An Evaluation of Medication Safety related Communications in the Patient Healthcare Pathway in Kuwait

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Submitted to the University of Hertfordshire in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

November 2022

Dedication

This thesis is dedicated to those who supported me the most, loved me unconditionally, believed in me and sacrificed for me.

My beloved late grandmother, Santa Alharbi

You always surrounded me with your love and tenderness; you were a source of happiness and joy to me. You supported me throughout my PhD journey until I lost you two months before submitting this thesis. I know you were looking forward to the completion of my PhD but Almighty Allah may have planned a better reunion in heaven for us.

My grandparents, Bejian and Atwaa Alharbi

Your unconditional love, support and prayers that you always surround me with mean the world to me. I have always found comfort in your advice and safety in being near you.

My parents, Bandar Alharbi and Nashmeyah Alharbi,

Words cannot express the amount of support you have provided. You sacrificed your time, health, and happiness so that my siblings and I could reach for the stars.

My husband, Mohammad AlMalek,

You believed in me the most, encouraged me and provided me with the unconditional love and support that I needed to complete my thesis. Without your endless sacrifices and motivation, I could not have reached this point.

Acknowledgements

I would like to express my gratitude to my supervisors Dr Nkiruka Umaru, Dr Nada Shebl, Dr Sherael Webly, and Dr Fatemah Alsaleh for their guidance, inspiration and support throughout this process. Not only have I learnt from their valuable discussions, but they have also inspired me with their professionalism. I extend my gratitude to Dr Abdullah Al Hamid for supporting me during the first year of my PhD, and to Dr Ilhem Berrou for preparing my PhD acceptance papers and for her invaluable support with the systematic review. I would also like to acknowledge Dr Ahmad Alsaber for his valuable statistical advice.

I would also like to acknowledge the Department of Civil Commission in Kuwait for sponsoring my scholarship.

This thesis would not have been completed without the support of my colleagues, the healthcare professionals in Kuwaiti hospitals and everyone who participated in this research, from the preliminary stage to the final stage.

I would also like to thank my support system—my family—my grandparents, my parents, my husband, my loving siblings, my mother- and father-in-law, aunts and uncles and sisters- and brothers-in-law for all their support and prayers. I would like to thank my study buddy, my stepson Athbi for encouraging me and motivating me, and my nephews and nieces for being my bundles of joy. Last but not least, my gratitude goes to my cousin, Dr Shorouq Alharbi, whose support lifted a heavy weight during difficult times.

Finally, I attribute having a memorable experience during my journey to my friends for their support and valuable discussions. Thank you Hessah Alaslawi, Hessah Alshammari, Ruba Azfar-Ali, Narjis Alshurafaa, Safia Sharif, Sarah Alsubaei, Mariam Jawdat and Yousraa Shoqui.

Abstract

Background: Patient safety is a recognised public health issue. When post-market medication safety information emerges, the benefits and risks of the medication concerned are usually evaluated by drug regulatory agencies. The outcomes of such pharmacovigilance activities are communicated to the public, patients and other healthcare professionals (HCPs). The aim of these medication safety communications might vary from improving the intended recipients' knowledge or attitudes to outlining specific actions to be followed by them. However, it is currently recognised that sharing medication-related information does not improve patients' safety on its own if not accompanied by an accurate implementation of these recommendations in clinical practice. Despite their importance in protecting patient safety and subsequently affecting public health, no previous study was found to have evaluated or described the process of creating and disseminating medication safety communications by the Kuwaiti drug regulatory agency. Equally, no study was found to have investigated the impact of or the factors affecting the implementation of regulatory-related medication safety communications in Kuwait. Therefore, this thesis aimed to address these gaps in knowledge by evaluating medication safety communications in the patient healthcare pathway in Kuwait.

Methods: This multiphase study was preceded by a systematic literature review of the factors affecting HCPs' implementation of regulatory-related medication safety communications, using a narrative synthesis approach. Following the systematic review, multiphase research was initiated. This consisted of three phases, each of which focused on a specific stakeholder group involved in the process of medication safety communication. Phase 1 involved Kuwait Drug and Food Control (KDFC), an administration within the Ministry of Health (MOH), as the regulatory agency responsible for pharmacovigilance activities. This was a convergent mixed-methods study. Data collection in this phase included documents produced by KDFC or issued to KDFC relating to medication safety and three face-to-face interviews with KDFC employees involved in pharmacovigilance activities. Documents were analysed using a descriptive quantitative approach and a framework analysis technique.

Phase 2 focused on healthcare professionals working in MOH hospitals in Kuwait. This phase was an exploratory mixed-methods study, where focus group discussions were conducted followed by the distribution of an online survey. The focus group discussions were analysed using a thematic analysis technique. In the second part of this phase, an online survey was

developed based on Phase 1, the focus group discussions and the systematic literature review. Survey data analysis included descriptive analysis (frequency and percentile) and statistical analysis including principal component analysis (PCA) and the Kruskal–Wallis H test, which was followed by a post hoc analysis of variables that had significant results. Other statistical tests applied included Fisher's exact test, the Mann–Whitney U Test, and multivariate regression analysis. Participants' answers to open-ended survey questions were analysed using a conventional content analysis technique.

Phase 3 was an interpretive phenomenology study. This phase involved semi-structured phone interviews with six female patients of childbearing age who used a valproate-related medication for epilepsy or migraine. These patients had been prescribed the valproate-related medication in one of six secondary hospitals and one specialist neurology hospital within the MOH hospitals. An interpretive phenomenological analysis technique was applied to analyse the transcripts.

Results: The results of the systematic literature review indicated that the factors affecting HCPs' implementation of medication safety communications occur at multiple levels. These levels included the sources or senders of the safety information (delays in the delivery of medications safety communications), healthcare institutions (hospitals' position and interpretations of the recommendations), the HCPs (knowledge of the content of medications safety communications), and the patients and/or their carers (willingness to use the medication concerned). Phase 1 revealed a lack of legislation and a pharmacovigilance-specific policy.
Results from Phase 2 reflected poor knowledge of the concept of medication safety communications within the context of pharmacovigilance and a lack of familiarity with the tools used by KDFC to communicate emerging medication information among HCPs. In the survey, although the majority of HCPs who responded were aware of the teratogenicity of VRM (65.1%, (n = 110/169)), only 2.6% had responded correctly to the statements of the VRM KDFC recommendations. More than half of the participants (57%) reported changing their practice to accommodate at least one intended KDFC recommendation. Providing female patients with written information (37.2%) and counselling female patients about contraceptive use (37.2%) were the most reported intended changes in practice. The most reported barriers to implementation included not having the capacity in terms of time and/or the infrastructure to implement the recommendations (33.8%).

Four themes originating from patient interviews included (1) the timeline of the patient's experience (2) varied knowledge and perception with valproate use, (3) patient's expectations from HCPs and (4) experiences and preferences towards medication safety communications.

Conclusion: Medication safety communications are essential tools for disseminating information related to medication safety updates to HCPs, patients and the public. This research identified challenges at the level of the sender (KDFC) and the intended recipients (HCPs and patients) that could reduce the ability of KDFC's medication safety communications to reach clinical practices. The first step in increasing their reach is to adapt electronic methods for disseminating such information. Involving stakeholders, such as HCPs and patients, in evaluating the clarity and understandability of KDFC's medication safety communications should be the focus of future research.

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Research output

Papers

Alharbi, A. B., Berrou, I., Umaru, N., Al Hamid, A., & Shebl, N. A. (2023). Factors influencing the uptake of medicine risk communications by healthcare professionals in clinical practice: A systematic review. *Research in Social and Administrative Pharmacy*, 19 (1). https://www.sciencedirect.com/science/article/pii/S1551741122002078.

Alharbi, A. B., Berrou, I., Umaru, N., Al Hamid, A., & Shebl, N. A. (2022*). Factors influencing the implementation of medicine risk communications by healthcare professionals in clinical practice: a systematic review using the theoretical domains framework.* (Submitted for publication-manuscript under review).

Posters

Alharbi, A., Al Hamid, A., Umaru, N., & Shebl, N. A (2019, February). The uptake of medications risk communications in clinical practice [poster presentation-selected for oral presentation]. DUPHAT, Dubai, United Arab Emirates.

Alharbi, A., Al Hamid, A., Umaru, N., & Shebl, N. A (2019, March). Factors influencing the uptake of medication risk communications by healthcare professionals in clinical practice [poster presentation]. International Forum on Quality & Safety in Healthcare, Glasgow, United Kingdom.

Alharbi, A., Umaru, N., Webley, S., Alsaleh, F., & Shebl, N. A (2022, September). Healthcare professionals' knowledge and implementation of valproate related safety communications in Kuwait [poster presentation]. 80th FIP World Congress of Pharmacy and Pharmaceutical Sciences, Seville, Spain.

Alharbi, A., Umaru, N., Webley, S., Alsaleh, F., & Shebl, N. A (2022, November). Healthcare professionals' perceived barriers to the implementation of valproate-related regulatory recommendations in Kuwait [poster presentation-selected for oral presentation]. UKCPA Virtual Conference, 10 November 2022, United Kingdom.

Abbreviations

ADE	**Adverse Drug Event**
ADR	**Adverse Drug Reaction**
AES	**Adverse Events**
ATC	**Anatomical Therapeutic Chemical**
BW	**Black Box Warning/Box Warning**
CMS	**Central Medical Stores**
DHCP	**Dear Healthcare Professional**
DSC	**Drug Safety Communication**
EMA	**European Medicines Agency**
EU	**European Union**
GCC	**Gulf Cooperation Council**
GMP	**Good Manufacturing Practice**
HCPS	**Healthcare Professionals**
ICH	**International Conference on Harmonisation Steering Committee**
ICSRS	**Individual Case Safety Reports**
KDFC	**Kuwait Drug and Food Control**
LSE	**London School Of Economics and Political Sciences**
MedDRA	**Medical Dictionary for Regulatory Activities**
MHRA	**Medicines And Healthcare Products Regulatory Agency**
MM	**Mixed Method**
MOH	**Ministry Of Health**
NICE	**National Institute for Health and Care Excellence**
NHS	**National Health Service**
PSUR	**Periodic Safety Update Report**
PV UNIT	**Pharmacovigilance Unit**
RMM	**Risk Minimisation Measures**
SGLT2	**Sodium-Glucose Cotransporter 2**
SSRI	**Selective Serotonin Reuptake Inhibitors**
TDF	**Theoretical Domains Framework**
UK	**United Kingdom**
US	**United States**
VRM	**Valproate-Related Medication**
WHO	**World Health Organization**

Chapter 1: Introduction and Background

1.1 Introduction

1.1.1 Patient safety

Patient safety is a globally recognised public health challenge (World Health Organization [WHO], 2019). Ensuring patient safety is not the sole responsibility of a particular individual or organisation. However, it requires the active collaboration of patients and their families, healthcare facilities in all sectors and services, various groups of health professionals and government bodies such as ministries of health (WHO, 2021a). Patient safety is defined as:

> A framework of organized activities that creates cultures, processes, procedures, behaviours, technologies and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make errors less likely and reduce impact of harm when it does occur (WHO, 2021a, p. 1).

Globally, patient harm ranks as the 14th leading cause of disease burden (Jha et al., 2013). Patient harm is the "impairment of structure or function of the body and/or any deleterious effect arising there from", and this includes "disease, injury, suffering, disability and death" (Runciman et al., 2009, p. 21). Patient harm may be physical, psychological, or social (WHO, 2009). Patient harm is not exclusive to a specific healthcare setting. It can occur both in hospitals and in primary care settings. Different reasons could, but not necessarily, lead to patient harm. Among these reasons are medication-related events (e.g. medication errors) or reactions (e.g. adverse drug reactions) (Assiri et al., 2018; Insani et al., 2021; Slawomirski, Auraaen, & Klazinga, 2017). Medication-related harm are defined in the next section (1.1.2).

1.1.2 Definitions of medication-related harm

Following the introduction of Aspirin, the first synthetic medicine in 1897, there have been remarkable advances in medication developments. This included the synthesis of medications that aided in the prevention and treatment of diseases that were once considered to be fatal (Eder & Herrling, 2015; WHO, n.d). Public regulatory authorities play an essential role in ensuring that manufacturing companies adhere to medications-related regulations in terms of medicinal products manufacturing (Rick, 2004). This includes making sure that animal studies follow Good Laboratory Practice (GLP), that clinical trials follow Good Clinical Practice (GCP), and that drug manufacturing is conducted according to current Good Manufacturing Practice (cGMP) (Rick, 2004). Before a medicine reaches the market, its quality, efficacy and safety should be established (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH], 1997, 2003, 2005, 2011, 2020). Depending on the setting, the medicine use process in the post market-phase involves multiple steps, including procurement, prescribing, transcribing, order entry, preparation, dispensing, administration and monitoring (United States [US] Pharmacopeia, 2010).

Medication-related harm is considered when the medication is the potential source of an undesirable outcome. This undesirable outcome could take different forms, such as morbidity, or failure to produce a beneficial effect (e.g. due to drug–drug interaction, or mortality (Aronson, 2012; Panagioti et al., 2019). Latent injury could also occur, which includes the susceptibly of patients to injury during the process of care (Hepler, 2003, cited in Ackroyd-Stolarz, Hartnell & MacKinnon, 2006). Different scenarios surround, and result from, latent injuries. Examples in this regard include errors which are not significant enough to cause injury, as they are recognised and corrected before leading to damage; in some cases, years could pass before such errors cause harm due to a triggering event. Another example is an injury (harm) which occurs in some patients but not others, due to patients' characteristics [i.e., the presence or absence of risk factors (e.g. obesity) in patients with untreated hypertension that could result in a stroke (Ackroyd-Stolarz et al., 2006)].

Patient harm might result from adverse reactions. The WHO (1969, p.6) defines adverse reactions as "noxious and unintended, and which occurs at doses used in man for prophylaxis,

diagnoses or therapy". Edwards and Aronson (2000) employed the term *adverse drug effect* to describe all forms of toxic effects and unwanted side-effects. The purpose of this was to remove assumptions and ambiguity with respect to the dose and mechanism of the toxic effects and side-effects, as well as whether a side-effect is beneficial. They suggested that ADRs and adverse drug effects are interchangeable. However, the first term is patient-focused, whilst the second is medication-focused. Neither of these terms, however, is interchangeable with the term *adverse drug events* (ADEs; or adverse drug experience), which is a wider term that describes harm occurring during medicine use but not necessarily caused by a medication according to the authors (Edwards & Aronson, 2000). The European Parliament and the Council of the European Union expanded the definition of an ADR in 2010; the definition was changed so that, in addition to unintended and noxious effects that result from authorised use of medicines within their normal doses, it also included undesirable effects which stem from medicine errors or medicines used outside the scope of authorisation, such as misuse or abuse.

Patient harm can also occur when optimal care is interrupted. Hepler and Strand (1990, p.535) stated that a drug-related problem (DRP) is "an event or circumstance involving drug treatment that actually or potentially interferes with the patient's experiencing an optimum outcome of medical care". According to Ackroyd-Stolarz et al. (2006), DRPs encompass drug-related morbidity and medication misadventures (adapted from Manasse, 1989), which include medication errors, adverse drug reactions, and adverse drug events. The American Society of Health-System Pharmacists (ASHP) also classified medication harms as inherent, regardless of whether they are caused by prescribing or omission, and referred to it as medication misadventure, which encompasses all types of drug-related risks, including medication errors, ADEs and ADRs (ASHP, 1998; Manasse, 1989). Unlike the ASHP (1998), both Bürkle et al. (2013) and the Pharmaceutical Care Network Europe ([PCNE] 2020) differentiated between the harm itself and the potential reasons leading to the harm's occurrence. Bürkle et al. (2013) considered ADRs and ADEs to be forms of medicine harm that are part of a larger class of patient signs and symptoms. These clinical signs and symptoms could result from healthcare professionals' (HCPs) and/or patients' decisions and actions manifested as MEs. The authors separated ADE from errors related to drug omissions, as omissions are not linked to a certain drug or a specific drug pathway. However, they classified Harm resulting from medicine omission as *omission-related events* (Bürkle et al., 2013). In contrast with Bürkle et al. (2013), the PCNE (2020) specified the causes of medicine-related harm without categorising these causes as ME or not. The PCNE (2020) described actual or potential harm as drug-related

problems. These problems could be lack of treatment effectiveness, possible or actual ADE, unnecessary treatment, or ADR occurring at normal doses. In contrast with Bürkle et al. (2013), the PCNE considered medicine omission to be a potential cause of a drug-related problem (PCNE, 2020).

1.1.3 Preventable medication-related harm

Medication-related harm could be preventable. A systematic review and meta-analysis that pooled the results of 70 studies involving 337,025 patients in different healthcare settings was conducted by Panagioti et al. (2019). This review included quantitative observational studies (e.g. prospective or retrospective cohort studies) and cross-sectional studies carried out mostly in the US (47%), followed by Europe (39%), and other countries (14%). The majority of these studies were conducted in a general hospital involving patients from different specialities (64%), whilst 17% were conducted in advanced care specialties, including intensive care and surgery. This systematic review concluded that at least one in 20 patients suffered from preventable patient harm in the different medical care settings. Approximately 20% of the preventable patient harm led to permanent disability and death. The greatest percentage of patient harm was related to medications (25%) and other non-medications therapeutic treatment incidents (24%). These were followed by surgical procedures (23%), healthcare infections (16%) and diagnosis (16%) (Panagioti et al., 2019). Patient harm due to medications could be prevented. Based on a meta-analysis conducted by Hodkinson et al. (2020) involving 285,687 patients across 81 studies located primarily in Europe (32%) and the US (28%), one in 30 patients is subject to preventable medication harm. This review mostly included a prospective cohort (72%), followed by retrospective cohort studies (19%), and cross-sectional studies (10%). These studies involved general hospitals or internal medicine (36%), highly-specialised care settings (17%), emergency departments, ICU (10%), and primary care (5%). The prevalence of medication harm identified in this review was 9%, of which 3% was preventable. More than a quarter of the preventable medication-related harm estimated in this review was severe or life-threatening (Hodkinson et al., 2020).

A systematic literature review evaluated the definitions of "preventable harm" related to specific harm (e.g. drug-related events) and more general harm in 127 publications. The three

most common concepts of preventable harm include: (1) harm caused by identifiable and modifiable factors, (2) harm that can be prevented from recurring through reasonable adaptation to a process, and (3) harm that occurred where an existing guideline was not followed (Nabhan et al., 2012). However, external validity was not evaluated in most publications reporting these concepts (Nabhan et al., 2012). Hepler and Strand (1990) suggested that claiming an injury resulted from a drug-related (therapy) problem which was preventable requires meeting four conditions, namely: (1) the DRP leading to the injury was recognisable, (2) the adverse outcomes were foreseeable, (3) the causes of the outcomes were identifiable, and (4) the causes of the outcomes were controllable. However, not all medicine-related harm is preventable, and not all ADRs are known. When ADRs differ, in terms of their nature or severity, from the expected drug characteristics, deviating from domestic labelling and regularity marketing authorisation, these ADRs are regarded as unexpected ADRs (Edwards & Aronson, 2000). However, unrecognised ADRs are expected throughout the lifecycle of a medicine. This is because before any medication reaches the market, clinical trials are conducted with a limited number of individuals, excluding certain groups, such as pregnant women and the elderly (WHO, 2004). Thus, although the balance between benefit and risk is acceptable in the premarketing stages, a shift in this balance is possible. On the one hand, emerging evidence from the post-market phase may suggest that a medicine has broader efficacy than that identified from the pre-market phase, and that its safety in the actual population is acceptable (Rawlins, 1987). However, efficacy might be lower than expected, and safety concerns might arise (Rawlins, 1987). One of the international strategies used to mitigate patient harm resulting from ADRs includes pharmacovigilance activities. The WHO (2002) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (p.42).

1.1.4 Unrecognised ADRs and pharmacovigilance

ADRs have been associated with hospitalisation (Bénard-Laribière et al., 2015; Oscanoa, Lizaraso, & Carvajal, 2017; Patel & Patel, 2018), extended hospital stays (Khan, 2013), increased healthcare costs (Khan, 2013; Kuula, Backman, & Blom, 2022) and mortality (Kuula et al., 2022; Patel & Patel, 2018). It is inevitable that previously unknown ADRs might occur with a medication throughout its lifecycle as premarketing clinical trials are

usually underrepresent the actual population (WHO, 2004). The significance of unrecognised or post-market ADRs was acknowledged after the thalidomide disaster, where thousands of infants were born with congenital deformities due to maternal exposure to thalidomide, which was once promoted as being safe for consumption during pregnancy. This disaster led to a rise in international efforts related to detecting and sharing post-market medicine safety information (WHO, 2002). In its 16th assembly, the WHO (1964) called for the creation of a system through which ADR information could be shared. In 1968, the WHO launched a programme for international drug monitoring [The WHO for International Drug Monitoring (WHO PIDM)], which includes more than 170 full and associate members from different countries worldwide (World Health Organization Collaborating Center for International Drug Monitoring at Uppsala [WHO-UMC], 2023a). To minimise and manage ADRs, pharmacovigilance includes four basic activities, namely risk identification, assessment, mitigation and communication (Beninger, 2018). Pharmacovigilance is necessary for both public health, and to support the rational and safe use of medicines (WHO, 2002). The Oxford English Dictionary defined safety (2022) as the "state of being protected from or guarded against hurt or injury; freedom from danger". In the context of pharmacovigilance, Aronson (2012, p. 11) defined medication safety as the "avoidance, prevention, or mitigation of harms or hazards that arise from the use of medicinal products". Pharmacovigilance activities could achieve their goals of safeguarding patients by disseminating their regulatory action into clinical practice and having this action translated by HCPs and patients in clinical practice. Background information related to pharmacovigilance are provided in the next section (1.2).

1.2 Background

1.2.1 National pharmacovigilance centres

Upon the WHO meeting in 1972, developing national centres for medication safety monitoring was encouraged (WHO, 1972). A national pharmacovigilance centre was defined by the WHO (2002) as a "single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyse and give advice on all information related to drug safety" (p. 42). The functions of a pharmacovigilance system were drawn up by the WHO (2018), and a set of minimum requirements were indicated. The requirements include the following: (1) At least one full-time staff member, source of funding and clear structures and roles, (2) A spontaneous reporting system with national forms for safety reports, (3) A system for the collection and management of the safety reports, (4) An advisory committee with expertise in ADR or pharmacovigilance to provide support in different aspects of the pharmacovigilance centre's activities, and (5) A clear communication strategy for both routine and crisis situations.

Upon meeting the previous requirements and establishing a national center, the activities of the center, along with those of other parties, will be guided by established guidelines for good pharmacovigilance practices. There was a need for such guidelines because of the varying strategies applied by the worldwide centres, the effects of pharmacovigilance centres on communities, and the need to protect different stakeholders involved in, or affected by, the centers' activities (Meyboom, 1997). The targeted parties of these guidelines could be the member countries, stakeholders involved, or pharmaceutical industries performing pharmacovigilance activities. An example of a good pharmacovigilance practice guideline targeting the pharmaceutical industries is the document issued by the Food and Drug Administration (FDA) of the US (US FDA, 2005). This clearly states that there is no legal obligation on the industries to adhere to the guideline itself; rather, it reflects the current FDA's thinking on certain topics. These topics are grouped into three categories: safety signal identification; pharmaco-epidemiological assessment and safety signal interpretation; and

pharmacovigilance plan development. Another example is the high-quality pharmacovigilance practice guideline produced by the European Union (EU) and administered to the Member States (European Medicine Agency [EMA], 2022a). It stands on a legislation framework that applies to the centrally- or nationally authorised medicinal products across the EU and shows the responsibilities of the marketing authorisation holders. This guideline considers all the aspects of pharmacovigilance, including: the process, products and population. It also identifies patients as reporters of adverse reactions. Moreover, it recommends including representatives of patients and healthcare providers in the Pharmacovigilance and Risk Assessment Committee. Finally, the guideline on good pharmacovigilance practice in Arab countries was developed in 2014 and declared effective in 2015 (The League of Arab States, 2014). This guideline was influenced by that of the EU and developed by different national medicines authorities from the following countries: Egypt, Jordan, Oman, Saudi Arabia, Tunisia, and the United Arab Emirates. Although it aims to harmonise the pharmacovigilance activities across the Arab countries, it takes into account the current varying practices and declares that it should be considered as an ideal model to be followed by the Arab states. This document provides the obligations to be fulfilled by the marketing authorisation holders, as well as detailed descriptions of the risk identification, risk assessment and risk mitigation processes. Different Arab countries approved this guideline, including all the Gulf Cooperation Council (GCC) countries, namely: Saudi Arabia, the United Arab Emirates, Qatar, Bahrain, Oman and Kuwait (Al-Essa, Al-Rubaie, Walker, & Salek, 2015). A total of fifteen modules are included in this guideline relating to pharmacovigilance activities and marketing authorising holders' responsibilities, such pharmacovigilance: systems, system master file and inspection, risk management systems, signal management, safety communication and risk minimisation measures (RMMs). Three of the fifteen modules were not published (i.e., they were underdevelopment), including public participation in pharmacovigilance, international cooperation, and continues pharmacovigilance, ongoing benefit to risk evaluation, regulatory action and planning of public communication (The League of Arab States, 2014).

Despite the common pharmacovigilance guideline, harmonisation in pharmacovigilance is still lacking amongst the Arab countries (Alshammari, Mendi, Alenzi & Alsowaida, 2019). Pharmacovigilance systems across the Arab countries countries differ in terms of their levels of complexity and maturity, ranging from well-established to poorly-established systems (Alshammari et al., 2019). Data from the WHO-UMC (2023a) indicates the variabilities in the status of the Arab countries in terms of their membership of the WHO-UMC. Amongst the

Arab countries, Tunisia was the first to establish a national pharmacovigilance centre in 1984, followed by Algeria in 1988, and Morocco in 1989 (Alshammari, Alenzi, & Ata, 2020). Morocco (in 1992) and Tunisia (in 1993) were also the first Arab countries to join the WHO-UMC. As of April 2023, 19 Arab countries were members of the WHO International Drag Monitoring programme (WHO-UMC, 2023a, 2023b). The details of this are in Figure 1.1.

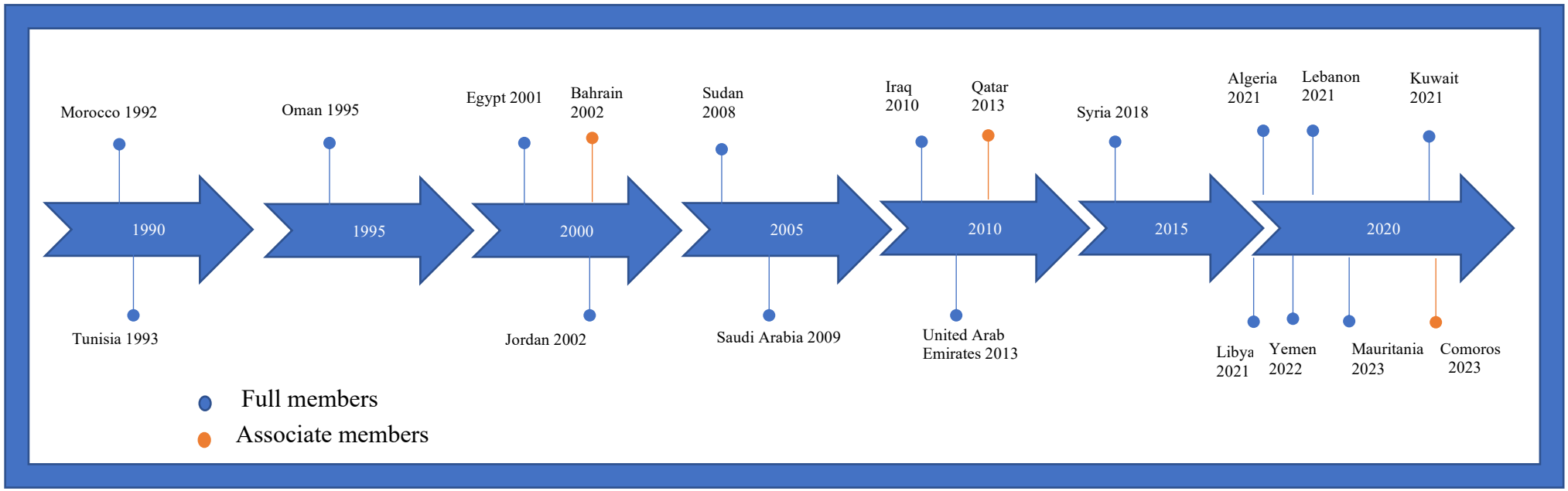


Figure 1.1 Arab countries' membership status with the World Health Organization (WHO) Collaborating Center for International Drug Monitoring at Uppsala (WHO-UMC)

Figure 1.1 represents the membership status of Arab countries according to the year of status update, last updated 11 April 2023 (WHO-UMC, 2023a, 2023b). Three Arab countries are not members of the WHO-UMC, including Djibouti, Palestine, and Somalia (Alshammari et al., 2019).

1.2.2 Pharmacovigilance activities

Pharmacovigilance involves four basic activities, namely risk identification, assessment, mitigation and communication (Beninger, 2018). Countries with pharmacovigilance centres rely on spontaneous ADR reporting, which could be from the patients, healthcare professionals, or the manufacturer, for risk identification (Pal, Duncombe, Falzon, & Olsson, 2013). Spontaneous reporting is a passive form of pharmacovigilance and relies heavily on the motivation of the reporter, whether a healthcare professional or a patient, to report. This voluntary form of reporting, although mandatory in some countries, requires training of the healthcare professionals and the community regarding the mechanism of reporting (WHO, 2013). However, underreporting remains a widespread challenge for pharmacovigilance (Hazell & Shakir, 2006). Another way in which ADRs can be detected is the cohort event monitoring [CEM (WHO, 2013)]. Such a reporting system complements spontaneous reporting systems (Pal et al., 2013). This prospective observational cohort study focuses on the detection of adverse events related to new medicines, although it was also used for other medicines (Pal et al., 2013). Cohort event monitoring is an active form of pharmacovigilance, which involves detecting adverse events by enquiring directly with patients or reviewing their medical records (WHO, 2013). Examples of cohort event monitoring are the Intensive Medicines Monitoring Program (IMMP) in New Zealand, and prescription event monitoring (PEM) in England (WHO, 2013). China also uses a similar method for monitoring contraceptives in rural areas (WHO, 2013). Targeted spontaneous reporting is another method for detecting risks derived from both spontaneous reporting and cohort event monitoring. This form of pharmacovigilance involves considering ADR monitoring as a standard of care as much as the routine practice of monitoring treatment success or failure and other forms of practice within a patient cohort (WHO, 2012a). Targeted spontaneous reporting involves the reporting of adverse events by HCPs who manage a defined group of patients, such as those with drug-resistant tuberculosis. This type of spontaneous reporting addresses a specific set of questions and provides detailed monitoring that is affordable and feasible (Pal et al., 2013).

Following data entry from ADR reports, a causality assessment is conducted. Whilst a quantitative estimation of a drug–ADR relationship that is both reliable and precise cannot be achieved,

causality assessments involve a systematic assessment of the reports of ADRs to identify a causal link between the medicinal product and an ADR (Kaeding, Schmälter, & Klika, 2017; WHO-UMC, 2018). The WHO-UMC (2018) involves six criteria (certain, probable/likely, possible, unlikely, conditional/unclassified, unassessable/unclassifiable) based on the information written in individual case safety reports (ICSRs), including time of occurrence of the ADR in relation to the drug use, whether or not the ADR could be explained by the underlying disease, and the clinical response to drug withdrawal.

A core activity of pharmacovigilance is signal detection aimed at identifying side-effects of a drug product that were either previously unrecognised or were incompletely described (UMC-WHO, 2022). It is not feasible to evaluate all submitted ICSRs due to the huge number of reports regarding the submitted ADRs, which were approximately 14 million in the WHO database since 1968 (Ralph Edwards, 2017). Thus, the WHO-UMC utilises a mixed approach which includes the data mining process and clinical evaluation of the prioritised ADR–drug combinations, along with qualitative screening of the scientific literature. Selected combinations are then individually evaluated to check if the side-effects were previously described in the drug product information, and whether a further deep evaluation is required (WHO-UMC, 2022).

Decisions made by regulatory agencies are usually communicated to HCPs, patients and the public. Such communications are issued by regulatory agencies or pharmaceutical companies (after prior approval from the regulatory agency) and relate to the post-market use of medicines (de Vries et al., 2018). These communications usually include emergent information regarding the benefit to risk balance, decisions on whether to withdraw medicines from the market, recommended changes to practice, or the provision of changes to healthcare professionals without specifying practice changes (EMA, 2014; Weatherburn, Guthrie, Dreischulte, & Morales, 2020). Between 2014 and 2017, 86 label updates and 17 direct healthcare professional communications took place in the European Union (Farcaş, Măhălean, Bulik, Leucuta, & Mogoșan, 2018). Moreover, 19 medications were withdrawn between the years 2002 and 2011 in the EU due to safety reasons (McNaughton, Huet & Shakir, 2014). The underlying reasons for these withdrawals were cardiovascular events or disorders (n=9), hepatic disorders (n=4), neurological disorders (n=4) or psychiatric disorders (n=4). Between the years 1953 and 2013, 462 medications withdrawals

occurred in different geographical areas including, Africa (n=63), Asia (n=150), Australia and Oceania (n=32), Europe (n=309), North America (n=134), South America (n=65). Hepatotoxicity accounted for 18% of the withdrawals, followed by immune-related reactions (17%), neurotoxicity (16%), cardiotoxicity (14%), carcinogenicity (13%), haematological toxicity (11%) and drug abuse and dependence (11%). Death was related to 25% of the withdrawals (Onakpoya, Heneghan & Aronson, 2016). Figure1.2 presents examples of post-market withdrawals of medications from the years 1954 to 2022 (Aronson, 2012; EMA, 2010; US FDA, 2018a, 2018b, 2020, 2022).

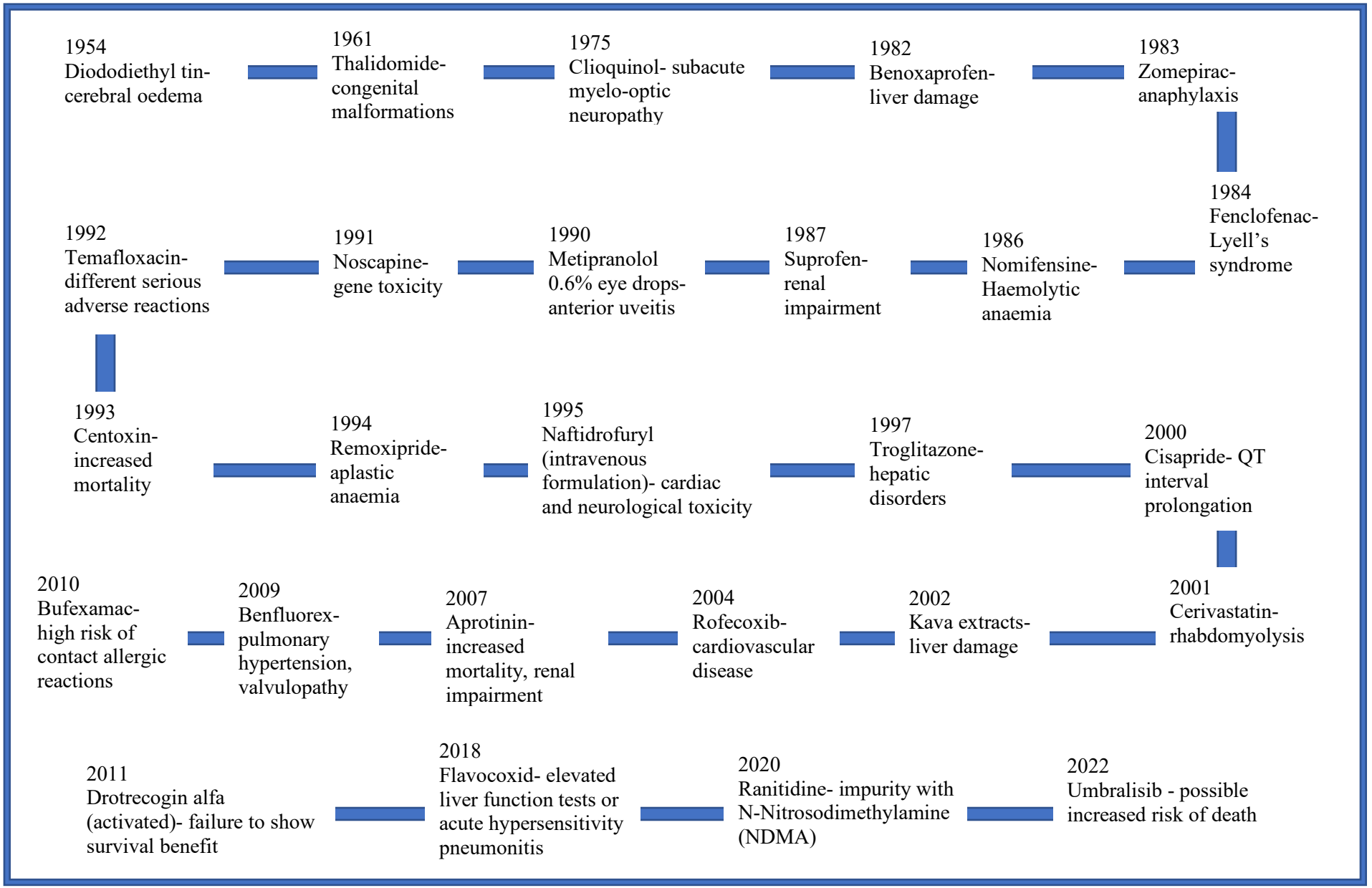


Figure 1.2: Examples of post-market medication withdrawals (Aronson, 2012; EMA, 2010; US FDA, 2018a, 2018b, 2020, 2022)

1.2.3 Pharmacovigilance regulations

In 1995, the European Union established a pharmacovigilance legislation in order to reduce the number of ADRs within the European Union. Based on the European Union pharmacovigilance legislation and the good pharmacovigilance practice (GVP) modules, EMA developed 20 tasks for centrally- and nationally-authorised products. Examples of these include risk management systems (GVP module V), periodic safety update reports (GVP module VII), ADR management (GVP model VI), post-authorisation studies (GVP module VIII), signal management (GVP model XI), management of the listed products under additional monitoring (GVP model X), safety communications (GVP module XV), risk minimisation measures and monitoring of effectiveness (GVP module XVI), and coordination of pharmacovigilance inquiries (EMA, 2021a). These new tasks, or reinforced tasks, mainly fall under four groups, including pharmacovigilance system master files, periodic safety update reports (PSUR), post-authorisation safety and efficacy studies, and risk management plans (EMA, n.d.-a). The first three are discussed in this section, and risk management plans are discussed in the following section. A pharmacovigilance system is defined as:

> a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities listed in Title IX [Pharmacovigilance] and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance (The European Parliament and the Council of the European Union, 2001, p. 14).

Moreover, a pharmacovigilance system master file is "a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products" (The European Parliament and the Council of the European Union, 2001, p. 15). Any marketing authorisation applicants should provide an overview of the pharmacovigilance system, including proof that a qualified person responsible for pharmacovigilance is at the applicant’s disposal. The file should also include the Member States where the qualified person carries out his/her pharmacovigilance- related activities, the contact details of this qualified person, and a statement from the applicant stating that they have the

necessary means to carry out, and undertake, the pharmacovigilance tasks and responsibilities, respectively. The marketing authorisation holder should also indicate the location of the master pharmacovigilance file of the medicine (EMA, 2017a).

PSUR is a post-authorisation evaluation tool presented by the marketing authorisation holder at specific time points during a medicine's lifecycle in order to provide a comprehensive, concise, and critical analysis of the risk–benefit balance of the medicine, taking into account new and emergent information that accumulates after the medicine is marketed. Thus, this tool takes into account the population that was not included in the preauthorisation phase. As a result of this process, a new risk–benefit balance might be established, and more information regarding the product's safety could be obtained. Although this tool is not used to deliver urgent safety or efficacy information, the said tool might lead to the discovery of new safety issues (EMA, 2013).

Post-authorisation safety studies may include interventional or non-interventional studies relating to an authorised medicinal product, either initiated by the marketing authorisation holder or requested by the regulatory agency, to identify, characterise, or quantify a safety hazard, verify the safety profile of the medicine, or assess the efficacy of risk management measures (EMA, 2017b; The European Parliament and the Council of the European Union, 2001).

Post-authorisation efficacy studies might be requested by a regulatory agency, either at the point of approving an initial marketing authorisation, when the agency has concerns about certain aspects of the efficacy of a medicine, which need to be addressed post-marketing, or post-authorisation, when the understanding of the disease and clinical methodology or the medicine's use in real life situations indicate that the previously-stated efficacy needs to be revised significantly. Additionally, these kinds of studies could be requested in certain instances, such as marketing authorisation approved in exceptional circumstances (EMA, 2022b).

1.2.4 Risk management plans

The importance of pharmacovigilance activities became widely recognised in the second half of the twentieth century. Most of these activities focus on the detection of adverse drug reactions in post-marketing phases. Decades after the first implementation of pharmacovigilance functions, the Japanese Ministry of Health and Welfare proposed "*Early phase post marketing vigilance*" at a meeting of the ICH in Tokyo in 2001. This concept was provided by Japanese regulators as an illustration of an early-phase post-market risk management plan (Hartford et al., 2006). Thereafter, the ICH provided guidance on early pharmacovigilance activities that should be continued throughout the lifecycle of medication (Hartford et al., 2006; ICH, 2004). Likewise, the Council for International Organizations of Medical Sciences (CIOMS) VI guidance in 2005 recommended that the concept of pharmacovigilance and its related activities be applied to pre-marketing phases. It was considered by this working group that risk management plans should be formally developed and be drug-specific. This recommendation aimed to guard safety during clinical trials and ensure the availability of as much safety information as possible. At that time a risk management plan was not a legal requirement, but it was recommended that the produced document be legally sound (CIOMS, 2005).

A risk management plan is a document that is submitted by an applicant of a drug marketing authorisation to a regulatory agency (EMA, 2017b). This document describes the risk management system that is required for the identification, characterisation and minimisation of risks associated with certain medications (EMA, 2017b; The European Parliament and the Council of the European Union, 2010). Risk management plans should be differentiated from the management of medications' single risk, which involves the detection, assessment, minimisation and communication of that particular risk (Calvo Hernaez & Zúñiga, 2011).

Article 30 European Commission Implementing Regulation No. 520/2012 illustrates the elements of risk management plans (The European Commission, 2012). These elements require applicants to identify or characterise the safety profile of a drug, indicate how to further characterise the safety profile of the drug, report risk minimisation measures related to risks associated with the drug of

concern, and report how these risk minimisation measures will be evaluated for their effectiveness. Moreover, applicants are required to report post-authorisation obligations. Besides these elements, applicants are required to report whether post-authorisation studies (if relevant) are indicated, managed or financed by the applicants or marketing authorisation holders.

Risk management plans involve two parts. The first part involves a safety specification and pharmacovigilance plan, while the second part involves the evaluation of a need for risk minimisation activities and risk minimisation plans (Calvo Hernaez & Zúñiga, 2011). A safety specification is a summary that includes important identified risks, important potential risks, and any important missing information (ICH, 2004). Furthermore, this summary describes the population at risk and any unanswered safety questions that could influence the benefit–risk balance of the medication (ICH, 2004).

A pharmacovigilance plan is part of a risk management plan, wherein applicants discuss how they will further characterise safety concerns, and is based on information provided in a safety specification (EMA, 2017b; ICH, 2004). A pharmacovigilance plan focuses on actions with which to address risks, possible risks, and important missing information (ICH, 2004). If additional risk minimisation activities are not required in the pharmacovigilance plan, routine pharmacovigilance, including the minimum set of activities that are necessary for all medications, will be sufficient (ICH, 2004).

The second part of risk management plans involves evaluating the need for risk minimisation measures and designing actions for these measures (Calvo Hernaez & Zúñiga, 2011). Risk minimisation measures required in such plans differ from routine risk minimisation measures required for every medicinal product, such as a summary of the product characteristics, labelling, package leaflet, packet size, and the legal status of the product in cases of potential misuse (EMA, 2017b). For routine risk minimisation measures, product information could be located on the inner or outer packaging (CIOMS, 2014). Moreover, it could be directed to HCPs (summary of product characteristics [SmPC and SPC], data sheet, drug data sheet, safety data sheet, package insert, and product information) and to patients (package leaflet, patient information leaflet, patient product information, patient information, consumer medicine information, patients' instructions for use, patient package insert [PPI]) (CIOMS, 2014). In the US, pharmaceutical companies are expected to submit structured

product labelling (SPL) with all of its submissions that involve changes or modifications to the medicine labelling or changes being affected. In addition, they should submit SPL with the submission of the final approved content of labelling, and with annual reports, unless no changes have been made to previous final SPL. In this case an annual report would include a reference to previously submitted electronic SPL (US FDA, 2009).

1.2.5 Risk minimisation measures

Risk minimisation measures (or additional risk minimisation measures) that are required to be specified in the second part of risk management plans are specific, and are required if they are essential for supporting safe and optimal medicinal use. The need for such measures should be evaluated periodically (EMA, 2017b). Risk minimisation measures differ from other parts of risk management plans because they need the cooperation of different stakeholders, including regulators, marketing authorisation holders, healthcare professionals, and patients, to ensure their success (EMA, 2017b). Applicants are required to provide five sections in their description of risk minimisation measures. These include the rationale, objectives, descriptions, and implementation and evaluation plans (EMA, 2017c). Similar to the risk minimisation measures required by EMA, in the US a Risk Evaluation and Mitigation Strategy (REMS) can be required by the FDA, which includes educating or implementing actions to prevent, monitor and/or manage specific serious risks (US FDA, 2021).

Examples of risk minimisation measures include educational programmes, such as guidance for prescribers, guidance on special administrative procedures, and patient alert cards. Moreover, risk minimisation measures can include pregnancy prevention programmes and controlled-access programmes (different from legally controlled programmes), e.g. the requirement of a specific test to ensure patients' compliance, or documentation from a prescriber, pharmacist or patient that acknowledges their understanding of the information received (EMA, 2017c). Another strategy could be that of restricted-access tools, including reminder systems and performance-linked assessment systems. Reminder system tools are manifested as patient agreements or consent, registration programmes for wholesalers and retailers (e.g. restricted pharmacy distribution), certification programmes for HCPs, and a limited amount/prescription or number of prescriptions or a limited

amount/pack (CIOMS, 2014). Among performance-linked assessment system tools are product access linked to laboratory test results, prescribing allowed only by specialists, reimbursement allowed only when a drug has been prescribed within the indication (not off-label), and prescribing allowed only to patients with the correct pharmacogenomic profile (CIOMS, 2014). A controlled regulatory framework is another form of additional risk minimisation measure. This strategy is performed when the public health impact has been deemed to be significant. This strategy includes regulatory scheduling (such as narcotic drugs) and the ordering of drug market withdrawal (CIOMS, 2014). Manufacturing restrictions are a further strategy that involves altering a drug's physical appearance, packaging or dose (CIOMS, 2014). This form of risk minimisation measure is used for both routine risk minimisation measures as well as for additional risk mitigation strategies. This strategy includes low-dosage formulations, coloured and/or coded dosages, and restricted packaging (CIOMS, 2014).

Communication is a useful additional risk minimisation strategy to consider whenever routine product information is considered to be inadequate. It should be used for an important risk where an increased awareness of circumstances for use beyond routine product labelling may minimise or mitigate a risk (CIOMS, 2014). Communication, such as Dear Health Care Provider Letters, is used to deliver information (DHPL and DHCP). They are intended as a fast method of delivering emergent information, while being able to reach a wide range of audiences (CIOMS, 2014). Patient brochures targeted at specific patient populations aim at providing both information and education to patients (CIOMS, 2014). These tools have the advantage of empowering patients (CIOMS, 2014). In addition, they might aid in early recognition of an adverse event, leading to earlier treatment. On the other hand, their impact needs to be evaluated, especially as patients' literacy levels might play a role in the success of these tools (CIOMS, 2014).

1.2.6 Medication safety communication

Medication safety communication is the "active dissemination of safety information for an intended audience" (EMA, 2017d, p.4). It is one of the dynamic activities of pharmacovigilance that is required in order to achieve the goal of reducing patients' harm resulting from an adverse drug reaction (ADR) or medication error within the context of its benefits (Bahri et al., 2015; Beninger, 2017; Leong, Salek & Walker, 2015; Nebeker, Barach & Samore, 2004). This communication of safety information is expected to differ from unstructured communication in its intentionality, content, audience, source of information, and flow of safety messages (Plough & Krimsky, 1987). Messages involved in medication safety communication have a defined intentionality and specific expectations in terms of their outcomes, created by experts, directed to target audiences, and flowing from experts to audiences through established pathways (Plough & Krimsky, 1987). Medication safety communication is also required to be accurate (US FDA, 2011). Safety communication is not to be confused with transparency, which aims to share information related to authoritative activities with the public and enable democratic decisions (Bahri, 2010; EMA, 2017d). There are different objectives of medication safety communication according to the US FDA (FDA, 2011). These can be either for ethical or responsibility fulfilment, regardless of whether people have understood them or not (e.g. package information inserts), to facilitate a change in people's beliefs, knowledge, attitudes or opinions, where a unified course of action cannot be advised to all patients, or for behavioural change, where a course of action is known to be best for patients. The expectation of the final objective is that audiences will act upon receiving safety information or messages. Medication safety communication can be divided into statutory information (e.g. package leaflets) or that which involves new safety information, defined by the EMA (2017d) as "new information about a previously known or unknown risk of a medicine which has or could have an impact on a medicine's risk-benefit balance and its condition of use" (p.4).

Pharmacovigilance centres have different strategies for communicating medication safety information. EMA publish safety information on its website or via media and requires direct healthcare professional communications to be sent through marketing authorisation holders (EMA, 2014; EMA, 2017d). The

Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK) publish 'Dear Healthcare Professional' Communications on their website (de Vries et al., 2017; UK MHRA, n.d.). Furthermore, the MHRA disseminate medication safety information through posting alerts on their website, and providing broadcasts and news headlines on their Central Alerting Network (UK MHRA, n.d.). In addition, educational materials are also utilised in Europe, although to a lesser extent than previous methods (de Vries et al., 2017). The US FDA used to communicate safety information via different methods, but this was standardised in 2010 to the use of a single method, i.e. Drug Safety Communication (DSC), in posting safety information on their website that is aimed at both healthcare professionals and patients (US FDA, 2007; US FDA, 2015). In the most serious situations, the FDA will issue a black box warning (or box warning) on their website, medication package inserts, and on the websites of marketing authorisation holders (O'Connor, 2010). The FDA also establishes relationships with different professional and trade associations, safety organisations, and patient groups that aid in the dissemination of safety information if needed (US FDA, 2016). In Japan, "Dear Doctor" Letters are issued by the Japanese Medication Regulatory Agency in two types, namely yellow and blue letters. Both involve important safety information regarding medications and medical devices. The yellow letters include emergent information to be communicated to HCPs, but the blue letters do not require emergent communication as the yellow letters, although rapid communication is required (Japan Pharmaceuticals and Medical Devices Agency, n.d.). In Arab countries, the guideline on good pharmacovigilance practice in Arab countries stated the channels for delivering emergent safety communication. These include Dear Healthcare Professional Communications, press releases, websites, and newsletters, although they have not yet been implemented by many countries in this region (Alshammari et al., 2019; The League of Arab States, 2014).

1.2.7 Risk communication in the context of benefits and risk perception

In order to approve a medication for marketing, safety and efficacy data are based on the results of randomised controlled trials. Usually, patients participating in these trials are under controlled conditions, and patients with other diseases and using different medications long-term are excluded from these trials. Thus, limited information on the use of medications in these subgroups will be available. In addition, in clinical trials, participants are intensively monitored for adverse events, while in real-life situations a broader spectrum of patients, who could be older in age, using different

medications or with genetic abnormalities, are using medicines with less close monitoring. Thus, adverse events that are too rare to occur in clinical trials might occur in real-life situations, hence the need for continuous analysis of efficacy and safety through the lifecycle of a product. Such analysis is conducted immediately after the appearance of an issue, as well as periodically to assess accumulating data. Such periodic evaluations will mostly present data on the safety of a product; however, they will also add information on the effectiveness, the limitations of use, alternative treatments, and other aspects that are important to the benefit–risk assessment of a product (ICH, 2012). Disseminating accumulating evidence that affects the benefit–risk balance of a medicine is important from both regulator and recipient perspectives. Besides updating the benefit–risk balance based on recent evidence, benefit–risk communication facilitates regulators' decision-making process transparency, where the evaluation of harm is presented within the context of efficacy (Leong et al., 2015). Communicating both risks and benefits might reflect regulators' recognition of the possible influence of risk perception on recipients' response to the communicated safety issue. Components of risk perception are important to regulators when designing medication safety communication. In their strategy, the US FDA (2011) mentioned the importance of affective perceptions for the responses of target audiences. In their strategy of risk–benefit communication, the US FDA (2011) recommend providing information on both the risks and benefits of a medication, instead of only delivering information on the risks. Moreover, they highlight the importance of delivering information on the risks and benefits of not taking action. Furthermore, they recommend the use of evaluative tools to ease the access to information by recipients who are suspected to be influenced by affective perceptions.

Risk perception is an intuitive judgement that people make regarding risks (Slovic, 1987). Research on risk perception became recognised in the twentieth century and it was believed that it would help policymakers in health and safety to understand the different perceptions of risks across different recipients that might affect their responses. Such research examined what people really mean when they refer to risky situations and what factors may influence them. As a result, different studies were conducted in order to uncover the differences in risk perceptions between experts and laypeople (Slovic, 1987). Factors contributing to responses to risk were classified as key characteristics of low risk perception or key characteristics of high risk perception (Gibson et al., 2012). This classification is based on a dual characterisation of risk perception as being either high or low. Some of these factors

include benefits, familiarity, knowledge, type of risk, uncertainty, manifestation, and social or scientific status (Slovic, 2000, cited in Gibson et al., 2012). Table 1.1 illustrates the differences between the aforementioned factors and the characteristics of risk perception.

Table 1.1: Factors contributing to low or high-risk perception (Slovic, 2000, cited in Gibson et al., 2012)

Factors	Low risk perception	High risk perception
Benefits	High benefits	Low benefits
Familiarity	Old risk	New or novel risk
Knowledge about risk	Known to exposed people	Not known to exposed people
Type of risk	Chronic (e.g. kills one person per time)	Catastrophic (e.g. kills many people per time)
Uncertainty	Known to science	Not known to science
Manifestation	Immediate/reversible damage	Delayed/irreversible damage
Scientific status	Consensus possible	Controversial

In a review of risk perceptions, components of risk perceptions were differentiated as deliberative, experiential or affective (Ferrer & Klein, 2015). Deliberative risk perception was described by Ferrer and Klein (2015) as the process in which individuals depend on a set of reason-based strategies to reach an estimation of the likelihood that an event will occur. The authors further provide examples of this type of perception such as the "percentage likelihood of disease" or the "likelihood of disease compared to others". When discussing experiential risk perception, Ferrer and Klein (2015) explained it as being the process of making a rapid judgement resulting from the integration of deliberative and affective information (Damasio, 1994, cited in Ferrer and Klein, 2015; Sinclair, Ashkanasy & Chattopadhyay, 2010). Slovic and Peters (2006) characterise this component as the rapid handling of risk by feelings. In their research on risk perception, health behaviour, intention, and determinants of health behaviour, Dillard, Ferrer, Ubel and Fagerlin (2012) reported that this form of risk perception was the most predictive of participants' intentions

and attitudes towards colon cancer screening, except for worries about colon cancer that were predicted by comparative risk perceptions.

Affect is one of the most studied components of risk perception (Sinclair et al., 2010). It was described by Slovic, Finucane, Peters, and MacGregor (2004) as the "faint whisper of emotion" (p. 312). It refers to the feeling state (be it consciously or unconsciously) regarding whether stimuli are good or bad (Slovic et al., 2004). One of the early studies that investigated the influence of affective evaluation on people's judgement of risks and benefits was conducted by Alhakami and Slovic (1994). The results of their study suggested a strong inverse interdependent relationship between risk and benefit judgements across the different items of their study. This meant that the higher the perceived risk, the lower the perceived benefit. However, they found a difference between the distance between these correlations (i.e. between risk and benefit) across the items. Participants' affective evaluation was a major predictor of these correlations. In situations in which individuals had favourable attitudes, high benefit and low risk correlations were noticed. Meanwhile, weak negative correlations (low benefit and high risk) were observed in individuals who had unfavourable attitudes (or evaluations) regarding the items. Affective situations were found to cause insensitivity to numbers and probabilities when strong affective meaning underlined the consequences (Slovic & Peters, 2006). Based on previous research, Slovic and Peters (2006) reported that the importance of rescuing one's life would be perceived to be great if it were the only life (or the first life) to be saved. However, this feeling will decrease as well as the difference that saving this one life will not be much valued when the total number of lives to be saved is 87 in comparison to 88 (Slovic and Peters, 2006).

1.2.8 Public right in transparent risk communication

In 1997, the Eric declaration emphasised open communication and transparency in pharmacovigilance activities (Hugman, 2006). The declaration was approved by 34 countries, and it highlighted the public's right to receive information regarding optimal medication use. In addition, it required that information about the safety of medications be openly, ethically, and effectively accessible to all (Hugman, 2006). Even though an accurate description of the

transparency of regulation requires a consideration of their practices and transparency frameworks, several laws are in place to hold regulatory bodies responsible for hiding information (Coplan, Noel, Levitan, Ferguson, & Mussen, 2011). A new level of transparency was sought by European Union legislations, for example, by making information about the different processes of pharmacovigilance, such as decision-making and monitoring, publicly available (EMA, 2017d). In the United Kingdom, the MHRA is accountable for transparency based on the Freedom of Information Act of 2000 (Grigg, O'Sullivan, Goldacre & Heneghan, 2019). Additionally, the US FDA posts quarterly reports on its Center for Drug Evaluation and Research website based on its 2007 FDA (FDAAA) legislation (Chakraborty & Lofstedt, 2012). In Arab states, the Arab pharmacovigilance guideline recommends that the regulatory authorities maintain a list of medications requiring monitoring, and make this list publicly available on their website (The League of Arab States, 2014).

1.2.9 The challenges of medicine safety communication within the modern age

With current modern advances in communication and the flow of information, medication safety communication can be challenging. Information system technologies have advanced over the years. In the 1970s, the Bulletin Board System allowed software, data, messages, and news exchange among its users. Homepages gained popularity in the 1990s, through which an individual could share personal information. In 1995, online shopping and corporate webpages emerged with Amazon and eBay, and in 2001, dot-coms emerged. Kaplan and Haenlein (2010) defined social media as "a group of Internet-based applications that build on the ideological and technological foundations of Web 2.0, and that allow the creation and exchange of User Generated Content" (p. 61). Web 2.0 (a term introduced in 2004) describes a new way in which end users and developers started to use the World Wide Web. In particular, it is a platform through which content and applications are developed and published by all users collaboratively, no longer being created by individuals. Meanwhile, user-generated content describes the different forms of publicly available media content which are developed by end users. Health communication via social media was found in different forms. Social media is used to share health information with HCPs, patients, and the public. In addition, it is used to enable patient–patient and patient–HCP dialogue. What is

more, it is used to obtain information on patients' experiences, as well as their opinions on health services. Moreover, social media is used for health promotion and health education, as well as providing social support and influence to health interventions (Moorhead et al., 2013). In addition to facilitating interactions, social media has been used to share and receive health messages (Moorhead et al., 2013).

Huo et al. (2019) used the National Cancer Institute's Health Information National Trends Survey, which collects data in the US on changes in the field of health communication, to evaluate the temporal trends and predictors of social media use for health communication. It included exchanging health information in general public forums and exchanging medical information with healthcare professionals. Questions on sharing health information through social media were undertaken in the years 2013 and 2017 and included 4242 respondents. In contrast, questions regarding the use of social media for exchanging medical information with healthcare professionals were conducted in 2013 and 2014 and involved 4834 respondents. From the years 2013 to 2017, the authors reported that social media use for the purpose of sharing health information had significantly declined over time, specifically from 24.7% to 15.7% ($p<.001$). However, the use of social media for the exchange of medical information with a healthcare professional had nearly doubled from the year 2013 (2%) to the year 2014 (3.8%, $p=.025$).

Media in its various forms is a source of health-related information. In general, the media has played a role in health communication by connecting all stakeholders, including governmental sectors, healthcare institutions, and the public. This was clear during the COVID-19 pandemic, where international and local news networks played a role in promoting public awareness. Websites and social media platforms, such as Facebook, Instagram, and Twitter, were also used during the COVID-19 pandemic, where health guidelines and governmental instructions were posted. However, social media served as a channel for the fast spread of information, both true and false. This rapid spread of misinformation could have hindered the spread of awareness and risk mitigation strategies and promoted ineffective measures that lack supporting evidence (Mheidly & Fares, 2020).

The term “infodemic” (reflecting an information epidemic) was introduced in 2003 in relation to severe acute respiratory syndrome (SARS), but has not been limited to it. As it originated before the age of social media, multiple channels were traditionally used to spread information, such as mainstream media, specialist media, internet websites, wireless phones, text messages, pagers, faxes, and email (Rothkopf, 2003). An infodemic was explained by Rothkopf (2003) as follows: “A few facts, mixed with fear, speculation and rumor, amplified and relayed swiftly worldwide by modern information technologies, have affected national and international economies, politics and even security in ways that are utterly disproportionate with the root realities” (p. 1). Infodemics can occur when there is an excess of information, including misinformation and disinformation, during an epidemic. Digital and physical information systems facilitate the spread of infodemics between people. This makes it difficult for people to find credible guidance and trustworthy sources. The exacerbation of an infodemic was noticed during the COVID-19 pandemic. This led the WHO to launch the Information Network for Epidemics (EPI-WIN). The EPI-WIN is an information-sharing network that connects technical and social media teams within the WHO. This network disseminated and amplified COVID-19-related evidence-based information, while also tracking and responding to rumours. The WHO also collaborated with the US Centers for Disease Control and Prevention (US CDC) and conducted extensive research to produce a competency framework for infodemic managers as a new workforce to assist healthcare institutions in strengthening their infodemic managers’ capacity through recruitment, training, and human resource planning. Specifically, this framework was aimed to be a reference tool for different activities, such as job description development and revision, shaping responsibilities, and training need assessments and training plan development (WHO, 2021b).

A two-day online technical consultation on managing COVID-19 was held by EPI-WIN, involving technical experts and other stakeholders (e.g. academia, representatives of technological, web, and social media platforms and companies, and staff from ministries of health and institutes of public health). This consultation was aimed at collecting a range of information, evidence and ideas from the participants to draft an information response framework. Day one involved 1375 attendees, and day two 1169 (WHO, 2020a). In total, 594 ideas were obtained via brainstorming, which resulted in a framework that included the five following areas:

1. To strengthen the process of scanning, revising and verifying evidence and information.
2. To enhance knowledge interpretation and explanation, fact-checking activities, and misinformation handling.
3. To enhance the message amplification process from credible sources to those who need the information.
4. To strengthen the impact quantification process, which involves infodemic analysis, information flows, public acceptance of public health interventions, factors affecting infodemics, and individual and public behaviours.
5. To improve systems for infodemic management during health crises.

In this section, the researcher provided a background to pharmacovigilance. This included defining pharmacovigilance centres and stating the minimum requirements for a functioning pharmacovigilance centre set by the WHO. After this, the role of pharmacovigilance guidelines was explained with examples from the US FDA, EMA, and The League of Arab States. The main pharmacovigilance activities, including risk identification, assessment, mitigation and communication, were then stated. This was followed by introducing pharmacovigilance regulations, which included pharmacovigilance system master files, PSURs, post-authorisation safety and efficacy studies, and risk management plans. Both parts of risk management plans, including safety specification and pharmacovigilance plan, were also discussed. As an element of the pharmacovigilance plan, risk minimisation measures were differentiated from routine risk minimisation measures. Medication safety communication, as one form of risk minimisation measures, was explained with examples of strategies applied by different pharmacovigilance centres for medication safety communications. The importance of communicating risk within the context of benefit in medication safety communications was stated, and risk perception was presented. Following this, the challenges of medication safety communications in the modern age were presented. In the following section, background information about Kuwait, Kuwait's healthcare system, the patient healthcare pathway in Kuwait, medications registration, expenditure and consumption in Kuwait, and pharmacovigilance in Kuwait.

1.2.10 Kuwait

The State of Kuwait is located on the Arabian Peninsula of Western Asia and was established in 1716 A.D. (Al-Nakib, 2016). The surface area of Kuwait is 17,188 square kilometres, which is divided into six governorates: Al-Ahmadi, Mubark Al-Kebir, Hawali, Al'Asima, Al-Farwania and Al-Jahra (WHO, 2014). The official language of the state is Arabic, whilst English is also commonly understood across the country (Casey, Thackeray & Findling, 2007). Kuwait has a high literacy status, with education being compulsory for nine years (children aged from six to 14 years old). The literacy rate in Kuwait was estimated, in 2018, to be 99.1%, 96.1% and 72.7% amongst the age groups of 15-24, 15 years and older, and 65 years and older, respectively (United Nations Educational Scientific and Cultural Organization [UNESCO], n.d.).

The economic background of Kuwait has had a noticeable effect on the population growth, and on the development of the healthcare system. Up until the 1930s, the Kuwaiti natural pearling industry was recognised around the world and brought rewarding income to the state's economy (Casey et al., 2007; Crystal, 2016). However, the development of the cultural pearls in Japan led to a remarkable decline in the Kuwaiti pearling business. Whilst diving for pearls was fading in Kuwait, the petroleum industry started to develop with the discovery of oil on Kuwaiti land. Just after World War II, Kuwait began to export its oil to the rest of the world, building a strong foundation for its growing economy (Casey et al., 2007; Crystal, 2016).

The total population of Kuwait rose from 153,096 individuals in the year 1950 to approximately 4 million (Kuwaitis: 30.36%; Expatriates: 69.64%) in 2015. Similarly, the net rate of migration to Kuwait per 1,000 of the population grew from 4.6 in 1950 to 38.7 in 2015 (The Public Authority for Civil Information, 2018; UNESCO, n.d.; United Nations, 2017). The Kuwaiti Public Authority for Civil Information (2022) shows that the current population of Kuwait is 4,464,427 (60% males and 40% females). Approximately 66.35% of the total population are non-Kuwaitis, and 33.65% are Kuwaitis. The most common nationalities in Kuwait, in descending order, are: India, Egypt, Bangladesh, Philippines, Syria, Saudi Arabia, Sri Lanka, Pakistan, Jordan and Nepal (Kuwait

Public Authority for Civil Information, 2022). The distribution of females and males amongst Kuwaitis is almost equal, at 51% and 49% respectively. However, males represent 66%, and females 34%, of the non-Kuwaiti population (Kuwait Public Authority for Civil Information, 2022).

The life expectancy at birth (years) for the population in Kuwait is 78.7 for men and 79.4 for women. The crude death rates (deaths per 1,000 of population) declined from 13.5 in the 1950s to 2.6 in 2010 to 2015. The infant mortality rate (per 1,000 live births) also improved dramatically from 124 in the years 1950 to 1955, to eight deaths during the years spanning 2010 to 2015 (United Nations, 2017). The three major causes of death in Kuwait for the period of 2011 to 2015 were: circulatory and cardiovascular diseases; external causes (especially transport/road accidents); and neoplasms (Kuwait Ministry of Health [MOH], 2015). The burden of disease in Kuwait (in 2012) was mostly related to noncommunicable diseases (72.9%) followed by communicable diseases (16.1%) and injuries [11% (WHO, 2017)].

1.2.11 The Kuwaiti healthcare system

One of the earliest documented events aimed at improving the Kuwaiti health system occurred at the beginning of the 20th century. On that occasion, the Kuwaiti leader Shaykh Mubarak AlSabah asked doctors from the Arabian Mission of the Dutch Reformed Church in the US to develop a clinic in Kuwait. By the years 1911 and 1919, two hospitals for men and women, respectively, had been established in Kuwait (Metz, 1993). After Kuwait started to receive earnings from the oil industry, the Amari Hospital was opened in 1949 (Metz, 1993). Today, Kuwait has a total of seven general public hospitals and 32 specialised hospitals and health centres (Kieft, Alhmad, & Azim, 2012; Kuwait MOH, 2018). In 2015, the majority of outpatient hospital visits reported by the MOH were to secondary hospitals (66.3%), and the remaining were to tertiary hospitals or clinics (six secondary hospitals and 12 tertiary hospitals/centres were included in the comparison). The differences between the general (secondary) governmental hospitals in the Kuwait MOH in terms of hospital beds and patient visits are presented in Table 1.2 (Kuwait MOH, 2015). Moreover, the differences between these hospitals in terms of manpower are listed in Table 1.3 (Kuwait MOH,

2018). Primary care in Kuwait is provided through clinics in each area (Kieft et al., 2012). Figure 1.3 illustrates the distribution of the healthcare governmental services amongst the different health areas. In terms of the workforce, approximately 8,778 physicians, 1,576 pharmacists, and 22,580 nurses practise in the Kuwaiti MOH healthcare system (Kuwait MOH, 2018).

The healthcare services in Kuwait (except the emergency departments) are provided for 14 hours daily in hospitals and clinics (Kieft et al., 2012). Before the year 1994, neither Kuwaitis nor expatriates had to pay for governmental healthcare services (Kieft et al., 2012). After that year, however, expatriates were expected to pay a certain fee for clinics and hospital services, although they could receive support from the help desks in the hospital based on their financial status (Kieft et al., 2012; WHO, 2012b). Regarding services related to the pharmaceuticals, medications in governmental health institutions are distributed free of charge to both Kuwaitis and expatriates, provided that they show a valid prescription with their civil identification number (Kieft et al., 2012; WHO, 2012b).

Table 1.2: Comparison of secondary hospitals in Kuwait (Kuwait MOH, 2015)

Health area	Hospitals	Beds (%)[3]	Discharges (%)[3]	Emergency visits (%)[3]	Total outpatient visits (%)[3]	New outpatient visits				Follow-up outpatient visits			
						FK	MK	FN	MN	FK	MK	FN	MN
Al-Ahmadi	Adan	826 (11.6%)	39,432 (17.6%)	528,142 (14.5%)	464,084 (14.7%)	82,734	61,054	42,176	39,031	88,445	60,931	47,559	42,154
Capital (or Al-Asimah)	Amiri	417 (5.9%)	17,012 (7.6%)	259,822 (7.1%)	187,675 (6.0%)	29,695	28,288	15,475	22,648	37,006	26,480	11,082	17,001
Al-Farwaniya	Farwaniya	869 (12.2%)	36,268 (16.2%)	918,377 (25.2%)	638,117 (20.2%)	98,209	66,830	71,350	114,518	89,529	60,107	63,179	74,395
Hawally	Mubarak	731 (10.3%)	22,605 (10.1%)	510,145 (14.0%)	320,473 (10.2%)	24,132	19,762	20,444	22,177	70,756	62,155	43,417	57,630
Al-Jahra	Jahra	757 (10.6%)	34,196 (15.3%)	868,277 (23.8%)	241,133 (7.6%)	23,640	15,983	23,078	17,078	53,951	25,824	49,022	32,557
Mubarak	Jaber	-	-	-	-	-	-	-	-	-	-	-	-
Al-Sabah	Sabah	433 (6.1%)	12,753 (5.7%)	287,681 (7.9%)	240,805 (7.6%)	29,687	22,770	10,355	15,557	67,216	45,346	28,189	21,685

[1] No relevant information found for Jaber Hospital. [3] Percentage in relation to all **MOH** hospitals in Kuwait (specialised and secondary). **FK**: Female Kuwaiti. **MK**: Male Kuwaiti. **FN**: Female Non-Kuwaiti. **MN**: Men Non-Kuwaiti. Green shaded: highest figures amongst the hospitals.

Table 1.3: Comparison of secondary (general) hospitals in Kuwait in terms of manpower (Kuwait MOH, 2018)

Health area	Hospitals	Nurses (%)	Pharmacists (%)	Physicians (%)	Medical tech posts (including pharmacy technicians) (%)	Other	Reported total for single hospital manpower (%)
Al-Ahmadi	Adan	2,187 (48.3%)	87 (1.9%)	1,049 (23.2%)	675 (14.9%)	526 (11.6%)	4,524 (100%)
Capital (or Al-Asimah)	Amiri	1,463 (47.3%)	64 (2.1%)	675 (21.8%)	552 (17.9%)	337 (10.9%)	3,091 (100%)
Al-Farwaniya	Farwaniya	2,117 (49.5%)	47 (1.1%)	1,057 (24.7%)	640 (15%)	413 (9.7%)	4,274 (100%)
Hawally	Mubarak	1,572 (41.3%)	110 (2.9%)	970 (25.5%)	640 (16.8%)	517 (13.6%)	3,809 (100%)
Al-Jahra	Jahra	1,900 (50.8%)	47 (1.3%)	588 (15.8%)	554 (14.9%)	635 (17.1%)	3,724 (100%)
Mubarak	Jaber	94 (34.8%)	27 (10%)	25 (9.3%)	112 (41.48%)	12 (4.44%)	270 (100%)
Al-Sabah	Sabah	1,445 (54.1%)	64 (2.4%)	478 (17.9%)	347 (13%)	335 (12.6%)	2,669 (100%)

Information was about pharmacy technicians' numbers in each health governate were not reported separately, but reported as part of medical tech posts.

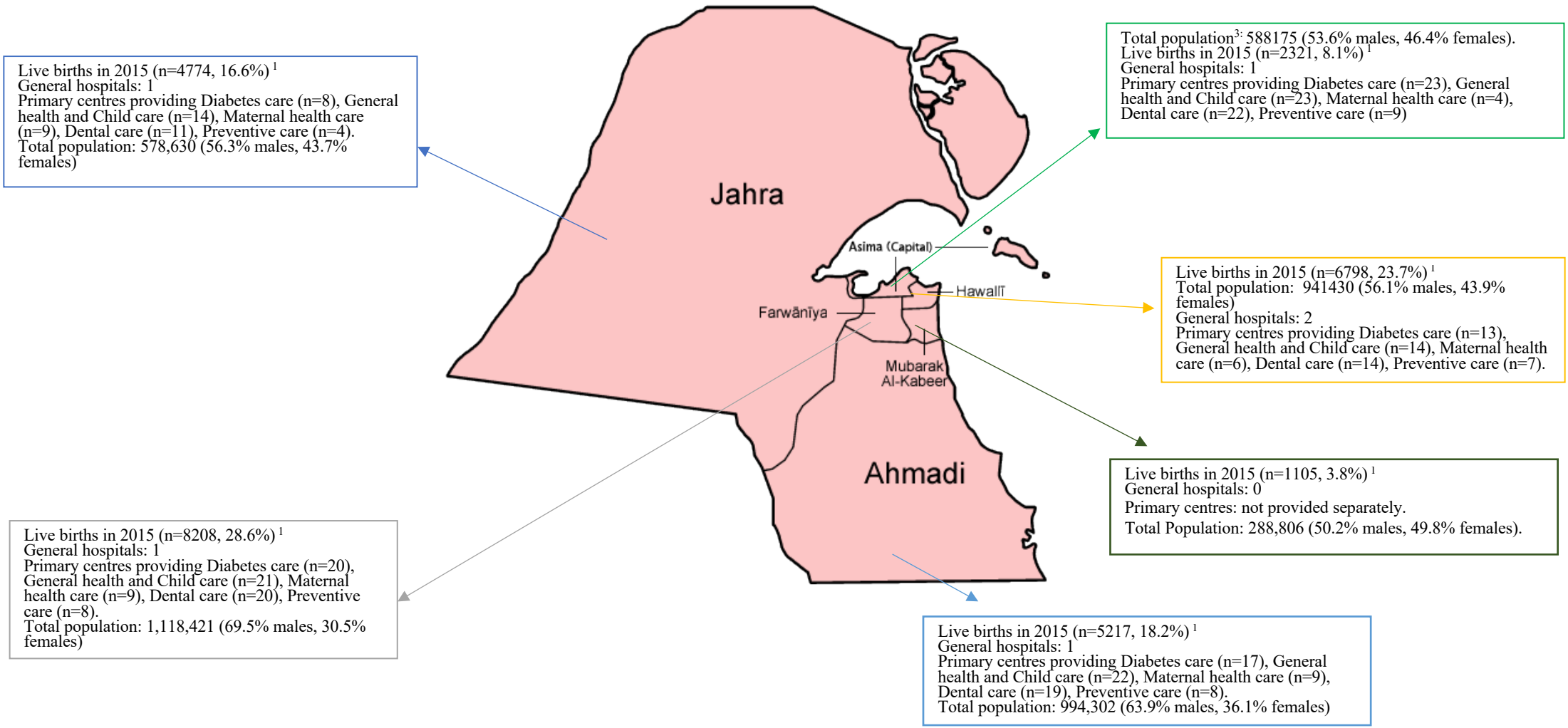


Figure 1.3: Distribution of the healthcare governmental services amongst the six six governates

[1] Represents the percentages of all births in Kuwait; does not complete to 100% due 1.0% (n=282) that were unstated (Kuwait MOH, 2015). Colours are just for illustration.). Information on Map based on Kuwait Public Authority on Civil Information (Updated June 2022 From: http://stat.paci.gov.kw/arabicreports/). Map credit to User:Golbez. Copyright (C) 2000,2001,2002 Free Software Foundation, Inc.51 Franklin St, Fifth Floor, Boston, MA 02110-1301 USA. Everyone is permitted to copy and distribute verbatim copies of this licence document, but changing it is not allowed.

In the health sector, a variation is noticed in terms of the healthcare professionals' nationalities (Kuwait MOH, 2018). Healthcare professionals working in the Kuwait MOH are from 87 nationalities (Kuwait MOH, 2018). The most noticeable variation is in the nursing sector, where 95% of the total registered nurses in the MOH are non-Kuwaitis (Kuwait MOH, 2018; Table 1.4). In addition to the multinational Kuwaiti healthcare system, Kuwaiti healthcare professionals might have different academic backgrounds that could have been gained in countries other than Kuwait, such as Bahrain, Egypt, Saudi Arabia, Hungary, Tunisia, the United Kingdom, the US, the Republic of South Africa, Spain, Tunisia, Canada, and the Netherlands (National Bureau for Academic & Education Quality Assurance, 2019). The diversity of the manpower in the Kuwaiti healthcare system can be identified from published studies conducted within the Kuwait MOH. Of particular note here is a study concerning the knowledge, attitude and practices of pharmacovigilance and adverse drug reaction reporting amongst pharmacists working at secondary and tertiary governmental hospitals in Kuwait. The study was conducted by Alsaleh, Alzaid, Abahussain, Bayoud, and Lemay (2017), and saw 172 Kuwaitis and 157 non-Kuwaitis participate. The non-Kuwaitis were from other Middle Eastern countries (Saudi Arabia, Iraq, Syria, Lebanon and Egypt), as well as from South Asia (India and Pakistan), Europe (the United Kingdom, Ukraine and Montenegro), or North America (Canada). The academic backgrounds of the participants in this study (country of graduation) were as follows: Kuwait (115), Egypt (124), Jordan (28), the UK(16), India (12), Pakistan (8), the United Arab Emirates (7), Syria (4), the US (3), Saudi Arabia (2), Lebanon (1), Italy (1), Russia (1), Ukraine (1), Yugoslavia (1), and Australia (1).

Table 1.4: Distribution of healthcare professionals as Kuwaiti or non-Kuwaiti (Kuwait MOH, 2018)

Professional group	Kuwaiti	Non- Kuwaiti	Total
Nurses	1,097	21,483	22,580
Pharmacists	749	827	1,576
Pharmacy technicians	805	188	993
Physicians	3,580	5,199	8,778

1.2.13 The patient healthcare pathway in Kuwait

Kuwait has a relatively modern healthcare infrastructure, and the Ministry of Health (MOH) is responsible for ensuring the promotion and protection of individuals' health in the country. Most of the healthcare services are provided by the public sector, which involves three levels of care, including primary, secondary (general) and tertiary [specialised (WHO, 2014)]. Within the public sector, the patient healthcare pathway begins, in non-emergency cases, with primary care clinics where a patient will visit a family physician or a general practitioner. The primary care clinic is located within the catchment area of the patient, as indicated by the patient's civil ID card. In cases where the primary care clinic is closed, the patient is directed by the MOH to another primary care centre. Unlike other healthcare systems, no patient has a specific GP or family physician, which makes an individual's health difficult to track over time. If the patient requires further medical attention, he/she is referred by the GP or the family physician to a secondary care hospital that is located within his/her catchment area (Mossialos, Cheatley, Reka, Alsabah, & Patel, 2018). Based on the physicians' judgment, the patient may then be referred to a tertiary care hospital or centre for more specialised care (Alhuwail, 2021).

A global strategic goal for healthcare services is to achieve high quality of care (WHO, 2020b). Quality of care is a multi-dimensional concept that encompasses healthcare effectiveness, patients' satisfaction and experiences, and patient safety (Darzi, 2008; UK Secretary of State for Health, 2008). Besides being an essential dimension of quality, patient safety also constitutes a public health matter (WHO, 2019). Improving both the public health sector and patient safety have long been aims of the MOH. Steps have been taken in order to improve these sectors, such as making patient safety one of the criteria for hospitals' accreditation in Kuwait (Mossialos et al., 2018). Additionally, the Kuwait Foundation for the Advancement of Sciences (KFAS) invited the London School of Economics and Political Sciences (LSE) to develop Kuwait's public health strategy (Mossialos et al., 2018). Moreover, improving patient safety was recognised in the Kuwaiti national health plan 2010–2014 (WHO, 2014). Furthermore, a recent ministerial decree – aimed at expanding the role of pharmacists from dispensaries concentrated to more patient-focused care – provided pharmacists with the authority to improve patient safety through participating in

pharmacovigilance activities and reporting of adverse drug reaction (Kuwait MOH, 2022). However, improving patient safety remains one of the challenges for the MOH reform (WHO, 2014).

1.2.14 Medication's registration, expenditure and consumption in Kuwait

Medications in Kuwait are mostly imported from international industries with established good pharmaceutical practice due to the lack of pharmaceutical industries in Kuwait. Moreover, medications importing is carried out in accordance with the US FDA, as well as the British and European administrations. The processes of importing, testing and inspecting medications are regulated by different acts produced by the Prince of Kuwait, and they are a function of different departments within the MOH, as there is no autonomous medicine regulatory agency in Kuwait (WHO, 2012b). The process of registering a medicinal product in Kuwait is regulated by minstrel decree number 302/80, which was put in place by the Kuwait Drug and Food Control (KDFC), and consists of three steps, described in Table 1.5 (Kuwait MOH, n.d.).

All imported medications are required to hold a marketing authorisation, except if they were previously registered in one of the Gulf Cooperation Council (GCC) countries. All registered medications are tested for prequalification purposes and required to have a published summary of the product characteristics. Medication procurement to fulfil the requirements of governmental health institutions is held by the Central Medical Stores (CMS) in the Ministry of Health. The CMS is also responsible for distributing medications to these health institutions. Only physicians are authorised to carry out medication prescribing, and medication dispensing can only be undertaken by a pharmacist, in a pharmacy setting. Inspections of medications are then conducted based on these settings by pharmacists working in the inspection department of the MOH (WHO, 2012b).

Table 1.5: Steps of registering medicinal products in Kuwait (Kuwait MOH, n.d.)

Step	Requirements
• Step 1: Registration of the MAH	• Obtain an institution or a company licence from the Ministry of Commerce that indicates (import pharmaceuticals) • Obtain a drug store licence from the Drug Inspection Administration • A pharmacist should be present and registered as being in charge of the store
• Step 2: Registration of the manufacturer	• Original and authenticated certificate between the manufacturer and the agent in Kuwait, stating that the agent in Kuwait is the exclusive marketing authorisation holder of that manufacturer or product • Original and verified manufacturing licence for a manufacturer, issued by the responsible authority in the country of origin • Original and authentic GMP certificate from the health authorities in the country of origin • A comprehensive file about the manufacturer that includes all data, from equipment information, production lines, products, and certificates obtained by the factory, to plans, control processes, and quality, etc. • 250 KD as a registration fee
• Step 3: Registration of the product	• Ensures the effectiveness and safety of the product • Compliant with international standards for registration of preparations • Laboratories at the KDFC perform analysis of the preparation to ensure that it complies with official specifications and drug constitutions

MAH: Marketing Authorization Holder; **KDFC**: Kuwait Drug and Food Control; **GMP**: Good Manufacturing Practice

The estimated percentage of the Kuwaiti Government's expenditure on medications is more than 15% of total governmental expenditure on health and approximately; 1.15% of the total government budget (Kuwait MOH, 2009, cited in WHO, 2012b; WHO, 2012b). Kuwait MOH (2015) reported that the 2014 government's expenditure on medications reached 178,202,235 Kuwait Dinar (KD [£395,608,961.7 using pound sterling equivalent to 1 KD on 02/01/2015]). This increased to 189,218,061 KD (£429,524,998.47 using pound sterling equivalent to 1 KD on 08/01/2016 [Kuwait MOH, 2015]).

Figure 1.4 and Figure 1.5 show the most requested medicinal products in the period spanning 2017–2019 (Kuwait CMS, unpublished records, 2018, 2019).

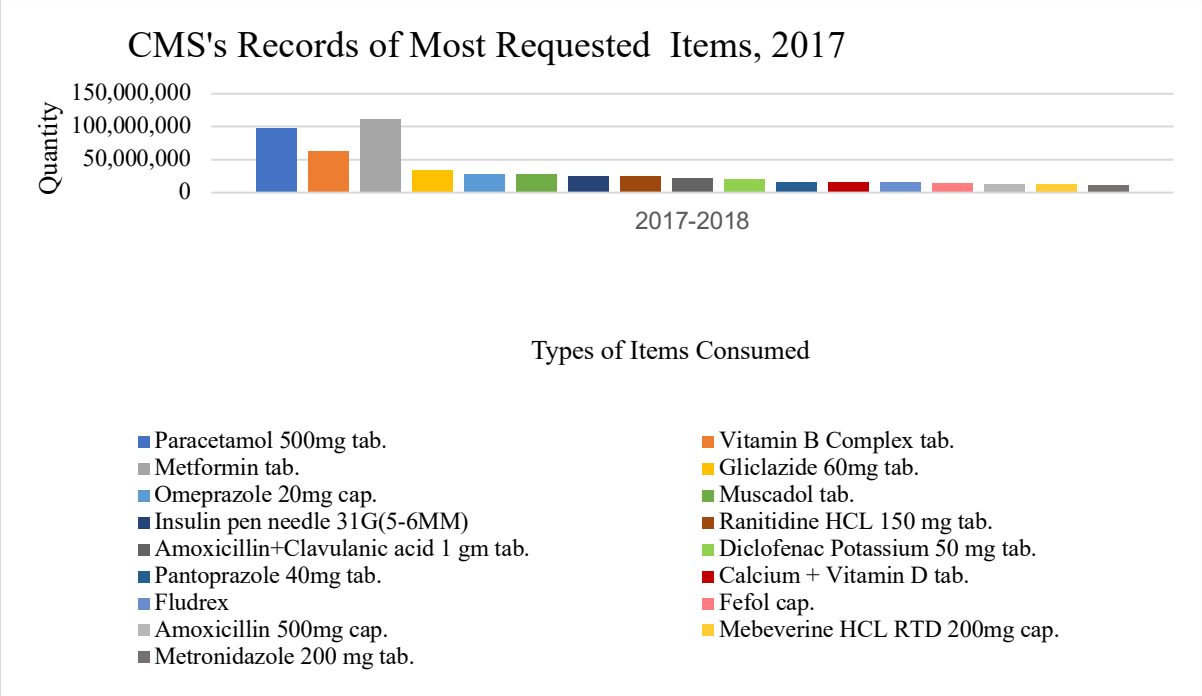


Figure 1.4: Central Medical Stores' records on most requested medications from April/2017 to April/2018

Figure 1.4: Most requested items based on the Central Medical Stores' records. The records show the top 20 items by quantity (here the quantities metformin 850mg, 500mg, 1000mg and XR 1000mg, which ranked 3rd, 4th, 12th and 16th, respectively, were combined). Fefol: Ferrous sulphate + Folic acid. Tab: tablet, Cap: capsule. Note: total number reflects medications that were distributed to healthcare institutions by the CMS based on their requests [not a direct measure of patient consumption].

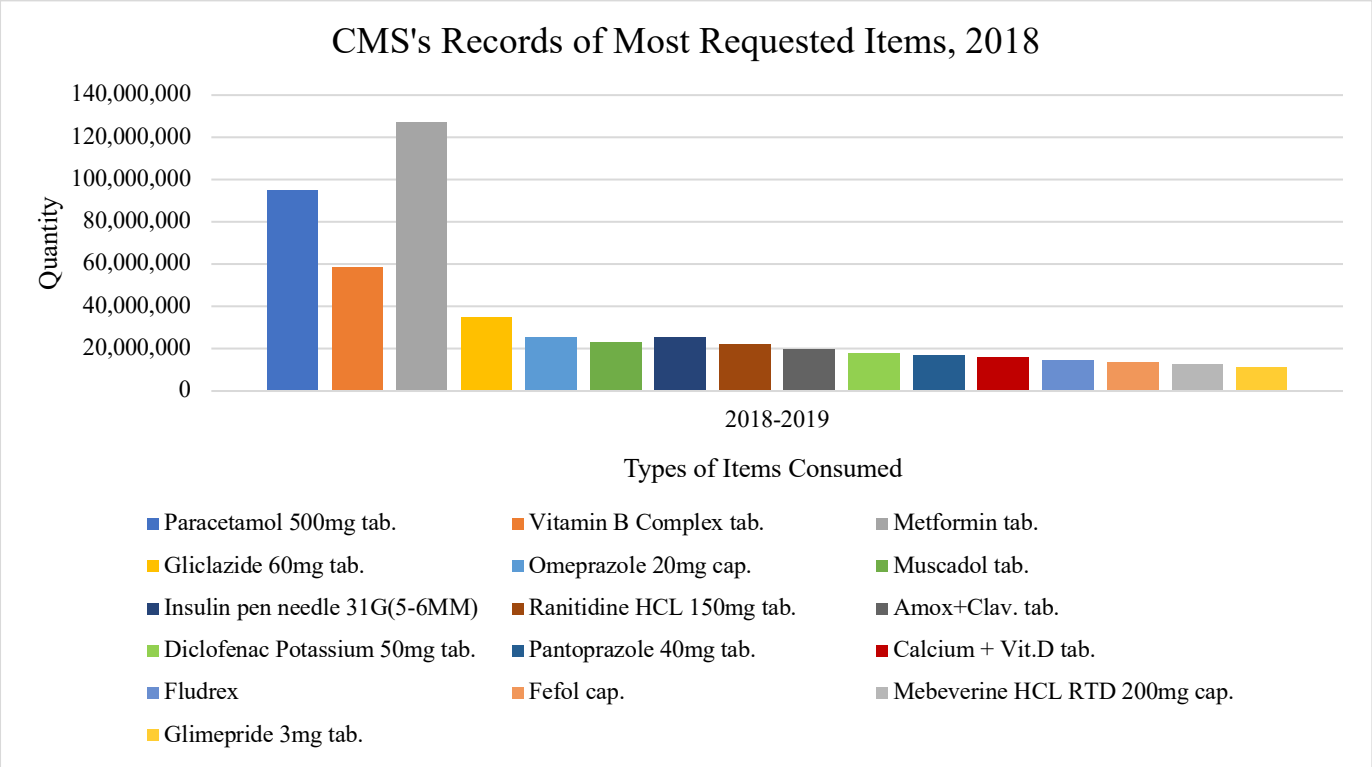


Figure 1.5: Central Medical Stores' records on most requested medications from April/2018 to April/2019

Figure 1.5: The records show the top 20 items by quantity (here the quantities metformin 500mg, 850mg, 1000mg, XR 1000mg, and XR 750mg, which ranked 3rd, 4th, 12th, 14th, and 18th, respectively, were combined). Fefol: Ferrous sulphate + Folic acid. Tab: tablet, Cap: capsule. Note: total number reflects medications that were distributed to healthcare institutions by the CMS based on their requests [not a direct measure of patient consumption].

1.2.15 Pharmacovigilance in Kuwait

The idea of starting a pharmacovigilance centre in Kuwait emerged in the 1980s (Moussa, Bayoumi, Al-Khars, & Thulesius, 1985). However, it was reported, in different documents, that Kuwait had no active pharmacovigilance centre, no legal provisions for monitoring adverse medication reactions, and no official standardised form for reporting an adverse medication reaction (WHO, 2012b; Wilbur, 2013). This contradicted the findings of a survey conducted in 2015 across 21 Arab countries (Qato, 2017). It was discovered in the latter study that Kuwait had established a pharmacovigilance centre in 2007 with dedicated full-time staff members to perform the activities. However, it was also reported that this pharmacovigilance centre was not accompanied by national regulations, a specified budget, or standard operating procedures regarding how to perform its activities. Moreover, the same cross-sectional study found that Kuwait neither had a database for adverse medication reaction reports, nor was it actively collecting the reports themselves. In 2015, the presence of a pharmacovigilance centre performing basic activities was evident (Al-Essa et al., 2015). Around that time, Kuwait had agreed to adopt the guideline on good pharmacovigilance practice in Arab countries, developed in 2014 and pronounced effective in 2015, along with all the GCC countries, namely: Saudi Arabia, the United Arab Emirates, Qatar, Bahrain, Oman and Kuwait (Al-Essa et al., 2015; The League of Arab States, 2014).

Most of the spotlight on the activities of the Kuwaiti pharmacovigilance centre was related to the establishment of the online adverse medication reaction reporting system by the KDFC (KDFC, 2016), which is a department in the Ministry of Health (KDFC, 2016). Following that, the "Report Me" project, led by Reem Al-Essa[1], was initiated to increase the public's awareness of pharmacovigilance by utilising different social media platforms, including: LinkedIn, Instagram, Facebook, Twitter, Snapchat and YouTube (WHO-UMC, 2017). In 2018, Kuwait became an

[1] Dr Reem AlEssa obtained her PhD in pharmaceutical regulations, and co-authored Pharmaceutical Regulatory Environment Challenges and Opportunity in the Gulf Region.

associate member of the WHO Uppsala Monitoring Centre (Alshammari et al., 2019). In 2021, Kuwait became a full member of the Uppsala Monitoring Centre (WHO-UMC, 2023a).

Several studies concerning the area of pharmacovigilance in Kuwait were published. One of the first papers was a three-year population-based study conducted by Moussa et al. (1985) with the objective of creating a reference system for initiating an adverse drug reaction monitoring centre, as well as proving a benchmark for the patterns of adverse drug reactions in Kuwait. In this study, a total of 704 reports were received from different health institutions, with more than 90% of those reports classified as having a positive possible causal relationship. The most commonly reported medications in this study were anti-infective (32.2%), and the most common adverse effects were cutaneous reactions (48.6%).

Another noteworthy study was conducted by Al-Essa et al. in 2015. It aimed to describe the current state of pharmacovigilance across the GCC countries. The authors reported that Kuwait had a pharmacovigilance unit with no more than three employees. They also found that the adverse drug reaction information in this unit was from the following sources: literature reviews, pharmaceutical companies, industry and reference agencies. Moreover, Al-Essa et al. (2015) indicated that this unit receives adverse drug reaction reports from physicians, pharmacists and patients based on a standardised form.

Three further studies were conducted in Kuwait to evaluate the knowledge, attitudes and practices (KAP) of adverse drug reaction reporting amongst different healthcare providers. One study targeted pharmacists at secondary and tertiary governmental hospitals in Kuwait (Alsaleh, Alzaid et al., 2017). Pharmacists in this study showed positive results in terms of their knowledge of pharmacovigilance and adverse drug reactions (61.5%; 72.6%). Although the majority were willing to report an adverse drug reaction (88.6%), only 26.8% of the participants indicated that they had previously reported an adverse drug reaction.

Another study was conducted amongst physicians at private and governmental hospitals in Kuwait (Alsaleh, Lemay et al., 2017). The results revealed that physicians in the private sector had a better understanding of pharmacovigilance (75.2% vs 64.8%) and adverse drug reactions (75.8% vs

65.3%). The majority of the physicians had positive attitudes towards adverse drug reaction reporting and had previously identified such reactions in their careers. However, only 34.2% of the participants from both sectors indicated that they had previously reported an adverse drug reaction.

A further study was undertaken in primary care settings with the aim of comparing the KAP of pharmacists and physicians regarding the reporting of adverse medication reactions (Lemay et al., 2018). The authors found that both groups were knowledgeable about the concepts of pharmacovigilance and adverse drug reaction. However, most of the participants were not aware of the presence of an adverse drug reaction reporting centre in Kuwait. In the above study, it was also found that 97.7% of the participants felt it is necessary to report an adverse drug reaction; yet, only 27.8% of the participants had actually reported such reactions, with physicians having submitted a significantly higher number of reports than pharmacists (30.8% vs 21.7%).

A recent overview of pharmacovigilance in Arab countries and a cross-sectional survey revealed the current state of pharmacovigilance in Kuwait (Alshammari et al., 2019; Alshammari et al., 2020). It was reported that the pharmacovigilance centre in Kuwait has access to both computer facilities and libraries (Alshammari et al., 2020). Initiatives have been implemented in Kuwait for pharmacovigilance improvement. Between the years 2016 and 2017, fewer than 600 reports were received by the KDFC, 30 of which were spontaneous. Kuwait follows the four GVP Arab countries. However, not all pharmacovigilance activities indicated in the guidelines were followed. Submission and preparation requirements for periodic benefit risk evaluation reports and periodic safety update reports follow GVP for Arab countries and the EU GVP. The pharmacovigilance centre also requires the submission of a risk management plan as follows: at the time of a product's registration, either an EU risk management plan or a local risk management plan should be submitted. In addition, market authorisation holders should submit an updated risk management plan upon request of the pharmacovigilance centre or whenever there are significant changes to the previously-submitted risk management plan. The pharmacovigilance centre mandates that pharmaceutical companies should submit a pharmacovigilance system master file, which must include both a global and local summary upon the first submission. However, the pharmacovigilance centre does not mandate a qualified person for pharmacovigilance or a local

safety expert responsible for the pharmaceutical companies. These studies did not include an evaluation of safety communications disseminated by the KDFC (Alshammari et al., 2019), and thus they did not provide an insight into safety communications conducted by the KDFC.

This chapter provided an overview of patient safety, background information on pharmacovigilance, background information about Kuwait, Kuwait's healthcare system, the patient healthcare pathway in Kuwait, medication's registration, expenditure and consumption in Kuwait, and pharmacovigilance in Kuwait. The next chapter provides a systematic review of the factors influencing the implementation of medication safety communications by HCPs in clinical practices. The next chapter ends by presenting the rationale, overall aim and objectives of this research.

Chapter 2: Factors influencing the implementation of medicine risk communications by healthcare professionals in clinical practice: A systematic review

2.1 Introduction

Pharmacovigilance is defined by the WHO (2002) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (p.42). The importance of this sector of clinical science arose from the fact that clinical trials, in the pre-marketing phase, test the efficacy and safety of medications for a short period of time and on a limited number of people, ranging from 500 to 5000 (WHO, 2004). These individuals usually underrepresent the actual population, where people from different age groups use different medications for long periods of time and have various life-styles, which might lead to the occurrence of unexpected adverse drug reactions (WHO, 2004).

Pharmacovigilance involves four basic activities to minimise and manage the threats of adverse drug reactions. These included: Risk identification; assessment; mitigation; and communication (Beninger, 2018). Without an effective risk communication pharmacovigilance may fail to prevent patient harm (Bahri et al., 2015).

Pharmacovigilance centres have different strategies for communicating medication safety information. The EMA publishes safety information on their websites and requires direct health care professional communications to be sent through marketing authorisation holders (EMA, 2017d). The US FDA used to communicate safety information through different methods, but this was standardised in 2010 to a single DSC. This is an FDA independent analysis and communication process for posting safety information on their website, aimed at HCPs, the patients, and the public (US FDA, 2015). After the DSC is posted on the FDA website, it would then be sent out through different channels, such as listservs, MedWatch and HCPs' newsletters

(US FDA, 2015). In more serious situations, the FDA issues a BW on its website, medication package inserts, and the websites of the marketing authorisation holders (O'Connor, 2010).

The success of a risk message is typically determined by the source sending it (US National Research Council, 1989). This includes the extent to which the recipient audience matches the sender's intended outcome (US National Research Council, 1989). Evaluating the impact of medication's safety communications is a way of determining the success of the communication and will also highlight the barriers for implementation (EMA, 2021b). Furthermore, measuring the impact of medications' safety communications on HCPs' behaviours is only a surrogate for patient outcomes, and HCPs' behaviour in response to these communications could compromise patient safety. Cisapride, for instance, has been linked to ventricular arrhythmia, resulting in fatalities and sudden death (Ferriman, 2000; Wysowski, Corken, Gallo-Torres, Talarico, & Rodriguez, 2001). In response, the FDA issued a BW, a press release, and the manufacturer disseminated Dear Healthcare Professionals letters (Klausner cited by Smalley et al., 2000; Smalley et al., 2000). Based on an analysis of databases from three pharmacoepidemiologic sites, only minor changes were observed in contra-indicated prescribing that could lead to QT-prolongation complications (Smalley et al., 2000). Eventually, cisapride was voluntarily withdrawn from the market (Ferriman, 2000; Henney, 2000; WHO, 2001). This led to a subsequent market shift (Glessner & Heller, 2002) and raised concerns relating to potential safety issues associated with alternative agents (Drolet, Rousseau, Daleau, Cardinal, & Turgeon, 2000; Glessner & Heller, 2002).

In another example, following the warning from EMA and the FDA related to the suicidal risk for children and adolescents taking selective serotonin reuptake inhibitors (SSRIs), Gibbons et al. (2007) reported a significant increase in the rates of suicide in children and adolescents in US and the Netherlands, which appeared to be parallel to the decrease in SSRIs prescriptions for patients within the same age group. Although this association was not found in another ecological time-series study conducted in the UK, the prescriptions of SSRI in youth younger than 18 years of age declined following the warning compared to the prescription rates before the warning (Wheeler, Gunnell, Metcalfe, Stephens, & Martin, 2008).

A number of systematic reviews explored the impact of regulatory related communications and actions. Piening, Haaijer-Ruskamp, de Vries et al. (2012) reviewed the literature published

between 1996 and 2010 that measured the impact of direct healthcare professional communications, BWs and public health advisories on clinical behaviours. They identified a total of 50 articles, more than half of which measured the impact associated with third generation oral contraceptives, SSRIs and cisapride. The intended impact on clinical practice was reported in 72% and 41% of studies using before/after analysis and interrupted time series analysis, respectively. Unintended effects were reported in 19 of the 22 studies relating to SSRIs and in 4 of the 5 studies relating to third-generation oral contraceptives.

Dusetzina et al. (2012) review focused on the impact of FDA regulatory actions on health outcomes and the utilisation of medication and healthcare services. Their search included studies published between 1990 and 2010. This search yielded a total of 49 studies relating to 16 medications or therapeutic groups. About one third of the medications covered were antidepressants. They found that advisory warnings regarding increasing laboratory or clinical warnings had a transient and modest effect on the intended actions, while mainly leading to a decreased use of medications. Spill-over effects were also evident in their review. A common example was that associated with FDA communications in 2003 -2004 regarding the use of antidepressants in children, where the authors also reported decreases in the utilisation of these medication in the adult population. However, while most studies evaluated databases (medical or pharmacy claims) to measure the impact of these communications, only 9 of the 49 studies explored HCPs' beliefs and attitudes regarding safety communications.

Three systematic reviews reported factors that could affect HCPs' implementation of medicines' safety communications. The authors of one study reported communication factors that could affect the effectiveness of the dear healthcare professionals letters, including the clarity of the content and medium of delivery, as different HCPs have different preferences (Møllebæk et al., 2019). It was also reported by Møllebæk et al. (2019) that HCPs prefer safety communications from authoritative agencies rather than the pharmaceutical industry. However, this systematic review focused on including studies focusing on communication factors relating to the sender, message, the use of media, and recipient related factors (Møllebæk et al., 2019). However, the review did not explore environmental factors such as lack of resources (Cabana et al., 1999). The second systematic review identified reasons for the unintended impact of safety communications, including the service receivers' (patients, their parents, or guardians) refusal to use the medicine

of concern, liability concerns and perceiving that there is no risk or the risk is minimal (DeFrank, McCormack, West, Lefebvre, & Burrus, 2019). However, it only included studies that reported unintended effects of the alerts (DeFrank et al., 2019). Excluding studies that reported intended effects or studies that did not involve an unintended effect could have led to missing studies that reported on factors without reporting any type of alert-related impact. Dusetzina et al. (2012) provided insights on HCPs' awareness and levels of agreements with medications safety communications. They found that healthcare providers had high awareness of general safety communication, and less awareness of more specific recommendations, like antidepressants follow-up schedules (Dusetzina et al., 2012). The extent to which providers agreed with the content of medication risk messages varied from high, with messages relating to the use of over-the counter cough medications in children, to low in other cases, such as monitoring patients taking antiepileptic medications (Dusetzina et al., 2012). However, this systematic review focused only on US FDA related safety communications. Thus, factors that could be identified from other regulatory areas or knowledge and attitudes of HCPs from different geographical arears were not captured.

Some of the outcomes of a risk communication could be related to changing knowledge (Goedecke, Morales, Pacurariu, & Kurz, 2018), perceptions or attitudes. At the same time, knowledge and attitudes could be barriers to implementing the intended outcomes (Cabana et al., 1999). With minimal information on causational reasons that could be related to the specific type of risk communication uptake (DeFrank et al., 2019), it is important to identify the range of possible factors that could influence the uptake of medications risk communications by the targeted audiences. Understanding the factors that influence HCPs actions and responses to regulatory agencies medicine risk communication could improve the effectiveness of risk communication and, ultimately, could enhance patients' safety and clinical outcomes. This systematic review aimed to identify the factors that could influence HCPs' implementation of medication risk communications. A narrative synthesis approach, including two synthesis processes, thematic analysis and concept mapping using a theoretical framework were employed. In this review, alerts and medications safety communications are used interchangeably.

2.2 Methods

This section explained the methods applied in the conduction of this systematic review.

2.2.1 Systematic review registration

This is a systematic review as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guideline (Page et al., 2021). The protocol of this review was PROSPERO registered (CRD42018116468).

2.2.2 Literature search and study selection

Search terms were developed based on concepts derived from the population, intervention, and outcome strategy as clarified in table 2.1 (O'Connor, Green & Higgins, 2008). These terms were reviewed independently by another researcher and an information manager. The final search terms were adjusted per database requirements. MESH terms and alternative terms were used in PubMed and CINAHL PLUS, respectively. The search strategy is provided in Appendix 1 and the details of the search strategy employed in Scopus, PubMed, Web of science, and OVID are provided in Appendices 2 to 6, respectively.

Table 2.1: Population, Outcome, Intervention (O'Connor et al., 2008)

PICO	Criteria
Population	Healthcare professionals; type or rank of healthcare professionals was not prespecified.
Intervention	Medicines' risk-related regulatory communication.
Comparator	Not applicable
Outcome (with variation)	Factors that could possibly affect healthcare professionals' uptake and implantations of medicines' risk-related communications.

The search was conducted between April and May 2018 including the following databases: AMED; EMBASE; Embase classic; Global Health; HMIC; International Pharmaceutical Abstracts; Health and Psychosocial Instruments; PsycEXTRA; PsycINFO; MIDIRS; OpenGrey; Web of science; PubMed; Scopus and CINAHL PLUS. AB (Amal Alharbi) and IB (Dr Ilhem Berrou) independently screened the titles and abstracts of all studies retrieved against the inclusion and exclusion criteria. Disagreements were resolved through discussion and providing the justification for including or excluding a certain study based on the inclusion and exclusion criteria.

A first update was conducted by AB between May-August 2019 using the same search strategy including the following databases: Web of science, PubMed; Scopus and CINAHL PLUS. No extra studies that meet the inclusion criteria were identified at this point.

A second update was conducted by AB in June 2021 using the same search strategy and the following databases PubMed; Scopus and CINAHL PLUS. One study was identified to meet the inclusion criteria. IB reviewed the study against the inclusion criteria and agreed on its inclusion.

The references of the included studies, and the references of relevant reviews (i.e., reviews focused on the impact of post-market medication safety communications) were also manually searched by AB.

2.2.3 Inclusion & exclusion criteria

Studies were included if HCPs reported any possible factor(s) influencing their uptake of alerts. English Oxford Dictionaries was used to define factor (Factor [Def.1, n.d.]) and uptake (Uptake [Def.1, n.d.]). these definitions are provided in Appendix 7. Studies that did not have an abstract written in either English or Arabic were excluded. This was to avoid translation biases, as the research team are fluent in both languages.

Studies that did not involve pharmacovigilance or patient safety regulatory agencies were excluded. Studies were also excluded if they only measured HCPs' practice after alerts or only evaluated the effectiveness of risk minimisation measures. Studies related to occupational hazards, case reports, interventional studies, and studies not involving HCPs were also excluded. AB contacted authors of primary studies when the published information was insufficient to decide inclusion or exclusion. Additionally, AB contacted the authors of seven eligible abstracts, including an abstract of an article in Spanish, two conferences, two meetings, and two research letters, but none of the authors contacted could provide the English full text. Thus, these abstracts were excluded.

2.2.4 Data extraction

A data extraction form was developed to retrieve essential information. AB conducted the data extraction. Data from seven studies was independently extracted by NS (Dr Nada Shebl). The two sets of extracted information were compared and differences were resolved, which were mainly related to the level of details to be included. Moreover, one heading of the data to be extracted appeared to be confusing. This was "targeted patient population", and it was changed to "targeted population from the alert" to reflect the aim of this heading.

Extracted information included the author and year of publication, country, name of the regulatory agency involved, medication of concern and type of regulatory action, targeted population from the alert, study participants and settings, objectives of the study, method of data collection, method of data analysis, factors and processes identified as impacting implementation. The data extracted were utilised to inform the table of characteristics. However, it was not utilised in the analysis process as the analysis was conducted inductively.

The Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization Collaboration Centre for Drug Statistics Methodology, 2019) was utilised to code medicines and the Medical Dictionary for Regulatory Activities ([MedDRA]The National Center for Biomedical Ontology, 2018) to code safety concerns. This information was reported in the table of self-reported impact in Appendix 12.

2.2.5 Quality assessment

Quality assessment was conducted using the Mixed Method Appraisal Tool (MMAT) version 2018 (Hong et al., 2018). AB assessed the quality of all the included studies. IB and NU (Dr Nkiruka Umaru) independently repeated the assessment of 9 and 7 studies respectively. Initial disagreements were resolved by discussions and by agreeing on the criteria to judge the items of MMAT. Full text articles were not excluded based on their quality assessment. Decisions on quality assessment process are provided in Appendix 8.

2.2.6 Data analysis

A narrative synthesis approach, involving four steps was used, based on the Economic and Social Research Council guidance (Mays, Pope, & Popay, 2005; Popay et al., 2006). This is a systematic approach to qualitatively synthesise data from various types of studies when meta-analyses are deemed unsuitable (Mays et al., 2005; Popay et al., 2006). In contrast to narrative reviews, this approach provides new insights and supports decision-making, rather than solely

summarising the included studies (Mays et al., 2005).

2.2.3.1 Step 1: Developing a theory

The first step, developing a theory, involves thinking about how interventions work, why they work, and for whom they work (Popay et al., 2006). The Theoretical Domains Framework (TDF) was used at a later stage of the synthesis to identify different factors. This framework integrates 128 theoretical constructs from 33 theories (Michie et al., 2005). TDF's first version was refined and validated in 2012, resulting in a second version (Cane, O'Connor, & Michie, 2012) that was used in this review. This version includes the following 14 domains: knowledge; skills; social/professional role; assumptions; beliefs about consequences; reinforcement; intentions; goals; memory; attention; environmental contexts and resources; social influences; emotions; and behavioural regulations (Cane et al., 2012).

2.2.3.2 Step 2: Preliminary synthesis

In the second step, preliminary synthesis, both tabulation and thematic analysis were employed since combining tools leads to a comprehensive description of studies compared to using only one tool (Evans, 2002; Popay et al., 2006). While tabulation was initially used in this review to develop an initial description that eases the process of comparing the studies (Evans, 2002; Popay et al., 2006), thematic analysis was also chosen because it could be flexibly applied across different study approaches (Braun & Clarke, 2006). As the included studies had heterogeneous participants, outcomes, settings, regulatory actions involved, and types of medicines, it was not possible to mathematically pool the data; therefore, the quantitative data was converted to qualitative at the data stage (Hong, Pluye, Bujold, & Wassef, 2017). However, percentages and significance levels were sometimes presented for illustrations.

Using thematic analysis at this stage addresses the limitations of content analysis, the alternative tool for translating the data (Popay et al., 2006). Contrary to content analysis, recurrences of a particular theme do not necessarily reflect its vitality. Furthermore, in content analysis, un-reported evidence is considered as unimportant (Dixon-Woods, Agarwal, Jones, Young, & Sutton, 2005).

However, thematic approaches have been criticised for lacking transparency (Dixon-Woods et al., 2005). To mitigate this, we followed Braun and Clarke's guidance (Braun & Clarke, 2006). The analysis process was completed by AB, and co-authors reviewed and confirmed the final product of the thematic analysis.

To facilitate coding, MAXQDA was used. MAXQDA is a user-friendly software package (Oliveira, Bitencourt, Teixeira & Santos, 2013). This software allows the researcher to code both text and image files (Oliveira et al., 2013). This was important as some of the articles retrieved during the search process could only be retrieved as scanned files. Therefore, it was impossible to code them as text. Besides supporting coding that is controlled by the researcher, this software also has other features, such as visually providing the number of segments assigned for each code via the code matrix browser, as well as facilitating comparing between the codes and the coded segments both directly in the software and through exporting them to an EXCEL® or HTML® spreadsheets (Oliveira et al., 2013). MAXQDA also supports the storage and retrieval of complete analytical work through a MAXQDA Reader for free. This also allows an independent reviewer who does not have the software to read the complete analysis (Kuckartz, & Rädiker, 2019).

The results sections (and open-ended questions in one study's discussion section) were read line by line and inductively coded. Components that were irrelevant to the review (e.g. patient interviews) were not coded. This resulted in 456 codes that were grouped into initial common themes. Within the knowledge theme, Knowledge levels were classified as high (70% or more), fair (50 to < 70%), or poor (knowledge level <50%) (Madison, Donner, Mutter, Mingrino, & Alvaro, 2019).

2.2.6.3 Step 3: Concept mapping

The third step is to explore relationships within and across studies (Popay et al., 2006). Exploring relationships between empirical studies in systematic reviews is challenging, and is further complicated by the heterogeneity of the data (Mulrow, Langhorne, & Grimshaw, 1997). Therefore, an analytical framework is necessary to link the pieces of evidence (Mulrow et al., 1997). Thus, concept mapping was employed. This tool visually explores the relationships among the extracted

data and highlights concepts related to the review's questions (Popay et al., 2006). The codes from the preliminary analysis were reviewed to identify the range of possible factors. The factors were then matched with TDF constructs, which were presented in a table and the behaviour change wheel (Atkins et al., 2017; Cane et al., 2012; Michie, Van Stralen, & West, 2011; Westland et al., 2017). After that, the TDF table was reviewed to extract the sources of the factors. As a result, different sources of factors have been identified, including the source and sender of the medication safety communication, the HCPs themselves, the healthcare institutions, and the patients and their carers. A figure illustrating the sources of factors is presented in this chapter. This step was conducted by AB, and the final product was reviewed and approved by the co-authors. Examples of the data analysis process are presented in Appendix 9.

2.2.6.4 Step 4: Critical reflection

This narrative approach includes a critical reflection on the synthesis process, which reflects the limitations relating to the processes undertaken during the conduct of the systematic review (Popay et al., 2006).

2.3 Results

2.3.1 Studies' characteristics

Twenty-eight full-text articles were included in this review (Barker et al., 2019; Bell, Matsumoto, Shaw, Brandt, & Krauss, 2013; Bhatia et al., 2008; Cheung, Sacks, Dewa, Pong & Levitt, 2008; Cordero, Rudd, Bryan & Corso, 2008; de Vries et al., 2017, 2018; Esterly, Steadman, & Scheetz, 2011; Flood et al., 2015; Fogler, Weber, Mahoney, & Goldschmidt, 2009; Garbutt, Sterkel, Banister, Walbert & Strunk, 2010; Habib & Gan, 2008; Harder & Hawboldt, 2009; Karpel, Peters, Szema, Smith, & Anderson, 2009; Kesselheim et al., 2017; Kloet, Lohr, Smithburger, Seybert & Kane-Gill, 2017; Mazor, Andrade, Auger, Fish, & Gurwitz, 2005; Morrato, Curbow, Crum, Nowels, & Feinleib, 2008; Piening, Haaijer-Ruskamp, de Graeff, Straus, & Mol, 2012; Reed,

Gough, Ho, & Brown, 1999; Richards, Weiss, Bretz, Schneir, Rinetti, & Derlet, 2003; Richardson, Lewis, Casey-Goldstein, McCauley, & Katon, 2007; Saad, Cassagnol, & Ahmed, 2010; Sabblah, Darko, Asamoa-Amoakohene & Ashie, 2016; Shneker, Cios, & Elliott, 2009; Smollin, Fu, & Levin, 2016; Théophile et al., 2011; Yaghmai, Cordts, Ahlers-Schmidt, Issa, & Warren, 2010) (Figure 2.1 PRISMA (Page et al., 2021)). Most of these studies (n=19) were conducted in the US (Bell et al., 2013; Bhatia et al., 2008; Cordero et al., 2008; Esterly et al., 2011; Fogler et al., 2009; Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Kesselheim et al., 2017; Kloet et al., 2017; Mazor et al., 2005; Morrato et al., 2008; Reed et al., 1999; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Shneker et al., 2009; Smollin et al., 2016; Yaghmai et al., 2010). Two studies were part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE), and were conducted in nine European countries(de Vries et al., 2017, 2018). A correction of de Vries (de Vries et al., 2017) was recently published(de Vries et al., 2020) and the information was updated in the table of characteristics. Four studies were qualitative (Barker et al., 2019; Kesselheim et al., 2017; Morrato et al., 2008; Richardson et al., 2007) and 24 were quantitative (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2017, 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Habib & Gan, 2008; Harder & Hawboldt, 2009; Karpel et al., 2009; Kloet et al., 2017; Mazor et al., 2005; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Reed et al., 1999; Richards et al., 2003; Saad et al., 2010; Sabblah et al., 2016; Shneker et al., 2009; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). Studies were conducted in different care settings with a range of 10 to 3625 participants, except for one cohort study that reported the number of patients for whom medicines were reviewed, but not the HCPs involved (Kloet et al., 2017). The most studied alert was issued by the FDA regarding antidepressants-associated suicidality in children and adolescents (n=4) (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Richardson et al., 2007). The characteristics of the included studies are presented in Table 2.2. Tabulation of the results of the included studies is displayed Appendix 10.

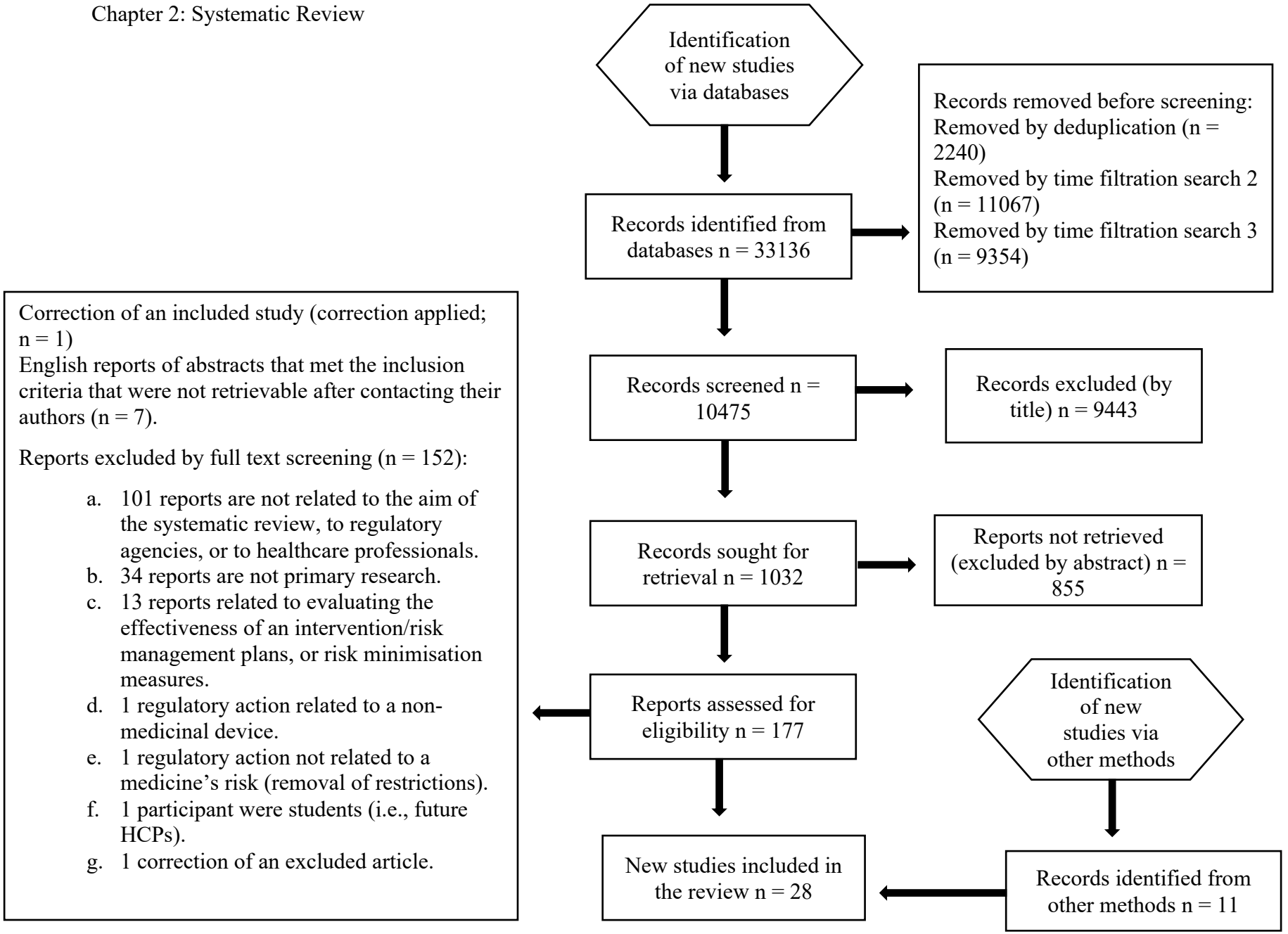


Figure 2.1: PRISMA flowchart

Table 2.2: Characteristics of the included studies

First author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
Qualitative studies							
Richardson (2007)	US Washington state	US FDA	Black box warning. All antidepressant medicines, including all SSRIs, may cause suicidality risk.	Adolescents	Nine practices, of which five were in rural and four in urban settings. The total number of individuals participating were 35, of whom 32 were paediatricians and three paediatric nurse practitioners.	To examine the changes in depression treatment practices after the black-box warning	Focus groups' interview and an individual interv iew
Morrato (2008)	US	Not specified	Not specified	Not specified	Twenty physicians (specialty: psychiatry (n = 10) or internal medicine (n = 10))	To identify the range of drug safety information sources used most by US physicians; To explore their perceptions of the relative advantages and disadvantages of different scientific, drug company and third-party sources; To improve drug risk communications (based on physicians' recommendations)	Semi-structured interviews

Kesselheim (2017)	US	US FDA	Zolpidem: DSCs label changes due to impaired driving and alertness issues. Eszopiclone: FDA issued a DSC related to eszopiclone, reporting label changes because patients could experience diminished driving skills, memory and coordination.	Men and women, but women were more likely to be affected by the risks with Zolpidem.	Ten physicians who practised primary care were listed as prescribers of zolpidem or eszopiclone. sometime between 1 July 2012 and 30 June 2013.	To evaluate physicians ' awareness and understanding of emerging drug safety information related to zolpidem or eszopiclone	Semi-structured interviews
Barker (2019)	Canada	The study included different sources of quality-related events, including recalls and safety alerts from Health Canada.	Not specified	Not specified	15 community pharmacy managers (12 females); the participants were from different community pharmacies, including nine large corporates, two small banner chains, and four independent pharmacies.	To explore the barriers that might limit the use of patient safety information sources with community pharmacies	Semi-structured interviews
Quantitative nonrandomised studies (cohort study)							
Kloet (2017)	US	US FDA	No prespecified medication warnings. However, in-patients medications for boxed warnings were checked.	Not reported	The study involved reviewing medications of 393 general medicine and ICU patients (18 years and older) who were cared by physicians at an urban, academic medical centre.	To determine prescriber adherence rates to BWs in adult in-patients (they also sought to assess prescriber reasons for nonadherence	Prospective cohort quality improvement project

						and detect ADRs as a result of nonadherence.)	
Quantitative descriptive studies (surveys)							
Reed (1999)	US	US FDA	FDA had reported 130 deaths in the US that may be related to patients' use of sildenafil in May 1998. Pfizer Pharmaceuticals distributed a letter to all emergency physicians alerting them to potentially severe drops in systemic blood pressure that may occur when patients prescribed sildenafil are administered nitrates.	The patients included in this study were all male with chest pain, for whom base-station contact was required and for whom prehospital nitroglycerin was either requested or ordered.	94 paramedics	To explore whether paramedics and online physicians consider the use of sildenafil prior to ordering nitrate therapy in the prehospital setting (however, the objective of the survey, which is the part included in this systematic review, was not reported.)	Survey
Richards (2003)	US	US FDA	A black box warning for droperidol was released by the Canadian Health Protection Branch. Concern was raised over potential prolongation of	Not specified as it occurred with patients with no known risk factors. Also, the contraindication is specified for patients with known or suspected QT prolongation,	506 emergency physicians (working in private/community n=278 (55%); academic/county n=187 (37%) and health maintenance organisation n= 41 (8%) hospitals. Of the total number of participants, 124 (25%)	To determine if droperidol's use by emergency physicians has changed since the FDA warning	Web-based survey

			the QT-interval, torsade de points, and sudden death after administration of droperidol.	including patients with congenital long QT syndrome. The extreme caution was related to patients who may be at risk of developing prolonged QT syndrome. Other risk factors may include age over 65 years, alcohol abuse and use of agents such as benzodiazepines, volatile anaesthetics and IV opiates.	practise in the inner city, 299 (59%) in urban and 83 (16%) in rural settings.		
Mazor (2005)	US	A sample of DDLs identified through the Medwatch website or direct contact with pharmaceutical companies	Not specified; Those were issued between 2000 and 2001.	Not specified	Ten primary care physicians (internists) were recruited to serve as raters.	To describe key characteristics of recent DDLs in terms of content, organisation and format, and to examine the extent to which these characteristics influenced physicians' perceptions of the importance of the information provided and the	The recruited physicians served as raters. Each physician rated each letter on eight items intended to assess the presentation of the information, the perceived importance of the information and whether the information would be likely to impact

						likelihood that they would change prescribing practices as a result.	their prescribing behaviour. Letters were randomly ordered for each physician.
Habib (2007)	US	US FDA	Black box; Droperidol; Concerns raised for serious cardiac arrhythmias, secondary to QT prolongation.	Patients with postoperative nausea and vomiting (for the study).	A total of 295 physicians completed the survey; 176 (62%) of 282 practised in a private hospital and 106 (38%) of 282 in an academic institution. Two hundred fifty-seven (93%) of 277 respondents were attending anesthesiologists, 9 (3%) were fellows and 11 (4%) residents in training; 176 (87%) of 203 respondents practised in a surgery centre, 44 (22%) of 203 practised in an office practice, and 48 (24%) of 203 practised in a procedure facility or other location; 233 (81%) of 287 indicated that ambulatory surgery constitutes 50% to 100% of their practice.	To determine the practice of members of the Society of Ambulatory Anesthesia (SAMBA) in the management of postoperative nausea and vomiting (PONV) before and after the FDA black box warning on droperidol.	Survey posted on the website

Bhatia (2008)	Nebraska, US	US FDA	Black box warning; All antidepressant medicines, including all SSRIs, may cause suicidality risk.	Children and adolescents	605 family medicine clinicians with the following specialities: family medicine physicians, family medicine nurse practitioners, family medicine physician assistants, family medicine residents, general practice; 139 paediatric clinicians with the following specialities: paediatricians, paediatric nurse practitioners, paediatric physician assistants, developmental and behavioural; 122 psychiatric clinicians with the following specialities: general psychiatrists, child and adolescent psychiatrists, psychiatric nurse practitioners, psychiatric physician assistants, psychiatric residents; 739 clinicians practising in urban and 127 in rural settings	To determine the clinical implications of the FDA warning	Survey
Cheung (2008)	Canada	US FDA	Black box warning; All antidepressant medicines including all SSRIs may cause suicidality risk.	Children and adolescents.	670 paediatricians	To examine the impact of the FDA Black box warning on the practice of paediatricians in	Mailed surveys

						the management of children and adolescents with antidepressants	
Cordero (2008)	South-West US	US FDA	Black box warning; All antidepressant medicines including all SSRIs may cause suicidality risk.	Children and adolescents less than 24 years of age	115 primary care providers working in medical centres affiliated medical schools or primary care clinics	To explore the accuracy of primary care providers' understanding of the FDA black box warning label for SSRI antidepressants for children and adolescents	Web-based survey
Fogler (2009)	US	US FDA	Nelfinavir mesylate; In 2007, the FDA and Pfizer Inc. announced the presence of a process-related impurity in nelfinavir mesylate, ethyl methanesulfonate, which was teratogenic, mutagenic and carcinogenic in animals.	Pregnant women in need of antiretroviral medicine	26 infectious disease physicians; 36 obstetrician/gynaecologists ; 29 primary care physicians (family/internal medicine); 5 other physicians; 18 nurse practitioners/certified nurse midwives; 7 pharmacists	To determine how widely the information has been disseminated and how many clinicians had pregnant patients whose care was affected by the change in the recommendations	Phone survey
Harder (2009)	Canada	US FDA and Health Canada	Ceftriaxone and calcium-containing solutions; Health Canada issued notice to hospitals.	Specific recommendation for patients under 10 weeks of age and	152 pharmacists from nine provinces and one territory evenly divided between teaching or tertiary care and	To assess the opinions and responses of pharmacists and their respective	Online survey

				another for patients older than 10 weeks of age.	community or general hospitals where the participants commented that they represented paediatric hospitals	institutions regarding warnings of the calcium-ceftriaxone interaction	
Karpel (2009)	US	US FDA	Long-acting ß-agonist (LABAs); Black box warning was placed by the FDA on all LABAs and products that contained the combination of inhaled-corticosteroids and LABAs, suggesting that LABAs are associated with increased mortality in asthmatic patients.	Asthmatic patients	1107, in total, consisted of the following: 429 pulmonologists, 395 allergists, 141 internists, 132 family physicians and 10 paediatricians; The setting for the entire sample was as the following: 64.4% were in private practice, 24.1% in academic practice, 4.8% in training programmes and 6.6% in other settings (i.e. clinic groups, military or hospitals).	To investigate physicians' knowledge of the black box warning for LABA	survey via e-mail
Shneker (2009)	US	US FDA	FDA issued an alert regarding antiepileptic drugs (AEDs) and suicidality (defined as suicidal ideation and behaviour).	Risk is higher in patients with epilepsy.	175 clinicians who treated patients with epilepsy	To understand neurology health practitioners' reaction to the FDA alert and explore how it may affect or change their clinical practices	E-mail survey
Garbutt (2010)	US	US FDA	Nationwide Public Health Advisory released about the use of over the counter (OTC) cough and cold medicines (including decongestants, anti-	Children younger than six years of age	105 community paediatricians	To determine paediatricians' attitudes towards and use of these products	Mailed survey

			histamines and cough expectorants and suppressants) in children younger than two years of age (serious and life-threatening side effects) and older children (they only provide symptom relief and do not cure the cause of illness or reduce its duration).				
Saad (2010)	US	US FDA	Boxed warning about antipsychotic medicines and cerebrovascular accidents.	Elderly patients with dementia	65 geriatric practitioners (pharmacists (94%) physicians (3%) and nurses (3%) from different settings, including nursing home facilities, teaching, veterans affairs, clinical private practice, community hospital, university health care or other specialities, including neurology, psychiatry, hospice, geriatrics, internal medicine and family medicine	To determine the influence of the FDA's boxed warning on the management of psychosis in elderly patients with dementia	Web-based survey
Yaghmai (2010)	US	US FDA	Nationwide Public Health Advisory released about the use of over the counter (OTC) cough and cold medicines	Children younger than six years of age	33 general paediatricians	To assess the effects of the FDA recommendations on parent counselling and	Cross-sectional survey conducted by phone

			(including decongestants, antihistamines, and cough expectorants and suppressants) in children younger than two years of age (serious and life-threatening side effects) and older children (they only provide symptom relief and do not cure the cause of illness or reduce its duration).			prescribing practices of community paediatricians	
Esterly (2011)	US	US FDA	Ceftriaxone and calcium containing solutions; FDA alert	In 2007: all patients. In 2009: patients older than 28 days were removed from the 2007 warning; however, the FDA mentioned their recommendation in terms of using both medicines subsequently in patients older than 28 days	Members of the Society of Infectious diseases pharmacists (SIDP) with a hospital practice site affiliation; 94 responses were included in the analysis. From those, 11% described their roles as administration, 78% as clinical and 54% reported their professional role as antibiotic stewardship pharmacists. 77% of the respondents reported a university affiliation.	To quantify the impact of the FDA warning on healthcare institutions	Survey was distributed in a paper form in a national meeting. A link to the online survey was also e-mailed to the members of the Society of Infectious Diseases Pharmacists.

Théophile (2011)	France	French Medicines Agency	The manufacturer, at the request of the French Medicines Agency ((DDL) the AFSSAPS, placed a press release. Also, an e-mail with a link to the press release and the DDL was sent to the subscribers of the AFSSAPS mailing list. Malaise in neonates and infants caused a safety concern related to an incorrect method of medicine administration and to a pipette not adapted for neonates. These malaises occurred immediately after the administration of two brands of an oral solution of vitamin D, the first alone and the second in combination with vitamins A, E and C.	Neonates and infants	The participants included paediatricians (31%, n = 45), GPs (37%, n = 255) and pharmacists (40% , n = 92).	To assess the effectiveness of such DDL and collect the opinions of healthcare professionals on the best way to provide them with information	Mailed survey

Piening (2012)	Netherlands.	Lareb = Netherlands Pharmacovigilance Center; MEB = Dutch Medicines Evaluation Board	Rimonabant (depression risk); Moxifloxacin (hepatoxicity, skin reactions); Clopidogrel (Proton pump inhibitor interaction); etoricoxib (hypertension)	Not specified	Total 1,141 healthcare professionals, including 233 general practitioners, 410 internists, 223 community pharmacists and 175 hospital pharmacists	To explore healthcare providers' experiences and their preferences for risk communication of safety issues of medicines, comparing the views of GPs, internists and community and hospital pharmacists	Mailed survey
Bell (2013)	US	US FDA	FDA safety warnings for antiepileptics included (1) Suicidal thoughts with 11 antiepileptics. (2) High risk of birth defects in offsprings of mothers receiving Divalproex (valproate semisodium). (3) Cognitive impairments in offspring of mothers receiving Divalproex. Only preliminary findings were reported in the drug product insert. (4) Risks of hypersensitivity reactions related to	Patients using antiepileptics. Two of the risks were raised for pregnant women. One of the risks was raised for patients of Asian descent.	505 neurologists	To evaluate the knowledge of the US neurologists of recent antiepileptics warnings, their sources of medicine safety information and whether they incorporate this safety information into their practices	Survey sent by e-mail

			carbamazepine use were associated with the HLA-B*1502 haplotype marker, which is more common in patients of Asian descent. This study also included a control question: neurologists were asked whether they knew that lacosamide did not have 'black box' safety warnings.				
Flood (2014)	UK	National patient safety agency (NPSA)	A rapid response report, released by the NPSA, indicated that adult patients were being overdosed with high-strength midazolam injection when used for conscious sedation.	Not specified	100 gastroenterology clinicians	To evaluate potential reductions in risks associated with midazolam injection, a sedating medicine, following a UK National Patient Safety Alert	Online survey
Sabblah (2016)	Ghana	Ghana Food and Drugs Authority (FDA)	Azithromycin (cardiovascular risks); risks with the use of codeine for analgesia in children and adolescents; diclofenac (risk of cardiovascular events); paracetamol (risk of severe skin reactions); incidents	Children and adolescents for codeine related risks; not specified for other letters	913 health workers, who included 597 (65.39%) pharmacists, 136 (14.90%) doctors, 95 (10.40%) nurses and 85 (9.31%) physician assistants	To assess the effectiveness and relevance of DHP letters as an effective risk minimisation tool and seek opinions of health workers about the most effective way of	Structured questionnaire

			reported of therapeutic ineffectiveness and restrictions on the use of ketoconazole due to severe liver injury, adrenal gland problems and drug interactions. All were issued in 2013 by Ghana Food and Drugs Authority (FDA).			communicating safety information	
Smollin (2016)	California, US	US FDA	Black box warning was associated with five medicines: (1) ciprofloxacin (increased risk of tendonitis and tendon rupture; it should be avoided in patients with a history of myasthenia gravis). (2) Midazolam IV (respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. (3) Naproxen (increased risk of serious cardiovascular	Ciprofloxacin to avoid in patients with a history of myasthenia gravis; haloperidol in elderly patients with dementia. Not specific for the other warnings.	81 physicians, including 50 emergency medicine physicians and 31 paediatricians; 16 of them were in their first postgraduate (PG) year, 20 in the second year, 16 in the third year, 5 in the fourth year and 24 were attending fellows.	To assess physicians' awareness and knowledge of boxed warnings (black box warnings); To gain a better understanding from where physicians obtain information regarding serious adverse medicine reactions for commonly prescribed medicines	Survey distributed via e-mail

			thrombotic events, myocardial infarction, and stroke. Increased risk of serious gastrointestinal adverse events). (4) Haloperidol (increased mortality in elderly patients with dementia-related psychosis. (5) Metformin (Lactic acidosis is a rare but serious complication.)				
de Vries (2017)	SCOPE project: Norway, Sweden, Denmark, Ireland, UK, Spain, Italy, Netherlands and Croatia	National competent authorities	Not specified	Not specified	1766 general practitioners (25 from Denmark, 847 from Spain, 85 from Croatia, 144 from Ireland, 183 from Italy, 72 from Netherlands, 105 from Norway, 108 from Sweden and 197 from UK); Of the 1766, 1551 were community-based, 39 hospital-based and 32 practised in other settings.	To assess healthcare professionals' awareness and preferences regarding risk communications	Survey
de Vries (2018)	SCOPE project: nine European countries (Croatia, Denmark, Ireland, Italy,	National competent authorities	Distribution of DHPC (direct healthcare professionals communication); Combined hormonal contraceptives (2014): Risk of VTE;	Diclofenac patients with ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and	3288 participants; of them, 54% were GPs, 40% pharmacists and 7% cardiologists. Their country-wise was as follows: (General practitioners: Croatia 85; Denmark 25;	To assess and compare the familiarity of GPs, cardiologists, and pharmacists with DHPCs as communication tools, their	Cross-sectional web-based survey

	Netherland, Norway, Spain, Sweden and the UK)	Diclofenac (2013): Risk of cardiovascular events; Valproate (2014): Risk of teratogenicity; Ivabradine (2014): Risk of cardiovascular events.	congestive heart failure.	Ireland 144; Italy 183; Netherlands 72; Norway 105; Spain 847 Sweden 108; UK 197); (Cardiologists*: Croatia 4; Denmark 7; Ireland 5; Italy 63; Netherlands 17; Norway 40; Spain 56 Sweden 15; UK 15); (Pharmacists*: Croatia 104; Denmark 35; Ireland 281; Italy 104; Netherlands 64; Norway 381; Spain 13; Sweden not available; UK 318).	awareness of specific drug safety issues and the sources through which they had become aware of the specific issues

AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé (the French Medicines Agency); **DDL**: Dear Doctor Letter; **ED**: Emergency Department; **FDA**: Food and Drug Administration; **NPSA**: National Patient Safety Agency; **SCOPE**: Strengthening Collaboration for Operating Pharmacovigilance in Europe; **SSRI**: Selective Serotonin Reuptake Inhibitor; **UK**: United Kingdom; **US**: United States; * based on published correction of de Vries et al. (2018) published in de Vries et al. (2020).

2.3.2 Quality assessment

Qualitative studies scored 80% to 100% (Barker et al., 2019; Kesselheim et al., 2017; Morrato et al., 2008; Richardson et al., 2007) on the MMAT, while quantitative studies scored 20% to 80% (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2017, 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Habib & Gan, 2008; Harder & Hawboldt, 2009; Karpel et al., 2009; Kloet et al., 2017; Mazor et al., 2005; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Reed et al., 1999; Richards et al., 2003; Saad et al., 2010; Sabblah et al., 2016; Shneker et al., 2009; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). Lack of reporting was a main reason for quantitative studies not fulfilling the MMAT items (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Habib & Gan, 2008; Harder & Hawboldt, 2009; Karpel et al., 2009; Reed et al., 1999; Richards et al., 2003; Saad et al., 2010; Smollin et al., 2016; Théophile et al., 2011). The details of the studies quality assessment are presented in table 2.3.

Table 2.3: Quality assessment of the included studies using the MMAT (Hong et al., 2018)

Qualitative studies								
First author (year)	Screening question 1: Clear research question	Screening question 2: Collected data allow to address the research question	Item 1: Qualitative approach appropriate to answer the research question	Item 2: Qualitative data collection method adequate to address the research question	Item 3: Findings adequately derived from data	Item 4: Interpretation of results sufficiently substantiated by data	Item 5: Coherence between qualitative data sources, collection, analysis and interpretation	Calculated score (%) (excluding the screening questions)
Kelsselheim (2017)	Yes	Yes	Yes	Could not be determined	Yes	Yes	Yes	80%
Richardson (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Morrato (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Barker (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Quantitative nonrandomised studies								
First author (year)	Screening question 1: Clear research question	Screening question 2: Collected data allow to address research question	Item 1: Participants representative of the target population	Item 2: Measurements appropriate regarding both outcome and intervention (or exposure)	Item 3: Complete outcome data	Item 4: Confounders accounted for in the design and analysis	Item 5: Intervention administered during the study period (or exposure occurred) as intended	Calculated score (%) (excluding the screening questions)
Kloet (2017)	Yes	Yes	Could not be determined	Outcome: yes Exposure: yes	No. 26% of general medicine patients with box warning non-adherence were discharged before the pharmacists	No	Yes	40%

					talked with physicians.			
Quantitative descriptive studies								
First author (year)	Screening question 1: Clear research question	Screening question 2: Collected data allow to address research question	Item 1: Sampling strategy relevant to address the research question	Item 2: Sample representative of the target population	Item 3: Measurements appropriateness	Item 4: Risk of nonresponse bias is low.	Item 5: Statistical analysis appropriate to answer the research question	Calculated score (%) (excluding the screening questions)
Bhatia (2008)	Yes	Yes	Yes	Yes	Could not be determined; validity and reliability not reported	No; Response rate 57.5% of 1521; Difference in subpopulations	Yes; Did not mention if normally distributed or not to measure the mean	60%
Habib (2008)	Yes	Yes	Yes	No	Could not be determined; Validity, reliability, pretesting of the questioner were not reported.	No; Response rate 25% of 1179	Yes	40%
Smollin (2016)	Yes	Yes	Yes	Yes	Could not be determined; Validity and pretesting of the questioner were not reported.	Could not be determined; Response rate 41%; Difference in respondents' subgroups	Could not be determined; All included tests (mean, SD; T-test; ANOVA) would be appropriate if the data were normally distributed.	40%

							This information was not reported.	
Sabblah (2016)	Yes	Yes	Yes	Yes	Yes	Could not be determined; Response rate 83.15% of 1098; Difference in respondents' subgroups	Yes	80%
Yaghmai (2010)	Yes	Yes	Could not be determined	Could not be determined	Could not be determined	Could not be determined; Response rate 71.7% of 46	Yes	20%
Bell (2013)	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability, pretesting of the questioner were not reported.	No; Response rate 13.1% of 4627; Then, 100 were excluded because they did not meet the inclusion criteria.	Could not be determined; Not reported where ANOVA test was performed	40%
de Vries (2018) Authors of this study reported that ethics approval was not considered necessary.	Yes	Yes	Yes	Yes	Yes	No. Response rate not reported; Total 3625 respondents, 377 of them were excluded because they were not from the targeted population. Excluded HCPs who were not familiar with DHPC from the assessment of awareness about safety issues,	Yes	80%

						although HCPs could know the issue from another source. Difference in subpopulations		
Esterly (2011)	Yes	Yes	No	Could not be determined	Could not be determined; Validity, reliability, and pretesting of the questioner were not reported.	Could not be determined; Response rate reflected the initial respondents before being excluded due to duplication in institutions.	Yes	20%
Fogler (2009)	Yes	Yes	No	No	Could not be determined; Validity, reliability, and pretesting of the questioner were not reported.	No. All individuals approached agreed to participate; however, they only included individuals who called a hotline service within a certain year.	Yes; Not clear x^2 test was performed	20%
Garbutt (2010)	Yes	Yes	Yes	Yes	Could not be determined; Validity and reliability were not reported.	No; 53% of 197 (physicians, not patients); Matched respondents and non-respondents	Yes; Did not report if data were normally distributed or not to be judged for mean/median	60%
Piening (2012)	Yes	Yes	Yes	Yes	Yes	No; Totally, 1141 from 3488 responded.	Could not be determined; Not clear which type of ANOVA test was	60%

							performed; Not clear why Wilcoxon signed rank test was performed, although it is for paired data	
Richards (2003)	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported.	No; Response rate 25% of 2000	No	40%
Saad (2010)	Yes	Yes	Yes	No	Could not be determined; Validity, reliability and pretesting of the questioner were not reported.	No; Response rate was not reported. Most respondents were pharmacists (61/65).	Yes	40%
Shneker (2009)	Yes	Yes	Yes	Yes	No; Did not assess for validity and reliability; Pretesting of the questioner was not reported.	No; Response rate 22% of 780	Yes; Correlation reported in the discussion but did not specify which test was performed;. Did not report if data were normally distributed or not	60%
Mazor (2005)	Yes	Yes	Could not be determined;	Could not be determined	Yes	Could not be determined	Yes;	40%

			No information about how physicians were chosen				Did not report if data were normally distributed or not to be judged for the mean; Average rating of the letters had classification for each result; however, the basis was not clear.	
de Vries (2017)	Yes	Yes	Yes	Yes	Yes	Could not be determined; Differences among participants from different countries	Yes; Not reported if data were normally distributed (for the mean)	80%
Cheung (2008)	Yes	Yes	Yes	Yes	Could not be determined; Validity and reliability were not reported. Variables for the reason of changes in prescribing practices were not clear.	No; Response rate 38% of 1748	Yes	60%
Reed (1999)	Yes	Yes	Yes	No. The survey only included paramedics,	Could not be determined Validity, reliability and	No; Response rate 47% of 200 paramedics.	Yes	20%

				although the observation part (not covered in this review) and the aim includes both paramedics and physicians.	pretesting of the questioner were not reported.			
Theophile (2011)	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported	No; Response rate for paediatricians: 31% of 145. Response rate for general practitioners 37% of 680; Response rate for pharmacists: 40% of 230	Yes	60%
Flood (2015)	Yes	Yes	Yes	Could not be determined; Not clear why only gastroenterologists were targeted	Could not be determined; Overall, the study is valid as multiple different sources were used. Reliability was reported in one point in the study but not in the survey (which is the only part included in this review). Variables were clear. It was not reported if the	Could not be determined; Response rate not reported; 100 gastroenterologists responded.	Yes [for the survey part only].	40%

					survey was pretested or not.			
Karpel (2009)	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported.	No; Response rate was 9.9% of 11147. Difference in subgroups of population; Large differences with the paediatricians' groups, but they were not analysed independently.	Yes; For the Pearson X^2 test and the Fisher exact test, only reported that they used either test for relationships, but did not give details on where each test of the two was performed	60%
Harder (2009)	Yes	Yes	Yes	Yes	Could not be determined; Reliability and pretesting of the survey were not reported.	Could not be determined; No response rate	Yes	60%
Cordero (2008)	Yes	Yes	Yes. Although excluded primary care practitioners whose information were not available.	Yes.	Could not be determined. Validity, reliability, and pretesting of the questioner were not reported.	No; Response rate was 15.15% of 764. 74% of the respondents practised with medical centres affiliated with medical schools.	Yes	60%

2.3.3 Preliminary synthesis

2.3.3.1 Healthcare professionals' knowledge of medicine alerts

In total, this theme was identified from 22 studies (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2017, 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Kloet et al., 2017; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). Diverse areas of knowledge were reported regarding medicine alerts. The majority of studies (n=19) explored HCPs' awareness of an alert's release (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). However, only five studies assessed healthcare professionals' knowledge of the content of the alert (Bell et al., 2013; Kesselheim et al., 2017; Richardson et al., 2007; Sabblah et al., 2016; Smollin et al., 2016). In two studies, HCPs were evaluated with regard to their knowledge of an evolving medicine risk (Bell et al., 2013; Yaghmai et al., 2010). In one, the knowledge of a study that led to the regulatory decision that prompted the alert was evaluated (Karpel et al., 2009). Four studies reported HCPs' familiarity with tools used in medicine safety communications (de Vries et al., 2017, 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Smollin et al., 2016), while only two studies reported HCPs' knowledge of the existence of the regulatory agency or its website (Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012). One study did not investigate knowledge directly, yet a lack of knowledge was provided as a reason for physicians' nonadherence to boxed warnings (Kloet et al., 2017). In this study, the area of knowledge deficiency was not specified (Kloet et al., 2017).

Studies reported on knoweldge using a variety of methods. Three studies were qualitative (Kesselheim et al., 2017; Morrato et al., 2008; Richardson et al., 2007), one was a cohort observational study (Kloet et al., 2017), and the rest were quantitative surveys (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2017, 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). Most studies (n=14) investigated HCPs' knowledge in relation to one medicine or one medicine class (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Théophile et al., 2011; Yaghmai et al., 2010), while five studies involved more than one medicine (Bell et al., 2013; de Vries et al., 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Sabblah et al., 2016; Smollin et al., 2016) Fourteen studies reported the knowledge across one professional group (Bell et al., 2013; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2017; Esterly et al., 2011; Flood et al., 2015; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Kloet et al., 2017; Morrato et al., 2008; Richards et al., 2003; Smollin et al., 2016; Yaghmai et al., 2010), while eight studies did so among at least two professional groups (Bhatia et al., 2008; de Vries et al., 2018; Fogler et al., 2009; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Théophile et al., 2011). Knowledge was reported in most studies within a single country (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Kloet et al., 2017; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010), while two articles, relating to the same project, investigated knowledge across different countries (de Vries et al., 2017, 2018).Only two studies used a control medicine (a medicine without specific alerts, e.g., without a BW, at the time of the study) (Bell et al., 2013; Smollin et al., 2016). None of the studies specified a cut-off point or a threshold for acceptable knowledge levels.

2.3.3.1.1 Healthcare professionals' knowledge of the release of an alert

In total, 13 studies reported physicians' awareness of alerts, resulting in 64 physician–alert combinations (Bell et al., 2013; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2018; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Richards et al., 2003; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). As a whole, physicians possessed poor knowledge in 29 of the physicians–alert combinations, followed by high knowledge in 25 and fair knowledge in 10 of the combinations. In the included studies, the knowledge levels of primary care providers (PCPs), general practitioners (GPs), emergency physicians, and paediatricians were reported in at least two studies, while the rest were repeated once. Family medicine and internists were reported in two studies (Fogler et al., 2009; Karpel et al., 2009), but in one study their knowledge percentage was presented collectively (Fogler et al., 2009).

Primary care providers demonstrated high levels of knowledge of alerts related to antidepressants (Cordero et al., 2008) and of zolpidem and eszopiclone alerts (Kesselheim et al., 2017). Similarly, there was a high level of knowledge among general practitioners regarding alerts relating to OTC cough and cold medicines (Yaghmai et al., 2010), valproate (birth defects) (de Vries et al., 2018), diclofenac (de Vries et al., 2018), contraceptives (de Vries et al., 2018), and ivabradine (de Vries et al., 2018). Interestingly, general practitioners also demonstrated a high level of knowledge regarding the FDA consideration to remove cough and cold active ingredients from medicines for children below the age of six years (Yaghmai et al., 2010). However, GPs possessed poor levels of knowledge of the alert related to vitamin D (Théophile et al., 2011). In addition, emergency medicine physicians possessed high levels of knowledge of two alerts, namely dropiredol(Richards et al., 2003) and haloperidol(Smollin et al., 2016), and fair levels of knowledge of a metformin-related alert (Smollin et al., 2016). Among these physicians, there were poor levels of knowledge of alerts related to midazolam (Smollin et al., 2016), ciprofloxacin (Smollin et al., 2016), and naproxen (Smollin et al., 2016). Paediatricians also demonstrated high levels of knowledge regarding antidepressants alerts (Cheung et al., 2008) and OTC cough and cold medicine alerts (Garbutt et al., 2010), but poor knowledge regarding six alerts relating to vitamin D (Théophile et

al., 2011), midazolam (Smollin et al., 2016), ciprofloxacin (Smollin et al., 2016), haloperidol (Smollin et al., 2016), metformin (Smollin et al., 2016), and naproxen (Smollin et al., 2016). The details of the physicians' levels of knowledge are presented in Table 2.4.

Table 2.4: Physicians' knowledge of the release of an alert

First Author (year)	Speciality	Medicine																		
		Zolpidem & Eszopiclone	Droperidol	Antidepressants	Nelfinavir Mesylate	LABA	OTC Cough & Cold	Vitamin D	Carbamazepine	Newer Antiepileptics	Valproate Birth Defects	Valproate IQ Changes[†]	Midazolam	Ciprofloxacin	Haloperidol	Metformin	Naproxen	Diclofenac	Contraceptives	Ivabradine
Kesselheim (2017)	PCP	100%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Richards (2003)	EP	-	91%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cheung (2008)	Paediatricians	-	-	72%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cordero (2008)	PCP	-	-	96%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fogler (2009)	Infectious disease physician	-	-	-	80.8%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Obstetrician/gynaecologist	-	-	-	33.3%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Family/internal medicine	-	-	-	51.7%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Other physicians	-	-	-	60%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Karpel (2009)	Allergists	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Family physicians	-	-	-	-	93.2%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Internists	-	-	-	-	87.8%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pulmonologists	-	-	-	-	98.1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Garbutt (2010)	Paediatricians	-	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-		-
Yaghmai (2010)	GPs	-	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-	-	-
Théophile (2011)	Paediatricians	-	-	-	-	-	-	49%	-	-	-	-	-	-	-	-	-	-		-
	GPs	-	-	-	-	-	-	48%	-	-	-	-	-	-	-	-	-	-	-	-
Bell (2013)	Neurologists	-	-	-	-	-	-	-	81.2%	80.6%	79%	83.2%	-	-	-	-	-	-	-	-
Flood (2015)	Gastroenterologists	-	-	-	-	-	-	-	-	-	-	-	63%	-	-	-	-	-	-	-
Smollin (2016)	Emergency medicine	-	-	-	-	-	-	-	-	-	-	-	10%	40%	82%	50%	20%	-	-	-
	Paediatrics	-	-	-	-	-	-	-	-	-	-	-	16.1%	22.6%	38.7%	38.7%	32.2%	-	-	-
	PGY1	-	-	-	-	-	-	-	-	-	-	-	12.5%	25%	56.3%	43.8%	25%	-	-	-
	PGY2	-	-	-	-	-	-	-	-	-	-	-	10%	35%	60%	55%	30%	-	-	-
	PGY3	-	-	-	-	-	-	-	-	-	-	-	12.50%	12.5%	50%	43.8%	25%	-	-	-
	PGY4	-	-	-	-	-	-	-	-	-	-	-	20%	40%	80%	60%	0%	-	-	-
	Attending/fellow	-	-	-	-	-	-	-	-	-	-	-	12.5%	50%	83.3%	37.5%	25%	-	-	-

de Vries (2018)	GPs	-	-	-	-	-	-	-	-	-	76%	-	-	-	-	-	-	96%	88%	70%
	Cardiologists	-	-	-	-	-	-	-	-	-	34%	-	-	-	-	-	-	79%	61%	91%

[1] At the time of the study the authors reported that the valproate product insert did not mention this specific risk, while it mentioned that there had been reports of developmental delay, autism, and/or autism spectrum disorders in children born to mothers who were exposed to valproate during pregnancy.
Smollin (2016) classified participants in two ways, namely speciality and years of training.
PGY: Postgraduate Year.
PCP: Primary care providers; **EP**: Emergency Physicians; **GP**: General Practitioners

Studies that described pharmacists' levels of knowledge included alerts released on vitamin D (Théophile et al., 2011), ceftriaxone and calcium interaction (Esterly et al., 2011), valproate (birth defects) (de Vries et al., 2018), contraceptives (de Vries et al., 2018), diclofenac (de Vries et al., 2018), and ivabradine (de Vries et al., 2018) (Figure 2.2). Pharmacists demonstrated high levels of knowledge of five alerts relating to calcium and ceftriaxone interaction (Esterly et al., 2011), nelfinavir (Fogler et al., 2009), valproate (de Vries et al., 2018), diclofenac (de Vries et al., 2018), and contraceptives (de Vries et al., 2018). Meanwhile, fair levels of knowledge were demonstrated in the pharmacist groups with respect to alerts related to vitamin D (Théophile et al., 2011) and ivabradine (de Vries et al., 2018).

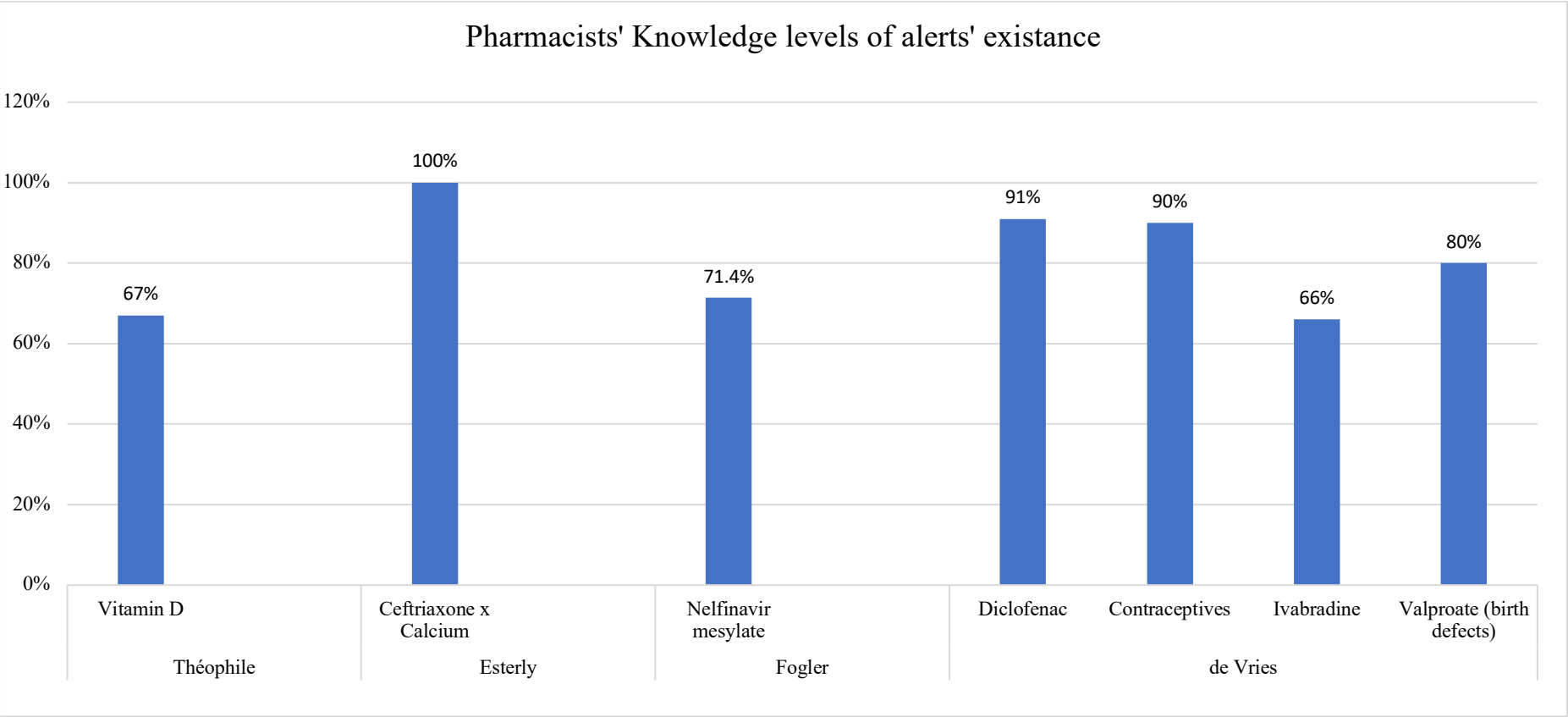


Figure 2.2: Pharmacists' levels of knowledge of the release of an alert

Ceftriaxone x Calcium: ceftriaxone and calcium interaction. Citations: Théophile et al., 2011; Esterly et al., 2011; de Vries et al., 2018; Fogler et al., 2009.

One study reported the exact level of knowledge of nurse practitioners and nurse midwives in relation to the release of a nelfinavir-related alert (Fogler et al., 2009). The level of knowledge was high among this group of practitioners (Fogler et al., 2009).

There were three studies that provided the collective levels of knowledge of different health professional groups with regard to the release of an alert related to antidepressants in youth (Bhatia et al., 2008; Richardson et al., 2007) and of an antipsychotics-related alert (Saad et al., 2010). All three US-based studies found high levels of knowledge among the participants, with the first including paediatricians and paediatric nurses (only a minority of the sample were nurses) (Richardson et al., 2007), the second involving physicians, physician assistants (also called physician associates), and nurses from different specialities (Bhatia et al., 2008), and the third involving pharmacists (94% of the sample), physicians and nurses (Saad et al., 2010). Two other studies revealed the range of knowledge levels among different groups of healthcare professionals in relation to the existence of different alerts (Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Sabblah et al., 2016). One of these studies was conducted in the Netherlands and involved GPs, internists, community pharmacists, and hospital pharmacists (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). A fair level of knowledge of etoricoxib, and a high level of knowledge of clopidogrel were reported in this study (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). The second study was conducted in Ghana and included pharmacists, nurses, physician assistants, and doctors (the study did not specify the types of doctors). The study participants ranged in their level of knowledge from possessing poor knowledge of codeine alerts to possessing a fair knowledge of diclofenac alerts (Sabblah et al., 2016).

2.3.3.1.2 Healthcare professionals' knowledge of alerts' content

Five studies assessed HCPs' knowledge (Bell et al., 2013; Fogler et al., 2009; Kesselheim et al., 2017; Richardson et al., 2007; Sabblah et al., 2016; Smollin et al., 2016) of the content of alerts. The researchers targeted physicians in most studies, but one study also examined nurses (Richardson et al., 2007). In one study, the authors reported that only a few knew about the recommendations of the alert. However, the study did not report specific percentages (Richardson et al., 2007). In the remaining studies, 40 profession–alert combinations were found. Among these combinations, one demonstrated high levels of knowledge, including of carbamazepine (Bell et al., 2013); two showed fair levels of knowledge, including of zolpidem (Kesselheim et al., 2017) and newer antiepileptics (Bell et al., 2013); and 37 combinations reported poor levels of knowledge, including of valproate (Bell et al., 2013) (related to both birth defects and IQ changes), midazolam (Smollin et al., 2016), ciprofloxacin (Smollin et al., 2016), haloperidol (Smollin et al., 2016), metformin (Smollin et al., 2016), and naproxen (Smollin et al., 2016). Further details of the participants' knowledge of the content of alerts are presented in Table 2.5. One study (based in Ghana) reported the collective levels of knowledge of healthcare professionals in relation to the content of different alerts (Sabblah et al., 2016). In this study, a high level of knowledge was observed regarding the content of alerts among those who knew about the release of the alerts (Sabblah et al., 2016).

Table 2.5: Healthcare professionals' knowledge of alerts' content

First author (year)	Speciality /Professional Background	Medicine									
		Zolpidem	Carbamazepine	Newer Antiepileptics	Valproate Birth Defects	Valproate IQ Changes[1]	Midazolam	Ciprofloxacin	Haloperidol	Metformin	Naproxen
Kesselheim (2017)	Physician	50%	-	-	-	-	-	-	-	-	-
Bell (2013)	Physician	-	73.9%	60.2%	33.5%	48.9%	-	-	-	-	-
	Emergency medicine	-	-	-	-	-	6%	22%	4%	38%	12%
	Paediatrics	-	-	-	-	-	13%	10.3%	0%	13%	10.3%
	PGY1	-	-	-	-	-	0%	12.5%	0%	25%	6.3%
	PGY2	-	-	-	-	-	5%	15%	0%	30%	10%
	PGY3	-	-	-	-	-	12.5%	6.3%	0%	31.3%	12.5%
	PGY4	-	-	-	-	-	0%	0%	0%	40%	20%
Smollin (2016)	Attending/fellow	-	-	-	-	-	12.5%	33.3%	8.3%	25%	12.5%

[1] At the time of the study the authors reported that the valproate product insert did not mention this specific risk, while it mentioned that there had been reports of developmental delay, autism, and/or autism spectrum disorders in children born to mothers who were exposed to valproate during pregnancy.
Smollin et al., (2016) classified participants in two ways, namely speciality and years of training.
PGY: Postgraduate Year.

2.3.3.1.3 Other knowledge areas

Other knowledge areas included healthcare professionals' knowledge of the existence of the regulatory agency (Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012), the tools that they used (de Vries et al., 2017, 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Smollin et al., 2016), and their awareness of the research that led to the regulatory decision (Karpel et al., 2009). The majority of participants in the Netherlands-based quantitative survey were aware of the Dutch Medicines Evaluation Board (MEB) (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). However, all general internists (n=10) participating in the qualitative US-based study were not aware of the US FDA free email alert service regarding new medicine warnings (Morrato et al., 2008). Healthcare professionals' familiarity with DHPCs was reported in three studies, two of which were related to the same project across different European countries (de Vries et al., 2017, 2018), and the third was conducted in the Netherlands (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). A high level of DHPCs' familiarity was observed among the participants in the three studies (de Vries et al., 2017, 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012). Similarly, general practitioners from different European countries possessed high levels of awareness of the national competent authorities' communications, and fair levels of awareness of educational materials (de Vries et al., 2017). Only one study of those reporting HCPs' familiarity with alert communication tools was conducted in the US (Smollin et al., 2016). In this study, physicians (emergency medicine physicians and paediatricians with different levels of training) showed a high level of awareness of the concept of US FDA BW (Smollin et al., 2016). Furthermore, a high level of knowledge of the Salmeterol Multicenter Asthma Research Trial (SMART), a study reported by the authors as leading to the US FDA LABA BW, was noted among physicians (pulmonologists, allergists, internists, family medicine, and paediatricians; a difference in sample sizes was reported, ranging from 10 paediatricians to 429 pulmonologists) (Karpel et al., 2009).

2.3.3.1.4 Demographic characteristics associated with healthcare professionals' level of knowledge

Different studies explored demographic associations with healthcare professionals' levels of knowledge. Eight of these studies focused on healthcare professionals' knowledge of the existence of an alert. Studies investigated different demographic characteristics including professional groups (Fogler et al., 2009; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Sabblah et al., 2016), settings (Saad et al., 2010), years of training (Smollin et al., 2016), specialities (Karpel et al., 2009; Smollin et al., 2016), the number of patients treated in practice (Bell et al., 2013; Fogler et al., 2009), and the sources for obtaining general information on the safety of medicines (Bell et al., 2013). Professional groups that were reported to have significantly increased levels of knowledge included nurses (higher knowledge in at least one of the six alerts relating to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole) (Sabblah et al., 2016), pharmacists (in alerts related to rimonabant, moxifloxacin, and clopidogrel) (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), and primary care HCPs, including GPs and community pharmacists with the etoricoxib-related alert (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). On the other hand, with regard to the nelfinavir-related alert, the lowest level of knowledge was observed among obstetricians, who demonstrated almost half of the levels of knowledge of all other groups collectively (Fogler et al., 2009).

Two studies identified a significant association between knowledge and speciality (Karpel et al., 2009; Smollin et al., 2016), and one with the level of training (Smollin et al., 2016). In the first, pulmonologists and allergists possessed a greater level of knowledge related to the LABA alert than did primary care providers (Karpel et al., 2009). In the second, attending physicians and fellows were more knowledgeable about medicines with or without BW than were residents (Smollin et al., 2016). In the same study, greater levels of knowledge were observed among the resident groups with increasing years of training (Smollin et al., 2016). One study found that most HCPs who reported being very familiar with the antipsychotics-related alert were practising in a nursing facility and in teaching hospital settings (Saad et al., 2010). Furthermore, two studies reported that healthcare professionals' levels of knowledge increased as the number of patients

treated in their practice increased (Bell et al., 2013; Fogler et al., 2009). In the case of the nelfinavir-related alert, awareness was significantly higher as the number of HIV-infected patients in participants' practice increased (Fogler et al., 2009). Similarly, being aware of antiepileptics-related alerts modestly increased as the number of epileptic patients treated each year increased (Bell et al., 2013). In the same study, only specialist organisations as sources of obtaining general knowledge of the safety of medicines were associated with increased levels of knowledge of the release of an alert (Bell et al., 2013). However, the type of practice, region, years of practice, and age of respondents were not associated with their knowledge of medicine safety issues (Bell et al., 2013).

Only three studies reported significant associations or differences with HCPs' levels of knowledge of the content of alerts. One study reported that nurses were more likely to remember the content of the letters released by the Ghana FDA in 2013 (six letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole) compared to the other participating healthcare professionals (Sabblah et al., 2016). As with the knowledge of the release of an alert, knowledge of the exact risk reported in five alerts related to antiepileptics increased only slightly with the increased number of epileptic patients treated each year (Bell et al., 2013). Moreover, using specialist organisations as a general source of medicine safety information was associated with HCPs' increased knowledge of the exact risk of alerts (Bell et al., 2013). However, the participants' type of practice, region of practice, years in practice, and age were not associated with their knowledge of the exact risk reported in the alerts related to antiepileptics (Bell et al., 2013). The third study reported that there were no statistically significant differences between attending physicians and residents when identifying the content of a BW (Smollin et al., 2016). Furthermore, there was no statistically significant difference in residents' abilities to identify the content of the BW based on their years of training (Smollin et al., 2016).

Two studies reported significant associations or differences with healthcare professionals' familiarity with the tools used in communicating the alerts, and one study reported differences in terms of HCPs' familiarity with the regulatory agency (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In a study based in the Netherlands, the authors reported a significant difference when reporting the range of healthcare professionals' unfamiliarity with DHPCs, which was lowest

among hospital pharmacists and highest among general practitioners (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In the same study, the authors reported that hospital and community pharmacists were more familiar with the Dutch Medicine Evaluation Board (knowing about it and visiting its website) than internists and general practitioners (Piening, Haaijer-Ruskamp, de Graeff et al., 2012).

In another survey that was distributed to HCPs in nine different European countries, pharmacists in Italy were found to be significantly more familiar with direct healthcare professional communications than were GPs from the same country (de Vries et al., 2018).

Only one study reported characteristics associated with HCPs' knowledge of a potential regulatory decision regarding the safety of medicine. In comparison with physicians who were not aware of the FDA's consideration to remove active ingredients from cough and cold products in children below the age of six years, physicians who were aware of the potential recall had significantly more years in practice (Yaghmai et al., 2010).

2.3.3.1.5 Possible factors affecting healthcare professionals' knowledge of medicine alerts

One factor possibly affecting healthcare professionals' knowledge is whether they took action in order to increase their knowledge, such as reading the alert. Although most HCPs in one study reported reading the antidepressants-related BW (Cordero et al., 2008), healthcare professionals reported different actions related to reading other alerts that they received, whether they read all of the alerts (Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012) or only those relevant to them (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). Further action involved visiting the regulatory agency's website or using one of its services. Although some HCPs reported visiting the regulatory agency's website (Piening, Haaijer-Ruskamp, de Graeff et al., 2012) or using one of its services (Morrato et al., 2008), the majority of participants in one study had never visited the regulatory agency's website (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In addition, HCPs reported subscribing to journals as a means to keeping up to date about the safety of medicines (Morrato et al., 2008). However, not actively searching for information (Barker et al., 2019) and not reviewing the in-store website on a daily basis were also reported (Barker et al.,

2019). Healthcare professionals also reported using multiple sources for information confirmation (Kesselheim et al., 2017) and for ensuring information quality (the latter reported by only one participant) (Morrato et al., 2008).

The participants in the included studies reported using different sources to become aware of specific alerts, or sources they use generally to update their knowledge of the safety of medicines. The sources were divided into those related to regulatory agencies, pharmaceutical companies, medical sources, non-medical sources, and point-of-care sources. A sixth category was that of information reporting the mode of delivery without specifying the exact source. Table 2.6 includes details of these sources. However, some participants reported that they did not update their knowledge or did not have a method with which to update their knowledge (Smollin et al., 2016). Some HCPs also reported not using any source to obtain information about alerts (Morrato et al., 2008; Sabblah et al., 2016). Healthcare professionals' satisfaction with the current ways of delivering medicine safety information could also influence their motivation to update their knowledge (Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012). They also had different preferences regarding future alerts in terms of sources or senders (Barker et al., 2019; de Vries et al., 2017; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012) format (Barker et al., 2019; de Vries et al., 2017; Théophile et al., 2011), content (Barker et al., 2019; Bell et al., 2013; Morrato et al., 2008), and mode of delivery (Barker et al., 2019; Bell et al., 2013; de Vries et al., 2017; Kesselheim et al., 2017; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Sabblah et al., 2016; Théophile et al., 2011). These are presented in Appendix 11. Furthermore, different beliefs towards the sources of medicine safety information were expressed. These beliefs are presented in Table 2.7.

Table 2.6: Sources of specific and general knowledge of medicine alerts

Category	Type of Source (First author, year)	Was a Source for Knowing about a **Specific** Alert	As a **General** Source to Obtain Information about Alerts
Related to regulatory agencies	US FDA website/MedWatch/Listserv (Bell, 2013; Fogler, 2009; Kesselheim, 2017; Morrato, 2008; Smollin, 2016)	√	√
	MEB website (Piening, 2012)	√	√
	Pharmacy regulatory authority website, Institute for Safe Medication Practices (ISMP) Canada sources (Barker, 2019)	-	√
	Canada's Community Pharmacy Incident Reporting (CPhIR) system (Barker, 2019)	-	√
	Health Canada (Barker, 2019)	-	√
	Ghana FDA (letter) (Sabblah, 2016)	√	√
	National competent authority's information centre(de Vries, 2018).	√	-
Related to pharmaceutical companies	Pharmaceutical representative (Bell, 2013; Fogler, 2009; Kesselheim, 2017; Morrato, 2008)	√	√
	Drug company websites (Kesselheim, 2017)	-	√
	Mail from manufacturers (Kesselheim, 2017)	-	√
	Pharmacy inserts/product inserts/product labelling (Bell, 2013; Kesselheim, 2017; Morrato, 2008)	√	√
	DHCP(Fogler, 2009; Morrato, 2008; Piening, 2012)	√	√
	Drug advertisement (Kesselheim, 2017)	-	√
Related to medical sources	Specialist organisations/professional associations (Bell, 2013; de Vries, 2018; Sabblah, 2016)	√	√
	Medical/health newspapers (Garbutt, 2010; Kesselheim, 2017; Morrato, 2008)	√	√
	Professional journals (Bell, 2013; de Vries 2018; Garbutt, 2010; Kesselheim, 2017; Morrato, 2008; Piening, 2012)	√	√
	Drug software (web-based/mobile applications) (Fogler, 2009; Sabblah, 2016; Kesselheim, 2017; Morrato, 2008; Smollin, 2016)	√	√
	CME or other educational programs (Bell, 2013; Morrato, 2008; Smollin, 2016)	-	√
	Conferences (Kesselheim, 2017)	-	√
	Medical insurance companies (Morrato, 2008)	-	√
	Medical meetings (Morrato, 2008)	-	√
	Professional regulatory bodies/councils (Sabblah, 2016)	√	-
	College website (no further information was provided) (Barker, 2019)	-	√
Related to non-medical sources	Popular press (lay media, newsletters, news reports) (de Vries, 2018; Garbutt, 2010; Kesselheim, 2017; Morrato, 2008; Smollin, 2016)	√	√
	Social media (Kesselheim, 2017)	-	√

Point-of-care sources	Colleagues/peers (Bell, 2013; Fogler, 2009; Garbutt, 2010; Sabblah, 2016; Kesselheim, 2017; Morrato, 2008)	√	√
	Formularies (Kesselheim, 2017)	-	√
	Clinical pharmacists (Smollin, 2016)	-	√
	Word of mouth (Smollin, 2016)	-	√
	Electronic medical records (Kesselheim, 2017; Morrato, 2008)	-	√
	Prescribing alerts/pharmacy system alerts (Morrato, 2008)	-	√
	Company owning the community pharmacy (Barker, 2019)	-	√
	Community pharmacy webpage/pharmacy intranet (Barker, 2019)	-	√
	Database provider folder in the pharmacy's general email account (Barker, 2019)	-	√
	Managers supplying the information to their staff (Barker, 2019)	-	√
	Patients/parents (Garbutt, 2010)	√	-
	Hospitals /healthcare facilities where HCPs practise (Esterly, 2011; Sabblah, 2016)	√	√
Related to the mode of delivery	Internet services and internet-based resources (de Vries, 2018; Fogler, 2009; Morrato, 2008; Sabblah, 2016)	√	√
	Email notifications/Listserv (Barker, 2019; Fogler, 2009; Smollin, 2016)	√	√
	Computer-aided (Morrato, 2008)	-	√
	Podcasts (Smollin, 2016)	-	√
	Journals (types of journals not specified) (Smollin, 2016)	-	√
	DHPCs (de Vries, 2018)	√	-
	Hard-copy letters (Sabblah, 2016)	√	-
	Soft-copy letters (Sabblah, 2016)	√	-

Table 2.7: Healthcare professionals' beliefs towards the sources of medicine alerts

Source Category	Positive Beliefs (First author, year)	Negative Beliefs (First author, year)
Related to regulatory agencies	• MEB are knowledgeable about medicines (Piening, 2012) • Information from MEB is more trustworthy than information from pharmaceutical companies (Piening, 2012). • FDA is reported to be much better than a colleague opinion (Morrato, 2008).	• The findings and recommendations of the FDA are controversial (Bell, 2013). • FDA is biased towards the industry and it is a bought and sold group (Morrato, 2008).
Related to pharmaceutical companies	• Pharmaceutical companies provide trustworthy information (Kesselheim, 2017) • Pharmaceutical companies are knowledgeable about medicines (Piening, 2012) • Believing that pharmaceutical companies would provide all of the information on safety issues associated with their products (Morrato, 2008). • Pharmaceutical companies' DHPCs are viewed more favourably than other pharmaceutical companies' sources (Morrato, 2008)	• Pharmaceutical companies are not reliable due to potential bias and conflicts of interest (Kesselheim, 2017) • The information from pharmaceutical companies is less trustworthy than that from MEB (Piening, 2012) • Perceived as being the least credible and biased (Morrato, 2008). • Information from pharmaceutical companies' representatives is viewed with scepticism (Morrato, 2008) • Pharmaceutical companies may have limited targeted audiences based on medicine's indications and a physician's prescribing habits (Morrato, 2008).
Related to medical sources	• Online sources such as Medscape, Medline, Monthly Prescribing Reference, Epocrates, and DynaMed are considered reliable (Kesselheim, 2017) • Academic sources (journals were given as an example) are considered the most trustworthy by healthcare professionals and are not directly impacted by financial interests (Kesselheim, 2017)	• Physician Desk Reference was not trusted because it is developed by pharmaceutical companies (Morrato, 2008) • Credibility of medical meetings was questioned because they are often sponsored by pharmaceutical companies (Morrato, 2008) • Medical meetings were not perceived to be an efficient source of information because these meetings do not usually address safety-related issues (Morrato, 2008)
Related to non-medical sources	• Medications' risk issues can be brought to the attention of HCPs through news reports (Morrato, 2008) • News reports are believed to improve physician–patient dialogue (Morrato, 2008)	• Information from popular press might reach the public before physicians — as the public becomes aware of risks first, there is concern that physicians will not have the time to read the resources and form an opinion on the issue before being asked by patients (Morrato, 2008)
Point-of-care sources	-	• Pharmacy alert systems do not account for the whole clinical picture (Morrato, 2008)
Only reported mode of delivery	• Computer-aided and online sources are considered timely and reliable (Morrato, 2008).	-

One study reported healthcare professionals believes towards groups of sources in general, including (1) scientific sources (this included medical newsletters, medical journals, colleagues, and continuing medical education) are most credible and provide in-depth information, (2) third party sources (internet services, popular press, drug software/personal digital assistant, Physician Desk Reference, product labelling, US FDA, medical insurance companies electronic medical records/prescribing alerts) are considered to be fast, readily accessible electronically, and can be customised according to the physicians' needs; however, they have mixed credibility (Morrato, 2008).

In addition to healthcare providers, healthcare institutions and managers may also play a role in ensuring that healthcare professionals receive information about the safety of medicines. Healthcare institutions and managers of community pharmacies reported providing their staff with such information (Barker et al., 2019; Esterly et al., 2011; Harder & Hawboldt, 2009). Not permitting pharmaceutical company representatives in the workplace (Kesselheim et al., 2017) and pharmacy managers filtering the information received (Barker et al., 2019) have also been reported. Only one study reported managers taking steps to ensure that staff were informed about the alert, which involved asking HCPs to sign after reading the information (Barker et al., 2019).

Different barriers to healthcare professionals updating their information on the safety of medicines were identified. The information-seeking process was perceived to be time-consuming (Barker et al., 2019; Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012) and not enough time was available to search for and read updates related to the safety of medicines (Barker et al., 2019; Kesselheim et al., 2017). Workload and interruptions at work were other barriers to healthcare professionals searching for and reading medicine safety information (Barker et al., 2019). Another barrier was that of overwhelming information, which was reported in two studies (Barker et al., 2019; Kesselheim et al., 2017). This included receiving information that is irrelevant to HCPs' practical setting but related to other practices (Barker et al., 2019), as well as being overwhelmed by information related to medicines' regulatory aspects rather than specific information regarding the safety of medicines when using the website of a regulatory agency (Kesselheim et al., 2017). In one of these studies, a participant reported feeling inundated by the volume of emails received (Barker et al., 2019). Healthcare professionals (community pharmacy managers) reported being overwhelmed by the number of sources and the need to combine information from different sources (Barker et al., 2019). However, a physician in another study reported receiving excessive amounts of sources including journals, brochures and newsletters through the mail (Morrato et al., 2008). Although many of them were redundant, the participant felt that it was better to receive a large amount of information than not receive enough (Morrato et al., 2008).

In one study a participant expressed that they are either not receiving the information that they desire or they do not know how to access the information (Barker et al., 2019). Similarly, two

other studies reported difficulty in using regulatory agency websites (Kesselheim et al., 2017; Morrato et al., 2008). Difficulty in using information systems and a need for guidance on how to access the information were also reported (Barker et al., 2019). Time delays in receiving alerts (Morrato et al., 2008; Sabblah et al., 2016;) and the possibility that the alerts may not be seen by HCPs (Kesselheim et al., 2017; Morrato et al., 2008), or that they might be mistakenly discarded by HCPs thinking that they are advertisements (Morrato et al., 2008), were also reported challenges.

2.3.3.2 Healthcare professionals' perceptions of alerts

HCPs' perceptions of alerts were identified in six studies (Cordero et al., 2008; Esterly et al., 2011; Harder & Hawboldt, 2009; Reed et al., 1999; Richardson et al., 2007; Shneker et al., 2009). Inaccuracies in perception were identified to be related to either the nature of the risk included in the alert (Cordero et al., 2008; Reed et al., 1999; Richardson et al., 2007; Shneker et al., 2009) or the recommendations regarding the alert (Esterly et al., 2011; Harder & Hawboldt, 2009). These inaccuracies were found at the individual level of healthcare professionals themselves or at the level of the healthcare institution in which they work (e.g. the hospital level). In all studies reporting perceptions at the level of healthcare professionals, perceptions were risk-related, while perceptions at the level of healthcare institutions were recommendation-related. Both types of perception-related inaccuracies are discussed in subsequent sections.

2.3.3.2.1 Inaccurate perceptions of risk

Inaccurate risk perceptions were identified in four studies (Cordero et al., 2008; Reed et al., 1999; Richardson et al., 2007; Shneker et al., 2009). Three of these studies involved physicians (Cordero et al., 2008; Richardson et al., 2007; Shneker et al., 2009), and one study involved paramedics (Reed et al., 1999). Underestimation of the risk appeared in three studies. They included primary care providers who thought that there was no risk of suicidality or that the risk was low in comparison to the benefits of antidepressants (Richardson et al., 2007). The second was also related to the risk of suicidality, where physicians in open-ended survey answers indicated that suicide in epileptic patients was linked neither to antiepileptic medicines nor to epilepsy, but rather to comorbid psychiatric conditions (Shneker et al., 2009); the study also stated that suicide rates

were low or not an issue in epileptic patients (although the risk involved suicidality) (Shneker et al., 2009). Paramedics in the third study stated that chest pain medicines administered to patients would not be affected by sildenafil (Reed et al., 1999). In this study, however, it was not reported whether or not paramedics were aware of the release of the alert. Overestimation of the risk included in the alert was reported in one study, in which primary care providers inaccurately thought that patients had died from suicide in aggregated clinical trials related to antidepressants (Cordero et al., 2008).

2.3.3.2.2 Inaccurate perceptions of recommendations

Inaccurate perceptions of recommendations were identified in two studies, both of which were related to calcium and ceftriaxone interactions (Esterly et al., 2011; Harder & Hawboldt, 2009). Both studies involved pharmacists describing their healthcare institutions' positions in relation to the alerts. One of these studies specified perceptions of the US FDA 2007 alert, which indicated that ceftriaxone and calcium IV solutions should not be administered within 48 hours of each other, regardless of the patient's age (Esterly et al., 2011). This study reported the different forms of institutional interpretations of the alert, including both correct and inaccurate interpretations (Esterly et al., 2011). Examples of inaccurate interpretations included that ceftriaxone should never be used in neonates, and to avoid any form of calcium-containing products within 48 hours of administering ceftriaxone to adults (Esterly et al., 2011). The second study addressed Health Canada's alert to hospitals involving the same issue but differing in the timeframe for separation depending on age (to avoid administration within five days for patients below 10 weeks of age, and to avoid administration of both products within 48 hours of each other for all other ages) (Harder & Hawboldt, 2009). Although both an accurate interpretation and no interpretation were reported, the alert was interpreted by most healthcare institutions as a relative contraindication, in which the benefits outweigh the risks in some situations (Harder & Hawboldt, 2009).

2.3.3.3 Characteristics associated with inaccurate perceptions

Only one of the six studies investigated characteristics associated with wrongful perceptions (Cordero et al., 2008). This study found that overestimation of the risk was associated with the participants' disagreement with the risk, in which those who were more likely to disagree with the

release of the alert were more likely to perceive that death occurred within patients in aggregated clinical trials (Cordero et al., 2008). The same study reported that the length of a licence and experience was not associated with the likelihood of having a wrongful perception of the risk (Cordero et al., 2008).

2.3.3.4 Facilitators of accurate perceptions of safety alerts

Different factors that may contribute to optimising the perception of alerts were derived from four studies (Cordero et al., 2008; Esterly et al., 2011; Reed et al., 1999; Sabblah et al., 2016). However, none of these studies assessed how those facilitators influenced healthcare professionals' understanding of the alerts. Facilitators were present at the level of the source of the alert (one study) (Sabblah et al., 2016), the level of the healthcare institution (two studies) (Esterly et al., 2011; Reed et al., 1999), and the level of the healthcare professionals (one study) (Cordero et al., 2008). A source-related facilitator involved writing letters in a language that would be easily understood by the healthcare provider (Sabblah et al., 2016). This was demonstrated in one study in which most participants positively evaluated the language understandability of safety letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole sent by the Ghana FDA (Sabblah et al., 2016). Two studies mentioned facilitators at the level of healthcare institutions. More than half of the participants in one study reported receiving a guideline on the management of chest pain in patients who take sildenafil, although the sender of this guideline was not specified (Reed et al., 1999). The second study reported healthcare institutions' investment in employee hours to interpret the US FDA alert relating to ceftriaxone and calcium IV solution interactions, which for most participants ranged from one hour to more than 100 employee hours (Esterly et al., 2011). Nevertheless, the nature of the activities undertaken by these healthcare institutions to interpret the alerts was not reported. One study reported the steps that were taken at the level of healthcare professionals to obtain an accurate understanding of the alert related to the risk of suicidality of antidepressants in youth (Cordero et al., 2008). These steps involved primary care providers reading, seeking information, further supervision, continuing education, and consultation (Cordero et al., 2008).

2.3.3.2.5 Barriers to accurate perceptions of safety alerts

Barriers to accurate perceptions of safety alerts were obtained from six studies (Barker et al., 2019; Bell et al., 2013; Mazor et al., 2005; Saad et al., 2010; Sabblah et al., 2016; Shneker et al., 2009). Most of these barriers were source-related, specifically to alert creation (four studies) (Bell et al., 2013; Mazor et al., 2005; Sabblah et al., 2016; Shneker et al., 2009). The remaining barriers were related either to the development of guidelines (one study) or to time and workplace-related barriers (one study). Three studies included source-related barriers in terms of the formatting of alerts (Mazor et al., 2005; Sabblah et al., 2016; Shneker et al., 2009). One of these studies reported primary care physicians' ratings of alerts issued between the years 2000 and 2001, which were identified through MedWatch (FDA) and pharmaceutical companies (Mazor et al., 2005). Some letters had deficiencies in the clarity of the writing, readability, and overall communication effectiveness (Mazor et al., 2005). Moreover, relevant information was not always apparent and it was reported that such information was obscured by less critical information (Mazor et al., 2005). In this study the use of special formatting was associated with higher ratings (Mazor et al., 2005). In the same study, the length of letters or the placement of key information was not associated with the ratings of letters. The the effect of the letter content was not evaluated as the letters had similar content characteristics (Mazor et al., 2005). Similarly, a US-based study relating to suicidality associated with antiepileptics showed that physicians did not rate the clarity of the FDA alert highly (Shneker et al., 2009). In another study relating to the risk of suicidality with newer antiepileptics alerted by the US FDA, many neurologists revealed that suicidality is a vague concept (Bell et al., 2013). In Ghana, however, only a few participants were not satisfied with the language used in the Ghana FDA's 2013 letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole (Sabblah et al., 2016). A barrier related to the development of guidelines was identified in one study (Saad et al., 2010). In this study, most of the geriatric practitioners indicated that there was a need to develop guidelines in response to the FDA BW regarding the use of antipsychotics in patients with dementia (Saad et al., 2010). A lack of guidance was reported in the same study as a reason for not considering the alert in clinicians' practice (Saad et al., 2010). One study identified multiple tasks in the workplace and time constraints as obstacles to assessing and reflecting on medicines' safety information (Barker et al., 2019).

2.3.3.3 Healthcare professionals' attitudes and concerns regarding medicine alerts

The majority of studies reported healthcare professionals' attitudes towards alerts' placement (i.e. issuing of the alert) (Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Kesselheim et al., 2017; Richards et al., 2003; Yaghmai et al., 2010) or content (Bell et al., 2013; Harder & Hawboldt, 2009; Mazor et al., 2005; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richardson et al., 2007).

2.3.3.3.1 Mixed attitudes towards the placement of alerts

Studies that investigated the attitudes of HCPs towards placing an alert focused on the FDA's US-based alerts (Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Kesselheim et al., 2017; Richards et al., 2003; Yaghmai et al., 2010). Three of these alerts were BW (two related to droperidol (Habib & Gan, 2008; Richards et al., 2003) and one to LABA (Karpel et al., 2009)), two were nationwide public health advisories (both related to OTC cough and cold medicines (Garbutt et al., 2010; Yaghmai et al., 2010)), and one was related to DSC label changes, which involved the hypnotic medicines zolpidem and eszopiclone (Kesselheim et al., 2017). All of these studies investigated physicians' attitudes towards the placement of the alert (Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Kesselheim et al., 2017; Richards et al., 2003; Yaghmai et al., 2010).

Noticeably, studies that reported that most of their participants had positive attitudes towards the placement of an alert involved non-BW alerts. These studies were related to DSC label changes regarding hypnotic medicines (Kesselheim et al., 2017), as well as the nationwide public health advisory concerned with OTC cough and cold medicines (Garbutt et al., 2010; Yaghmai et al., 2010). On the other hand, nearly half of the participants of two studies reported negative attitudes towards the placement of the alert. These studies involved droperidol (Richards et al., 2003) and LABA's (Karpel et al., 2009) FDA BWs. Only one study reported that the majority of its participants had negative attitudes towards the placement of the alert, which involved droperidol's BW (Habib & Gan, 2008).

2.3.3.3.2 Mixed attitudes towards the content of alerts

Two studies reported healthcare professionals' attitudes towards the importance of medicine safety information (Mazor et al., 2005; Piening, Haaijer-Ruskamp, de Graeff et al., 2012). However, individual studies reported on HCPs' attitudes towards the recommendations of an alert (Richardson et al., 2007), the importance of knowing the details of an alert (Bell et al., 2013), and their attitudes towards following those recommendations (Harder & Hawboldt, 2009).

Healthcare professionals from the Netherlands, including physicians and pharmacists (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), and physicians from the US (Mazor et al., 2005) had positive attitudes towards the importance of medicine safety information both generally (Piening, Haaijer-Ruskamp, de Graeff et al., 2012) and within specific letters (Mazor et al., 2005) respectively. However, negative attitudes were reported among US-based healthcare professionals (mostly physicians and a few nurses) towards antidepressants' BW recommendations (Richardson et al., 2007). Similarly, negative attitudes were reported among US-based physicians regarding the importance of knowing the exact risk of both suicidality with newer antiepileptics and birth defects with valproate (Divalproex) (Bell et al., 2013). Negative attitudes towards the need to strictly adhere to Health Canada's alert regarding calcium and ceftriaxone interaction were also reported by almost half of participating pharmacists who were based in Canada (Harder & Hawboldt, 2009). In the same study, most of those who had or would have a direct role in the institution's position regarding the alert disagreed with strictly following the recommendation (Harder & Hawboldt, 2009).

2.3.3.3.3 Healthcare professionals' concerns regarding medicine safety communications

Healthcare professionals' concerns were identified in eight studies (Cordero et al., 2008; Flood et al., 2015; Habib & Gan, 2008; Harder & Hawboldt, 2009; Kesselheim et al., 2017; Richards et al., 2003; Richardson et al., 2007; Shneker et al., 2009). Six of these studies involved the US FDA (Cordero et al., 2008; Habib & Gan, 2008; Kesselheim et al., 2017; Richards et al., 2003; Richardson et al., 2007; Shneker et al., 2009), one involved Health Canada (Harder & Hawboldt, 2009), and one involved the UK's National Patient Safety Agency (Flood et al., 2015). Concerns were expressed in four studies involving physicians (Cordero et al., 2008; Flood et al., 2015; Habib & Gan, 2008; Richards et al., 2003), one including pharmacists(Harder & Hawboldt, 2009), one including clinicians who treat epilepsy (Shneker et al., 2009), and one involving both physicians (the majority) and nurses (Richardson et al., 2007).

The areas of concern included malpractice (Cordero et al., 2008) and media attention (Richardson et al., 2007) regarding antidepressants' BW, as well as liability with antidepressants' BW (Richardson et al., 2007), antiepileptics alerts (Shneker et al., 2009), and droperidol BW (Habib & Gan, 2008). Patient-related concerns were also expressed including patient risk (Cordero et al., 2008), patient compliance (Shneker et al., 2009), poor patient experience and/or outcomes(Flood et al., 2015), and patient dependence on the medicine of concern (although this was not the risk reported in the alert) (Kesselheim et al., 2017). Losing the medicine from the market was another concern reported by healthcare professionals(Richards et al., 2003). Other areas of concern were either not specified (Harder & Hawboldt, 2009) or were general (such as concerns surrounding adverse events (Cordero et al., 2008) and negative impacts (Shneker et al., 2009)).

2.3.3.3.4 Characteristics associated with healthcare professionals' attitudes and concerns

This subtheme was only identified in two studies relating to healthcare professionals' attitudes towards the placement of the alert (Karpel et al., 2009) and the content of alerts (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In the first study, primary care providers had significantly higher agreement with the placement of the US FDA LABA BW than did other specialists (Karpel et al.,

2009). The authors of the second study found that most healthcare professionals appeared to have a positive attitude towards the importance of safety information. However, the hospital pharmacists in the study had a higher appreciation of the importance of safety information compared to GPs (Piening, Haaijer-Ruskamp, de Graeff et al., 2012).

2.3.3.3.5 Reported explanations for healthcare professionals' attitudes and concerns

Two studies provided explanations for healthcare professionals' attitudes towards the alerts (Kesselheim et al., 2017; Richardson et al., 2007), and one of them clarified the nature of healthcare professionals concern in relation to the alert (Richardson et al., 2007). Having a positive attitude towards the placement of a hypnotics' alert was attributed by the authors to the participants' reluctance to prescribe these medicines, and the fact that the alerts supported their arguments against using them (Kesselheim et al., 2017). However, having a negative attitude towards the US FDA's antidepressants' BW was justified by different reasons including: a lack of space (the study did not specify space as being physical or temporal); the recommended frequencies not being acceptable to patients and their families; the participants feeling uncomfortable about recommending additional follow-up visits while not knowing their additional value; and concerns surrounding reimbursement as some participants suggested that they could see two to three patients with acute conditions in the time it takes to see one depressed youth (this study was conducted within the US healthcare system) (Richardson et al., 2007). Healthcare professionals in one study explained their liability-related concerns surrounding the US FDA antidepressants' BW stating that most use of antidepressants in youth is off-label, with no clear guidelines being available to treat depression in this patient group (Richardson et al., 2007).

2.3.3.4 Self-reported impact of alerts

Different forms of self-reported impact were highlighted in the included studies. These included HCPs' actions in response to the alert, whether to take no action (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Esterly et al., 2011; Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Shneker et al., 2009; Théophile et al., 2011; Yaghmai et al., 2010), take the intended action (Bell et al., 2013; Bhatia et

al., 2008; Garbutt et al., 2010; Kloet et al., 2017; Reed et al., 1999; Théophile et al., 2011; Yaghmai et al., 2010), change their practice in a certain way (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Garbutt et al., 2010; Habib & Gan, 2008; Karpel et al., 2009; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Shneker et al., 2009), or increase referrals (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; Richardson et al., 2007). Moreover, some physicians preferred to reduce the frequency of prescribing the medicine of concern (Bhatia et al., 2008; Esterly et al., 2011; Richards et al., 2003; Richardson et al., 2007; Yaghmai et al., 2010) or stop prescribing it (Bhatia et al., 2008; Cheung et al., 2008; Garbutt et al., 2010; Habib & Gan, 2008; Richards et al., 2003; Richardson et al., 2007; Yaghmai et al., 2010). It also appeared that alerts could influence the choice of medicine to be used (Cheung et al., 2008; Habib & Gan, 2008; Richards et al., 2003). For example, about half of providers in a qualitative study stated that as a result of the alert, they now only use fluoxetine to avoid using other antidepressants off-label in young patients (Richardson et al., 2007). Spillover effects were also reported in two studies (Esterly et al., 2011; Karpel et al., 2009). In one of these studies, a spillover effect was reported more with primary care providers than with specialists ($p<0.001$) in LABA prescribing in COPD (Karpel et al., 2009). The effect of alerts upon the medicine of concern, such as its formulary availability in at least one healthcare institution (Esterly et al., 2011; Habib & Gan, 2008; Harder & Hawboldt, 2009; Richards et al., 2003), and HCPs' opinions on its utility following the alert (Richards et al., 2003) were also reported. In studies related to the use of antipsychotics in dementia patients (Saad et al., 2010), as well as the use of OTC cough and cold medicines in children (Garbutt et al., 2010; Yaghmai et al., 2010), the authors investigated the use of supportive or non-pharmacological measures. However, two studies did not compare the use before and after the alert (Saad et al., 2010; Yaghmai et al., 2010). Possible impacts on HCPs were seen in different studies, such as amongst primary care providers indicating that they might provide a follow-up in coordination with a psychologist (Richardson et al., 2007), and amongst primary care physicians (internists) stating that they would likely change their practice in response to most of the letters that they rated (Mazor et al., 2005). Interestingly, HCPs reported that alerts affected service recipients' (patients, family members, or carers) willingness to use the medicine of concern (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008), as well as affecting healthcare institutions' policies and protocols (Esterly et al., 2011; Habib & Gan, 2008; Harder & Hawboldt, 2009; Reed

et al., 1999). Details of the different types of self-reported impact, in accordance with the type of medicine and the safety concern involved that were investigated by the authors of the included studies, are presented in Appendix 12.

Reasons for never prescribing droperidol in one study included medico-legal considerations; the medicine of concern not being available; believing that other medicines are more effective; and considering that droperidol is a dangerous medicine (Habib & Gan, 2008). In another study, physicians who observed activation, including aggressive behaviour or agitation, ($p<0.001$) or any side effects reported in the FDA alert regarding antidepressants ($p<0.001$) stopped treatment more than those who did not observe activation or any of the alert's side effects (Cheung et al., 2008). Pharmacy managers in a qualitative study reported a range of barriers, including source overload, content overload, a lack of information relevance, source system complexity, and a lack of time, which had affected their ability to access, filter, read, reflect and act on the safety information, despite their intention to use this information in their practice (Barker et al., 2019).

2.3.4 Matching the identified factors to the TDF

2.3.4.1 Knowledge

Knowledge has been investigated in most of the studies (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai et al., 2010). This included measuring HCPs' awareness that an alert has been issued (Bell et al., 2013; Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008; de Vries et al., 2018; Esterly et al., 2011; Flood et al., 2015; Fogler et al., 2009; Garbutt et al., 2010; Karpel et al., 2009; Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Richards et al., 2003; Richardson et al., 2007; Saad et al., 2010; Sabblah et al., 2016; Smollin et al., 2016; Théophile et al., 2011; Yaghmai

et al., 2010) for a medicine and their knowledge about the specific content of an alert (Bell et al., 2013; Kesselheim et al., 2017; Richardson et al., 2007; Sabblah et al., 2016; Smollin et al., 2016). One reason cited for physicians not implementing medicine safety communications was the lack of knowledge (Kloet et al., 2017). However, no clarification was provided as to what type of information was lacking. Healthcare professionals' familiarity with the regulatory agency responsible for regulating medicines safety communications, its website or email service (de Vries et al., 2017; Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012), and their familiarity with the tools used to communicate emerging medicines' safety information were also possible factors that have been reported in different studies(de Vries et al., 2017, 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012; Smollin et al., 2016).

Procedural knowledge was reported to a lesser extent and less directly as a potential factor than knowledge. This has been illustrated by reporting the provision of guidance to implement the recommendations (Reed et al., 1999), the time devoted by healthcare facilities to interpreting an alert (Esterly et al., 2011), the active efforts taken by healthcare professionals to understand the alert (Cordero et al., 2008), as well as their knowledge about the lead person responsible for implementing the recommendations within their healthcare facility (Flood et al., 2015). Another factor related to procedural knowledge was healthcare professionals' understanding of the implications of the risk on their clinical practices (Morrato et al., 2008). On the other hand, lack of guidance and needing guidelines to address the alert were reported (Saad et al., 2010). Additionally, it was reported that the lack of guidance hindered the implementation of FDA recommendations (Saad et al., 2010).

2.3.4.2 Memory, attention and decision process

Possible factors that potentially influenced decision-making were the establishment of the risk (Bell et al., 2013), the trustworthiness of the information and the credibility of the source of information (Kesselheim et al., 2017), as well as the trust that the information has been rigorously peer reviewed (Kesselheim et al., 2017). One study revealed that healthcare professionals were concerned about how the US FDA analysed and presented data (Shneker et al., 2009). Poor data quality and a lack of evidence were reported as barriers to implementation (Saad et al., 2010). When pharmaceutical companies provided information, HCPs reported difficulty differentiating

evidence-based information from promotional information (Morrato et al., 2008). Some physicians felt that knowing about the alert before their patients would not allow them to formulate their opinions on it before being asked by patients (Morrato et al., 2008).

Healthcare professionals weighed the risks and benefits of the medicine of concern (Kloet et al., 2017). In some cases, healthcare professionals believed there was no risk (Richardson et al., 2007), that the risk was low (Richardson et al., 2007; Shneker et al., 2009) or that the risk was related to a comorbid condition rather than the medicine of concern (Shneker et al., 2009). Moreover, medicines having an acceptable risk to benefit ratio was mentioned by physicians as one reason for nonadherence to alerts recommendations (Kloet et al., 2017). Balancing the information received from pharmaceutical companies' representatives with clinical experience was also a potential factor related to decision-making (Morrato et al., 2008).

Another possible factor that was related to healthcare professionals' decision-making process was the availability of an alternative agent. Healthcare facilities introducing an alternative agent for the medicine of concern to its formulary were reported (Esterly et al., 2011; Flood et al., 2015). However, alternative agent unavailability was also reported (Harder & Hawboldt, 2009; Saad et al., 2010). When available, healthcare professionals compare the effectiveness of the medicine of concern to its alternatives, determining whether the alternative is more effective, equally effective or worse than the medicine of concern (Habib & Gan, 2008; Richards et al., 2003). On the one hand, not using the medicine of concern was attributed to the availability of more effective alternatives (Habib & Gan, 2008). On the other hand, a lack of alternative agents was cited as a barrier to implementing alerts' recommendations (Saad et al., 2010).

Healthcare professionals were reportedly presented with alerts while on the job, which were considered as possible factors to memory and attention. This involved pharmacists' reviews to identify potential nonadherence to the alert (Esterly et al., 2011). In addition, healthcare facilities added the alert to the computerised medicine order entry system (Esterly et al., 2011), the label on medicine bags before dispensing (Esterly et al., 2011), and the pharmacists' computer system (Harder & Hawboldt, 2009). However, healthcare professionals expressed concerns about screening-out information due to becoming immune to electronic medical record flags or alerts, as much of the information appearing on these records is already known to them (Morrato et al.,

2008). Moreover, a physician expressed concerns about pharmacy alert systems that pharmacists do not know the whole clinical picture; thus, they ultimately override the pharmacists (Morrato et al., 2008).

2.3.4.3 Behavioural regulation

Physicians demonstrated action planning by creating electronic patient records to identify which patients were receiving which medicines, check for interactions between medicines, and contact patients if necessary (Morrato et al., 2008).

2.3.4.4 Environmental context

Two different aspects of organisational culture or climate were possible factors related to the environmental context. The first involved whether healthcare facilities had their own interpretation of the alert (Esterly et al., 2011; Harder & Hawboldt, 2009) or let healthcare professionals interpret the alerts themselves (Esterly et al., 2011). Decision-makers in policy changes at the healthcare facility (Esterly et al., 2011) and their interpretation of the alert (Harder & Hawboldt, 2009) might influence how the healthcare facility responds to the alert. The second aspect of organisational culture was staff education, as education of office staff was reported as one barrier to implementing alert recommendation (Garbutt et al., 2010).

The second aspect of the environmental context domain was the material resources. One possible factor contributing to this aspect was related to the medicine of concern that was mentioned in the alert. This involved the medicine of concern being no longer available in the healthcare facility (Habib & Gan, 2008; Richards et al., 2003). Healthcare facilities also imposed policy changes in response to the alert, including changing stocks of the medicine of concern (Habib & Gan, 2008), applying restriction on the medicine of concern use (Habib & Gan, 2008), prohibiting the use of the medicine of concern in certain situations (Esterly et al., 2011), and adjusting restriction policies or auto-substitution of the medicine of concern in favour of its alternative (Harder & Hawboldt, 2009). Formulary discontinuation of the medicine of concern was also reported (Esterly et al., 2011; Harder & Hawboldt, 2009). Some physicians reported that now (at the time of the study), they never use the medicine of concern due to its unavailability, yet it was not revealed whether this was due to the alert or not (Habib & Gan, 2008). Changes in the treatment protocols of disease

management were also reported in healthcare facilities after the release of the alert (Reed et al., 1999).

Lack of time (Barker et al., 2019), workload (Barker et al., 2019) and lack of space during high infectious diseases seasons (however, space was not specified in the study) were all resources-related barriers to implementing alerts recommendations (Richardson et al., 2007).

The final form of resources-related barriers was related to the message and information received. The possible factors within this aspect of the environmental context domain included the understandability of the language used in the letters (Sabblah et al., 2016), the relevance of the content to HCPs practice (Sabblah et al., 2016), clarity of the alerts (Shneker et al., 2009), and the use of special formatting in the letter (Mazor et al., 2005). Receiving a large amount of information that is irrelevant to the HCP specific practice (Barker et al., 2019), unsatisfaction with the quality of information received (Kesselheim et al., 2017), receiving letters that lacked clarity (Mazor et al., 2005) and readability (Mazor et al., 2005) were all reported by HCPs. Moreover, HCPs reported that relevant information was not always apparent in the letters, and important information was overshadowed by less important information (Mazor et al., 2005). Message formatting was associated with perceptions about the criticalness of the information and intent to change practice (Mazor et al., 2005).

2.3.4.5 Social influences

Social influences that were identified were related to group conformity and social pressure. Group conformity was illustrated by healthcare professionals obtaining consensus among their practice partners, in which this factor was reported as an implementation barrier (Garbutt et al., 2010). Social pressure, however, was mainly related to the service-receivers, including patients, their families or their carers. The willingness and refusal of service-receivers to take medicine of concern after becoming aware of an alert were reported (Bhatia et al., 2008; Cheung et al., 2008; Cordero et al., 2008). In addition, service-receivers who are already not attending appointments as required might reject additional visits to adhere to the alert were also voiced by the HCPs (Richardson et al., 2007). Patients' willingness to take the risk of a side effect (Kesselheim et al., 2017) and patients initiating the discussion about the alert with their HCPs were all reported

(Karpel et al., 2009). Lack of educational materials for parents and parents demanding treatments were both cited as barriers to alerts' implementation (Garbutt et al., 2010).

2.3.4.6 Reinforcement

A study revealed a possible need for incentives, as HCPs questioned reimbursement because they could see more patients with acute illness in the same amount of time it takes them to implement recommendations for just one patient (Richardson et al., 2007).

2.3.4.7 Emotion

This domain was covered by two studies, and it was related to the concerns or past experiences of HCPs. Healthcare professionals reported being concerned about the alert in one of these studies; however, the specific area of concern was not reported (Harder & Hawboldt, 2009). The number of physicians stopping medicine following the alert in the other study was significantly higher among those who had patients who experienced aggressive behaviour, agitation, or any side effects listed in the alert compared to those who did not experience this with their patients (Cheung et al., 2008).

2.3.4.8 Social/professional role and identity

Professional identity is the first aspect of professional roles and identity domain-related barriers. Clinicians' comfort level in prescribing the medicines of concerns to the targeted population of concern was a possible factor related to this aspect (Bhatia et al., 2008). In addition, physicians who were hesitant to treat welcomed the alert because it supported their reluctance (Kesselheim et al., 2017). Furthermore, healthcare professionals' motivation to treat the disease coupled with the availability of disease-related resources (specifically, access to mental health resources) and their views about the efficacy of medicines compared to counselling could influence the way they respond to the alerts (Richardson et al., 2007).

The second aspect of this domain was the professional role, which was identified in two situations. First, some paediatric primary care providers indicated that they might provide additional follow-ups as recommended in coordination with a psychologist (Richardson et al., 2007). Second, In-

patient physicians who were identified as having cases of nonadherence to alerts reported deferring intervention until communication with primary care providers was established (Kloet et al., 2017). The second situation was reported as a reason for some of the nonadherence to alerts that were identified in the in-patient settings (Kloet et al., 2017).

2.3.4.9 Beliefs about consequences

The first aspect of the beliefs about consequences domain was beliefs. Beliefs towards the sources of the alert were in relation to knowledgeability (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), credibility (Morrato et al., 2008), the trustworthiness of the sources (Morrato et al., 2008) or the information they provide (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), and reliability (Kesselheim et al., 2017; Morrato et al., 2008). Beliefs about the sources also included HCPs' trusting that the sources are not affected by potential biases or financial interests (Kesselheim et al., 2017). Some of the reported beliefs included that the regulatory agencies' findings and recommendations are controversial (Bell et al., 2013), regulatory agencies' information being more trustworthy than those of pharmaceutical companies (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), the regulatory agency being biased toward the pharmaceutical industry (Morrato et al., 2008), and pharmaceutical companies being biased (Morrato et al., 2008). An example of one physician not trusting the regulatory agency believed that they were bought and sold; the same physician reported no longer listening to the regulatory agency (Morrato et al., 2008). Beliefs about the appropriateness of the placement of the alert (Richards et al., 2003) related to whether they agreed or disagreed with the placement of the alert (Garbutt et al., 2010; Karpel et al., 2009; Yaghmai et al., 2010), and whether the placement of the alert was unjustified (Habib & Gan, 2008; Richards et al., 2003). Lack of agreement with the recommendation was one barrier to implementing it (Garbutt et al., 2010).

Consequents related factors were the second aspect of the beliefs about the consequences domain. Possible factors related to this aspect included concerns about media attention (Richardson et al., 2007), liability issues (Richardson et al., 2007), malpractice (Cordero et al., 2008) and lawsuit (Cordero et al., 2008). Concerns that alerts could trigger legal litigation were reported (Shneker et al., 2009)—One reason for not using the medicine of concern after the alert was due to medicolegal concerns (Habib & Gan, 2008). The use of a medicine that was licenced for use in the targeted

population was reported to avoid the off label use characterising the rest of medicines within the medicines group of concern (Richardson et al., 2007).

The last aspect of this domain is the outcome expectancies. Possible factors related to this aspect included concerns about risks to patients (Cordero et al., 2008), concerns that patients would receive inadequate therapy (Flood et al., 2015), and concerns that the alert would reduce the patient compliance and lead to negative impact (Shneker et al., 2009). In addition, not knowing the added value of adhering to the recommendation to patients made healthcare professionals uncomfortable with following the recommendation (Richardson et al., 2007).

2.3.4.10 Goals

Possible factors related to the goals domain were either related to goals priority or implementation intention. Considering medicines safety information in general (Piening, Haaijer-Ruskamp, de Graeff et al., 2012) and alerts' specific information (Mazor et al., 2005) as important by the healthcare professionals are related to the goal priority aspect. On the other hand, examples of possible factors related to the implementation intention included considering or not considering alerts when prescribing (Smollin et al., 2016) and a healthcare professional's agreement on how strictly an alert recommendation must be followed (Harder & Hawboldt, 2009). In addition, two studies reported that healthcare professionals counselled (Bell et al., 2013; Richardson et al., 2007) or prescribed the medicine of concern (Richardson et al., 2007) to patients with certain conditions or comorbidities. Likewise, healthcare professionals in a third study reported different choices of which patients to counsel about the alerts: whether all patients, patients with a particular diagnosis, patients with certain comorbidity, patients starting a certain medicine or drug within a medicine group, patients experiencing certain symptoms, or patients who initiated the discussion (Shneker et al., 2009). Moreover, healthcare professionals refusing to prescribe the medicine of concern unless an initial prescription from a specialist, or unless the patient had certain comorbidity, as well as healthcare professionals indicating that they would adhere to the alert if collaborated with a specialist were all reported (Richardson et al., 2007).

2.3.4.11 Beliefs about capabilities

Beliefs about the capabilities' domain were represented by the perceived behaviour control in two studies. In one study, physicians felt the alert had affected their ability to treat patients (Richards et al., 2003); whereas in another study, physicians feeling the need to prescribe something was reported as a barrier to implementing the recommendation (Garbutt et al., 2010).

The narrative synthesis approach utilised in the current systematic review involved utilising a theoretical framework to identify and characterise factors affecting HCPs' implementation. The result of this step of the synthesis is reported in a following review. Key players identified from this step to interact and affect HCPs' implementation involved the developers (the sources and senders) of the safety information and the receivers of safety information [healthcare institutions (e.g. hospitals), the healthcare professionals' themselves, and the patients and their carers). Figure 2.3 represents this conceptual mapping of the possible factors involving the key players. The developers involved the senders' and channels used to deliver alerts (e.g. failure or delays in alerts' delivery and patient access to information before HCPs, and the effectiveness of medium used to deliver the alert) and messages' (e.g. clarity and formatting) related factors. Healthcare professionals' factors included knowledge of alerts' existence and content, their knowledge of how to implement the recommendations, action planning and goals toward the implementation, their judgments and opinions, trust, and the influence of colleagues among each other. External factors include healthcare institutions (medicine of concern or alternatives availability, policies, position and interpretations of the alerts, availability of resources and staff education), and patients or carers (demands related to medicine use).

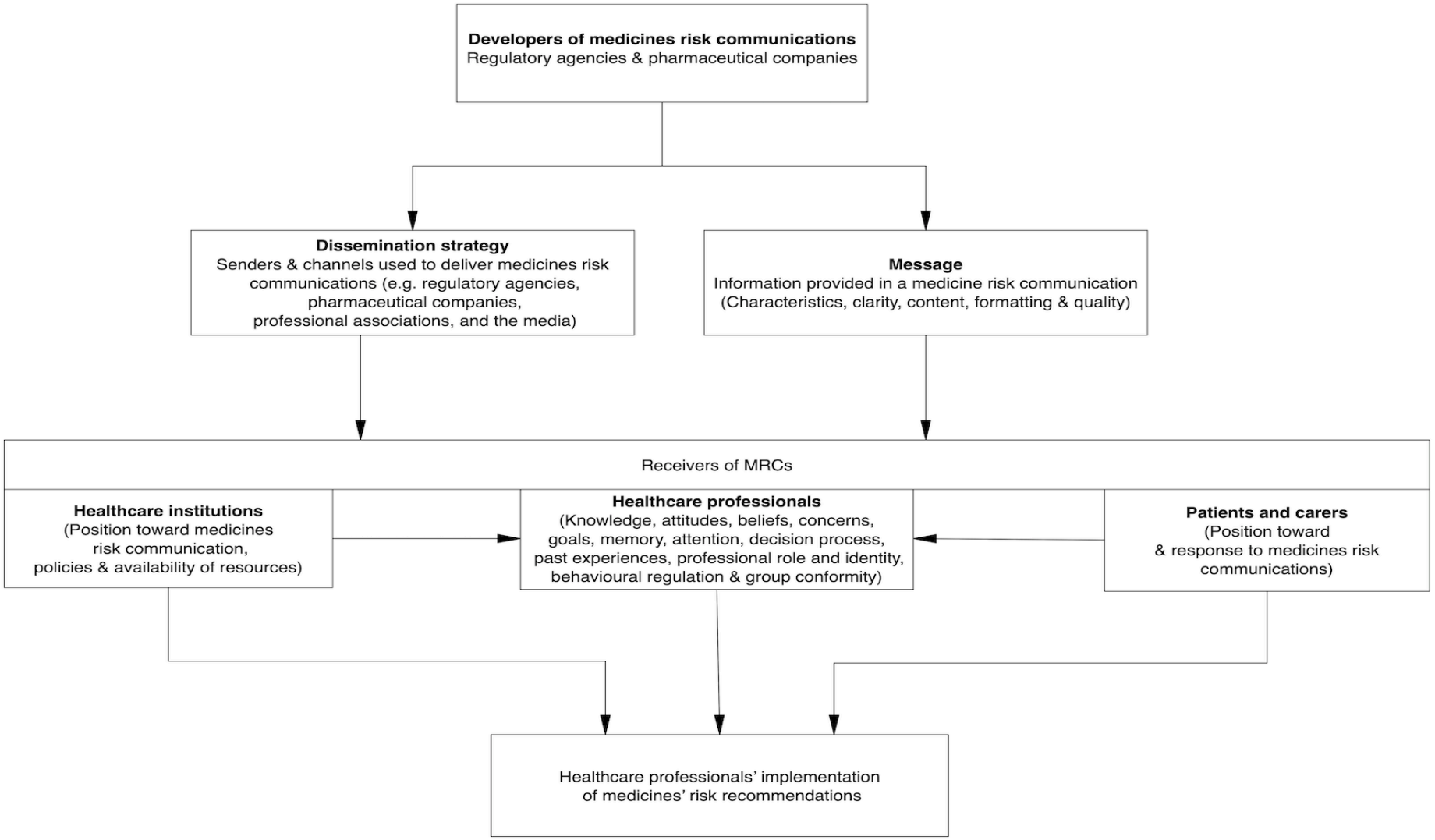


Figure 2.3: Concept mapping

2.4 Discussion

2.4.1 Summary of the results

This systematic review explored different factors that could possibly influence HCPs' uptake of alerts. Knowledge of alerts was the most frequently investigated factor at different levels, including HCPs' awareness of the alert release, their knowledge regarding the content of the alert, as well as their knowledge of regulatory agencies, and the tools used by them to disseminate emergent information concerning the safety of medicines. Possible factors that could affect HCPs' knowledge included their actions in terms of searching and reading alerts, whether they had sources to update their medicine safety information, the effectiveness of the sources in delivering such information, and HCPs' beliefs and trust in these sources. Barriers against healthcare professionals' action in updating their medicines safety knowledge were also identified, such as lack of time, workload, and being overwhelmed with information that could be irrelevant to one's practices. This systematic review uncovered that HCPs had inaccurate views in terms of their perception towards information reported in the alerts, although this was demonstrated by a smaller number of studies than those reporting HCPs' knowledge. Different possible facilitators were identified that could influence the perception of HCPs about the alerts, including the understandability of the alert, receiving updated clinical practice guidelines involving the alerts, time invested to address the alerts, and HCPs' actions to understand the alert, such as seeking supervision and continued education. On the other hand, barriers to accurate perceptions were also identified, including alert formatting and clarity, and lack of guidelines to address the alerts' recommendations. Moreover, HCPs demonstrated mixed attitudes towards the placement of the alerts and their contents. Few explanations for HCPs' attitudes were identified, like having multiple barriers that affect the implementation of the alert leading to HCPs' negative attitudes towards the alerts' recommendations. Various areas of concern of the HCPs' towards the alerts were also identified, including liability issues, and negative patients outcomes. This systematic review also revealed an interaction between different key players that could affect HCPs' implementation of the alerts, which involved the developers (sources and senders) of the safety information, and the receivers of safety

information [healthcare institutions (*e.g.,* hospitals), the healthcare professionals' themselves, and the patients and their carers].

2.4.2 Healthcare professional-related factors

Knowledge about the existence of an alert and familiarity with its content is essential to its implementation. This was consistent with findings by Cabana et al., who highlighted that lack of awareness hinders physicians' implementation of guidelines (Cabana et al., 1999). Familiarity with the content of an alert would at least require that HCPs' read the alerts. Barriers to HCPs' reading of alerts were also identified by Faied, El Wakeel, Saad and Sabri (2019), including their busy schedules and lack of trust in alerts' sources. Although altering HCPs' knowledge might be the expected outcome of an alert, it should be viewed as a modifiable factor when it comes to implementing actionable alerts. Sending an additional email from the RA to HCPs (Piening, de Graeff, Straus, Haaijer-Ruskamp, & Mol, 2013), or including the alert in continuing medical education (CME) activities (Kraus, Baldwin, & McAllister, 2013) could improve HCPs' knowledge of medicines safety information.

A Netherland-based RCT was conducted by Piening et al. (2013), and included ophthalmologists and hospital pharmacists, who were the targets of a DHPC related to pegaptanib. Both the control and intervention groups received a paper-based DHCP, while only the intervention group received an additional email newsletter from the MEB. A survey was sent two weeks later to both groups. The results of the RCT revealed a significant increase in awareness about the existence of the alert among the intervention group. In addition, more participants in the intervention group reported conducting a form of action in response to the alert, compared to the control group participants who reported that they did not take any action as a result of the alert. Interestingly, among those who were aware of the existence of the alert in both groups, similar knowledge levels about the recommendation presented in the alert were highlighted. The majority of the participants of this RCT worked in a general hospital, which might affect the generalisability to other settings. The findings of this study might be limited by those who prefer to receive an email from the MEB, as both the control and the intervention group reported a high preference to receiving an email from the MEB regarding drug safety information. As the response rate was 18.6%, it could be that those who answered the online questionnaire (invitation sent by email) are those who prefer to receive an additional email.

Moreover, the effect was measured two weeks post the additional email. Thus, information sustainability and retaining information might not be reflected.

Kraus et al. (2013) investigated the impact of internet-based CME on clinicians' knowledge of the US FDA alerts. In this study, Medscape sent a Safe Use Alert (SUA) email to 176,988 registered members. This email included the "Dear Healthcare Provider" letter about ipilimumab at the time of its approval for the treatment of unresectable or metastatic myeloma, aligning with the FDA risk evaluation and mitigation strategies (REMS) for distributing the letters. At the same time, a CME-certified activity was posted on the Medscape website, made available on the specialty website, and sent through specialty-specific email alerts to members. This study used a pre-test/post-test learning assessment. Targeted populations included both physicians, nurses, and pharmacists required by the REMS, as well as other HCPs who might be involved in managing patients receiving ipilimumab. In these assessments, the test takers acted as their own controls. Totally, 40,842 HCPs became aware of the FDA's REMS requirements for ipilimumab. Of these individuals, 20,642 learned about the REMS only through the SUA, and 20,764 individuals learned about it by undertaking the CME activity. Similar improvements in test scores were noticed among those who read the CME activity in the cohort who did not receive the SUA (47.8%), and those who both received and opened the SUA (47.6%). HCPs who read the CME materials, whether or not HCPs received and/ or opened the SUA, had a similar degree of knowledge improvement. Unaffected participants (who responded incorrectly to both pre-assessment questions and post-assessment questions, or who responded correctly to pre-assessment questions but incorrectly to post-assessment questions)–were lower in the cohort who read both the SUA and the CME activity (9.5%) compared to those who read the CME activity alone (14.7%). The impact of this intervention on healthcare professionals' actions in response to the safety information was not evaluated. Moreover, the safety issue communicated in this study was related to pre-market safety issues rather than emergent safety information. Thus, it is not clear whether HCPs would be more in agreement with pre-market safety information compared to post-market information; and whether their information-seeking behaviour would also be different in both situations.

Unlike knowledge, perception was less frequently reported in the included studies. In the current systematic review, the lack of a guideline to address the alert can result in inaccurate perceptions regarding the alert. Incorporating alert information into clinical practice guidelines (CPG) is already practiced. For example, the UK-based National Institute for Health and Care

Excellence (NICE) acknowledges that clinically significant medicine safety updates or medicine withdrawal from MHRA are examples of events that could affect the guidelines (UK NICE, 2014). An example of a recent NICE-published guideline incorporating information from MHRA in their clinical guidelines included fluoroquinolone antibiotics (UK NICE, 2022). However, two potential obstacles might preclude the usefulness of incorporating post-market alert information into clinical guidelines. First, whether HCPs would adopt and adhere to these guidelines (Cabana et al., 1999; Francke, Smit, de Veer, & Mistiaen, 2008). Second, whether guidelines are updated in a timely manner, to include emerging information about medicines alerts. Between March and July 2009, Alonso-Coello (Alonso-Coello et al., 2011) carried out a survey of international institutions involved in developing clinical guidelines. Most of these institutions reported updating their guidelines. The timeframe to check the need for updates was three to five years for about 61% of the institutions, followed by less than three years for 30.6% of the participating institutions. Vernooij, Sanabria, Solà, Alonso-Coello and Martínez García (2014) published a systematic review of methodological handbooks related to guidelines updating. Only 8.6% of the handbooks recommended less than or equal to one year, 40% recommended two to three years, and 22.9% recommended four to five years. Further research is required to explore the process and evaluate the impact of incorporating emerging medicines safety information into clinical guidelines, and whether such information is incorporated in a timely manner.

Francke et al. (2008) found that guideline complexity is an influencing factor in its implementation, as guidelines that are easy to understand and do not require specific resources have a high chance of being implemented. In this meta-review of systematic reviews, the authors focused on the importance for the developers to take into account the complexity of the guidelines, and their comprehensiveness by the different targeted audiences (Francke et al., 2008). Lack of relevance was one of the reasons reported in our review for not reading alerts. Further research could explore whether alerts that are tailored to each professional group, clearly indicating what is expected and how this could be clearly translated into their clinical practice, are effective in improving alerts uptake.

Even when being aware of an alert, HCPs did not always follow the recommendations. One possible factor was the (dis)agreement with the issuance of an alert and/or its recommendations. The extent to which HCPs agree with recommendations was also an influencing factor in clinicians' adherence to clinical practice guidelines (Cabana et al., 1999;

Ismaile, 2014; Lugtenberg, Zegers-van Schaick, Westert, & Burgers, 2009). In the RCT conducted by Piening et al. (2013) concerning the value of an additional email sent by the MEB to HCPs, there was a significant increase in the awareness about the existence of the alert among the intervention group, and a bigger proportion of participants from the intervention group agreed with the alert compared to the control group. It was noticeable that almost all respondents (93%) considered medicine safety information as important. Thus, having a positive attitude or agreeing with the alert could be different for those who do not consider medicine safety information important to their clinical practice. Further studies are required to investigate HCPs' reasons for disagreement with the importance of a safety alert and/ or its recommendations.

One of the reasons for negative attitudes towards alerts' recommendations reported in the current systematic review was the lack of resources. Other reasons were unreasonable scheduling due to cost, or lack of space-related issues. Involving stakeholders, to not only assess the comprehensiveness of the alert's recommendation, but also to identify barriers that might affect their attitudes towards the recommendations, is warranted. However, having a positive attitude towards the intervention does not assure implementation by the HCPs, thus its possible effects on HCPs' implementation should also be further studied (Li, Cao, & Zhu, 2019).

A qualitative study examined barriers to the implementation of a hospital-developed policy to ensure naloxone distribution to patients at risk of overdose. One reported barrier to implementation was that those staff who would be expected to implement the policy were not involved in its development (Drainoni et al., 2016). However, contradictory evidence is available for the usefulness of involving end-users in guidelines development (Francke et al., 2008). EMA has taken steps to involve the different stakeholders through public hearings. Since 2017, the EMA has held two public hearings regarding valproate(EMA, n.d.-b, 2017e), quinolone, and fluoroquinolone antibiotics safety issues (EMA, n.d.-b, 2018). Research is needed to understand the impact of initiatives such as the EMA's initiative on improving HCPs' attitudes towards the alerts, as well as in implementing medicines safety alerts. It was also identified in the current review that HCPs have different views towards alerts' senders. Thus, it might be important to evaluate initiatives for strengthening HCPs' trust in different senders.

In the current review, HCPs' trust of the sender was found to be possibly affected when the alert lacked the evidence supporting its recommendations, or when they anticipated the sender to be biased towards the industry. A recent retrospective study comparing post-market drug alerts on cardiac harm in Australia, Canada, the UK, and the US regulatory advisories, issued between 2010 and 2016, found that these regulators reported a range of evidence of harm, and US FDA was the only regulatory agency reporting the evidence used in decision making (Hooimeyer et al., 2020). Among the studies included in the current review, only one study investigated HCPs' knowledge about the evidence leading to regulatory decisions. Further studies are needed to assess HCPs' awareness of evidence underpinning the regulatory decisions, and whether facilitating their access to transparent, straightforward, and scientifically based decision-making processes would improve their confidence in regulatory agencies' decisions (Baden, Solomon, Greene, D'Agostino, & Harrington, 2020).

Møllebæk et al., (2019) reported that, in most studies, HCPs preferred non-industry and medical authority sources with no financial interests. Trusting guidelines' sources were further reported as a promotor for nurses' adherence to clinical guidelines (Ismaile, 2014). The Center for Regulatory Research on Tobacco Communication conducted a national telephone survey in the US, between September 2014 and June 2015, which included 5,014 adults over 18, and 1,215 adolescents (Kowitt, Schmidt, Hannan, & Goldstein, 2017). Among the adults, 64.6% reported trusting the CDC, and 62.5% reported trusting the FDA, demonstrating moderate levels of trust for both (Kowitt et al., 2017). On the other hand, adolescents had a high level of trust in the CDC (72.2%) and the FDA (78.8%) (Kowitt et al., 2017). Regulatory agencies and researchers should also explore trust towards alerts' senders, and identify what might cause a lack of trust, and how this impacts alert implementation by HCPs (US Institute for Public Relations, 1999; Men & Stacks, 2014; Slovic, 1993).

Trust was one of six elements proposed by public relationship academics, Dr. Linda Childers Hon of the University of Florida, and Dr. James E. Grunig of the University of Maryland, for evaluating organizational public relationships. One contributing element of trust was transparent communication (US Institute for Public Relations, 1999). A total of 502 participants in the US answered an online survey in April 2020. The authors investigated the role of transparent communication and trust in influencing public perception, attitude, and social distancing behaviour during the COVID-19 pandemic (Lee & Li, 2021). For this purpose, they utilised three aspects of transparent communication, including substantiality,

accountability, and participation (Lee & Li, 2021). The authors explained these three components based on previous literature (Lee & Li, 2021). First, substantial information is demonstrated through the disclosure of information (Yang, Kang, & Cha, 2015), by acknowledging that it is the human right to be provided with comprehensive and complete information (Grimmelikhuijsen, Porumbescu, Hong & Im, 2013), by open administrative procedures and government hearings (Beaumont, 1999; Finel & Lord, 1999), and by recognizing that openness is essential to the disclosure of information. Second, participation of other parties (Lee & Li, 2021), as information sharing by itself does not ensure transparency (Rawlins, 2008), audiences involved in addressing the interests of both sides (Heald, 2006), and a mutual understanding of a message (Albu & Wehmeier, 2014) could maximise transparency. Thus, organisations are responsible for ensuring that interested audiences can actively acquire, create, and provide information (Cotterrell, 1999). Third, accountability refers to organizations' acceptance of responsibility and mitigation of problems (Grunig & Hunt, 1984; Lee & Li, 2021). Accountability involves making the decision process visible, to ensure public understanding (Grimmelikhuijsen et al., 2013). The results of this survey revealed that public trust in state government and health institutions during the COVID-19 pandemic was significantly increased by information substantiality (Lee & Li, 2021). Only trust in health institutions (the CDC) was enhanced by audiences' participation, while accountability had no effect on public trust, in either health institutions, or state government (Lee & Li, 2021). In turn, organisational trust was an important element in increasing the perceived risks, subjective norms, and behavioural control of the public, which all promoted social distancing behaviour (Lee & Li, 2021). It is noticeable that attitudes also impacted public behaviours into social distancing (Lee & Li, 2021). However, the organisational trust did not affect the public's attitudes (Lee & Li, 2021). Nevertheless, it is not clear if the same results would be obtained in non-crises medicine safety communications. Moreover, this study was based on a cross-sectional survey that targeted around 500 individuals in the US, thus it might not be generalisable to larger populations, or those living in other geographical areas. Furthermore, the survey was administrated for one week in April 2020 (Lee & Li, 2021), so information on behaviour sustainability is not clear, and more longitudinal studies might be required.

2.4.3 External factors: Healthcare institutions and patients

External factors might also affect HCPs' implementation, even with sufficient knowledge and attitudes (Cabana et al., 1999). Regulatory agencies should consider collaboration with

healthcare institutions (*e.g.*, hospitals) in the dissemination and interpretation of the alerts. A framework might be provided to hospitals to deal with alerts, and to be aware of what is expected from healthcare organisations in terms of alerts implementations. Regulatory agencies could partner with healthcare organisations, in order to improve the uptake and implementation of medicines safety communications.

An example of such collaboration included The National Patient Safety Alerts Committee (NaPSAC). The NaPSAC was formed in 2018 at the request of the Secretary of State for Health and Social Care after evidence that safety advice and guidance issued to HCPs in the National Health Service (NHS) was not having the intended effect (Glasper, 2019). The initiative was launched by the collaboration of a regulatory agency (MHRA) and healthcare organisations (Public Health England, and NHS England and NHS Improvement Patient Safety Team) (NHS England, n.d.). One of the goals of NaPSAC is to ensure the alignment of alerts produced by different bodies, by using National Patient Safety Alerts. Additionally, it aimed to ensure that the required actions were evaluated for feasibility, risk of unintended consequences, equalities impact, effectiveness, and cost-effectiveness, and that the actions were specific, measurable, achievable, realistic, and timely (SMART) (NHS England, n.d.). Evaluating the roles of such initiatives in improving HCPs' implementation of emerging medicines safety information is important to further enhance patient safety. Establishing a feedback channel from healthcare organisations and HCPs, and carefully evaluating the effectiveness of alerts could also be considered, to ensure that the targeted audiences receive and accurately interpret these alerts (Moreland & Denham, 2019). Such evaluation should consider the role of healthcare institutions in promoting or hindering the implementation.

As only one of the included studies in the current review reported a role of a lead person for implementing the alert (Flood et al., 2015), further research should investigate the roles of the lead persons in ensuring implementation of the alerts by the multi- disciplinary HCPs, as well as providing such leads with evidence-based implementation strategies, and helping them with identifying barriers and facilitators to alert implementation (Morrow et al., 2022).

In the current systematic review, patients, their families, and carers' acceptance or refusal of the medicines of concern were identified as possible external factors affecting HCPs' implementation of alerts' recommendations. Patients were also identified as a factor in an overview of systematic reviews (Francke et al., 2008), since patients' resistance and

perceptions of lack of necessity for a guideline were barriers to implementation. More research is needed in terms of determining the influence of patients-related factors on the implementation of medicines safety alerts. The utilisation of the TDF to characterise factors affecting HCPs' implementation of alerts in the current review (results reported in a separate publication) identified that HCPs' goals, priorities and implementation intentions could be affected by patient factors, such as the patients' health status (Richardson et al., 2007; Shneker et al., 2009). Patient-related factors such as patients' demographics, health condition, presence of comorbidities, and use of polypharmacy have been reviewed by Medlinskiene et al. (2021).

Further research is required to identify whether evaluating patients' related health outcomes of an alert, and providing HCPs with such information, will influence their perception of the value of the alert, and their implementation of alerts-related recommendations. However, previous systematic reviews (Goedecke et al., 2018; Weatherburn et al., 2020) highlight the scarcity of studies measuring alerts' impact on patients- related health outcomes compared to other outcomes.

2.4.4 Other recommendations

It is important to consider the impact of alerts issued by international RAs' on HCPs' actions (Weatherburn et al., 2020). This is because on occasions, alerts may issue different guidance/ recommendations (Hooimeyer et al., 2020). During the "pill scare" in 1995, the UK Committee on the Safety of Medicines warned against the thromboembolic risk associated with third-generation oral contraceptives, and advised providers to only prescribe these agents for females who cannot tolerate the first and second generation contraceptives (Furedi, 2000; Williams, Kelly, Carvalho, & Feely, 1998). Although the Irish Medicines Board did not advise this, Williams and co-authors (Williams et al., 1998) found that both prescribers and users in Ireland were affected by the UK advice; with a noticeable reduction in consumption of third-generation oral contraceptives and an increase in use of second-generation ones.

Our findings support DeFrank et al. (2019) research recommendations when evaluating alerts' impact. It should focus on identifying the outcomes, reactions, and understanding of HCPs and patients, and evaluate the impact of different communication strategies on outcomes (DeFrank et al., 2019). We further recommend that RAs define or map out the unintended and the

spillover effects associated with alerts, and consider the factors behind HCPs undertaking unintended actions and the consequences of such actions on patient outcomes. Frameworks might aid in identifying possible barriers against their intended implementation. Development of interventions with psychological effects, and giving prescribers feedback on their performance should be considered (de Vries et al., 2017; Weatherburn et al., 2020).

2.4.5 Matching the factors to the TDF

Factors possibly affecting HCPs' implementations of medicines alerts were related to 11 domains. Most commonly, the included studies reported factors related to the knowledge domain. This was followed by a distance by beliefs about consequences, memory, attention, decision process and environmental contexts domains. The same number of studies reported both social influences and goals, followed by social/professional roles. Four domains were underrepresented: emotion, beliefs about capabilities, behavioural regulation, and reinforcement. In contrast, none of the identified factors was related to skills, optimism or intention.

The TDF was utilised in a cross-sectional study, nested within a cluster randomised controlled trial of a hand hygiene intervention (the feedback intervention trial). In this study, healthcare workers were directly observed and asked to explain episodes of noncompliance. The most commonly codded domain was 'memory, attention and decision-making', followed by knowledge and environmental context and resources (Fuller et al., 2014). Another systematic review included 15 studies that investigated the barriers and facilitators of prescribers' uptake of clinical guidelines that involved prescribing medication. Multiple barriers were identified relating to environmental context and resources, social influences, beliefs about consequences, knowledge and social and professional role and identity. However, the most common facilitators were beliefs about consequences, social/professional role and identity, knowledge, and social influences. In addition, some studies identified influences that were barriers and facilitators at the same study, including beliefs about consequences, knowledge and social influences (Paksaite, Crosskey, Sula , West & Watson, 2021). This systematic review had also grouped the identified determined according to the population group, which identified factors affecting specific patient groups but limited with the low number of studies in some of these

groups (ranged from 2 to 4 studies in each group). The identified domains related to the barriers for adhering to clinical guidelines based on the patient groups were beliefs about consequences (elderly and pregnancy and preconception groups), environmental context and resources (elderly, paediatrics, pregnancy and preconception and comorbidity groups), and knowledge (paediatrics, pregnancy and preconception, and comorbidity groups), and social influences (paediatrics, pregnancy and lactation, and the comorbidity groups).

Two studies had utilised interventions to improve the dissemination of alerts-related information to HCPs. One utilised an additional email from a regulatory agency to HCPs informing them about the alert (Piening et al., 2013), and the second was a CME-related intervention (Kraus et al., 2013). Both resulted in improved knowledge about the alert. Although, no evidence about the sustainability of the interventions on HCPs' knowledge and or uptake was investigated using these interventions. Furthermore, the impact on patient outcome was also not investigated. The additional email and the CME interventions match either education or education combined with training, using the BCW, respectively. From the identified factors in this review, training would target domains related to psychological capability (knowledge, memory, attention and decision-making, and behavioural regulation), physical opportunity (environmental context and resources), and automatic motivation (reinforcement and emotion). Education, on the other hand, would target reflective motivation (professional role and identify, beliefs about consequences, goals, and beliefs about capabilities). However, further evidence is required in terms of utilising the TDF in identifying barriers and facilitators within the context of alert implementation, as well as the suitability of these interventions for improving enablers and eliminating barriers. Further research should also aim at identifying whether a single implementation strategy that targets different domains would be more efficient than using multiple intervention techniques. Multiple stages' intervention had shown contradictory evidence regarding its usefulness compared to single strategies interventions in the guidelines implementation literature (Francke et al., 2008).

Current hospital responses, such as hospital restrictions and policy modification, could be utilised to improve implementation in proper contexts. Such intervention could be in accordance with the recommendation, consulted by the regulatory agency to avoid variances in institutions' responses. However, further research is required to assess their effectiveness, as well as their impact on patients related outcomes.

Compared to thematic analysis, TDF helped to identify how external influences affected healthcare professionals' implementation of alerts. As an example, the thematic analysis process revealed that healthcare facilities made changes (e.g. adding alternatives) to their formulary when they received the alert, while the TDF revealed that these changes might affect healthcare providers' decision-making process regarding the implementation.

A challenge with the TDF is not being able to differentiate between memory and knowledge of the content, or it could be more related to study design not differentiating lack of knowledge about the content whether it was related to not reading or not remembering the content. Nonetheless, both are within the psychological capability of the COM-B system (Michie et al., 2011). Lack of studies measuring the change in healthcare professionals' knowledge over different time periods post the alert release were noticed among the selected studies.

Another challenge was not accounting for the mediators that could affect the domain within the TDF. For example, we also identified from the included studies that possible factors could affect healthcare professionals' knowledge of alert, such as, healthcare professionals' not reading the alert or alerts not received, thus eventually influencing the implementation of the alerts' recommendations, and might enhance the effectiveness of the intervention as the intervention would be tailored to the root cause of the reason leading to lack of knowledge. A further challenge was classifying factors related to trust, as none of the TDF domains included trust. The trustworthiness of the information and the sources of information were either considered as factors affecting the decision process, or as factors relating to beliefs about consequences.

Craig et al. (2017) used a stepwise method based on French et al. (2012)
to develop implementation intervention. These steps included the following questions:
(1) Who needs to do what differently?
(2) Using a theoretical framework, which barriers and enablers need to be addressed?
(3) Which intervention components could overcome the modifiable barriers and enhance the enablers?
(4) How the behaviour change could be measured and understood?
(5) How can behaviour change be sustained?

A multidisciplinary team including frontline workers and researchers could be involved in such intervention development (Craig et al. 2017). Matrices for developing behaviour change techniques, such as that developed by Cane, Richardson, Johnston, Ladha, and Michie (2015) and that of Michie et al. (2013), could be used in the process of alerts development and dissemination.

2.4.6 Limitation of the systematic review

Most of the studies included were quantitative in nature, and data were collected through surveys, thus limiting the insights associated with qualitative data (Sandelowski, 1994). Since the findings were based on heterogeneous studies in the type of alerts, types of medicines, and populations targeted, the mathematical pooling of the data was not possible.

The majority of the included studies were based in the US, which could affect the generalizability of the results. Excluding papers that did not report possible factors might have affected the full exploration of both impact and preferences. Our synthesis is further limited by the inclusion of studies only concerning communications issued by RAs. Studies evaluating the effectiveness of risk minimization measures, and studies involving only pharmaceutical companies were excluded from the analysis. These studies could have provided additional insights into the factors relevant to the pharmaceutical industry.

Furthermore, the studies' inclusion was based on the author's assessment of RAs involvement. This could have possibly led to the omission of studies. However, the extensiveness of the search conducted reduced the risk of missing out papers.

Exclusion of papers without Arabic or English abstracts may have resulted in a language bias. It should also be highlighted that our search strategy was restricted by limiting the search to the titles of the study. This was done to manage the large number of citations resulting from limiting the search to abstracts. The wide range of search terms used in variable databases, as well as searching the references of the included studies helped mitigate the risk of missing papers. Moreover, the search update was limited to three of the databases searched in the first update.

2.4.7 Methodological limitation of the included studies

Most of the included studies used a cross-sectional survey, in which participants' answers might be affected by social desirability biases. Nearly one-half of the cross-sectional surveys were either web-based or distributed via email, which might affect the generalisability of these studies. Issues related to the sample size included one professional group being notably less represented than other professions within a single study (Richardson et al., 2007; Saad et al., 2010; Smollin et al., 2016) which might have affected the results representing the underrepresented groups. Bias related to the sample frame was identified in three studies, where knowledge levels might be higher in these participants, due to their interest in the topic (Flood et al., 2015; Fogler et al., 2009), or position within their institution (Esterly et al., 2011), which might have placed them in a better position to know about the alerts. The results should be interpreted with caution, as most of the studies scored less than 80% in their quality assessment. Only seven studies scored 80% or more; fulfilling at least 4 of the 5 MMAT questions.

None of the included studies had utilised the TDF in data collection and/ or analysis. This could explain the underrepresentation of some of the domains identified in this review. The most represented domains were “knowledge”, “beliefs about consequences”, “memory, attention and decision process”, and “environmental contexts”. With the exception of “beliefs about consequences”, most of the studies contributing to the other three domains had low scores (1 or 2 out of 5) on the MMAT quality assessment. While equal number of studies contributing to the “beliefs about consequences” domain had low (1 or 2 out of 5), and intermediate (3 out of 5) scores on the MMAT.

The risk of non-response bias was medium or high in all surveys included in this systematic review. As such, the possibility that non-respondents might have different factors could not be ruled out. None of the included studies had utilised the TDF in data collection and/ or analysis. This could explain the underrepresentation of some of the domains identified in this review. The most represented domains were “knowledge”, “beliefs about consequences”, “memory, attention and decision process”, and “environmental contexts”. With the exception of “beliefs about consequences”, most of the studies contributing to the other three domains had low

scores (1 or 2 out of 5) on the MMAT quality assessment. While equal number of studies contributing to the “beliefs about consequences” domain had low (1 or 2 out of 5), and intermediate (3 out of 5) scores on the MMAT.

2.5 Conclusion

Pharmacovigilance medicines risk communications aim at reducing patients' harm resulting from adverse drug reactions and medicine errors. Healthcare professionals have an essential role in translating these communications into their clinical practice. Not only do healthcare professionals’ actions might jeopardise patients’ safety and health-related outcomes, but having low knowledge levels about the content of the alert among HCPs, as well as having inaccurate perceptions about the alerts may affect patients' right to make informed decisions about their treatments.

Different factors were identified to have a possible influence on HCPs’ implementation of medicines risk communications. The most studied factor was HCPs’ knowledge of the alerts. Most of these studies focused on HCPs’ awareness of the release of an alert. Of these studies, the majority investigated physicians' knowledge followed by pharmacists. Awareness about the release of an alert does not reflect HCPs’ knowledge about the content of the alert. However, only a minority of the studies assessed HCPs’ content-related knowledge. More studies are required to assess healthcare professionals' knowledge and understanding of an alert. In addition, more studies are necessary to assess the different factors among other healthcare professional groups and in different geographical areas. The utilisation of the TDF aided in categorising the range of different factors affecting HCPs’ implementation from within their context. Although these factors were related to 11 domains, most reported factors were related to four domains only (“knowledge”, “beliefs about consequences”, “memory, attention, and decision process” and “environmental context domains”). Moreover, most of the studies contributing to three of these four domains were of low quality. Future research should focus on utilising implementation science in order to identify targets for behaviour change when it comes to actionable medicines risk communications. The employment of such science should be considered by regulators in order to create cost effective strategies for improving the implementation of medicines risk communications by HCPs.

According to the findings of this systematic review, there might be a non-straight path between the creation of an alert and the implementation of it. It may, however, be exposed to obstacles at different levels from developers to a complex-interactive healthcare system that involves different healthcare professionals at the ground level, healthcare institutions management and environment, and different groups of patients, as well as their guardians. There should be more research that accounts for the interactive-complex nature that might affect the alert-implementation trajectory and identifies the mediators for change and interventions to improve implementation.

Moreover, different disciplines of sciences should be considered when addressing the implementation of an alert, including communications, risk perception, implementation, and public relations sciences.

2.6 Research rationale, aim and objectives

Medication safety communication is an essential element of pharmacovigilance activities. It connects regulators and pharmaceutical companies with HCPs, patients, and the public. Transparency and ethical fulfilment are not the only purposes of this form of communication. Rather, it seeks to safeguard patients by having specific expectations regarding its outcomes, whether this is updating knowledge of the latest evidence regarding a medications' risks to benefits balance, or developing actionable recommendations based on the most recent evidence. Despite this, studies have shown that such communication can have varying impacts on healthcare practices in different geographical locations, whether they have an intended impact, an absence of impact, an unintended impact, or spill-over effects (DeFrank et al., 2019; Dusetzina et al., 2012; Piening, Haaijer-Ruskamp, de Vries et al., 2012). The unintended impacts and the absence of an intended impact, as well as negative spill-over effects, not only compromise patient safety but also might adversely affect patients' health outcomes, as well as the right of patients to make informed decisions about their treatment. Failure to communicate with HCPs also affects their rights to be informed about the latest evidence that may have an impact on their practice. Therefore, knowing the impact of these communications is vital to improving pharmacovigilance in Kuwait.

Medication safety communications are considered complex interventions as they settle at different destinations, including HCPs at different settings and levels, patients with different backgrounds/ demographics and the public, while it is complex in its expected outcomes (Skivington et al., 2021). Although the ultimate goal is to ensure the safe use of medications, the expected outcome might range from informing the targeted audiences about the risk, changing their attitudes or changing their behaviour (Arlett, 2020; US FDA, 2011). Changing a behaviour, however, would be challenging without at least being warned about the alert and having a proper understanding of its recommendations (Arlett, 2020). In complex research interventions, focusing on measuring the effectiveness of an alert might not guarantee implementation, cost-effectiveness or transferability regarding that alert in real-life situations (Skivington et al., 2021). According to the findings of the systematic review (Alharbi, Berrou, Umaru, Al Hamid & Shebl, 2023), there might be a non-straight path between the creation of an alert and its implementation. It may, however, be exposed to obstacles at different levels

from developer to a complex-interactive healthcare system that involves different HCPs at the ground level, healthcare institutions management and environment, and different groups of patients, as well as their guardians. Thus, it is imperative for regulatory agencies and pharmaceutical companies to understand the barriers that could affect the success of safety communication, whether related to the creation of the message, or the recipients of these messages. This is especially important with the competing sources of information in the modern age that might provide false information to the public.

The studies published in Kuwait to date in the field of pharmacovigilance were mainly focused on the establishment of a pharmacovigilance system due to the infancy of this system in Kuwait. According to a previous study, Kuwait has a clear communication strategy for medication safety (Al-Essa et al., 2015). However, none of the previous studies evaluated medication safety communications within the state of Kuwait. Based on the LSE report in 2018, strategic planning in relation to the healthcare sector in Kuwait is politically motivated, rather than grounded on evidence-based (Mossialos et al., 2018). According to the latest update to the framework for developing and evaluating complex interventions (jointly developed by the Medical Research Council and the National Institute of Health Research in the UK to maximise the value of complex intervention research to decision-makers), it is important to study both the complexity inherent in the intervention's components and their interaction with the context in which they are implemented (Skivington et al., 2021). Thus, this research aims to evaluate medication safety communications throughout the pathway of patient care within the Kuwaiti healthcare system. The research objectives were:

1. To identify and classify medications safety-related communications within the Kuwaiti healthcare system.
2. To explore the process by which Kuwait Drug and Food Control create and disseminate medications safety communications to the Kuwaiti healthcare system.
3. To explore HCPs' knowledge, attitude and experiences of medications safety-related communications.
4. To explore patients' experiences and views of medications safety communications.
5. To make evidence-based recommendations for the improvement of medication safety communications in Kuwait.

This section (2.5) presented the rationale for this research, its aim and its objectives. The next chapter presents the research methodology that was employed to fulfil the aim and objectives of this research.

Chapter 3: Research methodology

3.1 Introduction

Research is “the systematic investigation into and study of materials and sources to establish facts and reach new conclusions” as defined by the Oxford Online Living Dictionaries (Research [Def.1, n.d.]). The methodology is a set of principles and philosophy that forms the procedures and strategies applied by the researcher (Holloway, 1997). Whereas, research aims and objectives are linked to the appropriate methods by research design (Creswell & Plano Clark, 2018; Kroll & Neri, 2009). Research design transforms research questions into a framework of strategies and methods that enable the researcher to systematically answer the research question (Kroll & Neri, 2009). According to Creswell, Plano Clark, Gutmann and Hanson (2003) research design involves three processes: data collection, analysis and reporting of results. Research methods and techniques include methods of data collection, such as interviews, telephone, postal surveys, diaries and analyses of documents, and observational methods as well as the instruments and techniques used for data collection, such as interviews, surveys, document analysis, and observations (Bowling, 2014). This research uses both mixed method and qualitative research designs. It is composed of three phases (Figure 3.1).

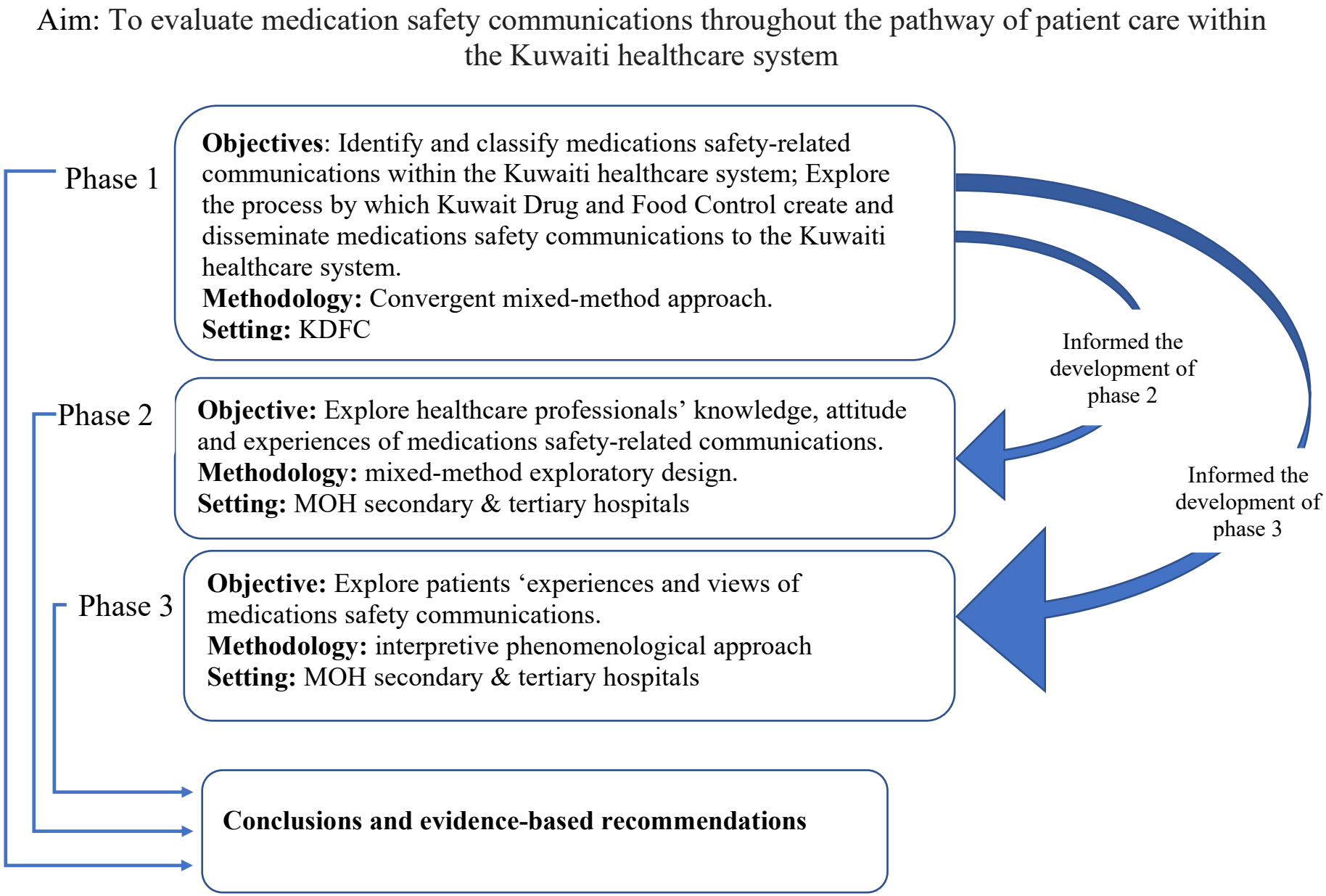


Figure 3.1: Overall methodological approach and flow of this research

MOH: Ministry of Health. **KDFC**: Kuwait Drug and Food Control

Phase 1 involves a convergent mixed-method approach. In this phase, both quantitative document analysis and semi-structured interviews (Chapter 4) with Kuwait Drug and Food Control (KDFC) staff members involved in medication safety communications are conducted. In this phase, a specified communication from KDFC related to medication safety was selected to be incorporated into subsequent phases. In Phase 2, a mixed-method exploratory design was employed. The qualitative aspect is a multiple-nested case study approach, where the medication chosen from phase 1 was used as a nested example for medication safety-related communications. The study included four focus groups with HCPs, including nurses, pharmacists, pharmacy technicians, and physicians practicing in a secondary general hospital setting. The four focus group interviews were conducted separately for each professional group (Chapter 5). Next, a mixed-method survey of HCPs in governmental hospitals was conducted (Chapter 5), which consists of open-ended and closed-ended questions. Phase 3 includes an interpretive phenomenological approach using semi-structured interviews with patients using the same medications as in phase 1 (Chapter 6). Based on the findings from all three phases, evidence-based recommendations were developed to optimise the implementation of medication safety communications in MOH hospitals. (Chapter 7).

Considering that the research process consists of eleven nonlinear stages (Figure 3.2), starting with defining the research paradigm (Mackenzie & Knipe, 2006), this chapter will follow this flow: Research paradigm (step 1 from Figure 3.2), Theoretical framework (step 7), Preliminary fieldwork (step 7), Applied methodologies (steps 3, 5 and 6), Research rigour and Ethical considerations (step 8). At the end of this chapter, data processing and analysis policy are presented.

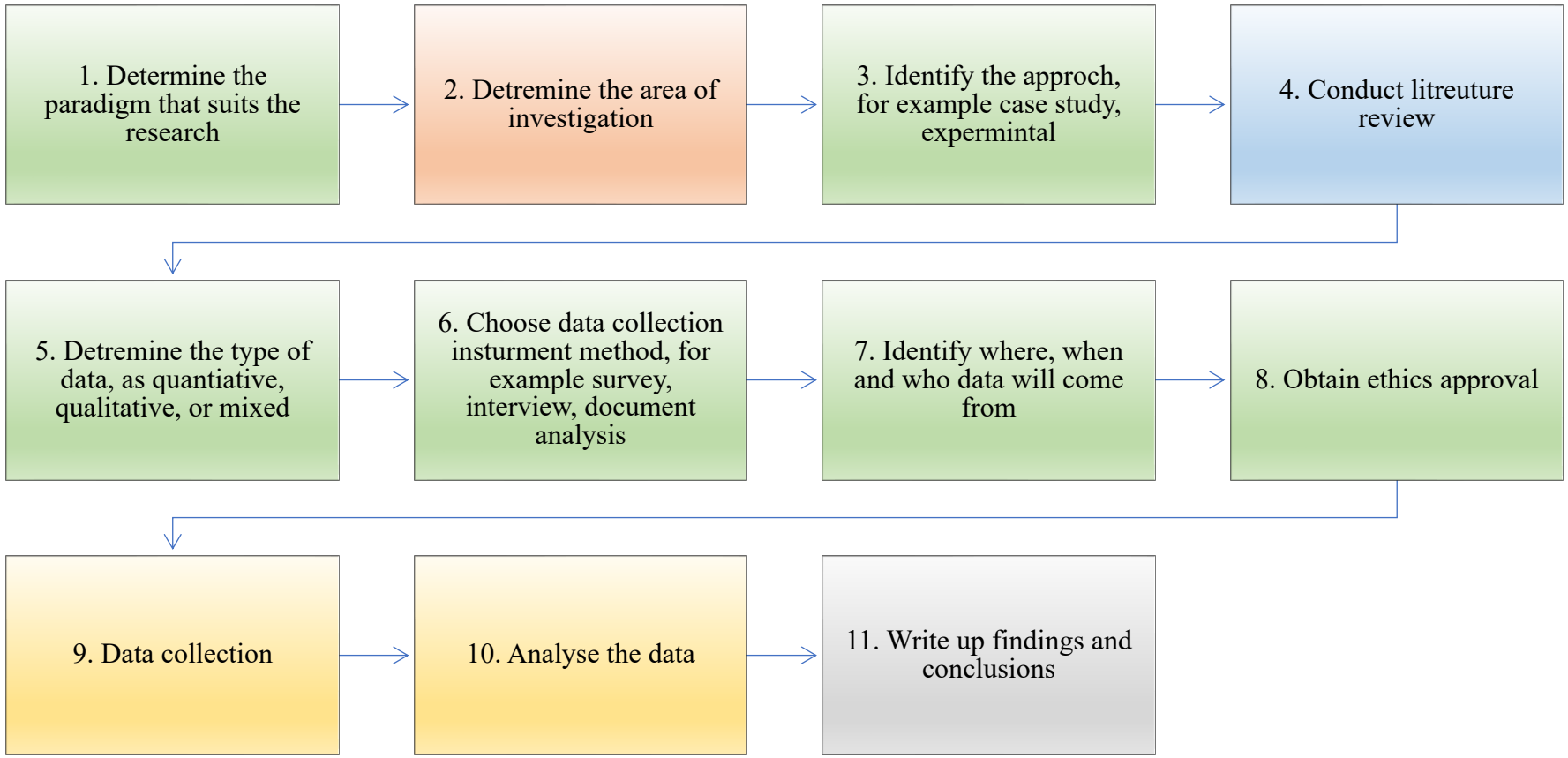


Figure 3.2: Eleven steps of the research process (Mackenzie & Knipe, 2006)

Areas shaded in green are presented in the current chapter (chapter 3). Areas shaded in orange are presented in chapter 1, and areas in blue are in chapter 2. The yellow shaded boxes are presented in chapters 4, 5, and 6;

and the grey shaded area is presented in chapters 4,5,6 and 7

3.2 Research paradigm

Paradigm originates from the Greek “pattern”, and it was first added to the word “research” by Kuhn (1970) driven by his aspiration to understand the underlying differences between social scientists (Kivunja & Kuyin, 2017). Patton (1978, P.203, cited in Lincoln and Guba, 1985; Patton, 2015, p. 89) described a paradigm as a “world view, a general perspective, a way of breaking down the complexity of the real world”. Paradigms are also viewed as the “philosophical intent or underlying theoretical framework and motivation of the researcher with regard to the research” (Mackenzie & Knipe, 2006). Paradigms could shape what is considered to be normal science among a certain community of scientists, setting for them the boundaries of their research (Holloway, 1997). There has been conflict among scientists for decades as a result of biases toward their paradigms (Patton, 2015). As a result, there has been long-standing disagreement over whether the only way to reveal reality is through measurements, hence the need for quantitative methods, or whether measurements cannot reveal complex human phenomena, hence the need for qualitative approaches (Patton, 2015). The first approach assumes a reality that is independent of the observer (Aliyu, Bello, Kasim & Martin, 2014; Creswell & Creswell, 2017; Zuber-Skerritt, 2001). This is manifested by the positivism paradigm and has been historically considered the core of medical research (Bunniss & Kelly, 2010). However, this approach has been accused of not acknowledging the humanity of people, posing both ethical and validity concerns (Lincoln & Guba, 1985). Meanwhile, interpretivist and constructivist paradigms were claimed by defenders of qualitative approaches to gain a deeper understanding of human interactions (Broom & Willis, 2007; Mackenzie & Knipe, 2006). Although interpretivism and constructivism have a concurrent presentation in paradigm discussions, both have their own assumptions about reality (Holloway, 1997). Interpretivism seeks to understand human experiences, assuming that these experiences are neither in isolation from their social construct nor are free from the researcher's influence (Holloway, 1997). The constructivist perspective, however, advocates the notion of multiple realities created by individuals, believing that these individuals construct their social world and that no world exists outside of humans (Holloway, 1997). It is also acknowledged in the

constructivism approach that overlaps between individuals' realities may occur because of their effort to adapt to the same phenomena, yet they differ in the meanings associated with their sense-making approaches related to the phenomena (Lincoln & Guba, 1985).

Unlike previous mono-approaches to worldview, pragmatism tends to combine both opposite ends of the paradigm spectrum, enabling researchers to choose the methos that are most appropriate to their inquiry (Kivunja & Kuyini, 2017). In addition, this approach permits the use of combinations of different types of methods that could lead to policy-related impact (Spicer, 2018). While pragmatism's paradigmatic nature has been questioned (Spicer, 2018), it is believed to enrich understanding of the strengths and limitations of qualitative and quantitative approaches (Patton, 2015). The conduct of this research is guided by two worldviews, pragmatism [in phases 1 and 2 (chapters 4 and 5)] and interpretivism [in phases 3 (chapter 6)]. This is explained by the researcher's belief that the mixed-method approach used in phase 1 (chapter 4) provides a better understanding and evaluation of the process of medication safety-related communications by utilising both quantitative document analysis and interviews with individuals involved in the creation and dissemination process. A mixed method approach, on the other hand, was employed in phase 2 by starting with a focus group interview with HCPs to gain insight into their experiences with medication safety communications within their workplace. As a result of this exploratory approach, the questionnaire for the cross-sectional survey was designed to facilitate the generation of evidence from a larger number of HCPs across all of the MOH hospitals. The interpretive approach utilised in phase 3 (chapter 6) provides the opportunity to understand the experiences of the patients on an individual basis.

3.3 Theoretical framework

The word theory has both Latin and Greek etymologies and it refers to contemplation and observation (Abend, 2008). Theories in communication have a role in minimising failures resulting from poor communication (Corcoran, 2007). In particular, theories could aid in predicting behaviours, disseminating messages, detecting the outcomes of communications, and providing

explanations for the resulting behaviours (Corcoran, 2007). Theoretical frameworks, on the other hand, aid in structuring the research (Osanloo & Grant, 2016). Two theoretical frameworks influenced this research. A communication persuasion matrix was used to help underline the research problem from a communication perspective (McGuire, 1984). To understand the research problem from an implementation perspective, the Theoretical Domains Framework (TDF) is applied (Cane et al., 2012). Using these two models provide an opportunity to overcome their limitations. In contrast with the theoretical framework domain, the communication/persuasion matrix focuses more on the message pathway, without any apparent emphasis on environmental or organizational factors. Conversely, the TDF does not explicitly acknowledge the credibility and trustworthiness of the senders of messages in influencing the behaviour of the receiver, whereas the communication persuasion matrix does (Alharbi et al., unpublished work, 2022; Lipworth, Taylor & Braithwaite, 2013; McGuire, 1984) acknowledge such factors.

3.3.1 The communication persuasion matrix

The communication persuasion matrix was adapted from the field of public health, where it was used particularly for designing effective campaigns. There are two processes involved in this model, input, and output. The input process consists of the following elements: source, message, channel, receiver, and targeted factors (Figure 3.3). The output process, however, is influenced by the engagement and the agreement of the receivers with the communicated message (Figure 3.4).

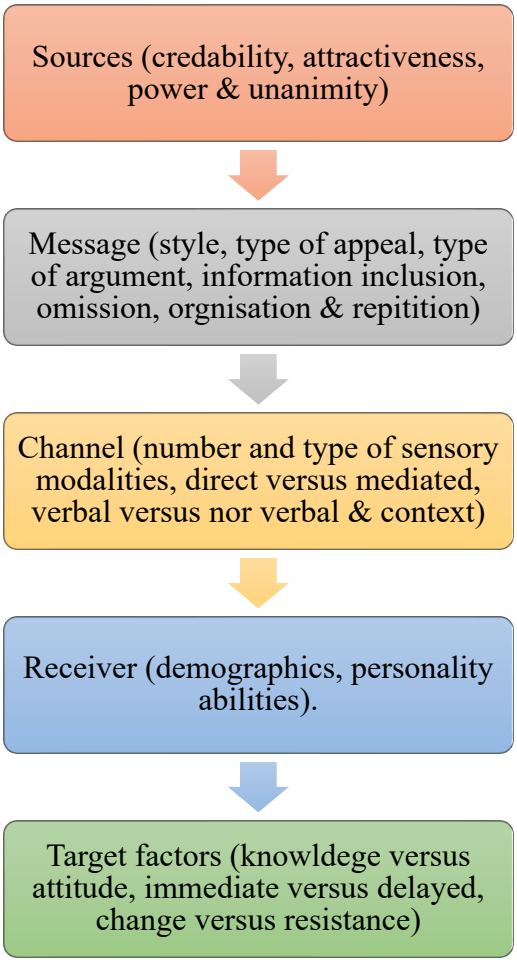


Figure 3.3: Input process of the communication/persuasion model (McGuire, 1984)

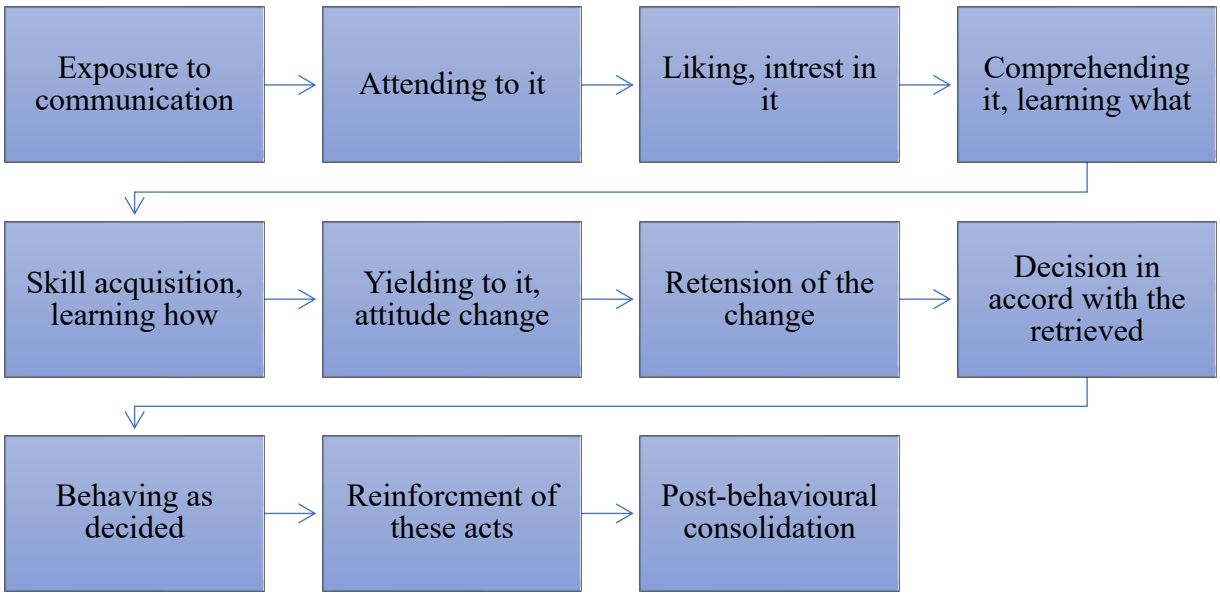


Figure 3.4: Output process of the communication/persuasion model (McGuire, 1984)

Both the input and the output processes are believed to contribute to communication success (McGuire, 1984). As with medication safety communications, effective communication focuses on changing the target audiences' knowledge, attitudes, or behaviours. This requires an evaluation that considers the process from where the safety message is created to its intended implementation. The use of the communication persuasion model focuses on two dimensions of the communication-intended impact process. Specifically, it aids in identifying the communication factors (input) as well as the recipient factors that influence the recipient's response to a persuasive message (Bator & Cialdini, 2000). In this research, the input factors are controlled by KDFC, the developers of the message (Bator & Cialdini, 2000). As discussed in phase 1 (Chapter 4), the output factors are related to the intended receivers, which are the HCPs and the patients. This model was adapted to draft the questions of the semi-structured interviews in Phase 1, which was conducted with staff members in KDFC involved in the process of medication safety communications (Chapter 4). In addition, the elements of the input model were also utilised in

phase 2 (Chapter 5, HCPs) and phase 3 (Chapter 6, patients). This Details of how this model was applied in the three phases of this research are presented in Table 3.1.

Table 3.1: Details of applying the communication persuasion matrix to this research

	Phase 1	Phase 2*	Phase 3*
Source	- MOH related sources was identified as PV unit in the KDFC. - PV unit sources for new emergent medicine safety information were identified.	- HCPs' awareness of KDFC as the sources of new emergent medicine safety information. - Sources that HCPs use to learn about emergent medicine safety information was identified. - HCPs' trust of KDFC and pharmaceutical companies was investigated.	- HCPs as sources for patients to learn about emergent medicine safety information were explored. - Patients' sources for learning about information about their medicines generally and to learn about medicines safety were explored.
Message	- The type of the different post-market medicine safety messages that are created or regulated by KDFC were identified. - The content of the messages (whether KuFDA newsletter or DHCPs) were analysed. - Repetition of the safety message was explored.	- HCPs' awareness of the existence of a specific medication safety communication (which was selected from phase 1) were assessed. - HCPs' knowledge about the specific recommendations	- Patients' awareness about the existence of a specific medication safety communication (which was selected from phase 1) were assessed.
Channels	- Channels used by KDFC to disseminate safety information were investigated.	- HCPs' preferences in terms of the channels to deliver future safety information and the communication format (e.g., electronic or paper-based) were investigated.	- Patients' suggestions for improving patients' medicines safety information were explored.
Receiver	- KDFC's targeted audiences from the medicine's safety communications were identified.	- Assessed whether HCPs received the KDFC's specific medication safety communication (which was selected from phase 1).	- Assessed whether patients received any materials related to a specific medication safety communication (which was selected from phase 1).
Destination	- KDFC's expected outcomes from medicines safety communications were identified.	- The impact of a specific medication safety communication (which was selected from phase 1) on HCPs practice was explored. - HCPs knowledge about the recommendations specified in a specific medication safety communication (which	- HCPs' implementation of a specific medication safety communication's (which was selected from phase 1) recommendations were explored from the patient experience.

	was selected from phase 1) was investigated.	- Patient knowledge about the nature of the safety issue associated with a specific medication safety communication (which was selected from phase 1) was explored.

*This model was intended for communication planning by the sender. **MOH**: Minstery of Health. **PV unit**: Pharmacovigilance unit. **KDFC:** Kuwait drug and Food Control. **DHCP:** Dear HealthCare Professionals communications.

3.3.2 The theoretical domains framework

The theoretical domains framework was developed to simplify the utilisation of behavioural change theories in implementation research. It was developed by integrating 128 theoretical constructs from 33 theories (Michie et al., 2005). This version was refined and validated resulting in the development of a second TDF version in 2012 (Cane et al., 2012). The second version is composed of the 14 domains, namely: knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention and decision processes; environmental context and resources; social influences; emotions; and, behavioural regulations. The domains of the TDF are explained in Table 3.2 along with examples of utilising this framework in this research

Table 3.2: Domains and constructs of the theoretical domain framework (Cane, et al, 2012)

Domain	Construct	Examples
Knowledge	Knowledge, procedural knowledge, knowledge of task environment.	- Assessed HCPs knowledge of the of a specific medication safety communication (which was selected from phase1). - Assessed HCPs knowledge of KDFC's recommendations of a specific medication safety communication (which was selected from phase 1).
Skills	Skill, skill development, competence, ability, interpersonal skills, practice, skill assessment.	- Assessed HCPs agreement to this statement: I do not have the necessary skills or knowledge to implement medication safety recommendations.
Social/professional role and identity	Professional identity, professional role, social identity, professional boundaries, professional confidence, group identity, leadership, organisational commitment.	- Assessed HCPs agreement to this statement: I do not think it is my role to implement the recommendations.
Beliefs about capabilities	Self-confidence, perceived confidence, self-efficacy, perceived behavioural control, beliefs, self-esteem, empowerment, professional confidence.	- Assessed HCPs agreement to a statement regarding their confidence in counselling patients about a specific medication safety communication (which was selected from phase 1).
Optimism*	Optimism, pessimism, unrealistic optimism, identity.	-
Beliefs about consequences	Beliefs, outcome expectations, characteristics of outcome expectations, consequences.	- Assessed HCPs agreement to this statement: Telling the patient about the safety recommendations may make the patient stop taking the medicine
Reinforcement*	Rewards, Incentives, punishment, consequence, reinforcement, contingencies, sanctions.	-
Intentions	Stability of intentions, stages of change model.	- Asked HCPs about their intention to implement the recommendations of a specific medication safety communication (which was selected from phase 1).
Goals	Goals (distal/proximal), goal priority, goal target setting, action planning, implementation intention.	- Assessed HCPs agreement to this statement as a barrier to implementing medication safety recommendations: When I have other work to do that has higher priority.
Memory, attention and decision process	Memory, attention, attention control, decision making, cognitive overload/tiredness.	- Assessed HCPs agreement to this statement as a barrier to implementing medication safety recommendations: When I think the medication safety recommendations are not evidence-based.

Environmental context and resources	Environmental stressors, resources/material resources; organisational culture/climate, salient events/critical incidents, person & environment interaction, barriers and facilitators.	- Assessed HCPs agreement to this statement: Lack of space for consultation is a barrier to implementing medication safety recommendations. - Assessed HCPs agreement to this statement: My hospital policies does not encourage me to implement the recommendations.
Social influences	Social pressure, group conformity, social comparisons, group norms, social support, power, intergroup conflict, alienation, group identity, modelling.	- Assessed HCPs agreement to this statement: patient resistance or refusal to accept medication safety recommendations is a barrier to implementing medication safety recommendations.
Emotions*	Fear, anxiety, affects, stress, depression, positive/negative effect, burn-out	-
Behavioural regulations*	Self-monitoring, breaking habits, action planning.	-

*Not asked directly but asked open-ended questions to allow for their exploration.

HCPs: Healthcare professionals. **KDFC**: Kuwait Drug and Food Control.

3.4 Preliminary fieldwork

Preliminary fieldwork was defined by Caine, Davison and Stewart (2009, p 491) as "the formative early stages of research in the field that allow for exploration, reflexivity, creativity, mutual exchange, and interaction through the establishment of research relationships with local people often before the development of research protocols and ethics applications". There are many ways in which it aids in research, including establishing the scope of the study, improving the researcher's understanding of context, bridging the gap between theory and practice, and building rapport with potential participants (Caine et al., 2009; US National Institute on Drug Abuse, 1990). Additionally, it was used to identify future research opportunities (Ahlin, Nichter & Pillai, 2016). Authors had different approaches to reporting their preliminary fieldwork. These included reporting it with the findings (Mcilfatrick, Sullivan & McKenna, 2003), within the methods section (Buabbas, Alsaleh, Al-Shawaf, Abdullah, & Almajran, 2018) or as a reflection of the experience (Ellis, 2018).

As part of this study, preliminary fieldwork was undertaken to inform the researcher about which administration was responsible for issuing communications regarding medication safety in Kuwait. In addition, preliminary fieldwork was undertaken to understand the structure of the Ministry of Health and the workflow in the possible research sites. It was also performed to gain information that was not available publicly and required permission to access, such as medication purchased at the Central Medical Stores. The preliminary fieldwork was conducted before the different phases of the research, like obtaining the specialties that prescribe valproic acid, and the type of MOH healthcare institutions where it is prescribed to inform the participants' selection in phase 2, as well as obtaining information on the number and characteristics of female patients taking valproic acid for phase 3 from a secondary general hospital.

Preliminary fieldwork was conducted by field visits to different MOH sectors, including the Pharmaceutical Services, Inspection Administration, Kuwait Drug and Food Control, Central Medical Stores, visits to a secondary general hospital, and telephone communications with a

drug company representative. The researcher collected information mostly by taking notes. The outcomes of the preliminary fieldwork on this research were as follows:

1. Kuwait Drug and Food Control was selected as it is the site where the pharmacovigilance unit functions. The term medication safety communication was chosen based on the term that was used within the KDFC.
2. Adjustments in the interview guide for phase 1.
3. In addition to introducing the researcher to the possible interviewees for phase 1, it also helped her build rapport with interviewees from the same phase.
4. The researcher was provided with some of the organisational frames that were helpful with the description of the context.
5. The sources for collecting the documents were identified which included the KDFC website and KDFC archives.
6. Provided insight about the possible cases to be selected for phase 2.
7. Provided insight into methods for recruiting patients for phase 3, including through pharmacies' electronic systems.

Conducting preliminary fieldwork had a variety of benefits in addition to informing the research. This included providing the researcher with examples of medication safety communications that were created within the MOH. In addition, it provided the researcher with insight into the current status of pharmacovigilance in Kuwait. As an example, the researcher was informed about the Pharmacovigilance Task Force team and their missions and met with some of their members. The researcher also gained insight into her interviewing skills as a result of her experience.

3.5 Applied methodologies

In this research, two methodological approaches were applied. These included mixed method approaches (phase 1[KDFC-related], Chapter 4; phase 2 [HCPs-related], Chapter 5), and a qualitative approach (phase 3 [patients-related], Chapter 6).

3.5.1 Mixed method research design

In literature, terms and definitions used to discuss mixed methods (MM) are not uniform (Kroll & Neri, 2009). It was noticeable that definitions of MM are commonly based on how previous MM researchers conducted their studies. While authors disagreed on the terms used to describe MM, they agreed that it involves both qualitative and quantitative approaches. In addition, they agreed that integration occurs in this type of research. Greene and Caracelli (1989) defined MM by its minimum requirement of having at least one quantitative and one qualitative method, independent of any specific paradigm. On the other hand, Teddlie and Tashakkori (2010) described MM as a methodology. They reported, "the broad inquiry logic that guides the selection of specific methods and that is informed by conceptual position common to mixed-method practitioners" (p.5). Some authors defined mixed methods in terms of what does not constitute MM research. For example, combining two or more types of research methods of similar nature (e.g., qualitative and qualitative, or quantitative with quantitative) is not considered MM, but under the triangulation umbrella (Pluye, Bengoechea, Granikov, Kaur & Tang, 2018). Creswell and Plano Clark (2018) also provided examples of what is not considered a mixed-method design, such as collecting qualitative data and analyzing it quantitatively using, for example, content analysis.

Creswell et al. (2003) provided a definition that highlighted the order of occurrence of the data collection (concurrently or sequentially), the degree of priority given to the quantitative or the qualitative parts, and the point where the integration takes place (i.e. in the data collection, analysis or the interpretation phase). However, this definition does not refer to the existence or absence of a theoretical framework that might be used by some researchers to guide their research. Moreover, it is focused on combining quantitative and qualitative divisions in a single study, regardless of when the interpretation might occur (Crewsell et al., 2003). Although some researchers agreed that MM is used within a single study, Creswell and Plano Clark (2018) indicated that in this study design, researchers might need to work at multiple phases and connect multiple studies to reach the overall objective of the study, especially in evaluation studies. Similarly, Johnson and Onwuegbuzie (2004) indicated that MM can occur within or across stages of the research process (from objectives and data collection to data analysis and interpretation.

For this research, Creswell and Plano Clark (2018) definition was used. These authors explained that in mixed methods:

> The researcher collects and analyses both qualitative and quantitative data rigorously in response to research questions and hypotheses, integrates (or mixes or combines) the two forms of data and their results, organizes these procedures into specific research designs that provide the logic and procedures for conducting the study, and frame these procedures within theory and philosophy (p.5).

This approach was conducted in phase 1 (within the study, Chapter 4) and phase 2 (across different studies, Chapter 5) in this research.

Some authors (Creswell & Clark Plano, 2018; Morse & Niehaus, 2009) differentiated two forms of mixed methods, “fixed” and "emergent" based on whether they were predetermined or considered during the process of conducting the other form of research, as one method was deemed inadequate. Emergent MM designs involve the use of MM due to issues that develop during the process of conducting the research. It usually occurs when a second approach (quantitative or qualitative) is added after a study is underway because one method was found inadequate (Morse & Niehaus, 2009). Based on the previous differentiation between the types of mixed methods, Phase 1 (document analysis and KDFC interviews) is considered to have a fixed mix method design, while phase 2 (survey and HCPs focus groups) is considered to be emergent, as the decision of including the quantitative part occurred after piloting the focus groups and editing the tools to be used in the focus groups. This was to ensure the generalisability of the data and support the recommendations of this research.

3.5.2 Reasons for using a mixed method approach

Different drivers for using MM were mentioned in the literature. According to Kroll and Neri (2009), MM can be used for following cases (1) research questions requiring the combined quantitative and qualitative data (2) exploratory research is needed due to the insufficient information in the literature, (3) availability of resources, such as expert team members and source of funding, (4) stakeholders and policymakers aiming for detailed coverage of the nature

and magnitude of a problem, and how they are interrelated, (5) journals accepting MM studies for dissemination. Kroll and Neri (2009) suggest that collecting data concurrently can be done for confirmatory purposes. It has been also proposed by Kroll and Neri (2009) that the use of MM can increase the depth and scope of the findings.

Creswell and Plano Clark (2018) provided other reasons that might lead a researcher to use MM, including (1) a need to obtain more completed and corporate results (2) a need to explain initial results (3) a need to explore before administering an instrument (4) a need to enhance an experimental study with a qualitative method (5) a need exists to explain and compare different case-studies (6) a need exists to develop, implement and evaluate a programme. There is also increased use of both qualitative and quantitative approaches within the same research study to collect more comprehensive data and a wider understanding of the research problem (Bowling, 2014). This was supported by Johnson and Onwuegbuzie (2004) who mentioned that the resulting mixture is not expected to be confirmatory or supportive, rather it is intended to widen the researcher's understanding (Johnson and Onwuegbuzie, 2004). The use of MM can also overcome limitations of using each method on its own, where qualitative methods might limit generalisation (Creswell & Plano Clark 2018); while quantitative methods may not provide deep understanding (Creswell & Plano Clark, 2018). In this research, MM was applied in phase 1(Chapter 4) as document analysis used as a confirmatory and to support the findings of the qualitative interviews. Moreover, MM was used in phase 2 for exploratory purposes as no previous research examined the interactions of HCPs practicing in Kuwait with medication safety communication. The findings from the qualitative stage of this phase (Chapter 4) were used in drafting the questionnaire survey used in the quantitative phase. In both phase1 and phase 2 the employment of a MM approach was intended to deepen the understanding of the research findings.

3.5.3 Mixed-method designs

Many designs of MM approaches are available in the literature; however, some researchers have grouped them into general approaches. According to Creswell et al. (2003) MM designs are based on four assumptions. Among these assumptions are the study's sequence of data collection, the integration point, the relative weight given to qualitative and quantitative

aspects, and its transformative value or action-oriented nature. Based on Creswell et al. (2003) researchers could use these four assumptions and be creative with the design they use. As it might be confusing to assign priorities, the researcher could have equal priorities in the results and then have different priorities in the discussion (Creswell et al., 2003). Different researchers have also based their classification on the sequence of research data collection, such as Kroll and Neri (2009), Johnson and Onwuegbuzie (2004), and Pluye et al (2018). Johnson and Onwuegbuzie (2004) also considered the dominant status of both the qualitative and the quantitative aspects of the research. Creswell and Plano Clark (2018) revised their earlier approaches to MM to focus on the intent of the research, whether convergent, explanatory sequential or exploratory sequential (referred to as explanatory or exploratory). In 2018, Creswell and Plano Clark moved from emphasising priority to focusing on the intent of the study to avoid vagueness associated with a priority. Typologies of MM designs in this research are based on Creswell and Plano Clark's (2018) revised approaches.

Phase 1 involves a convergent mixed-method approach. In this phase (Chapter 4), both quantitative document analysis and semi-structured interviews with KDFC staff members involved in medication safety communications are conducted. In phase 2, a mixed-method exploratory design was employed. The qualitative aspect is a multiple-nested case study approach, where the medication chosen from phase 1 is used as a nested example for medication safety-related communications.

3.5.4 Integration Point

The integration point is characteristic of MM (Kroll and Neri, 2009). Kroll and Neri (2009) explained that for a MM to be a true MM, there should be actual data integration, which might be possible at any point from data collection to the discussion (Kroll and Neri, 2009). Nevertheless, the researcher should clearly state this point (Kroll and Neri, 2009). According to Pluye et al., (2018), points of connection can generally be described as belonging to mixed-method processes or mixed-method products. Pluye et al (2018) suggested that points of integration would depend on the worldview of the researchers, thus resulting in different designs. For example, if worldview indicates that qualitative and quantitative approaches are different and separated, then the method of data collection and analysis for both quantitative

and qualitative data should be separated. A second example is if the worldview indicates that qualitative and quantitative approaches are different but interrelated, then the results of both should be integrated. The third assumption has two approaches or worldviews. First, one can combine qualitative and quantitative approaches regardless of worldview. Another assumption is that worldviews make it possible to transform one set of data into another. In this case, the qualitative data would be transformed into quantitative variables or quantitative data transformed into qualitative themes. Kroll & Neri, (2009) excluded an approach from being MM. They provided an example by saying that a quantitative study emerging from a qualitative study (even if conducted by the same main investigator) is not an MM because they revolve around different problems/questions and there is no integration of their findings (Kroll & Neri, 2009). However, Creswell et al. (2003) indicated that integration can occur at any stage of a study. In addition, Cresewll et al., (2003) extended the integration point to include the conclusion, as they indicated that the point where integration takes place can be related to the purpose of the research, the ease of integration, the researcher's understanding of the stages of the research, and the purpose of the study. Additionally, Creswell et al., (2003) indicated that the least seen type of integration is the integration in data collection. An example of this form of MM design is used in the survey (Chapter 5) as collecting both qualitative and quantitative data occurred at the level of the questionnaire. It should also be acknowledged that integration can occur at earlier levels, like the research question or problem. Integration could occur at multiple stages of the study, not necessarily at one point only (Creswell et al., 2003). In this research, the integration point for phase 1 was at the level of the interpretation (before the discussion section), and for phase 2 it occurred at the level of the discussion.

3.5.6 Qualitative research approach

Qualitative research has been defined in different ways. Often, these definitions had occurred as either a comparison of quantitative research, showing what is not a qualitative study, or describing what is expected from qualitative researchers. Denzin and Lincoln's (2018) definition has a naturalistic aspect highlighting the world as the source of data and the involvement of the researcher in data collection where the researcher is actively involved and present in the data collection taking field notes, doing interviews, conversation, taking photos, recordings and writing memos. They indicated that the researchers' activity of data collection

will transfer the world into data that would be analysed by the researcher in an attempt to interpret or make sense of it. Creswell's (2007) definition begins with the assumptions and worldview and the possibility of using a theoretical lens to the impact of the research. Creswell emphasises that this type of inquiry investigates the meanings an individual or group attached to a social problem. Similar to Denzin and Lincoln (2018), Creswell (2007) also has a naturalistic approach to data collection, indicating that data collection occurs in places sensitive to the places and people under study.

In qualitative research, the researcher is the instrument of the inquiry, and it is influenced by the researcher's background, skills, training, empathy, cross-cultural sensitivity, interpersonal (relating to the relationship or communication between people) competence, and how as a person the researcher engaged in the fieldwork and analysis (Creswell, 2007; Patton, 2015). The use of qualitative approaches in this research was because it allows for the understanding of people's perspectives and experiences (Patton, 2015). It also allows in-depth exploration and takes into account the complex nature of humans. This is seen by allowing the participant to elaborate more and the researcher probing with the questions, in which she/he understands that it might be unique to a participant (Patton, 2015). Moreover, qualitative research is advantageous over quantitative research when we have little knowledge about the research topic (as no similar study was conducted previously in Kuwait), researching sensitive or complex issues (sensitive topics teratogenicity, and epilepsy in women of childbearing age) and when there is an opportunity for exploration (Bowling, 2014).

3.5.7 Interpretive phenomenological analysis

Interpretive phenomenological analysis is the method used to answer patients' related objective in phase 3 (Chapter 6). Interpretive phenomenological analysis (IPA) examines qualitatively how people make sense of their major life experiences, according to Smith, Flowers and Larkin (2009). Besides focusing on participants' own experiences, IPA also acknowledges the active role of the researcher in the understating process (Smith & Osborn, 2008; Smith et al., 2009).

In this phase, IPA was employed using semi-structured interviews based on Smith and Osborn (2008) and Smith et al., (2009). Interpretive phenomenological approach was chosen instead of the descriptive approach. This is because descriptive approaches, such as Husserl's

phenomenological approach or Transcendental Phenomenology, relies on the researcher taking and becoming conscious of the participant's subjective experience, while the researcher is expected to disconnect from her preconceptions and background, thus focus on description (Welton, 1999; Koch, 1995). However, the process of doing a descriptive method is time-consuming for the researcher and the patients. In addition, it might allow for data waste; and, it claims that patients would not be affected by their environment. Moreover, the researcher cannot isolate her conceptions form participants experiences when trying to understand and make sense of them (Smith & Osborn, 2008). On the other hand, Heidegger's approach to phenomenology focuses on the experience of understanding, assuming that the researcher cannot separate their backgrounds in the understating process (Koch, 1995). Furthermore, IPA allows participants to describe their personal experiences with their concepts. It also allows these experiences to be seen through the individual account of the participant., rather than the researcher providing objective statements of the object or event.

3.6: Ethical consideration

Ethics were considered at the inception of this research. Before conducting the preliminary stage, the researcher contacted the Kuwait MOH ethics department and the University of Hertfordshire ethics to ask whether ethical approval was required to conduct this stage. While Kuwait MOH responded that such approval was required, the University of Hertfordshire ethics confirmed it was not required. Thus, ethics approval was obtained from Kuwait MOH for the preliminary stage, phases 1, 2 (focus group and not the survey) and 3, and for accessing the different settings related to these phases. This is presented in appendix 13 (916/2018; the year of obtaining the approval: 2018). The decision to conduct the survey was taken after the completion of phase 1 data collection, thus an amendment on the initial approval was obtained from Kuwait to include the survey (Appendix 14). Ethics approval was also obtained from the University of Hertfordshire for phases 1,2 (except the survey) and phase 3 (LMS/PGT/UH/03808; Appendix 15). An amendment to include the survey was approved by the University of Hertfordshire ethics committee in 2020 (Appendix 16).

Ethics are vital in the process of interviews because they investigate private lives and their findings affect our understanding of the research problem (Birch, Miller, Mauthner, & Jessop, 2012; Brinkmann & Kvale, 2015). In addition, the interviewees might be affected by the

interviewing process (Brinkmann & Kvale, 2015). Brinkmann and Kvale (2015) considered ethical issues throughout the interviewing process. The seven stages as stated by the two authors included thematising, designing, interview situation, transcription, analysis, verification and reporting. Thematising is the stage that involves formulating the purpose of the interview (the why and what of the investigation) before starting the interview. This purpose extends beyond scientific knowledge to improving human conditions that are investigated. In the designing stage, ethical considerations involved obtaining informed consent, ensuring confidentiality and considering the possible effects of the study on the participants. In the interview situations, the effects of interview interactions on interviewees, like stress during an interview, were considered when conducting interviews. In transcription, two main ethical issues were considered, which are confidentiality and accuracy of the written texts to the oral statements of the interviewees. In the analysis stage, ethical considerations involved the questions of how deeply can the researcher analyse the interviews. The last stage is reporting, where confidentiality and the effect of the published report on the interviewees as individuals and the communities they belong to were considered (Brinkmann & Kvale, 2015).

Based on Miller and Bell (2012) and Brinkmann and Kvale (2015) more ethical issues were considered. For the consent forms and the participant information sheet the researcher balanced between providing too much information that could affect the data and hiding information from participants. The participant information sheet that was given to the potential participants contained the aim of the study, the process involved in the study, and the reason and the process by which the participants were chosen. Potential participants were informed that they have the right to refuse or to withdraw from the study at any stage (Smith, 2010). Participants were also encouraged to ask questions. A special note on maintaining anonymity is that there is a risk of the deductive discloser, which threatens internal confidentiality, in phase 1 (Chapter 4) (Kaiser, 2009; Tolich, 2004). This is because these individuals could be identified by their age and years of experince despite removing their names. Thus, the previously mentioned information was also anonymised in the two phases. All data were anonymised after at transcribing stage. Similar principles were applied to the survey. An introduction explaining the purpose of the survey was provided to the participants in both English and Arabic. After this introduction, the participants were provided with the option to agree or disagree to proceed with answering the survey questions. Implied consent was considered when a participant chose to agree to participate. In addition, multiple responses by

the same participant were minimised by using the Prevent Multiple Submissions option in Qualtrics.

The rapport between the interviewer and the participants was achieved based on respect and not faking friendship. Transcripts were not sent back to the participants to confirm, rather the researcher verbally provided the participants with a summary of the interview just after conducting it. This is to avoid ethical dilemmas that might occur due to providing the transcripts for the participants. Ethical dilemmas that could arise from this process, include what if the participant was expecting a different outcome. Additionally sending the transcripts back to the participants might impose an extra burden on them and loss of time. Thus, the researcher finds that providing a summary at the end of the interview and asking the participants to correct her might provide a suitable balance between ethical consideration and the quality check (in the focus groups, a summary was provided after some discussion points). Furthermore, the effect of the interviewer on the interviewees especially those related to patients' experiences with adverse drug reactions was considered. For this, the interviewer focused on detecting such distress and planned to offer interviewees to take a rest or stop the interviewer and complete later, or stop the interview entirely, and inform the interviewee about their right to do so. The researcher also identified the appropriate department in the hospital, the social service department, that is responsible for providing emotional and mental support if such distress occurs in the participant. The researcher planned to refer the participant to the medical team to give the participant the necessary support if required (Brinkmann & Kvale, 2015; Miller & Bell, 2012).

Data were managed using an encrypted laptop, and recordings were kept in a locked cabinet that only the researcher had access to.

3.7 Research quality

Quality measures for increasing the trustworthiness of the results from the interview were adapted from Lincoln and Guba's (1985) criteria. First, credibility, which is concerned with how confidence in the truth of the findings; this was achieved by triangulation (with the document analysis) and member checking, by asking the interviewees about their feedback on

the summary (in the same setting after the interviews were conducted) (Lincoln & Guba, 1985; Pandey& Patnaik, 2014). Transferability, which aims to show that the results of the study are applicable in other situations, was aimed by making the other researcher's judgment possible by providing thick descriptions (Lincoln & Guba, 1985; Pandey& Patnaik, 2014). Conformity reflects the degree to which the findings of the study are formed by the participants rather than the researcher's biases; This was achieved by triangulation and keeping a reflective journal, as notes were taken by the researcher during the interviews and by the supervisor during the focus groups (Lincoln & Guba, 1985; Pandey& Patnaik, 2014). Triangulation was also applied in different stages of this research (Phase 1, Chapter 4, and Phase 2 Chapter 5). Transferability, which show that the results of the study are applicable in other situations, was addressed by making the judgment possible by providing thick descriptions (Lincoln & Guba, 1985; Pandey& Patnaik, 2014).

The reliability of the questionnaire included internal consistency, which describes the degree to which the questionnaire establishes stable and consistent results and the corrected item-total correlation, a measure of the correlation between an item and the total score of all the other items, using Cronbach's alpha (Gliem & Gliem, 2003; Taherdoost, 2016; Zijlmans, Tijmstra, Van der Ark, & Sijtsma, 2019). The test-retest reliability was assessed using Spearman's correlation and intraclass correlation coefficients (ICC). Face validity was also performed, which relates to whether the current questionnaire measures what it is supposed to measure (Gliem & Gliem, 2003). This involved reviewing the content of the questionnaire by the supervisors, who have expertise related to the themes included in the questions. Moreover, the questionnaire was reviewed by a statistician during the development stages. This is to confirm the suitability of the questionnaire for the targeted analysis to be performed. Moreover, HCPs participating in the survey pilot stage were given the opportunity to provide their opinions about the questions used in the questionnaire through open-ended questions.

To ensure the quality of the translation process, the English piloted questions were forward and backward translated in two rounds by translation services that were certified by the Association of Translation Companies (in the UK) or had a certification from the International Organization for Standardization. This process is explained in the following chapters (method section in Chapters 4, 5, and 6). The final Arabic translation was also piloted. Participants' quotas in two open-ended survey questions were translated by the researcher and confirmed by a bilingual supervisor. Discussion with a second bilingual supervisor took place when disagreements

occur. This is except for the patient experiences, where the coded segments (and one interview transcript where the patient demographics were removed) were translated by a local translator in Kuwait, who is familiar with the culture and has experience translating research interviews, including the field of pharmacy practice. The translated materials were then reviewed by the researcher for their accuracy. Medicines' safety-related press releases posted on KDFC's website that were written only in Arabic were translated by translation services certified by the Association of Translation Companies (in the UK) or with a certification from the International Organization for Standardization and checked by a bilingual supervisor and the researcher.

Pilot interviews, focus group discussions and survey administration were also applied with individuals with similar characteristics of those to be included in the study to help identify potential problems in the research instruments, help in identify questions that will be difficult to understand by the participants, and questions that are that needed to be modified, and helped in identifying the time required to complete an interview. Moreover, it was also an opportunity for the researcher to practice interview techniques (Berg, 2001).

All interviews and focus groups were audio-recorded and transcribed by the researcher. Moreover, the transcribing process of one interview in each phase was checked for accuracy by one of two supervisors, who were fluent in both Arabic and English.

Through training sessions, reading, and supervision, the researcher was developing herself in aspects related to this research. Training sessions attended by the researcher included different aspects of this research, such as developing questionnaires, conducting interviews and focus groups. The details of the training sessions attended by the researcher are presented in Appendix 17.

3.8 Data processing and analysis policy

This research involved the use of three main sources of data including documents, interviews (individual and focus groups) and a survey questionnaire. Both qualitative and quantitative techniques were applied to analyse the collected data. For the qualitative data, MAXQDA was used to facilitate the analysis process. MAXQDA was selected in this thesis because it supports

the analysis of Arabic transcripts (Kuckartz, & Rädiker, 2019). Whereas, SPSS was mainly used in the analysis of the quantitative data.

In phase 1 (Chapter 4), all documents were read and initially classified by the researcher according to their types. As described in Chapter 4, two tools were used to analyse the documents. The first tool was adapted from the literature, and the relevant sections were extracted. Then, descriptive statistical analysis was employed on the extracted data. The details of this process are provided in 4.2.5.1.

The second tool was developed and piloted by the researcher after reviewing all included documents. A supervisor (Dr Fatemah Alsaleh) then piloted this tool as described in 4.2.4. The researcher used the final version of this codebook to extract the data from the documents. Then, a descriptive analysis involving counting the frequency of the occurrence of a code was conducted by the researcher as described in 4.2.5.2.

After transcribing the interviews in phase 1 (Chapter 4), the researcher transferred the data to MAXQDA to facilitate the analysis process. For these interviews, a framework analysis technique was applied following Gale, Heath, Cameron, Rashid, and Redwood (2013). The details of this process are presented in 4.2.5.3.

In phase 2 (Chapter 5), focus group transcripts were transferred to MAXQDA. In this phase, a thematic analysis technique, based on Braun and Clarke (2006), was followed to analyse the focus group transcripts. This is discussed in detail in 5. 2.1.6. A survey was also utilised in phase 2. The survey data analysis is provided in 5.2.2.7. This involved quantitative data analysis for the closed-ended questions, and qualitative analysis for answers to the open-ended questions. For the quantitative data analysis, SPSS was utilised. This involved the use of descriptive statistics (frequency and percentile). Moreover, to reduce the set of variables in four questions into smaller sets of dimensions or components, principal component analysis (PCA) was performed. The researcher also set the hypothesis of this study (the survey questionnaire) in 5.2.2.7. To assess these hypotheses, the Kruskal-Willis H test, Fisher-Freeman-Halton Exact Test and Mann-Whitney U Test were performed. In addition, a multivariate regression analysis was conducted to detect predictors for implementing the intended recommendations specified in an example of KDFC's related DHCPs. For the qualitative data obtained from the survey, a descriptive analysis was performed on the participants' answers in the *others, please*

specify options. However, the answers to two specific open-ended questions (relating to the barriers to implementing the recommendations of medication safety communications both generally and specifically relating to a specific medication) were analysed using conventional content (Hsieh & Shannon, 2005). This is also described in details in 5.2.2.7.

Another source of qualitative was obtained from the patients' interviews (phase 3 Chapter 6). This phase was an interpretive phenomenology, and the data analysis was conducted following Smith et al. (2009). The details of this process are presented in 6.2.4.

3.9 Summary of Chapter 3

This chapter provided an overview of the research paradigm and theoretical frameworks underpinning this research. This chapter also included an explanation of the overall methodology of this research, including the three phases of this research. Phase one was a convergent mixed-method study, in which both quantitative document analysis of documents relating to KDFC's medication safety communications activities and semi-structured interviews with staff members engaged in this process at KDFC were conducted. Phase 2 involved a mixed-method exploratory approach using focus group discussions with HCPs working in a secondary hospital. This was followed by the administration of an online survey to HCPs working in MOH hospitals. Phase 3 consisted of semi-structured interviews with female patients of childbearing age who used valproate – related medication. The preliminary fieldwork, ethical considerations and research quality were also explained in this chapter.

The next chapter presents the methods applied in phase 1, as well as the results and discussion of this phase.

Chapter 4: Exploring the development of medication safety communications by Kuwait Drug and Food Control, A convergent mixed-method approach

4.1 Introduction

The objectives of this chapter were:

1. To identify and classify medications safety-related communications within the Kuwaiti healthcare system.
2. To explore the process by which Kuwait Drug and Food Control create and disseminate medications safety communications to the Kuwaiti healthcare system.

This chapter presents the methods, results and discussions of phase 1. As was previously discussed in chapter 3, KDFC is the responsible authority in Kuwait for developing and disseminating medication safety communications, as well as performing other pharmacovigilance activities. The senders of medicalisation safety communications, the issued communications and the channels used to deliver these communications could affect the implementation of their recommendations in clinical practices (Alharbi et al., 2023). However, as explained in chapter 1, no previous published research has been found to evaluate medication safety communications that were issued by Kuwaiti authorities. Thus, this phase aimed to uncover the processes of issuing and disseminating medication safety communications by conducting a mixed-method convergent study.

4.2 Methods

4.2.1 Study design

This is a convergent mixed-method study, where data are concurrently collected, analysed and integrated at the level of interpretation (Creswell et al., 2003). This design provides the advantage of overcoming the limitations of both methods alone, provides complementary data to understand the research problem, and allows for cross-validation of the findings (Creswell & Plano Clark, 2018). The quantitative part is the document analysis of written activities and communications of KDFC and the qualitative part is the semi-structured interviews with commissioners/staff members within the KDFC.

4.2.2 Setting

The setting of this study is the KDFC (Kuwait Drug and Food Control). Kuwait Drug and Food Control is one of four administrations related to pharmacy pharmaceutical products within the Ministry of Health (MOH). Other administrations are the Central Medical Stores, Pharmaceutical Services and Inspection administration. The KDFC was chosen based on a preliminary-field work that involved all the previously mentioned administrations to determine the most suitable place for answering the research question.

4.2.3 Data collection

4.2.3.1 Document analysis

The researcher obtained permission from the MOH and KDFC to retrieve documents that are related to medication safety communications. The administration in KDFC and the staff of the PV unit directed the researcher to the archives in the secretary office in February 2019. There, a file under the name of "safety" was handed to the researcher. This file included paper-based materials. These papers were not categorised in the file, and included different materials such as communications between KDFC and other MOH departments, pharmaceutical companies, and hospitals. It also included medication safety communications that were disseminated by KDFC. Using mobile phone, photos of all documents in the safety file were taken and scanned to the researcher email using CamScanner, except for two documents (one was not related (related to ADR reporting) and another was a second copy from a document that was already included). The total of the scanned documents from this file were 37. In addition to the documents identified in the archived files, seven medication safety communications that were previously disseminated by KDFC were given to the researcher by the pharmacovigilance staff members in KDFC. One document was provided by the Pharmaceutical Services and other six documents were identified from KDFC website (part of the MOH website). These six documents were uploaded as one file in the KDFC websites as well as KDFC Twitter account. This was last accessed in February/March, 2019 (MOH renewed its website after last access: https://www.moh.gov.kw/en/Pages/default.aspx , thus documents are no longer available at this website; but still available through: http://kdfcalerts.blogspot.com/?view=classic.

4.2.3.2 KDFC's interviews

Purposeful sampling approach was applied as staff members involved in the process of medications safety communications were interviewed (Patton, 2015). Interviews were conducted

in August and September 2019. The researcher identified that participants through the head of the department and the superintendent. Two of three interviewee were the only staff members in the pharmacovigilance unit. The third interviewee was a superior employee who oversee different KDFC-related activities including the functions of the pharmacovigilance unit. The researcher visited all three interviewees in their offices prior to the date of the interview to build rapport with them. All three interviewees were provided with a participant information sheet and consent forms. All interviews were conducted in participants' offices in KDFC based on their preference. Interviews were audio-recorded, and notes were taken during the interview by the researcher.

4.2.4 Documents inclusion, extraction tools and interview guide

Documents were classified based on their expected contribution to the research objectives. All documents related to medication safety communication were included to identify the process of medication safety communications. Excluded documents were those not related to medication safety, such as ADR reporting and documents related to medical devices. However, to classify KDFC's medications safety communications, only documents involving medication safety communications were included (e.g., DHCP letters from KDFC). These are the documents that were intended to disseminations medication safety information to HCP, patients or the public. However, documents that included medication safety information that were included in work reports of KDFC staff were excluded. The tools were initially created based on McGuire's (1984) elements of message flow, then adapted as appropriate for each objective. For the purpose of identifying and classify medication KDFC's safety-related communications, a survey instrument was adapted from Bjerre et al. (2018) with minor adjustments to suit the differences in the identified types of communications (i.e., those which were DHCP letters, newsletters prepared by KDFC staff, or those that were identified from the website). The instrument is presented in Appendix 18. For the purpose of identifying the process of creating and disseminating medications safety communications, a code book was developed by the researcher. After identifying the appropriate documents to achieve the objective, a coding book was developed by the researcher from reviewing documents. The coding book was piloted and discussed with a supervisor (Dr

Fatemah AlSaleh), and modified as necessary (four versions, last version in Appendix 19). Each document was considered the unit of analysis and they were hand coded by the researcher using the code book. Dr AlSaleh had also independently 5 of the documents, and overall, 84% consistency was recorded.

The interview guide was developed based on McGuire's (1984) model, Arab Pharmacovigilance Guideline (The League of Arab State, 2014), literature and EMA's standard operation procedure on safety communication to the public (EMA, 2014). They were initially checked by the supervisors to assess for its appropriateness against the objective of the study. Then, it was piloted with two pharmacists that have working experience with KDFC. The pilot resulted in the modification of the interview guide and attracted the researcher attention for the necessity to translate the interview questions. Figure 4.1 adapted from Brislin (1986), Jones, Lee, Phillips, Zhang and Jaceldo (2001), and Doris, Lee and Woo (2003), explained the translation process of the interview guide. Round 1 translation and backward translation round 2 were conducted by translation services that were certified by the Association of Translation Companies (in the UK) or had a certification from the International Organization for Standardization (Association of Translation Companies, n.d.; International Organization for Standardization, 2018). Forward translation round 2 was conducted by an independent researcher (native speaker of Arabic, postgraduate degree in pharmacy) and edited by the researcher. The final Arabic version was piloted with two pharmacists working in Kuwait and checked for grammar and spelling mistakes by a specialist. Table 4.1 represents the errors identified. The final version of the interview guide is presented in Figure 4.2.

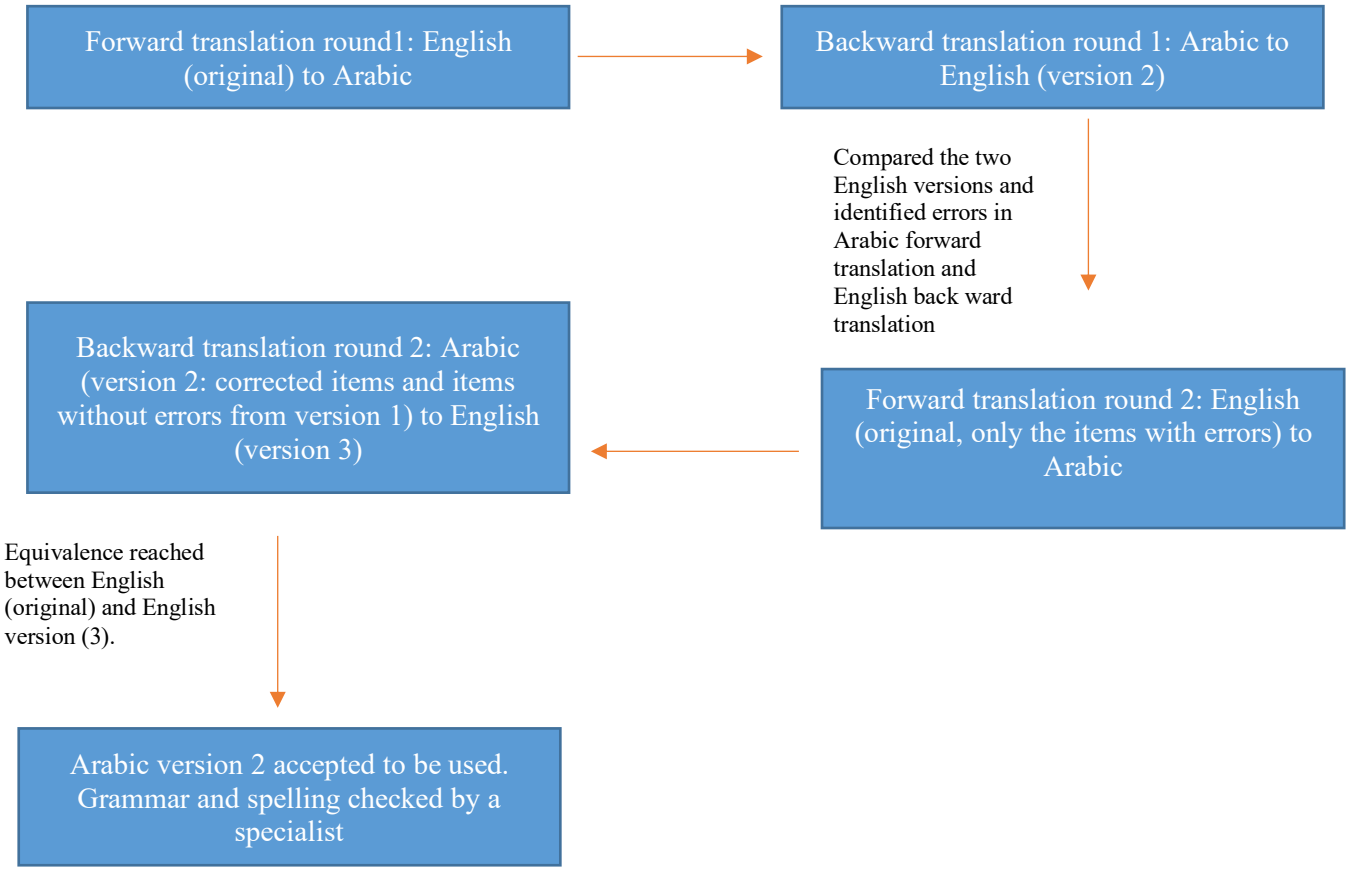


Figure 4.1: Translation process of the interview guide

Table 4.1: Comparison of the original and the backward translated English version of the interview guide (focusing on errors)

Original Interview guide in English	Back-translated interview guide (1)	Translation Error
Introduction statement: … and this includes the different forms of **delivering** medication (drug) safety information in Kuwait.	Introduction statement: … and it includes various forms of information related to the medication safety in Kuwait.	Missing word not written in the back translation. Although, the verb delivering is translated in the Arabic document, the word choice could have contributed to this error. The word refers more to presenting the information rather than delivering it. A better word that reflects the delivering meaning is present.
Item 4: Can you describe your role in the process of medication safety communications?	Item 4: Can you describe your role in the process of determining medication safety?	Error in the back translation.
Item 5: How would you know about a medication safety issue?	Item 5: Can you talk about a problem or issue related to the medication safety.	Error in the back translation.
Item 6: How would you decide on whether to communicate or not communicate the safety information?	Item 6: How can you decide on whether you want to provide information regarding the medication safety or not?	Error in Arabic Forward translation.
Item 7: On what bases would you choose the tool for medication safety communication?	Item 7: On what criteria will you choose a tool to determine the medication safety?	Error in the back translation. Although the Arabic forward translation is correct, it could be clarified; combining the Arabic translation of words in communication and tool made the sentence it a little ambiguous.
Item 8a: Do you know how it would be prepared?	Item 8a: Do you know how to prepare such drafts?	The passive voice in the original English translation and in the Arabic translation was assuming that the person does not prepare the draft and assuming that others create the draft. The English back translation used active voice, which made a slight difference. It is directly asking the interviewee whether s/he know how to prepare a draft her/himself.
Item 9a: Is there any quality control procedures for checking the draft before its final approval? E.g., pre-tested?	Item 9a: Are there any quality control procedures for checking the draft before final approval? For example, making the necessary tests in advance?	Error in the back translation, not in the question itself but in the given example.
Item 10: Marketing authorisation holders	Item 10: Marketing representatives.	Error in back translation.
Item 11: How would a draft be approved for communication?	Item 11: What required process at approve the draft to be used in determining the medicines safety?	Grammar mistakes. Error in the back translation

Item 17: After you send the safety communication, would you repeat **sending** the same information?	Item 17: After sending the information on medication safety related communications, will you repeat the same information?	Error in back translation.
Item 20: What medication safety communications have you been recently involved with following the process you have just described?	Item 20: What are the medication safety communications that you have recently participated in, and did you follow the process you just described?	Error in the back translation.
Item 23: Do you want to add any other information relevant **to this topic that we have not covered**?	Item 23: Do you want to add any other relevant information?	Missing words not written in the back translation.

Start with: My research area is about medications safety communications, and this includes the different forms of delivering medication (drug) safety information in Kuwait.

1. Ask general questions (years of experience, highest academic degree, and years of experience with medication safety).
2. To your knowledge, are there any legal requirements that influence medication safety communications in Kuwait?
3. What are the categories of medication safety communications that you deal with?
4. Can you describe your role in the process of medication safety communications?
5. How would you know about a medication safety issue?
6. How do you decide on whether to communicate or not communicate the safety information?
7. On what bases would you choose the tool for medication safety communication?
    a. Would you use more than one tool for the same information?
8. Do you usually prepare drafts for medication safety communications?
    a. What does it contain?
    b. Does it include information about the benefits of medications?
9. Is there any quality control procedures for checking the draft before its final approval?
    a. E.g., pre-tested?
10. Are there any stakeholders involved in the preparation process?
    a. E.g., patients, healthcare professionals, marketing authorisation holders.
11. How would a draft be approved for communication?
12. What is your deadline for the preparation process?
13. Who are your targeted audiences from medication safety communications?
    a. Ask about Ministry of Health departments if not mentioned.
14. How would you deliver a safety communication to these targeted audiences?
    a. Is there a deadline for the delivery process?
15. Do you have a channel for getting their feedback?
16. Would these targeted audiences be provided with training or guidance for implementation?
17. After you send the safety communication, would you repeat sending the same information?
    a. What if there was an update?
18. What would be your expected outcomes from these communications?
19. Do you monitor these outcomes?
    a. How?
20. What medication safety communications have you recently been involved with following the process you have just described?
21. To your knowledge, are safety communications developed by Kuwait Drug and Food Control publicly available?
22. From your perspective, are there any areas for improvement in the process of medication safety communications?
    a. Do you have any suggestions?
23. Do you want to add any other information relevant to this topic that we have not covered?
24. Summary.

Figure 4.2 Interview guide (phase 1: KDFC)

4.2.5 Data analysis

4.2.5.1 Document analysis: identifying and classify medication KDFC's safety-related communications

The generic names of nine medications were not reported, thus Drug Martindale and Lexicomp (Wolters Kluwer Clinical Drug Information) were used to identify their generic names (Brafield, 2019). Then, medications and the associated ADR were extracted and coded based on the Anatomical Therapeutic Chemical classification system (ATC) and MedDRA coding, respectively (MedDRA, 2019; The National Center for Biomedical Ontology, 2018; World Health Organization Collaboration Centre for Drug Statistics Methodology, 2019). About 20% of these medications and ADRs were reviewed by a supervisor (Dr Sherael Webley), no corrections were required. This is presented in Appendix 20. Then, for each type of document the relevant information was extracted using the first instrument explained in 4.2.1. Then, extracted answers were entered to SPSS 25 and descriptive quantitative analysis was conducted.

4.2.5.2 Document analysis: identify the process of creating and disseminating medications safety communications

After the extraction of the data using the code book (Appendix 21), the researcher analysed the data descriptively, i.e., by counting the frequency of the occurrence of the different codes within the different items (Boettger & Palmer, 2010).

4.2.5.3 KDFC's interviews

All three interviews were verbatim transcribed by the researcher (Appendix 22). A supervisor (Dr Fatemah AlSaleh) reviewed the transcript of one interviewee for accuracy. After this stage a framework analysis technique was applied for the interview analysis (Gale et al., 2013). The researcher uploaded the three interviews into MAXQDA to facilitate the analysis process.

After transcribing, the analysis process reading the transcripts for familiarisation. This was followed by an initial inductive open-coding of the transcripts. A supervisor (Dr Nkiruka Umaru) recoded one of the transcripts independently. This was followed by a comparison between the two coded transcripts and discussion with Dr Umaru. There was a general alignment between the two coded transcriptions, with minor difference in interpretation. This included *identifying no deadline* for the preparation and dissemination of medications safety communications as *no process in place* by Dr Umaru. This was corrected for all coded transcripts.

Following open-coding of the transcripts, the researcher adjusted the output process of the communication/persuasion model according to the coded transcripts (McGuire, 1984) (Final adjustment on framework and example from the analysis process available in Appendix 23). Then, the researcher indexed the open-ended codes to the items of this framework. After that, the researcher charted all quotations into the framework matrix, and interpreted these data into results (Gale et al, 2013).

4.3 Results

The results section of this chapter included two main sections. These sections are 4.3.1 the results of the document analysis and 4.3.2 the result of interviews with KDFC staff members.

4.3.1 Document analysis

A total of 51 documents were retrieved using the approach specified in the method section. After deduplication and applying the exclusion criteria, 29 document were included. Four of these 29 documents had multiple materials (i.e. two or more documents were attached as one). This resulted in 36, which were reduced to 33 after deduplication and removing an applying the exclusion criteria. The remaining documents were utilised for objective 1: identify the process of creating and disseminating medications safety communications. Of these documents, only 21 were medication safety communications. Figure 4.3 illustrates the process of the documents' inclusion and exclusion

The results of the document analysis have two sections representing each objective of this study. Results related to the first objective (identifying the process of creating and disseminating medications safety communications) is presented in 4.3.1.1. This explored the source of initial information to KDFC, the actions taken in response to the safety information, channels and tools used by KDFC to deliver medication safety information, receivers of safety communications sent by KDFC and involvement of stakeholders. The second objective (identifying and classify medication KDFC's safety-related communication) is presented in 4.3.1.2. This included the types of medication safety communications disseminated by the KDFC, format of the communications**,** information included in the communications and ADRs Involved.

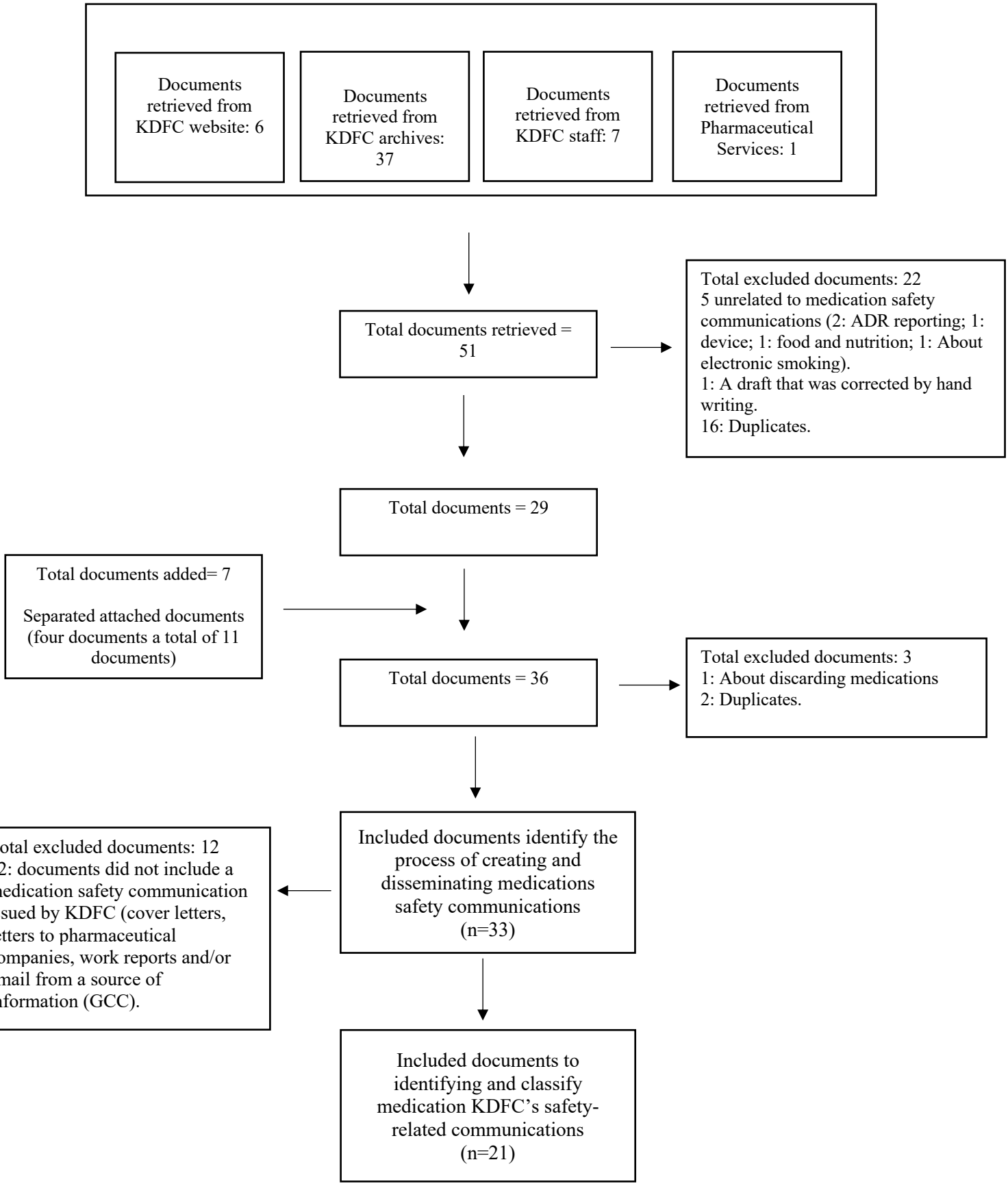


Figure 4.3: The process of the documents' inclusion and exclusion from the analysis

4.3.1.1 Identifying the process of creating and disseminating medications safety communications

4.3.1.1.1 The source of initial information to KDFC

A total of 25 (75.8%) documents included a source of the medication safety information. The majority of these documents (n=17, 68%) reported international sources (this included US FDA in 13 documents, EMA in 9 documents, MHRA in 7 documents, 2 WHO newsletters; one document could include more than one source). This was followed by the MAH in Kuwait (20%, n=5); in one of these, KDFC contacted the MAH to confirm whether they issued a warning or not. The Executive Office of the Gulf Cooperation Council of Health Ministries for the Cooperation Council Countries was also identified as a source of the medication safety information (16%, n=4). Three of the documents included United Arab Emirates Ministry of Health and Prevention being informed by their local MAH. Media or social media were identified in two documents (8%). Whereas one document had specified rumours (4%), and one (4%) specified a KDFC meeting with a special commission, but did not specify this commission.

4.3.1.1.2 Actions taken in response to the safety information

KDFC's Decisions on whether an action was required by KDFC were specified in 26 documents (78.8%). Of these documents, the most reported action was informing HCPs about the information, which was reported in 17 (65.4%) documents. Details of KDFC decision on actions are reported in Table 4.2.

Table 4.2: The details of KDFC's action in response to a safety information

Type of action	Number of documents
No action was required[1]	1
Risk minimisation measure by KDFC to HCPs (checklist/ prescribing guide/ added conditions for prescribing and monitoring)	3
Required pharmaceutical company to change label/ insert/leaflet/ patient guide	2
Asked for education workshops to be conducted with pharmaceutical companies	1
KDFC informed/ cautioned pharmaceutical company about the issue or any consequences or asked the pharmaceutical company whether they have applied or will apply the changes	2
KDFC withdrew the product (withdrawal from the market)	2
Suspension of the medication (suspension of the registration of the product, no mention withdrawal from the market)	1
KDFC asked patients to stop using the medication of concern and to contact their treating physicians for alternatives	2
KDFC asked pharmaceutical companies to send dear healthcare professional/ or approved pharmaceutical companies' letter.	2
KDFC assured following-up with the drug safety update from international agencies	6
KDFC informed HCPs about the information	17
KDFC issued advise, warned or clarified information to the public	2

[1]The product found to be not registered in Kuwait. **KDFC**: Kuwait Drug and Food Control. **HCP**: Healthcare professionals.

4.3.1.1.3 Channels and tools used by KDFC to deliver medication safety information

The channels used by KDFC for delivering medication-related information was identified from 23 (69.7%) documents. These included press release (n=5), fax (n=1), social media (n=5), KDFC website (n=5). These documents also included tools for delivering the medication safety information, these included DHCP by the KDFC (n=12), included in KuFDA newsletter (n=4), DHCP by MAH (n=2), workshops/lectures by KDFC and MAH (n=1), update included in drug leaflet/ package insert (n=2), or included in the patient guide (n=1).

A total of seven safety communications included one or more SGLT-2 inhibitors. Six of these communications were DHCP letters and one was a KuFDA newsletter. Ketoacidosis was reported in communications (all were DHCP letters); and, Urosepsis and pyelonephritis were reported in

three DHCP letters; bone fracture and decreased bone mineral in two DHCPs, and leg and foot amputations); while the KuFDA newsletter included a different safety issue (rare occurrence of serious infection [necrotizing fasciitis of the perineum] of the genital area). Azithromycin-containing products were included in three KUFDA newsletters. Two consecutive KuFDA newsletters (no 4 2018 and no 5 2018) included the same safety issue (Increased risk of cancer relapse and death with long-term use of azithromycin with donor stem cell transplant), while the third KuFDA newsletter included different information. Amphotericin B repeated in DHCP and KUFDA newsletter (potential confusion of formulation leads to fatalities). The details of the repeated safety issues are presented in Table 4.3.

Table 4.3: Medications that occurred in one or more of the KDFC's medication safety communications

Common medications /therapeutic group	**Type of communication**	**Name of the medication included in each communication**	**Reported safety issue**
Amphotericin B	DHCP letter	Fungizone (non –lipid- based formulation of amphotericin B)	Administration of fungizone instead of lipid-based formulations of Amphotericin B leading to fatal adverse reaction (overdose due to medication error)
	KuFDA newsletter no 4, 2018	Amphotericin B containing products [Fungizone, Amphotec, Abelcet, Ambisome]	Risk of potentially fatal adverse reaction if formulations confused.
Azithromycin containing products	KuFDA newsletter May 2016	Azithromycin containing products	Hypersensitivity: Drug Reaction with Eosinophilia and systemic symptom (DRESS). Angioedema Anaphylaxis Stevens-Johnson syndrome Toxic epidermal necrolysis Fatalities
	KuFDA newsletter no 4, 2018	Azithromycin containing products	Increased risk of cancer relapse and death with long term use of azithromycin with donor stem cell transplant.
	KuFDA newsletter no 5, 2018	Azithromycin containing products	Increased risk of cancer relapse and death with long term use of azithromycin with donor stem cell transplant.
All Ceftriaxone containing injections.	DHCP	Ceftriaxone injection	Anaphylactic shock Others included precipitation of ceftriaxone if administered with calcium at certain situation (but this is not the reason form the communication).
	KuFDA no 5, 2018	All Ceftriaxone containing injections.	Hypersensitivity reactions (anaphylactic shock)
Fluoroquinolone	DHCP	Fluoroquinolone (levofloxacin, ciprofloxacin, moxifloxacin,	Systemic: Hypoglycaemia, also reported hyperglycaemia depending on the fluoroquinolone class. Systemic: Psychiatric adverse reaction

		norfloxacin, ofloxacin and gemifloxacin)	Systemic: Grouped as mental health/CNS side effects: Agitation, nervousness, memory impairment, disturbances in attention , disorientation Systemic or inhalation: Aortic aneurysm and dissection Systemic or inhalation: Long lasting side effects involving bones, muscles, tendons and the nervous system.
	KuFDA newsletter no 4, 2018	Fluoroquinolone containing products	Coma from hypoglycaemia Blood sugar disturbances. Mental adverse effects, such as disturbance in attention, disorientation, agitation.
Metformin containing medicines	DHCP	Metformin containing medicines	For patients of GFR < 30ml/min: lactic acidosis. Still contra-indicated if the other active substance in a combination contains metformin contra-indicates its use (e.g. ebymect, xigduo, vokanamet, synjardy)
	KuFDA June, 2016	Xigduo [dabagliflozin and metformin HCL extended-release], Metformin HCL	Metformin associated lactic acidosis. Dapagliflozin causes acute kidney injury and impairment in renal function. Drug interaction: carbonic anhydrase inhibitors; cationic drugs, e.g. cimetidine), alcohol.
SGLT-2 inhibitors	DHCP Letters 5/10/2016	Canagliflozin Dapagliflozin Xigduo (metformin/dapagliflozin)	Diabetic Ketoacidosis Urosepsis and pyelonephritis Kidney injury Additional for canagliflozin: bone fracture and decreased bone mineral density Additional for canagliflozin: leg and foot amputations
	30/06/2015	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin[unregistered].	Diabetic Ketoacidosis
	15/06/2016	Canagliflozin Dapagliflozin	Acute Kidney Injury
	Not clear	Medicines containing empagliflozin (jardiance tablets and synjardy)	Diabetic Ketoacidosis Urosepsis and pyelonephritis
	4/08/2016	Canagliflozin Dapagliflozin	Diabetic Ketoacidosis Urosepsis and pyelonephritis Kidney injury

			Additional for canagliflozin: bone fracture and decreased bone mineral density Additional for canagliflozin: leg and foot amputations
	KuFDA newsletter no 4, 2018	SGLT2 inhibitors containing products: Canagliflozin [Invokana, Vokanamet). Dapagliflozin (Xidgudo XR, Forxiga). Empagliflozin (Synjardy, Jardiance)	Rare occurrence of serious infection (necrotizing fasciitis of the perineum) of the genital area

DHCP: Dear Healthcare professional; **SGLT-2**: Sodium-glucose cotransporter 2

4.3.1.1.4 Receivers of safety communications sent by KDFC

A total of 26 (78.8%) documents indicated the intended receivers of the documents. Although HCPs were the most frequently identified as intended receivers (n=15, 57.7%), none of the documents were sent directly to an HCP at the ground level. The details of the receivers are presented in Table 4.4.

Table 4.4: Details of the receivers of KDFC's safety communications

Receiver	Number of documents
Director of health area	4
Director of governmental hospital	4
Director pharmaceutical services at MOH	7
Director Health promotion department/ health awareness departments at MOH	2
Public	5
Chairman of the Council of Medical Departments (one related to ADR reporting).	5
Chairman of paediatric departments council	1
Head of pharmaceutical service office in a health area (in specific health area)	1
Chairman of diabetes specialised centre	2
HCPs as intended receivers (the letter stated dear HCP)	15
Kuwait Oil Company-related hospital	3

4.3.1.1.5 Involvement of stakeholders

Stakeholder involvement were only reported in one document to be involved in the development or approval of medications safety communications. These included physicians from the council of the medical department who attended meeting related to SGLT-2 inhibitor safety issues.

4.3.1.2 Identifying and classifying medication KDFC's safety-related communications

4.3.1.2.1 Types of medication safety communications disseminated by the KDFC

Three types of communications were created by KDFC: KuFDA newsletter (n=4) (Example: Appendix 24), Dear Healthcare Professionals (DHCPs) communications (n=12) (Example Appendix 25) , and communications to the public through the media (n=5). Each DHCPs and communications to the public involved one medication/therapeutic class of medications. However, KuFDA newsletter included a total of 38 medications. Thus, the total number of communications sent by KDFC by the number of medications involved were 55. The DHCPs were titled as "Urgent drug safety communication" in two letters (related to valproic acid and teratogenicity, and amphotericin B medication- related errors), "Drug safety communication" in eight letters, "Safety notification" in one letter, and did not include any title in one letter. Out of the 38 communications reported in the KuFDA newsletter, 27(71.1%) were created due to label/leaflet changes and updates, 2 (5.3%) were reminders, 8 to report updates from MHRA (n=2, 5.3%), EMA (n=2, 5.3%), or US FDA (n=4, 10.5%), and one (2.6%) communication was created due to both label changes and update from MHRA. Among the five communications aimed to the public, 2 (40%) were due to medications recall, 1 (20%) was due medication suspension, 1 (20%) was a response to a rumour (KDFC announced to the public that, contrary to social network rumours, no warnings or withdrawals for One-Alpha (alfacalcidol) were issued), and 1 (20%) was warning from an abuse to an unregistered product (the product name was Red Juice claimed for weight loss).

4.3.1.2.2 Format of the communications

A total of 21 documents were identified to be safety communications disseminated by the KDFC. These documents included 55 medications that were classified to ten ATC first level classes (Table 4.5).

Table 4.5: Anatomical Therapeutic Chemical (ATC) classifications of the identified medications

		Type of communication			Total	Medications/group of medications involved
		Public announcements	DHCP letter	KuFDA newsletter		
ATC class	Alimentary tract and metabolism	3	6	3	12	(1) Canagliflozin, Dapagliflozin, and Xigduo (metformin/dapagliflozin); (2) metformin containing medications; (3) SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin); (4) canagliflozin and dapagliflozin; (5) medications containing empagliflozin; (6) canagliflozin and dapagliflozin;(7) One-Alpha (alfacalcidol); (8) Reductil (sibutramine); (9) Avandia (rosiglitazone); (10) Xigduo (metformin/dapagliflozin) and metformin; (11) Dapagliflozin; (12) SGLT2 inhibitors containing products (Canagliflozin, Dapagliflozin and Empagliflozin).
	Blood & Blood forming organs	0	0	3	3	(1) Hydroxyethylstarch solution containing products; (2) Eltrombopag; (3) Rivaroxaban.
	Cardiovascular system	0	0	5	5	(1) Rosuvastatin; (2) Macitentan; (3) Doxazosin; (4) Nitroglycerin; (5) Valsartan containing medications.
	Genito urinary system & sex hormones	1	0	1	2	(1) Diane 35 and Daphne; (2) Medroxyprogesterone-acetate.
	Systemic hormonal preparations, excluding sex hormones & insulins	1	0	0	1	(1) Red Juice (unlicensed steroids).
	Anti-infective for systemic use	0	4	12	16	(1) Fluoroquinolone (levofloxacin, ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin and gemifloxacin); (2) Daclatasvir, Sofosbuvir/velpatasvir,Ledipasvir/sofosbuvir, Sofosbuvir, Dasabuvir, Ombitasvir/ paritaprevir/ritonavir and Elbasvir/grazoprevir; (3) Fungizone (non –lipid- based formulation of

						amphotericin B); (4) Ceftriaxone injection; (5) Azithromycin; (6) Viekirax (ombitasvir, paritaprevir & ritonavir); (7) Dolutegravir (8) Piperacillin and Tazobactam injection; (9) Tamiflu powder for oral suspension (Oseltamivir); (10) Darunavir; (11) Fluoroquinolone containing products; (12) Amphotericin B containing products; (13) Azithromycin containing products; (14) Azithromycin containing products; (15) Ritonavir-containing products; (16) Ceftriaxone containing injections.
	Antineoplastic & immunomodulating agents	0	0	8	8	(1) Neupogen (Filgrastim); (2) Ibrutinib; (3) Everolimus; (4) Bendamustine; (5) Adalimumab; (6) Leuprolide acetate for depot suspension; (7) Regorafenib; (8) Aubagio (teriflunomide).
	Musculoskeletal system	0	0	1	1	(1) Ibuprofen syrup.
	Nervous system	0	2	4	5	(1) Sodium valproate, Valproic acid and Valproate semi-sodium (Depakine and Generics); (2) Quetiapine Fumarate; (3) Bupropion; (4) Phenytoin injection; (5) Vigabatrin; (6) benzocaine (gels and liquids).
	Respiratory system	0	0	1	1	(1) Xyzal, Glencet (Levocetirizine).
Total		5	12	38	55	-

ATC: Anatomical Therapeutic Chemical; **DHCP**: Dear Healthcare Professional; **SGLT-2**: sodium-glucose cotransporter 2

The most common class was Anti-infective for systematic use (29.1%) followed by Alimentary tract and metabolism (21.8%). Only one communication (1.8%) specified genders (DHCP related to the use of valproic acid in females). Similarly, age was only specified in few communications (n=5, 9.1%). These included neonates in two ceftriaxone/calcium-related communications (DHCP & KuFDA), infants and children in one ceftriaxone/calcium-related communication, children less than three years in one communication related to Darunavir, and children less than two years in a communication related to benzocaine (gels and liquids).

Most of the issues related to the identified medications were communicated through KuFDA newsletter (69.1%) and only 9.1% were public communications (through press-release). Most of the communications were delivered in English (90.9%). Only 5.5% (n=3) and 3.6%(n=2) of these communications were delivered in Arabic or Both Arabic and English, respectively. All the five communications that were in Arabic (Red Juice, Reductil [sibutramine]; Avandia [rosiglitazone]; or Both Arabic and English (One-Alpha [alfacalcidol]; Diane 35 and Daphne [Cyproterone and Ehinylestradiol (ethinyl estradio)]) were aimed to the public.

Medications in the included communications were commonly referred to by both the generic and brand names (69.1%, n=38), followed by their brand (16.4%, n=9) or generic names (10.9%, n=6); and one communication (1.8%) used the therapeutic group in referring to the medications of concern.

4.3.1.2.3 Information included in the communications

More than half of the communications (60%, n= 33) reported the name of the pharmaceutical companies, while 40% (n= 22) did not. Only three communications (5.5%) included the name of the person responsible for the communication. All three were those aimed to the public. The source of the original information was clearly mentioned in 24 (43.6%) of the communications. The reported sources common of safety information were US FDA (23.6%, n=13), EMA (16.4%, n=9), MHRA (14.5%, n=8), meeting of commission (1.8%, n=1) and social network (1.8%, n=1 [single communications could have one or more sources]).

About 58.2% (n=32) of the communications did not include the indications of the medications of concern; while 41.8% (n=23) reported the indications. None of the included communications (0.0%, n=0) reported quantitative information on the efficacies of the medications of concern. The scientific justification for the communication was only reported by 21.8% (n=12); 63.6% (n=35) did not report any scientific justification, whereas 14.5% (n=8) included justification for certain parts of the communication.

Almost all the included communications (89.1%, n=49) described the adverse drug reactions of concerns (7.3% (n=4) not applicable; 3.6% (n=2) no). However, 14.5% (n=8) had provided quantitative information on the reported ADRs, 10.9% (n=6) had provided quantitative information only for certain parts of the communication (this was not applicable for four (7.3%) communications). About 63.6% (n= 35) of the communications described specific recommendations, 12.7% (n=7) described recommendations for certain parts of the communication and 23.6 % (n=13; does not sum to 100% due to rounding-up) did not include any recommendations. About 36.4% (n=20) of the communications listed references or additional links. A total of twelve items were included as attachments in the DHCPs communications; these attachments included HCPs guides (n= 1, 8.3%), prescriber checklists (n=1, 8.3%), risk information form (n=1, 8.3%) patient information guide (n=1, 8.3%), patient booklet (n=1, 8.3%), safety communications from EMA (n=3, 25%), or safety communications from US FDA (n=4, 33.3%).

4.3.1.2.4 Adverse Drug Reactions Involved

A total of 172 ADRs were reported in the included safety communications (Table 4.6).

Table 4.6: MedDRA classification of ADRs per type of KDFC's communications

		Type of communication			
		Public release	DHCP letter	KuFDA newsletter	Total
MedDRA class	Blood & lymphatic system disorders	0	1	2	3
	Cardiac disorders	2	0	6	8
	Congenital, familial & genetic disorders	0	2	0	2
	Eye disorders	0	0	2	2
	Gastrointestinal disorders	0	0	7	7
	General disorders & administration site conditions	0	1	16	17
	Hepatobiliary disorders	0	0	3	3
	Immune systems disorders	0	0	16	16
	Infections & infestations	0	3	4	7
	Injury, poisoning & procedural completions	1	3	8	12
	Investigations	0	2	7	9
	Metabolism & nutrition disorders	0	7	4	11
	Musculoskeletal & connective tissue disorders	0	1	3	4
	Neoplasm, benign, malignant & unspecified (including cysts & polyps)	0	0	1	1
	Nervous system disorders	0	2	13	15
	Pregnancy, puerperium & perinatal conditions	0	0	1	1
	Product issues	0	0	1	1
	Psychiatric disorders	0	3	14	17
	Renal & urinary disorders	0	6	3	9
	Reproductive system & breast disorders	0	0	1	1
	Respiratory, thoracic & mediastinal disorders	0	0	4	4
	Skin & subcutaneous tissue disorders	0	0	7	7
	Social circumstances	0	0	1	1
	Surgical & medical procedures	0	2	0	2
	Vascular disorders	1	3	8	12
	Total	4	36	132	172

ADR: Adverse Drug Reaction; **KDFC**: Kuwait Drug and Food Control; **MedDRA**: Medical Dictionary for Regulatory Activities; **DHCP**: Dear Healthcare professional

Most of these ADRs were communicated through (n=132, 76.7%) KuFDA newsletter. Most of the ADRs were related to general disorders and administration site conditions (n=17, 9.9%) or to psychiatric disorders (n=17, 9.9%). None of the communicated ADRs were related to ear and labyrinth disorders or endocrine disorders.

The previous section (4.3.1) presented the results of the document analysis. The following section (4.3.2) presents the results of the framework analysis of three interviews conducted with KDFC staff members involved in pharmacovigilance activities.

4.3.2 Framework analysis of interviews conducted with staff members involved in the pharmacovigilance in KDFC

A total of three individuals participated in the interviews. These included two staff members of the pharmacovigilance unit (PV unit), who were responsible for conducting pharmacovigilance activities in KDFC. The third participant was a superior employee whose responsibility was overseeing the PV unit's activities, as well as other units' activities within KDFC. All participants were pharmacists, with a highest academic degree being a bachelor's degree in pharmacy or clinical pharmacy. This section presented the results of framework analysis of the interview transcripts. The framework matrix was presented as a total of three themes and 19 subthemes. Table 4.7 Presents these themes and subthemes.

Table 4.7: Themes and subthemes resulting from KDFC's framework analysis

Themes	Subthemes
Defining Pharmacovigilance unit within KDFC	The establishment of the Pharmacovigilance Unit (PV unit)
	Legal frameworks and guidelines underlying PV unit's activities
	Communications within KDFC and MOH administrations
	Communications with pharmaceutical companies
	Communications with healthcare professionals
The process of creating medication safety communications	Accessing information
	Assessing information
	Actions selection in response to the information
	Drafting a medication safety communication
	Quality control of the prepared communication
	The expected outcomes of medication safety communications
Dissemination and post-dissemination activities of medication safety communications	Delivering medication safety communications to the intended receivers
	The possibility of receiving feedback from the intended receivers
	Providing training to HCP for implementing the recommendations
	Monitoring the implementation of the delivered communications
	Storage of medications safety communications and their availability to the public
	Resending a medication safety information
	Examples of previous safety communications from the participants
	Suggestions for improvement

4.3.2.1 Defining Pharmacovigilance unit within KDFC

The participants explained the pharmacovigilance unit (a unit in KDFC) in terms of its establishment, legal frameworks and guidelines underpinning this unit, and its communication responsibilities, including communication within KDFC and MOH administrations, communication with pharmaceutical companies and communications with HCPs.

4.3.2.1.1 The establishment of the Pharmacovigilance Unit (PV unit)

The PV unit was described as a small unit within the drug registration department that is responsible for pharmacovigilance activities. Recent changes relating to this unit were also described. The changes involved the name of the unit, the scope of its work, its interaction with other parties, and an awareness of pharmacovigilance guidelines and the concept of medication safety among the staff. These changes were attributed by one participant to two reasons, the influence of international interest in post-market drug data, and the recognised importance of efficacy and safety of drugs in the post-market phase. A change in the name of this unit from quality assurance to the current name pharmacovigilance unit was also reported. Another form of reported changes involved specifying the scope of work as this unit currently has more specified work related to the efficacy and safety of registered products in Kuwait. The changes to the PV unit were described by one participant as follows:

> *"I started working here the the name of this department was quality assurance and then after that recently we we are starting to change the the title of the unit for pharmacovigilance department or unit okay because internationally there is a huge interest in the pharmacovigilance and safety efficacy of the medications post-marketing and also ... there is an an importance so our work now more specified for the safety and the efficacy of the registered products in Kuwait"* (Participant 1).

Other described changes relating to this unit included their increased interactions with people outside the KDFC. These included increased interactions with HCPs, as well as increased interactions with other health authorities in Kuwait.

Besides the establishment and the changes that occurred to the PV unit, a discussion was undertaken about legal frameworks and pharmacovigilance guidelines underpinning the PV unit activities.

4.3.2.1.2 Legal frameworks and guidelines underlying PV unit's activities

The participants differed on whether they follow a legal framework unpenning pharmacovigilance activity, but agreed that a Kuwaiti PV guideline is currently under development. One participant indicated that the PV unit follows the legal framework of registration and following up on the registered products. Another participant, however, indicated that there is no law underpinning pharmacovigilance activities but there is a law for ethics which they are following as described in the following excerpts:

> *"I don't know ... I don't think there is law for this but for its ethics for it points we we are already committed or it's a like some... as I know it's no laws for this for ... laws by by exactly law I don't know for this"* (Participant 2).

Unlike the legal framework, all participants agreed that currently there is no local Kuwaiti pharmacovigilance guideline. Two participants reported following the Guideline for Good Pharmacovigilance Practices for Arab Countries, which was described as the common guideline for the Arab region. However, a third participant indicted that the Arab pharmacovigilance guideline was utilised in drafting the Kuwaiti pharmacovigilance guideline as follows:

> *"but we don't have now an a legal ministerial decree or guidelines up till now for pharmacovigilance in Kuwait although we drafted already a guideline aa the pharmacovigilance task force drafted a new guideline which is a compline guideline adopted from the Arab guidelines it's now under review and we hope that it would be*

published soon" (Participant 3).

Some characteristics of the Arab guideline were provided by one participant including that this guideline was adapted from EMA's guidelines, this guideline is concerned with medication efficacy and safety, it included information about pharmacovigilance documents (ICSRs, PSURs) and about medication safety communications (e.g., tools for communications including DHCPs, news and journals). Based on this guideline, the pharmacovigilance task force drafted a guideline specifically for Kuwait. Although it was stated that this guideline "*will be published soon"*, no specific timeline was provided for its completion.

Communication responsibilities overseen by the PV unit staff members were also reported. One form of these responsibilities is communicating with KDFC's departments and MOH administrations.

4.3.2.1.3 Communications within KDFC and MOH administrations

One of the described responsibilities of the PV unit is to communicate with other KDFC staff members and departments regarding the safety of their products or to answer their queries. In addition, the KDFC communicates with other MOH administration. According to one participant, communication with other staff members occur after the PV unit staff member check for the safety of the other department's products including food, supplements, cosmetic products and other types of products and other products, as explained by the participant:

> *"I'm saying medicine but I don't mean only pharmaceutical products okay as I told you before I'm I'm checking all the cosmetic products all the food supplements special foods which include for example baby baby milk okay special formulations like Red Bull like this we also check these products if there is any problem in the safety my work is to inform other departments here okay to for example there is alert there is new information regarding this product or something and they will do their work okay"* (Participant 1).

In case of the occurrence of a safety issue related to products that are not medicinal, the participant explained that the PV staff will contact the relevant department. This is to inform them about the new safety issue, ask them about the registration status of the product in Kuwait, and what action they plan to take. The execution of this plan, however, will be performed by the PV unit staff member as reported:

> *"but for example if there is medicinal for food supplements okay I will send the information or a letter to the department the food department that this product there is a recall for example for some batch or something okay and please inform me if it's registered in Kuwait or if this batch arrived to Kuwait and what the action that you will take they gonna tell me if this product should be recalled or we didn't receive this batch it didn't enter Kuwait okay so I I will inform them at the beginning they will tell me what to to do and then the action will be from me I will aa contact the company to tell tell them that they have for example to recall to make a leaflet update or something and then I will tell other regulatory departments for example inspection department central score central medical stores like this"* (Participant 1).

Other responsibilities of the staff members of the PV unit are answering queries related to the active ingredients of the product, which could be asked by other KDFC employees. On the other hand, the PV unit communicates with other MOH administrations, such as the Inspection Administration and CMS (Central Medical Stores) for information exchange

Besides communications within the KDFC and MOH administrations, the PV unit have the responsibility to communicate with pharmaceutical companies.

4.3.2.1.4 Communications with pharmaceutical companies

The participants discussed situations in which they communicated with pharmaceutical companies, their responsibility in evaluating pharmaceutical companies' decision to voluntarily recall medications, and obligations posted on the pharmaceutical companies to seek the PV unit's approvals before updating or disseminating any materials.

Communication with pharmaceutical companies would be initiated in medication safety updates or medication recalls. Based on emergent medication safety information, the participants stated that the pharmacovigilance unit could request that the company, through official letters from KDFC's administration, update their patient information leaflet (PIL) or SMPC, and send DHCP letters to HCPs, as quoted:

> *"we can ask f request for any safety updates for the PIL from the company regarding this aa a communication a from the aa FDA or like this"* (Participant 2).

> *"we issue letters to the manufacturers and the marketing authorisation holders asking them for example to disseminate dear doctor letters by themself or to update their PIL or SMPC"* (Participant 3).

A participant explained what changes the PV unit could ask pharmaceutical companies to make. These changes included clarifications and additions of phrases relating to warnings, precautions, restrictions, or contraindications. All participants reported at least one form of PV unit's responsibility in evaluating materials developed by the pharmaceutical companies or decisions made by the pharmaceutical companies. An example of the latter was provided by one participant, which included assessing pharmaceutical companies' voluntary recalls of medications. One participant indicated that pharmaceutical companies are required to submit their Risk Management Plan. On the other hand, two participants stated that pharmaceutical companies are obligated to get this unit's approval before disseminating risk minimisation tools, such as DHCPs, educational materials, patient consent forms, and patients guides, as described:

> *"by the way any anything should be published from the company should take approval from us first they will send me the copy okay I will study it and check that everything is need I need is included in the paper and then they will take approval also if there is a promotional material or something for the patient patient guide patient card everything should be approval approved from our department first okay so make sure that if the company is publishing anything it should be approved from us first" (Participant 1).*

Besides written materials, one participant stated that pharmaceutical companies should seek the KDFC's approval before launching disease management applications for patients, although not necessarily from the PV unit specifically.

> *"not only the written to be honest there is sometimes there is an application for it to be used by the patient for example the the patient who is taking insulin or something there is some applications to enter the dose the the everything have to be approved but maybe from not the PV the other departments pharmaceutical or something but I mean from the food food and drug control"* (Participant 1).

In addition to their responsibilities that require communications with other departments within KDFC and pharmaceutical companies, the PV unit also communicates with HCPs from clinical practices.

4.3.2.1.5 Communications with healthcare professionals

Two participants reported communicating with HCPs through conducting lectures by KDFC, with the emphasis on the role of the head of the department and superintendent in conducting these lectures. The PV unit is also responsible for conducting lectures to physicians and pharmacists to educate them about reporting ADRs directly to the PV unit, not necessarily through a pharmaceutical company. This was explained by one participant as follows:

> *"not us [the head of the department] sometimes make a lecture for how to submit for individual ICSRs cases how to the importance of this to to deal with us direct to the doctor to communicate us directly it's ... it's not a must to communicate us aa through the company sometimes we make this lecture but not too much"* (Participant 2).

Another participant indicated utilising these lectures to ensure future communications with HCPs by obtaining their email addresses, as quoted:

> *"okay so we are insisting on getting information from them many times in many aa presentations we took emails from healthcare providers to communicate with each other of course that's not from me only from [the head of the department and the superintendent] because they are the heads"* (Participant 1).

One of the PV unit's responsibilities is issuing medications safety communications. The issuing of medication safety communications requires different activities. Activities related to the process of creating medication safety communications are explained in 4.3.2.2.

4.3.2.2 The process of creating medication safety communications

Different activities were described different steps occurring before the dissemination of a medication safety communication. These steps were as the following: (1) accessing information, (2) assessing information and (3) action initiation, (4) drafting a medication safety communication, (5) quality control of the prepared communication, and (6) outcomes expectation of the medication's safety communications.

4.3.2.2.1 Accessing information

Generally, the three participants described two types of medication safety information the PV unit deals with. These included signals or established updates and safety communications. One participant explained the types of medication safety information they deal with as the following:

> *"all right we have the safety communications that we receive and have the safety communications that we issue any new signal or new safety communication regarding any warning any precaution any new update to the core safety data or to the a the leaflet or the summary of product characteristic the department responsible for the safety communication for drugs after marketing and pre marketing of course as well"* (Participant 3).

All participants mentioned two ways for accessing emergent safety information. These included actively searching for updates online or receiving them from other sources. Two of the participants

stated that they search for updates on medication safety daily. Similarly, a third participant indicated that a search is always conducted, without specifying who frequently. The participants mentioned multiple sources which are utilised in the PV unit for learning about emergent medication safety information. Sources that were mentioned by all participants included international drug authorities, pharmaceutical companies, and hospitals or HCPs in Kuwait. Examples of international drug authorities included EMA, US FDA and UK MHRA. Moreover, all participants had either mentioned the WHO or the Upsala Monitoring Centre as other international sources of medication safety information. Furthermore, two participants mentioned the GCC; and one of them mentioned the Saudi FDA and the United Arab Emiratis as other sources. The utilised sources were reported as follows:

> *"this we receive also from the international authorities and we make our own homework is that we always check the international authorities and a we we have also relations with Upsala and with other am international aa health care aa authorities to make sure aa that we we receive the updated safety information"* (Participant 3).

> *"I have many sources I have from the other international health authorities okay like EMA US FDA MHRA okay aa Saudi FDA Emirates okay from the meetings okay some here in the [Arabian gulf, i.e., GCC] okay they are doing meetings regular meetings together to discuss the situation of some products the safety and usually they are taking general decisions okay which will will be applied in all the countries okay this is the main main source"* (Participant 1).

The participants also reported receiving reports from hospitals in Kuwait, whether from the governmental or the private sectors, that are received through KDFC's ADR online reporting system or faxes. One participant noted an increase in the number of reports received by the PV unit as explained in the following quote:

> *"I get yearly 50 for example 50 reports or something now no last year we received more than 1000 1000 or something okay and this year no we exceed this number I I am receiving it from the companies some individual cases some doctors are contacting [the head of*

> *department] [superintendent] and sending faxes okay regarding special adverse event they can see or something so I feel that there is a a big increase in the awareness of the importance of PV work"* (Participant 1).

All participants reported pharmaceutical companies as a source of medication safety information. Examples of types of information received by pharmaceutical companies included ICSRs and PSURs. One participant indicated that these companies are the main source of ICSRs. Two participants reported that companies are obligated to submit PSURs based on the Arab pharmacovigilance guideline. According to one participant, companies are expected to submit PSURs during a defined period even if they included non-serious or incomplete information. On the other hand, ICSRs is anticipated by one participant to be submitted to the PV unit within 90 calendar days in none serious cases, and 15 calendar days in serious cases. In serious cases pharmaceutical companies are expected to inform the PV unit regardless of the product registration status, as explained by one participant in the following excerpts:

> *"by the way its obligatory if there is any adverse event serious adverse event they have to submit it to us within 15 days it is obligation okay it is international obligation okay especially inside Kuwait but if it is outside they have to inform us but there will be no regulations" (Participant 1).*

Although none of the participants stated that they previously received safety reports from patients, one indicated that patients could also submit ADR reports through KDFC's website.

After knowing about medication safety information, the PV unit staff members assess this information.

4.3.2.2.2 Assessing information

Assessing the received information was reported by all participants. Regarding information received through their ADR reporting system, one participant reported causality assessments are conducted, which result in conclusions regarding the reports. Another participant added that ICSRs

are entered into a database system within the PV unit for later checking whether they match the rate specified in the medication leaflet or not. If the rate differs from the rate specified in the leaflet, an action would be initiated by the PV unit as explained in the following quote:

> *"we are doing a signal detection we are counting the rates of the cases because sometimes as I told you it's listed but it's listed that it's rare okay but regarding the population and the number of cases no it's not it's it shouldn't be rare rare it have to be increased the seriousness of the seriousness of the case should to be increased sometimes we communicate with the company if the cases is not a complete for example or it needs a follow up we need a follow up report or something yeah we are taking action in some cases and most of the cases are kept in our aa documents okay to to check the rate of the cases"* (Participant 1).

The participants mentioned various processes by which emergent safety information is evaluated for whether to be communicated or not. A commonly described approach involved checking the seriousness of the case. However, no specific criteria were in place to evaluate the seriousness of the case. For one participant, everything is considered serious at the beginning until the participant finds that the new information was already listed, as the participant explained:

> *"for me at the beginning all everything is serous okay until I check that no maybe it's common side effect or its already aa written in the leaflet okay but rate is is will should be increased for example it's it's rare then I found after so many ICSRs or so many safety issues I find that no it should be not not rare it should be common aa we will upgrade the seriousness of the case okay"* (Participant 1).

Besides the seriousness of the case, the evaluation process by this participant involved considering whether the PV unit took a previous action regarding the same safety issue, and whether the pharmaceutical company is taking an action regarding the emerging safety information. Another participant reported evaluating safety information on a case-by-case basis and communicating the information according to the seriousness of the case. This participant also considered whether the emergent information was previously listed or not as an indicator of the seriousness of the

information. This participant had also considered life-threatening safety issues, and information advise for monitoring as serious information that requires communication, as explained in the following quote:

> *"seriousness like is this is life threatening issue is this … is this not listed if the signal [it]is a new an new safety issue it's not listed in the PIL because if it's already listed or it's common it's okay … It's already listed or already written in the PIL so the healthcare provider knows but if a new issue if a new side effect if we have to deal we have to tell doctor we have to take care we have to if something want to make monitoring for something for liver function for kidney function for heart for like this this is a serious you know [so] it's issue we have to communicate with health care provider to to monitor for this"* (Participant 2).

Similar to the two previous approaches, a third participant considered the criticality of the case as a determining element on whether to communicate the case and which communication tools to select. On the other hand, two participants reported the decision to communicate might be taken by a committee. while one participant did not specify the nature of the committee. The second participant reported one example of a committee with the Medical Counsel (physicians not staff members in KDFC).

After assessing a medication safety information, different actions could be taken by the PV unit.

4.3.2.2.3 Actions selection in response to the information

Depending on the type of safety issue, the PV unit might take different actions, as reported by the participants. These actions are either applied by the PV unit or the pharmaceutical company. The actions could include restriction the use of the medication to a specific patient group, changing the legal status of a medicinal product, applying changes to the PIL (removing or adding information), or issuing a recall of a medication. Before the recall of a medication, the PV unit staff member checks the registration status of the medication of concern in Kuwait, as well as whether the recall was for the whole batch or a specific batch. According to two participants, decisions related to

medication recalls would not be reported in a HCPs' medication safety communication, as explained in the following quote:

> *If there is a recall or something we we don't send a DHCP what what will happen if there is a recall first I check recall for the whole range or at the batch that depends okay first of all I have to check if we received for a sample … a this batch is registered a we received it in Kuwait or not if its available in the Kuwaiti market we will inform the company that the recall should be have taken okay* (Participant 1).

The actions could also be issuing a medication safety communication, or asking the pharmaceutical company to send a DHCP letter. Different tools were mentioned by the participants through which medication safety information is communicated. These included those created and delivered by the PV unit including DHCP letters and the KuFDA newsletter, which is reported to be issued every two months to include the updates that occurred during this period. Additionally, in very few cases, the media was utilised to deliver medication safety information to the public according to one participant.

One participant reported that the tools by which they communicate the safety information depend on the criticality of the case and whether or not they perceive it should be immediately communicated. Very critical information will be communicated by KDFC, and less critical cases that need to be immediately communicated will be communicated through the pharmaceutical company in the form of DHCP letters. However, the pharmaceutical company would be asked to update their SMPC in less critical cases that do not need to be communicated immediately. This process is presented in the following quotation:

> "*if it's very critical we are as an authority we issue the dear healthcare professional letter if it's less critical we let the company do the dear doctor letter or dear healthcare professional letter and they will disseminate and come back to us confirming that the already disseminated them if it's a safety communication that it can wait a little bit we can ask the company to include it in the leaflet in the SMPC so it depends on the case and how critical it is"* (Participant 3).

Another participant indicated that the choice of the tool depends on the recommendation from the source, such as international drug regulatory agencies as described by the participant:

> *"Mainly according to the recommendation the recommendation if FDAs so usually it's writing written that it must a send dear health care letter to the providers it must make a safety update for the PIL a [so] mainly it's like this" (Participant 2).*

According to a third participant, in choosing the tool, they would consider the action of the pharmaceutical company in response to the safety issue. The participant explained if the pharmaceutical company had previously issued a warning regarding the safety information, and the case was not serious or was a routine case, the PV unit will not take further action. However, the PV unit will issue a DHCP letter if the action taken by the pharmaceutical company was perceived to be insufficient by the PV unit.

The participants also mentioned that a combination of tools could be used for certain safety communications. The purposes of using two tools for communicating the same information are presented in Table 4.8 with illustrative quotations from the participants.

Table 4.8: Using a combination of tools for medication safety communications

Purpose of the combination of tools	Illustrative quotations
To avoid delays: A PIL update could take a long time, thus a DHCP, whether from the PV unit or the pharmaceutical company, is communicated in the meantime.	*"okay aa so sometime I say that DHCP letter is the first step if there is a safety communication there should be a DHCP letter okay for for the healthcare providers after that because you know sometimes the changing in the leaflet if pack the package if there is a change in the package or something okay it takes time so but first we have to tell the healthcare providers that there is a problem in this issue okay after that the action will take time"* (Participant 1). *"as usually it's when they need PIL update leaflet update it's you know it's to to make this update it's maybe take for one year or for six months according to you know it's a submit for the file undertaking the approval [so] during this we we have to send a dear doctor letter from us or from the company to circulate to to to be the communication for the providers to leave more quickly tell we finish for the approval for the new update for the PIL [so] usually it will be both of them"* (Participant 2).
To conclude multiple safety communications: multiple safety communications for the same medication could be issued at different time points, thus one DHCP would include the summary of theses communication; if the issue is serious and multiple updates occurred to it, DHCP could be sent from KDFC, even if the pharmaceutical company had previously sent one.	*"regarding Fluroquinolone okay so we we did the same we concluded every information from this and every action we did regrading this issue in one DHCP letter and we prepared here disseminated to all healthcare healthcare providers also we published it in the newsletter" (Participant 1).*

Once a decision was made to communicate a medication safety information and a tool for this purpose was selected, the process of drafting the content of a medication safety communication would be initiated.

4.3.2.2.4 Drafting a medication safety communication

The content of a safety communication depends on the safety issue (or the case). Two participants explained the template as what is included in the safety communications, and one indicated that currently no template is used specifically to draft medication safety communications, but the participant might consult superiors (i.e. the head of department and superintendent) in drafting the communication as explained in the following quote:

> *"no template no template its we we make a draft and we can discuss with doctor [X] or doctor [Y] and after that signed for it but no… not there is no exactly template according also to the issue"* (Participant 2).

Nevertheless, all participants mentioned similar contents of a medication safety communication, which are presented in Table 4.9.

Table 4.9: The contents of KDFC's medication safety communications as described by the participants

Type of communication	Content	Illustrative quotations form the participants
DHCP	Mention the safety issue (the case), which could be precautions or contraindications. They do not contain information related to a medication recall (DHCP is not the tool used for this type of information).	*"the usual content also depends on the case if it's a dear health care professional the content will be what are what's the case what's the advice for the health care professional sometimes advice for the patient and how to report if there any problem happen you should report it to drug control at the end usually this is the template or this is how the form looks like for a dear health care professional letter"* (Participant 3). *"information which doesn't contain an action what I mean doesn't contain a recall doesn't contain cancellation it contains precautions for the use sometimes it contains contraindications if the this product is contraindicated in some cases"* (Participant 1).
	Advise/ recommendations to HCPs.	Included in the first two quotations.
	Might include the conclusion of different previous safety communications for the same product.	*"if you want you can take a copy to to know the form of template of the DHCP usually giving a short short note about the the problem okay the points which the DHCP providers the the healthcare providers should take care of okay and in this case it's a conclusion because Lemtrada has a problem from the the beginning of nine 2019 okay so this summary for what happened during the last year okay"* (Participant 1).
	Sometimes it includes advice to patients (whom will be informed by the HCPs).	Included in the first quotation.
	The source or the reference of the information (international regulatory agencies).	*"You will find the references I'm always attaching everything which is published internationally our sources is US FDA okay and EMA okay you will find everything is here this is the latest okay"* (Participant 1).
	Information on how to report an ADR	Included in the first quotation.
KuFDA newsletter	The medication name	Interviewer: you told me about the newsletter that it contains [The interviewer started reading what it contained from the participant 1 computer's screen] the medication name and you showed it to me

		[Participant 1: "ehm"] the manufacture the classes and what's the warning or the update Participant 1: yes yes and the reference a you see here [the interviewee was showing the interviewer the newsletter at the computer screen] at the end of the column you will see the the action that we take okay food and drug administration had requested DHCP letter to be circulated to the aa healthcare providers from the company.
	The manufacturer	- Included in the quotation above.
	The therapeutic class of the medication	- Included in the quotation above.
	The safety update or the warning	- Included in the quotation above.
	The reference	- Included in the quotation above.
	Action taken by KDFC (contacted pharmaceutical company to disseminate a DHCP)	- Included in the quotation above.
Both DHCPs and KuFDA newsletter/ or not specified for a certain type.	Benefits (differed among the participants): - Include the benefit if it is important to be mentioned (a statement would be added to indicate that the medication is still beneficial for certain patients, and the benefit to risk balance is positive). - They are not mentioned in the safety communications. - The risk could be mentioned in the context of its uses (i.e., it is still used for a particular indication); however, the main focus of the communication is to deliver a new information, which is the risk.	*"if if it's important to be mentioned then we can add because most probably you will have a phrase that says that some population will still benefit from the drug and that the still the risk the benefit risk balance is positive so sometimes you have this phrase that says that the product is important for a special population and that that's why we need it we're gonna keep it it will not be suspended it not be recall we're gonna keep it but with extra precautions aa like 1 2 3"* (Participant 3). *"benefits of no no no benefits we also mention the problem and aa how to aa to deal with"* (Participant 2). *"... I think that the healthcare provider knows the the advantages or the benefits of the product so there is no need to illustrate but maybe it it can be mentioned like this there is a risk of for example hyperglycaemia but it still can be used in some cases like this this this this but it's contraindicated for example for diabetic patients okay"* (Participant 1).
	The active ingredient of the product	*"Kind of information is of course the product the active ingredient the problem and the recommendation aa [the] by for the for the doctors for the patient and if if we are want to change PIL or [or]*

		planning to to ask for the company to change PIL but mainly it's advice for healthcare professional and for the patient" (Participant 2).
	The name of the product	- Included in the quotation above.
	The safety issue	- Included in the quotation above.
	The recommendation/ advise for the HCPs	- Included in the quotation above.
	The recommendation/ advise for the patients	- Included in the quotation above.
	The action that will be taken (contacted company to change the PIL).	- Included in the quotation above.

KDFC: Kuwait drug and Food Control; **ADR**: Adverse Drug Reaction; **DHCP**: Dear HealthCare Professional; **PIL**: Patient information leaflet

Two participants reported dealing with medication safety information on an urgent basis. Once they see the safety information, they would make the DHCP letter, or once they receive a DHCP letter from a company they would review it. One of the two participants estimated that they take two to three days as a deadline. According to these participants, the PV unit does not have a written guideline specifying the deadline for the preparation process, as reported in the following quotation:

> *"so far we don't have a deadline yeah but we treat it on urgent basis because we know usually it's it's it's an urgent safety communication so usually we treat it on urgent basis but we don't have a written guideline specifying timeline"* (Particpant 3).

Following the completion of a medication safety communication, the process of revising the draft for quality purposes begins.

4.3.2.2.5 Quality control of the prepared communication

The quality control procedure of KDFC's medication safety communications described by the participants included individual checks (by the person who drafted the communication) and multiple checks (including others). Two participants reported individual checks. For one participant, individual check involved revising the safety medication drafts, assuring that the information is clear, not misleading, direct, simple and easy to understand by the HCP. Another participant reported reading the draft and making sure that it has a recommendation. On the other hand, discussions and multiple checks were also described. This included the department head, superintendent, and finally, the director of the administration before it is approved for dissemination. Two participants stated that the drafts are not pretested with the intended receivers. However, one participant reported the involvement of stakeholders on one occasion. According to this participant, a meeting including the Medical Council (physicians) and KDFC was conducted regarding the safety of SGLT2 inhibitors. On that occasion, the medical council, which recommended the issuance of a DHCP letter, approved the draft before it was disseminated, as explained by the participant:

> *"maybe only once we had this case I remember it was the case of SGLT-2 inhibitors Invokana and sitagliptin and these these type of medications because it it the recommendation came from a committee and the committee had the members of the committee where head of council's medical doctors pharmacists from different specialties and that's why we drafted for them the dear healthcare professional communication and they approved it before before being disseminated but usually it's not the case usually the case is from from the drug control"* (Participant 3).

In contrast, another participant indicated that quality control procedures or approving the draft are not the responsibility of a committee. There was a shared sense (by two participants) that it is their responsibility to revise the draft, and stakeholders outside KDFC. However, one participant clarified that the final decision regarding the draft is not a one-person decision as described in the following quote:

> *"no because it's an internal work okay but it ... the the information is based on the our knowledge here and also the information which is published as I told you internationally okay it's not a single decision okay"* (Participant 1).

According to the participants, DHCPs drafted by the pharmaceutical companies are revised by the PV unit, as described in the following quote:

> *"of course if we receive it from the company requesting to disseminate it then they already have done their homework and they checked it by the quality assurance departments in their safety and medical team and then we're gona check it again because sometimes the the their draft we'll not approve it exactly we'll make some changes on it before approving it so this is like a second check..."* (Participant 3).

The PV unit staff members have expected outcomes of the revised, completed draft of the medication safety communications before its dissemination. These outcomes expectations are discussed in 4.3.2.2.6.

4.3.2.2.6 The expected outcomes of medication safety communications

All participants reported their expected outcomes of medication safety communications, which resulted in four outcome expectations. These included that HCPs: (1) would be updated with the new safety information (all participants), (2) know how to deal with the risk (one participant), (3) take the appropriate actions related to the patients' care and communicate proper guidance to the patients (two participants), and (4) and be encouraged to report ADRs that were not published in the disseminated medication safety communications (one participant). For the fourth expected outcome, the participant considered medication safety communications as an opportunity to establish a communication bridge between HCPs in clinical practices and the PV unit. The four outcome expectations are reflected in the following quotations:

> *"usually the outcome that we are expecting from this is the the the practitioners or the healthcare professionals to to to be aware first of all of the the the the risk number two to know how to deal with the risk and to deliver the proper guidance for the patient"* (Participant 3).

> *"we are trying to encourage healthcare professional by getting this information to to inform us if there is they can see any anything that not published yet"* (Participant 1).

The following theme (4.3.2.3) involves the dissemination and post-dissemination activities of medication safety communications. At the end of this theme, participants' previous examples of medication safety communications, and their suggestions for improving future medication safety communications are listed.

4.3.2.3 Dissemination and post-dissemination activities of medication safety communications

The dissemination activities were related to delivering medication safety communications to the intended receivers. Whereas the post-dissemination activities allow feedback from the intended receivers, training the intended receivers on implementing the medication safety communication, monitoring the outcomes of medication safety communications, storing medication safety communications, and resending a previously disseminated medication safety communication. At the end of this theme, examples provided by the participants of recent medication safety communications developed and/or issued by KDFC are presented. This is followed by the participants' suggestions for improving medication safety communications in Kuwait.

4.3.2.3.1 Delivering medication safety communications to the intended receivers

The participants mentioned the channels by which KDFC disseminates medication safety communications. These included faxes, emails, and by hand. Noticeably, the only mentioned case of delivering safety communication directly to a healthcare professional at the ground level was through printed copies disseminated at exhibitions that could occur once or twice yearly. One participant indicated that mainly paper-based communications are sent to the heads of health areas, hospitals and medical centres with a delivery man. Delivering medication safety communications through fax was perceived by two participants. Emails were mentioned in two cases. One participant speculated that it is sent by emails to the head of the department by the undersecretary of drug control. However, the second participant reported sending medication safety communication to private hospitals, based on their preference. This was reported in the following excerpt.

> *"for now it's a paper mainly paper work unless a some a private hospital they do prefer that we send by e-mail but so far we are a delivering like paper a document to as I told you the head of the health areas and hospitals and am medical centres"* (Participant 3).

The perceived intended receivers indicated by the participants included HCPs such as physicians, dentists, nurses and pharmacists. The participants differed, however, in terms of whether healthcare professionals in the private sector are receiving KDFC's safety communications or not.

As one participant indicated that the KDFC delivers to the private sector. However, two participants indicated that the pharmaceutical company is responsible for delivering safety communications to the private sector. It was also mentioned by one participant that KuFDA of the newsletter is sent to the head of the departments of all governmental hospitals.

The intended receivers that were mentioned by the participants also included the heads of the health areas, heads of medical centres, and pharmaceutical services department; and depending on the case, they could be delivered to the inspection department or the CMS (central medical stores). One participant stated that patients are targeted indirectly. According to this participant, they are targeted by sending the DHCP letters to their HCPs. However, another participant indicated that patients were previously targeted, although they are not the main receivers. This was stated by the participant in the following quote:

> "*Yeah and sometimes we deliver to the patients I forget to say this sometimes the the communication [will] be for the patients sometimes yeah but mainly as as as mentioned before health care professionals and different like central medical stores or inspection in some cases"* (Participant 3).

One participant indicated that the CMS and the inspection department only communicated in the case of medication recalls, and not for the DHCP letters. The same participant indicated that HCPs are not targeted for medication recalls as this matter is only related to the pharmaceutical company, KDFC and the inspection department. The participant explained that this is because the information shared with HCPs should be focused on the patients and their medication use, as illustrated by the participant:

> *"No maybe it let me remember if we send before for doctor for any recall maybe for medical device sometimes we we we in the medical in the health care doctor we we can tell doctor that some batches we we can we have to recall sometimes sometimes but not in in general we have to send to healthcare provider because this is the issue of for the company or for and for the inspection and for us doctor ...healthcare provider only I think for the anything direct with the patient for their*

> *work aa for side effect for monitoring for something for asking patient for any contraindication for medication like this (Participant 2).*

It was indicated also that communications are not sent to HCPs participating in clinical trials, however, perceived that it might be sent by the company.

The participants explained the deadline for the dissemination of medication safety communications differently. According to one participant, it would take two to three days. A second participant reported there is no specific deadline, but dissemination takes place as soon as possible. A third participant, however, specified deadlines for disseminating non-serious safety communication based on Arab pharmacovigilance guideline. The dissemination would take place within 15 days of approval, regardless of whether the information is disseminated by KDFC or the pharmaceutical company, as explained in the following quote:

> *"by the way this DHCP is should be studied as fast as we can for example if we receive it at morning at the end of the day it has be approved or not approved okay then the company is getting approval after getting approval within 15 days they have to be disseminated okay for us also it's the same because if there is anything aa DHCP at the same day I get approval from up after signature and sending within 15 days it will be send it to to the healthcare providers"* (Participant 1).

According to the same participant, the dissemination will be more urgent in serious cases, as described by the participant:

> *"At the same time if it serous at the same time because sometimes for example there is action has been taken regarding a product for example Lemtrada there was a problem between these days these two months or something about this product okay Lemtrada because they did a study and they found that there is the the the risk assessment is negative the the uses of this product is is not useful okay so what we are making here the decision we are cancelling the we are cancelling this product regarding this issue this is an urgent issue okay so we prepare all the papers at the*

> *same time we get approval and then we disseminate it all over the people that we know so its regarding the seriousness of the case"* (Participant 1).

The possibility of receiving feedback from the intended receivers after the dissemination of a medication safety communication is presented in 4.3.2.3.2.

4.3.2.3.2 The possibility of receiving feedback from the intended receivers

All participants indicated a form of communication between HCPs and the PV unit after the dissemination of a medication safety communication. Two participants reported direct communication from the HCP, as HCPs, could send questions, feedback, and report ADRs. While, all participants stated an indirect form of communication, which involved confirmation for receiving the disseminated medication safety communication. Two participants indicated that HCPs could send their feedback through KDFC's online website or KDFC's email address. This information was reported to be included in DHCPs letters, as explained in the following quote:

> *"We have our e-mail address for getting the feedbacks and as I told you we always have it on the the the dear healthcare professional letter itself that please report regarding this issue you receive any signal or any adverse event that you think it's related to the issue or even if not related please report to the drug control throughout our online form or in our email so we are receive by e-mail yes"* (Participant 3).

One participant had also added preparing brochures that are disseminated in meetings or presentations, which include information about the PV unit work, KDFC's email address, phone number and fax for questions or information. All participants, on the other hand, indicated that they received confirmation from the pharmaceutical company after they disseminated medication safety communications to HCPs in the private and governmental sectors. This form of feedback was explained by one participant as follows:

> *"For If we send the the dear healthcare no we don't have but if we the company sent we we can take this feedback by as the sign of doctor to to deliver this a safety communication"* (Participant 2).

One participant, however, also reported receiving confirmation of KDFC's disseminated medication safety communications. This was explained in the following quote:

> *"The delivery a man will go to all the health areas like together and we get signatures that they receive"* (Participant 3).

The participants' perceptions of providing HCPs with training to implement the recommendations was captured. This is presented in 4.3.2.3.3.

4.3.2.3.3 Providing training to HCP for implementing the recommendations

All participants reported that no training is provided to HCPs regarding the implementation of medication safety communications. However, two participants indicated that such training is focused on how to report ADRs. One participant clarified that the steps that are required to be taken by the HCPs are written in the communication for them to read. While, another participant expressed that it could be the next step for the PV unit to provide such training as the current priority is providing training on ADR reporting, as noted in the following quote:

> *"that's the next step which should be taken okay we are working on this to to make workshops for the first healthcare providers pharmacists okay to how to report to us if there is any problem if there is any safety issue or something… okay and then after that our next step Insha'Allah will be the patients"* (Participant 1).

Monitoring the intended receivers' implementation of the medication safety communication is another post-dissemination activity. This is presented in 4.3.2.3.4.

4.3.2.3.4 Monitoring the implementation of the delivered communications

All participants stated that they do not monitor the outcomes and the implementation of KDFC's disseminated medication safety information in clinical practices, as explained in the following quote:

> *"we follow up the case but we don't follow up the practice what's going on with the practice between the medical doctors and the patients"* (Participant 3).

One participant added there is no process in place to monitor such implementation. However, two participants showed awareness about the possibility that medication safety recommendations might not be always be implemented clinically without specifying the source of this recognition. One of these participants indicated that the PV unit tries to avoid this by informing HCPs through multiple sources, such as pharmaceutical companies' DHCP letters and their representatives' verbal communication with the HCPs. The participant explained this in the following quotation:

> *"look we don't have a problem in the dissemination because we already do our work and get approval send send it sign and disseminate but the problem as the previous point we are talking of talked about the is the doctor is obeying this healthcare provider information or not okay but from our side we are doing the the the job the steps as it should be okay but we don't know after that what happen that's why in in many cases we are asking the company also to to send a DHCP not only sending they have the the medical [the] representatives which is working in the company also verbally have to inform the the doctor regarding this new information okay this new restrictions new precautions okay so the doctor will will know the information from many sources it written from the company written from us and also verbally from the a medical representative of the company okay"* (Participant 1).

The storage of medications safety communications after their dissemination and their availability to the public were reported in 4.3.2.3.5.

4.3.2.3.5 Storage of medications safety communications and their availability to the public

After the creation of medication safety communications, they are stored in two ways. One participant reported that the approved (signed by the superiors) communications are stored in KDFC's secretary's office. The PV unit staff members, according to two participants, also store communications within their office computers, as explained in the following quote:

> *"It's kept in our computers I have a template for every single safety communication"* (Participant 1).

However, they differed on whether they stored all communications conducted by the PV unit or only stored communications drafted by staff members himself/herself. On the other hand, the three participants differed on whether the safety communications were publicly available or not. One participant indicated that this is not practised, however, it should be made publicly available. Another participant stated that there was a technical issue with the website; however, the participant was not sure as it is not within her scope of work. A third participant, however, mentioned that they sometimes post KuFDA newsletters on KDFC's website, as expressed by the participant:

> *"I think we we we put newsletter sometimes on the our online site for the food and [drug] administration newsletter is is upload for for this if the do healthcare provider can go … they can already go …not a closed aa they can go and see the newsletter [the] updated one* (Participant 2).

The final post-dissemination activity is whether a medication safety communication could be resent. The situations where medication safety information might be resent are reported in 4.3.2.3.6.

4.3.2.3.6 Resending a medication safety information

All participants stated a medication safety information could be resent after its dissemination. Two participants indicated a reminder would be sent if there was a problem appearing with the case or if it was perceived to be important. One of them specified a worldwide increase in the rate and seriousness of the case as a reason for sending a reminder. However, a third participant reported that if the safety information was re-published in the WHO newsletter, then the PV unit would send a reminder to HCPs. Two participants indicated that these reminders would be sent through the KuFDA newsletter, and not through DHCPs, as one explained in the following quote:

> *"I put the reminder I will add it to the newsletter our newsletter okay but we write it's a reminder it's just a it's not a new issue it's just a reminder which means that the same issue is still ingoing okay so take the same precautions take the same steps the same contraindications there is no change the same issue okay but as I told it's not important but from our side because it's already published this month but we already take took action before we will just give them a reminder but we will not send a single DHCP"* (Participant 1).

Besides sending a reminder to the HCPs, the PV unit might also reevaluate the case for any changes that need to be applied, according to one participant. This revaluation might result in the conclusion that more studies are required. Thus, the pharmaceutical company would be contacted by the PV unit to address this issue. While waiting for the studies to be completed KDFC might suspend the registration of the medication of concern, as explained in the following excerpt:

> *"So there is other steps have to be taken maybe we will restudy the case maybe we will revaluate the medication maybe no this medication should be for example the dose should be changed the the indication should be contraindicated in some patients more patients there must be more studies sometimes the the information that we get is not sufficient for us so we will send the to the company to ask them for more studies if there is more studies*

> *can be done regarding this issue and in some cases we suspend the the the medication for some time until these studies is prepared"* (Participant 1).

The processes of creating and disseminating medication safety information were clarified. Following this, examples provided of previous medication safety communications, and suggestions for improving future medication safety communication are presented in 4.3.2.3.7 and 4.3.2.3.8, respectively.

4.3.2.3.7 Examples of previous safety communications from the participants

Following the process that the participants described in creating and disseminating medications safety communications, the participants provided some examples. The participants' examples involved four medications/ medication groups, namely Isotretinoin, antivirals, Denosumab and Lemtrada. These examples along with the participants' quotations are provided in Table 4.10.

Table 4.10: Examples of previous safety communications developed by the PV unit

Examples provided by participants	Illustrative quotations
Isotretinoin: a safety communication was drafted. It includes a reminder of the teratogenicity of Isotretinoin and emerging information related to psychological-related issues.	*" but there is one regarding the isotretinoin Roaccutane aa of course all of us we know that it has a problem with the pregnant woman and there is lot of programs for preventing any harm to the pregnant woman and to avoid any exposure even before pregnancy for women that the intent to do it but now also there is another warning regarding the ... psychological disorders and psychological problems so now we we drafted a new communication to include both it's as a reminder for pregnancy and as an addition of the new am psychological disorders and problems psychological problems"* (Participant 3).
Antivirals for hepatitis C (like Sovaldi): a reminder was sent to physicians regarding monitoring for hypoglycaemia.	"It's for antiviral for hepatitis C hepatitis C product like Sovaldi and like this there is an update in WHO for the systemic hypoglycaemia monitoring for for hypoglycaemia and this we we make a reminder to the doctors this is the most recent one I can remember now …" (Participant 2).
Denosumab (information written in the KuFDA newsletter regarding hyperglycaemia might occur if stopped suddenly).	"*As you see newsletter okay you will find for example there there was an alert published in the MHRA regarding a denosumab which is prolia and aa xgeva aa this products okay they found various cases of hypoglycaemia after discontinuation of this product hyperglycaemia sorry okay what happen there will be a leaflet update to inform the doctors when we stop the medication suddenly there is a risk of hyperglycaemia will happened to the patient okay and the MHRA EMA published instructions for the healthcare to inform the patient the signs of hyperglycaemia how to discontinue how to stop the medicine not immediately okay gradually okay and what's the cases that this product should be given to the aa patient and shouldn't and the cases that the patient shouldn't take this medicine okay"* (Participant 1).
Lemtrada (a DHCP related to Lemtrada risk was drafted. The risk was a serious risk of stroke and blood vessel wall tears; the PV unit sent a DHCP although the pharmaceutical company had previously sent another one).	*"From our side why why did we prefer to do from our side because this this issue have been published many times there was so many questions about this issue what will happen with Lemtrada so we concluded summarised all the information aa regarding this issue and put it in only one DHCP it will be much easier for the healthcare provider to get all the information the latest information regarding this product "*(Participant 1).

Besides providing examples of previous medication safety communications, participants' suggestions for improving future KDFC's medication safety communications are also reported.

4.3.2.3.8 Suggestions for improvement

Different suggestions were made to improve the current medication safety communication process. While one participant focused on improving the communication process, two participants perceived that the priority should be focused on improving ADR reporting. Improving the communication process included communicating electronically with HCPs at the ground level through email to ensure a timely receipt of the information. This electronic system was also perceived to be beneficial by the participant for receiving feedback from different HCPs on the same case. Disseminating medication safety communication electronically was explained in the following quote:

> *"A yes first of all one of the areas is that to deliver electronically not like receiving paper based because we need to make sure that it is …that the the the healthcare [professional] received it on the proper time because as you know this cycle takes time receiving it from the head of the hospital and then head of the hospital disseminating and maybe you receive and maybe not … but if the doctor found it in his inbox or in his system the alert this would would would make it more beneficial number two the the idea of taking the feedback on also an electronic system that ok he's he received it he can always get his feedback on the same case and we receive all the feedback from different hospitals different areas different healthcare professionals regarding this case in one electronic system so I think the electronic system is important in this stage"* (Participant 3).

Another suggestion was added by the participant, which was to make the KuFDA newsletter more publicly available. Considering utilising the media in the future was also suggested by this participant to deliver information to the public with considering proper communication to avoid public panic. Additionally, utilising a simplified language in such communication was suggested so the information would be comprehensible to the patient. On the other hand, another participant reported that she used to have suggestions but now she thinks efforts are being made and huge changes will be noticed in the field of pharmacovigilance in Kuwait. This participant's main concern is to increase the number of HCPs reporting ADRs directly to the PV unit and not necessarily through pharmaceutical companies. This was a shared aim by another participant. One

suggested method was to increase the lectures conducted by the PV unit to raise HCPs' awareness regarding this issue, as explained in the following excerpt:

> *"To improvement yes we can we can make more lecture with doctors to to to to make them more more like or how to deal with any any any issue for any medication … how to communicate with us directly [and] not through the company I think it will improve the safety communication because [the] doctor the the or the healthcare providers only one dealing direct with the patients this is the point I think this is very important"* (Participant 1).

4.3.3 Triangulation outcome

The triangulation of both the quantitative and qualitative data resulted in both confirmatory and novel results. The confirmatory data included the multiple sources used by the PV unit to know about emergent medication safety information. While both types of data showed that PV-unit staff members received information from different sources, as well as checked international sources. Furthermore, the criteria of assessment were also apparent in the document analysis (information from the extracted data, checking if the product was registered in Kuwait), however, additional information was obtained from the interviews regarding other components of this criteria. Additionally, the fax was mentioned as a channel for delivering medication safety communications in both data. There were differences in few of the interviewees answers due to lack of a specified guideline.

4.4 Discussion

The PV unit is a subsection of the Drug Registration Department within KDFC. The process by which the PV unit develops medication safety communications includes accessing the information, assessing it, deciding on appropriate action and initiating action. Common sources for KDFC's medication safety information include international drug regulatory agencies (US FDA, EMA, and UK MHRA). While regional sources related to the GCC's Health Council were also identified. KDFC issues three types of medication safety communications, which are the KuFDA newsletter, DHCP letters, and public releases. A PV unit staff member includes a range of information in KDFC's medication safety communications. This includes the risk itself, the advice or recommendation, and how to report a suspected ADR.

Assuring the quality of a draft involves different levels of superior checks. Stakeholders that are not KDFC's staff were only involved once in approving KDFC's DHCP related to SGLT-2 inhibitors. KDFC's communication with MOH hospitals is mostly manual or by fax. Despite that the PV unit's main intended receivers are HCPs at the patient-facing level, they were not targeted directly in the dissemination process. Currently, the impact of KDFC's medication safety communications on clinical practices in Kuwait is not monitored.

The lack of pharmacovigilance legislation or a unified guideline was reflected in the inconsistencies at certain points between the interviewees. This includes inconsistencies in terms of the assessment criteria for emergent information, whether information on benefits is included and how they are included, deadlines for both the preparation and the delivery process, the quality control measures taken by each assessor, as well as the storage of the delivered medication safety communications.

In the current study, the legal framework of registration and follow-up on the registered products was cited as a policy followed by KDFC for PV activities. In their study, Garashi, Steinke, and Schafheutle (2021) reported that PV-related policy is issued by KDFC to pharmaceutical companies in the form of memos. Specifically, Garashi et al. (2021) found that the pharmacovigilance-related policy was clear to KDFC staff, but not to the pharmaceutical industry who reported inconsistencies in terms of the information being provided to them.

In the current study, most KDFC's issued communications were related to information published by international regulatory agencies. Such regulatory reliance, which is the concept of relying on the output and assessments of other regulatory agencies, is encouraged for developing pharmacovigilance regulatory agencies as it aids in evolving and refining the developing pharmacovigilance system (International Federation of Pharmaceutical Manufacturers & Associations, 2019; Peters et al., 2021). It was revealed from the interviewees that one criterion for deciding on whether to communicate or not is based on the recommendations of the source of the information. However, such reliance might explain the differences seen with KDFC's issued communications in the current study. This is because the format, content, and timing of issuing medication safety communications lack consistency among established pharmacovigilance systems such as US FDA, UK MHRA, and Health Canada as reported by Bjerre et al., (2018). Similarly, a study comparing advisories issued by US FDA, Health Canada, UK MHRA, and Australian Therapeutic Goods Administrations (ATG) found discrepancies in the types of communications produced, their frequencies, and focus (Perry et al., 2020).

Compared to other regulatory agencies that were evaluated by Bjerre et al. (2018), medication safety communications issued by KDFC (per medication) had a lower percentage of reporting the indication of the medication (41.8%%) compared to US FDA (94.4%), UK MHRA (87.8%) and Health Canada (87.5%). While, none of the included KDFC's medication safety communications included quantitative information on medications' efficacies, a low proportion was observed in communication-related to three regulatory agencies (Health Canada 2.5%; US FDA 10.3%; UK MHRA 16.8%). The inclusion of a scientific justification using a specific reference to literature or reported cases was lower in the current study (21.8%) compared to Health Canada (33.8%), UK MHRA (48.9%) and US FDA (93.5%). However, a comparable proportion of KDFC's communications (89.1%) described the ADR of concern as those of the US FDA (95.3%), UK

MHRA (87.8%), and Health Canada (90%). Communications that included additional links or listed references in KDFC (36.4%) were lower than those in US FDA (65.4%) but higher than those by Health Canada (7.5%) and UK MHRA (0%). While 100% of the communications issued by Health Canada, the US FDA, and UK MHRA stated the generic names of the medications, 80% of KDFC's issued communications stated the generic names.

Similar to the current findings, Garashi, Steinke and Schafheutle (2022a) reported that decisions made by the PV unit are not made exclusively based on the PV data, but based on both local and external data. This was attributed to the lack of resources within KDFC to perform certain activities (such as the lack of a computerised case report management system); and the low number of ADR reporting to KDFC, which was perceived by participants from KDFC to be due to potential reporters' lack of knowledge and/or attitudes towards pharmacovigilance reporting (Garashi et al., 2022a). Similarly, in the current study, increasing ADR reporting through educational workshops conducted by KDFC was a priority for the PV unit staff. Although it was indicated that recently the number of ADR reports submitted to KDFC was increased, pharmaceutical companies were reported to be the main source of ADR reporting. Similarly, recent data shows that around 93% to 95% of submitted ADRs to KDFC were from manufacturers (Garashi et al., 2022a; Garashi, Steinke & Schafheutle, 2022b). This was explained by Garashi et al. (2021) to be due to the lack of mandatory ADR reporting legislation and the lack of incorporation of pharmacovigilance in local healthcare-related universities in Kuwait. According to Alghamdi, Albalawi, and Alshammari (2021), the only pharmacy college in Kuwait does not provide any health outcomes and policy courses related to pharmacoepidemiology, pharmacoeconomics, pharmacovigilance, and patient safety. However, the same authors reported that among the Arab League countries, 58.9%, 33.7%, and 14.5% of colleges offer pharmacoeconomics, pharmacoepidemiology, and pharmacovigilance, respectively. Additionally, the same study reported that only one college among the Arab League countries offered a patient safety course to its students.

Despite that all participants reported that medication safety communications are disseminated on an urgent basis, only one participant reported a specific deadline based on the Arab guidelines for pharmacovigilance. To avoid discrepancies in the time in which different targeted audiences receive communications from KDFC, a unified policy including timelines should be specified by KDFC.

To communicate safety information to patients, lay language should be used, such as using a question-and-answer format to make the communication more accessible and comprehensive (The League of Arab States, 2014). A challenge might arise from communicating information in Arabic, as common Arabic terminologies and definitions related to pharmacovigilance are not yet established. In the first Eastern Mediterranean/Arab countries Meeting on pharmacovigilance, a need for common Arabic terminologies and definitions was recognised. In this meeting, attendees agreed on 20 common Arabic terms that could be used related to pharmacovigilance (Bham, 2015). Collaboration with established pharmacovigilance systems among the Arab countries should be considered. Such collaboration is especially important when it comes to issuing medication safety communications in Arabic. This step might increase the acceptability of information for those who are not fluent in English, whether HCPs or patients. This is because all communications intended for HCPs found in the current study were written in English, while the public-aimed communication was written in either Arabic only or both Arabic and English. Notably, all communications targeting the public were either related to recalls, suspensions, or advising against unregistered products. Thus, none of the communications required informed decisions about benefit-risk balance to be made by the patient or the HCPs. Efforts should be undertaken to also write safety communications in Arabic, and to include relevant stakeholders in pre-testing these communications by different groups representing Kuwaiti society at large. Pre-testing of medication safety should be conducted with different groups of intended receivers. Not only do they need to be tested for their readability, but also their comprehension.

In their scoping review, Nualdaisri, Corlett, and Krska (2021) concluded from six studies conducted in Saudi Arabia that written medication information materials intended for patients, whether in Arabic or English, were found easy to read but lacked relevant content, and were difficult to understand. For example, Al Aqeel et al. (2018) conducted a descriptive study consisting of consumers and healthcare experts to assess the readability and understandability of different medication-related materials. They included a total of 4476 sentences from Abdullah Bin Abdulaziz Arabic Health Encyclopaedia (KAAHE) and medication leaflets submitted by the manufacturers to the Saudi Food and Drug Authority (SFDA). It was determined that most of the sentences were deemed easy by the evaluators: experts (SFDA: 68%; KAAHE: 76%), and consumers (SFDA: 76%; KAAHE: 84%). They found, however, that precautions and side effects

were primarily rated as difficult or intermediate in the vocabulary or sentence structure. However, this study did not include information on the nationalities and/or the cultural background of the consumer. Further bias might occur from the convenience sampling technique; although the consumer group did not have healthcare education, however, they were university-level educated. Thus, these results might not reflect people with less educational levels.

Both the EFPIA-IPVG and Arab PV guidelines recommend mentioning the risks in the context of benefits, as well as mentioning the competing risks, such as the risks of nontreatment (Peters et al., 202; The League of Arab States, 2014). Despite that, it was found in the current study that benefits were not included unless it was perceived to be important. Including benefits in medication safety communications both supports patients' and HCPs' rights to informed decision-making as well as supports transparency related to regulatory agencies' decision-making process (Pignatti et al., 2015). It is notable based on the registration requirements mentioned in Chapter 1 (Table 1.5) ensuring the effectiveness and the safety of the products was one of the requirements for registering medications in Kuwait, however, the means of it was not explained. A study conducted by Alshammari et al. (2019) indicated that the KDFC requires the submission of a risk management plan as follows: at the time of a product’s registration, either an EU risk management plan or a local risk management plan should be submitted. In addition, market authorisation holders should submit an updated risk management plan upon request of the pharmacovigilance centre or whenever there are significant changes to the previously-submitted risk management plan (Alshammari et al., 2019). The decision regarding product registration is based on an individual registration officer and the head of the department (Badawi, Alkhamis, Qaddoumi, & Behbehani, 2015). Adding a structured benefit-risk template to this process should be considered to support communicating KDFC's decisions in a structured manner, and to assure uniformity in the communicated information (Leong Wai Yeen, Salek & Walker, 2014).

In the current study, it was found that the impact of medication safety communications is currently not being evaluated by KDFC. However, the PV unit is aware of the possibility of communications not reaching HCPs, and the possibility of HCPs not implementing the intended actions even if they are aware of it. Against this, the PV unit took measures like asking pharmaceutical companies to provide them with signatures of intended recipients as proof of delivery and also attempting to send the same safety issue via communication tools by both the KDFC and pharmaceutical

company to increase the chances of HCPs being aware of the issue, but not with every communication. It has been shown in chapter (2) that HCPs may not always adhere to the intended actions; in addition, the communication may result in spill-over effects. Moreover, many factors, other than awareness, may contribute to under-implementation. In the current study, a fear of the safety communication not reaching the HCP was also expressed due to the long process of going through multiple levels of directors before reaching the intended HCPs. Thus, monitoring the impact of medication safety communications, and the effectiveness of communication tools and channels are necessary to optimise the uptake of such communication in clinical practice. In addition, monitoring is also necessary, to avoid unnecessary waste of efforts and resources, such as repeating messages without knowing what hindered their implementation. Monitoring implementation, as well as patient outcomes, would provide evidence on whether the recommended measures supported patient safety or not. As a result of measuring effectiveness, lessons can be learned about adapting tools and prioritizing decisions (The league of Arab States, 2014).

With the current limited resources of KDFC (only 2 staff members at the ground level of the PV unit, and three levels of superiors, namely a head of department (relevant to drug registration), superintendent, and a director), strategies for improving medication safety communications should avoid adding any avoidable burden to the PV unit (Peters et al., 2021). Thus, collaborations with different professional organisations and the MOH should be considered for delivering timely information to HCPs via the email list to their members. The use of media and social media should also be considered. As the pharmacy scope is currently being expanded and with the current aspirations of developing residency-based programmes for pharmacists in Kuwait, it is also imperative that pharmacovigilance-based training be incorporated into professional development and residency-based programs in Kuwait. Such training should focus on increasing the manpower within the pharmacovigilance unit to increase the functionality of pharmacovigilance in Kuwait.

4.3 Strengths and limitations

This study had multiple strengths. It highlighted the process of medication safety communications through triangulating of two types of sources, documents and interviewees. The documents included different forms of activities, such meetings minutes, medications safety communications, emails from the sources of information, summary of decisions reported to superiors, and letters from KDFC to pharmaceutical companies. These documents included important information on the recipients of medications safety communications, as well as the channels by which the communications were disseminated. The semi-structured interviews involved the staff members that are involved in medication safety communications. Their accounts of their work as well as the documents provided insight into the processes used by KDFC in order to issue and deliver medication safety communications.

The study was restricted by the number of documents related to medicines safety stored in KDFC. No single database or computer had all the communications created by KDFC, as an employee would have a copy if the he/she wrote the documents. Thus, most of the documents were searched manually in KDFC archives, and not all documents were found to be stored (e.g., despite that KuFDA newsletter is disseminated every two months only four versions were found). Moreover, only few communications (all were targeting the public) were found in KDFC website which were removed after the website was updated. Searching for the communications within the targeted destinations (e.g., hospitals archives, local newspapers archives) might have been a more thorough way, but it consumes more resources and depends on whether the targeted destinations had kept their archives. Moreover, the study was restricted in the timeline of the data collections, as communications created after March 2019 were not included. It was out of the scope of this research to include information from pharmaceutical companies. Such information could have added to information on collaborations of KDFC with the pharmaceutical companies, and the documents produced by the pharmaceutical companies.

4.4 Summary of Chapter 4

The objectives of this chapter were to identify and classify medications safety-related communications within the Kuwaiti healthcare system, and to explore the process by which KDFC creates and disseminates medications safety communications to the Kuwaiti healthcare system. The sources for KDFC's medication safety information included international drug regulatory agencies (US FDA, EMA, and MHRA), the WHO, MAHs and the Executive Office of the Gulf Cooperation Council of Health Ministries for the Cooperation Council Countries. KDFC issues three types of medications safety communications, namely KuFDA newsletter, DHCP letters, and public release. Channels used by KDFC to disseminate medications safety communications to MOH hospitals included fax, and manual dissemination. Although the intended receivers are HCPs at the ground level, communications sent to MOH hospitals are directed to health areas directors, directors of governmental hospitals, director of the pharmaceutical services, chairmen of medical counsels, and heads of pharmaceutical supervises offices. Stakeholders outside KDFC, who members of a medical, were only involved once in approving KDFC's DHCP. The most common medication safety issues that were communicated were related to anti-infective for systematic use, followed by alimentary tract and metabolism. This chapter had contributed to the subsequent phases of this research by selecting the valproate – related DHCP as an example that was investigated in this research (in phase 2 and phase 3). It also contributed to this research by using an example of KuFDA newsletters and KDFC's DHCPs to measure HCPs familiarity with KDFC's medication safety communications tools (in phase 2).

It is impossible to determine the success of KDFC's safety communications without engagement from the intended recipients. Previously, no study had evaluated HCPs' knowledge and experiences with such communications. Using a mixed method approach, the next chapter focuses on the experiences of HCPs with medications safety communications. One medication safety communication obtained from this phase (valproate-related medications' (VRM) teratogenicity, which was distributed by KDFC in 2016) was used as an illustrative example.

Chapter 5: Healthcare professionals experiences with medication safety communications, Exploratory mixed-method research

5.1 Introduction

Chapter objective: To explore healthcare professionals' knowledge, attitude and experiences of medications safety-related communications.

This chapter presents the methods, results and discussion of phase 2. The results of this chapter are presented in four sections, including 5.3.1 (the results of the focus group discussions), 5.3.2 (the results of piloting the online survey), 5.3.3 (the results of the survey relating to medication safety communications in general), and section 5.3.4 (the results of valproate section of the survey). The results of sections 5.3.1, 5.3.3 and 5.3.4 are triangulated in the discussion of this chapter.

The methods used in this chapter are presented in 5.2

5.2 Methods

5.2.1 Focus groups

5.2.1.1 Study design

This is a multiple-case embedded case-study design (Yin, 2018). The case study approach was chosen because it allows to study the contemporary-natured research problem "in depth and its real-world context" (Yin, 2018, p. 286). The subject of the case is medication-safety communications (with valproic acid as the nested example) and the experience of healthcare professionals (each professional group separately) with medication safety communications in their practice shapes the analytical frame of this case (Thomas, 2016).

5.2.1.2 Subject

The nested example of safety communication was chosen from the identified DHCP from phase 1. This was based on the consumption rate (surrogate based on healthcare institutions' requests) , the availability of the medication and the recommendation provided in the letter, whether it had clear advice for patients or healthcare professionals (Table 5.1 & Table 5.2).

Table 5.1: Comparison between medications communicated by DHCP in terms of their consumption and availability

Medication	Date of safety communication	Consumption of rate based on requests from CMS (monthly) (from 04/2018 to 03/19)	Setting where the medication is available
Direct acting antiviral therapy: a. Daclatasvir (Daklinza). b. Sofobuvir/velpatasvir (Epclusa). c. Ledipasvir/sofobuvir (Harvont) d. Sofosbuvir (Sovaidi). e. Dasabuvir (exviera). f. Viekirax. g. Zepatier.	25/12/2018	a. Stopped. b. 560 tablets. c. 224 tablets. d. Stopped. e. Stopped. f. Stopped. g. 3 patients/ year.	Hospitals
Ceftriaxone injection	30/09/2018	29,500 vials (26,000 from 1 gm & 3,500 vials for the 0.5gm).	Primary clinics & secondary hospitals
Nonlipid formulation of Amphotercin B with a lipid formulation	12/08/2018	1600 vials	Hospitals
Azithromycin	10/08/2016 27/072016	11,400 capsules. 2000 bottles	Primary clinics & secondary hospitals
Empagliflozin (Jardiance)	7/11/2016	70,436 (10mg & 25mg)	Hospitals.
Metformin	30/10/2016	11,598,527 (all forms).	Primary clinics & secondary hospitals
Canagliflozin (Invokana)	05/10/2016	30,850	Hospitals
Epistatus midazolam oromucosal solution 10mg/ml	09/08/2016	1500ml (300 bottles of 5ml).	National Bank of Kuwait Specialized Hospital for Children Secondary hospitals.
SGLT2 inhibitors	14/08/2016 15/06/2016 30/06/2015	See Empagliflozin, Canagliflozin & dapagliflozin	-
Canagliflozin and dapagliflozin	04/08/2016	Dapagliflozin (Forxiga): 320,000	Dapagliflozin: Primary clinics & secondary hospitals

Fluoroquinolone Antibiotics a. Levofloxacin. b. Ciprofloxacin. c. Moxifloxacin. d. Norfloxacin. e. Ofloxacin. f. Gemifloxacin.	17/01/2019	a. 40,000 tablets & 2250 vials. b. 195,000 tablets; 6000 vials & 30 bottles (suspension.) c. 6000 tables & 300 vials. d. 1050 tables. e. Stopped. f. Stopped.		-
Valproate-related medications.	26/06/2016	Drops: 3300 Syrup: 570 bottles. Tablets: 219000 tablets. Injection: 1000 vials.	Hospitals.	

CMS: Central Medical Stores; **SGLT-2**: sodium-glucose cotransporter 2

Table 5.2: Comparison between medications communicated by DHCP in terms of their risks and recommendations

Medication	Risk	Comments regarding the safety communication
Direct acting antiviral therapy	Risk of hypoglycaemia in patients with diabetes.	- Recent to the time of data collection, sent in December, 2018. - Has clear actions. - It involves different professional groups - Patients would be those who have Diabetes mellitus and hepatitis C
Ceftriaxone injection	The main risk is anaphylactic shock due to improper use. The letter is a reminder of 16 warnings/precautions related to the use of ceftriaxone.	- Multiple specialities are involved. - No advise to patients and if so only inpatients would be involved. - Neonatal care would be the most suitable speciality to be targeted for this risk. - It's a reminder. The risk related to neonates was first identified in 2007.
Nonlipid formulation of Amphotercin B with a lipid formulation	Fatal consequences due to confusion between the formulations.	No advice to patients.
Azithromycin	Risk of Eosinophilia and systematic symptoms. KDFC search was trigged by media and social media. Asked pharmaceutical companies to update their leaflet and it was also released by KDFC through KuFDA newsletter.	Multiple specialities were involved.
Empagliflozin	DHCP letter. Includes the risks and the risk factors of the risks [ketoacidosis, urosepsis and pyelonephritis]. Counsel patients about signs & symptoms of the risks and evaluate patients for signs and symptoms of urinary tract infection. Actions: discontinue medication in prolonged fasting, illness or surgery.	Among the different diseases related to the listed medications, Diabetes mellitus is the most common. But these medications specifically are not. Dispensing restricted to Kuwaiti nationals only.
Metformin	No specific recommendations except→ metformin could now be used in patients with GFR of 30 – 59 ml/min (dose reduction should be considered).	Metformin is the most used medication among this group and Metformin 500mg & metformin 850 mg are the third and fourth most meds used in Kuwait, respectively (after paracetamol and Vitamin B complex).

SGLT2 inhibitors SGLT2	Diabetic ketoacidosis, could be present with low blood sugar (atypical presentation). (Also similar to Empagliflozin, Canagliflozin and dapagliflozin)	
Canagliflozin and dapagliflozin	ketoacidosis, urosepsis and pyelonephritis. Kidney warnings→ evaluate & monitor pts. Bone fracture→ encourage patients to read medical guide and counsel patients about factors that might contribute to the risk, consider factors that lead to the risk before initiation. Canagliflozin→ increased risk of foot and leg amputation especially the toes.	Checklist distributed with the warning for physicians to use. As Empagliflozin.
Fluoroquinolone Antibiotics	Risk of hypoglycaemia, mental side effects, and increased rupture or tears in the aorta blood vessel. Counselling patients about risk of psychiatric adverse event even from first dose. HCP should stop Fluoroquinolone immediate if patients had any of those symptoms. Ask the patients if they were using medications for diabetes mellitus and ask them about their blood sugar levels. Advise patients especially elderly about aneurism. Do routine check-ups for patients with aortic aneurism.	Clear risk & advice to patients. Actions include to stop meds if symptoms occur and to counsel patients about the risks. It might be difficult to recruit patients as they would be in the acute state. Antibiotics might be more relevant to nurses. Very recent 17/01/2019.
Valproate-related medications.	Risk of teratogenicity and developmental issues.	Since 2016. Specific patients groups: pregnant and using valproic acid. Relevant to different specialities including: neurology, internal. DHCP. Includes a risk minimisation measure. Relevant and clear instructions to pts. [patients should understand: risk associated with it during pregnancy; need to use effective contraception; need for regular review of treatment]. HCP should not prescribe it to female children or adolescents, women of child bearing age or pregnant women, unless other treatment are not effective.

DHCP: Dear Healthcare Professional; **KDFC**: Kuwait Drug and Food Control; **HCP**: Healthcare professional; **SGLT-2**: sodium-glucose cotransporter 2

The subject of the focus group was chosen from phase 1 (Chapter 1) which was valproate. Valproate was chosen because it had the highest consumption rate based on the Central Medical Stores (chapter 1) records compared to the other medications identified from KDFC's DHCP. Valproate was also available in the governmental sector for both Kuwaitis and non-Kuwaitis, and it had clear advice to patients and healthcare professionals. Furthermore, valproate is also a focus medication safety intervention by international regulatory agencies such as UK MHRA (MHRA, 2018).

After the selection of valproate, the researcher developed the focus group schedule.

5.2.1.3 Tool development

Focus group questions were developed based on the systematic literature review. The questions and interview guide were initially checked by the supervisors to assess its appropriateness against the objective of the study. Then, the guide was piloted with nine pharmacists (one individually; eight as two groups), seven had previous work experience in a general secondary hospital in Kuwait. Modifications were made based on the pilot. The need to include an Arabic translated guide was realised from the pilot. This same approach of translation in Figure 4.1 (chapter 4) was adapted (Brislin, 1986; Jones et al., 2001; Doris et al., 2003). A second round of translation was not required (Table 5.3).

Table 5.3: Comparison of the original and the backward translated English version of the interview guide (focusing on errors)

Original Interview guide in English	**Back-translated interview guide (1)**	**Translation Error**
Item 2c: list the mentioned sources.	**Item** 2c: Publications of the above-mentioned sources	The Arabic word that was used could also mean publication, however no action is required as the action of listing the sources will be done by the researcher.
11a. Healthcare professionals	**Item 11a:** caregivers (pharmacists, pharmacy technicians, nurses or practitioners)	Error in the back translation. No action is required because specific profession between brackets will be used with its relevant focus group.

The focus group schedule including the Arabic and English questions was adjusted with discussion with a supervisor (Dr Fatemah Alsaleh). The final focus group schedule is presented in Appendix 26.

5.2.1.4 Setting

This study was conducted in a secondary general hospital in Kuwait that represents one governate. It involved the following professional groups because they have direct contact with patients: pharmacists, pharmacy technicians, physicians, and nurses

5.2.1.5 Data collection

A secondary MOH hospital was chosen based on convenience sampling. A homogeneous purposeful sampling of participants of the same professional background was performed. A

theoretical replication was applied (four types of professional groups were be chosen) to maximise the opportunities for developing saturation in concepts (Corbin & Strauss, 2014; Krueger & Casey 2015; Patton, 2015; Yin, 2018). Each of the focus groups included a unique HCP group. This was to avoid blaming or feeling uncomfortable to share information in front of other HCPs groups. A total of 5 physicians, 13 nurses, 20 pharmacists and 6 pharmacy technicians, participated in the homogenous focus group discussions. Only physicians and nurses from the medical department (including internal medicine and neurology) and obstetric gynaecology, psychiatry were invited as they are expected to have more female patients on valproate than other departments; however, all pharmacists and pharmacy technicians were invited. Focus group discussions were facilitated by the researcher and audio-recorded. Notes were taken by a supervisor (Dr Fatemah Alsaleh).

5. 2.1.6 Data analysis

Interviews were verbatim transcribed by the researcher (Appendix 27). One transcript was checked by a supervisor (Dr Nada Shebl). A thematic analysis technique was adapted from Braun and Clarke (2006). This included familiarising oneself with the transcripts by reading the transcripts. After that, inductive coding was conducted by the researcher by reading the transcripts line-by-line. MAXQDA was used in this step to facilitate the coding process. A supervisor (Dr Nada Shebl) independently coded the transcript. There was an alignment between the two coders, with an additional code added by Dr Shebl regarding nurses' work culture, which was added by the researcher. This step was followed by developing the themes, reviewing these themes and defining and naming these themes. The previous steps were conducted for each professional group (each transcript) separately. This was followed by comparing the resulting sub-themes from each transcript and grouping them into overarching themes. This was followed by interpreting and writing up the focus group results section. Examples of the analysis process available in Appendix 28.

5.2.2 Survey

5.2.2.1 Survey design

An online cross-sectional survey questionnaire was developed. The items of the survey were developed from previous literature (Alharbi et al., 2023; de Vries et al., 2017; de Vries et al., 2018; Piening, Haaijer-Ruskamp, de Graeff et al., 2012), the TDF (Cane et al., 2012), the findings of phase 1 (KDFC's document analysis and staff interviews, chapter 4), and the recommendations of the valproate-related DHCP that was sent by KDFC.

The survey had two sections. The first section was a general section that could be answered by all participants. The first section was followed by a "stop question". The survey automatically ended for those who answered "No" for the stop question. Those who answered "Yes" or "Not sure" to the stop question continued to the second section of the survey, which was specific to the medicine "Valproate". The objectives of both sections of the survey included the following:

(A) General objectives (from the general section)

1. Knowledge about medications safety communications.
2. Practices of HCPs in terms of updating their knowledge about medications safety communications.
3. Attitudes and perceptions of healthcare professionals towards different aspects of medication safety communications.
4. Preferences towards receiving future safety information (Format (hard vs soft copies) & Medium of delivery (e.g., emails).
5. Perceived barriers in implementing the recommendations related to medication safety communications.

(B) Specific to valproate:

1. Knowledge about valproate teratogenicity and recommendations by Kuwait Drug and Food Control in response to this information.
2. Sources by which Healthcare professionals became aware of the valproate safety information.
3. Self-reported impact of valproate safety information on healthcare professionals' clinical practice (change in practice).
4. Perceived barriers in implementing the recommendations related to the implementation of valproate related recommendations.

Table 5.4 presents the survey questions based on the objectives of the survey.

Table 5.4: Survey questions according to the survey objectives

Objective	Question
Demographics	1. Age
	2. Gender
	3. Nationality
	4. Education level
	5. Workplace description (e.g., secondary governmental hospital)
	6. Location of workplace (health region)
	7. Professional background (nurse, pharmacists, pharmacy technician, physicians)
	8. Job title 9. Job title 10. Job title 11. Job title
	12. Years of experience
	13. Speciality
Objective 1: Knowledge	14. Who is responsible for issuing recommendations related to any emerging safety information of medicines to the healthcare professionals in Kuwait?
	15. When does medications' safety assessment occur? Included three statements
	16. Are you familiar with the following forms of medication safety communications? Included two statements
Objective 2: Practices to update knowledge	17. Do you check for updates about medications safety even if you don't receive an alert about it?
	18. How often do you get to know about new information related to medication safety from the following sources? Included 16 sources.
Objective 3: Attitudes	19. Who do you think should know about emergent medications safety information? Included 9 individuals (e.g., nurses, family members, carers)
	20. How strongly do you agree or disagree with the following statement "Information about medication safety is important for my practice"?
	21. From the following sources of medication safety information, please indicate which sources in your opinion provide trustworthy information? Included 7 sources.
Objective 4: preferences for future communications	22. Formal (e.g., soft copies i.e., electronic based)
	23. Channel of distribution (e.g., emails)
Objective 5: Perceived barriers in implementing the recommendations related to medication safety communications.	24. Please indicate the perceived barriers to you implementing recommendations required by emerging information related to medications safety. Included 13 statements
	25. Are there other barriers to you implementing recommendations required by emerging information related to medications safety that we didn't cover in question 24?
Stop question	26. Have you previously prescribed, dispensed or provided care for patients who use valproate?
Objective 1 (valproate specific): Knowledge	27. Are you aware of the teratogenic effects of valproate?

Objective 2 (valproate specific): Identify the sources by which healthcare professionals became aware about the teratogenicity of valproate.	28. How did you know about this safety information?
Objective 1 (valproate specific): Knowledge	29. Which of the following statements were recommended by Kuwait Drug and Food Control in response to the teratogenic effects of valproate? Included 7 statements.
Objective 3 (valproate specific): Change in practice.	30. How did the safety information related to the teratogenic effects of valproate affect your practice? Included 8 statements.
Objective 4 (valproate specific): Perceived barriers in implementing the recommendations related to the valproate safety information.	31. Please indicate the barriers to you implementing recommendations related to the teratogenic effects of valproate. Included 13 statements.
	32. Are there other barriers to you implementing recommendations related to the teratogenic effects of valproate that we did not cover in question 31?

5.2.2.2 Participants and Sample size

The survey targeted healthcare professionals (nurses, pharmacists, pharmacy technicians, and physicians) working in secondary care and tertiary care governmental hospitals in Kuwait. Initially, the sample size was calculated for each healthcare professional group based on their population in the governmental sector in Kuwait [nurses (population: 20000, sample size: 377), pharmacists (population: 1500, sample size: 306), pharmacy technicians (population: 993, sample size: 278), physicians (population: 8000, sample size: 367)] to compare between the four groups (Kuwait MOH, 2018). However, this was not achieved, a possible reason could be that the survey was distributed during the COVID-19 pandemic (before and during the second wave of COVID-19 in Kuwait) (De Koning et al., 2021).

Thus, one sample size was calculated for the total population of the four groups (30556), which resulted in a sample size of 380.

The sample size calculation was assessed by and online calculator (Raosoft, 2004) based on the formula below:

$$x = Z(c/100)2r(100-r)$$
$$n = N\,x/((N-1)E2 + x)$$
$$E = Sqrt[(N - n)x/n(N-1)]$$

[N is the population size, r is the fraction of responses of interest, and Z(c/100) is the critical value for the confidence level c].

The following values were entered, margin of error: 5%, confidence level: 95%, population size: 30556, and response distribution: 50% (Israel, 1992; Raosoft, 2004).

A statistician was consulted during the sample size calculation process.

5.2.2.3 Survey validity

Face validity was performed as described in 3.7. This included a revision of the questionnaire conducted by the supervisors and by the statistician. Moreover, this was conducted at the pilot stage, where a sample of HCPs had the opportunity to report their opinions about the questions used in the questionnaire.

5.2.2.4 Survey translation

The survey instrument was bilingual, i.e. it included two languages Arabic and English. Including an Arabic translation in the questionnaire was considered to be necessary after conducting the pilot focus groups, where translation was required. The same principle described in the translation of

the focus group questions was applied to the survey. Examples of questions changes due to back translation process included the following:

1. The term *rank of employment* was changes to *job title* (both used in previous studies). This is because the back-translation of the Arabic version of this first term was *job description* while the second one was the same as intended.

2. a description of the expected teratogenic effects as birth defects and early developmental issues were written. However, the back-translation of the Arabic term of *developmental issues* came as *growth*. Thus, a description the of same sentence used by SANOFI (the marketing authorisation holder) in Arabic and English (the KDFC also uses the English) versions were used.

5.2.2.5 Survey pilot

The sample size of the pilot survey was determined with the statistician to allow for comparisons between the four HCPs groups. The survey participants were identified initially through convince sampling. Then, those participants identified other participants. No nurses were identified through this process. Thus, nurses' participants were contacted by the Staff Development Unit of a secondary MOH hospital. The contact numbers of those who agreed was shared with the researcher. For all participants, the researcher sent a link of the anonymous survey to their WhatsApp contact number. A unique code was provided to each participant in order to be used in the test and re-test analysis.

The survey was piloted by administering the survey to the same individuals twice (included nurses, pharmacists, pharmacy technicians' physicians, and dentists) with at least a two weeks period separating the two administrations (50 HCPs included the test, and 46 HCPs included in the re-test). The answers of those who completed the survey at the two administration times were joined

in one data set, resulting in a third data set consisting of 92 participants (test and re-test). The reliability of the questionnaire was measured using the test data set (n=50) using Cronbach's alpha.

A total of 68 ordinal items were tested for test-retest reliability (46 participants) using Spearman's correlation and ICC (intraclass correlation coefficients). In the case of the ICC, the absolute agreement was assessed using a two-way-mixed model for single measurements (McGraw & Wong, 1996; Shrout & Fleiss, 1979). Spearman's correlation coefficients of 0.7 or higher were considered acceptable (DeVon et al., 2007). For the ICC, the coefficient values were categorised into poor (<0.5), moderate (between 0.5 and 0.75), good (between 0.75 and 0.9) and excellent reliability (> 0.9) (Koo & Li, 2016).

Internal consistency describes the degree to which the questionnaire establishes stable and consistent results (Taherdoost, 2016). For internal consistency, a minimum value of 0.7 was considered acceptable (Nunnally, 1978). The corrected item-total correlation defines the correlation between an item and the summed score of the other items (Gliem & Gliem, 2003; Zijlmans, Tijmstra, Van der Ark, & Sijtsma, 2019). Item to the total correlation of the variables in the test sample (n= 50), retest sample (n=46), and the test and retest sample (n=92), along with Cronbach's alpha score possible change if the variable would be removed, which represents the internal consistency of the scale if the designated item is removed (Gliem & Gliem, 2003). Variables were considered problematic if the total correlation of the corrected item was less than 0.2, and its removal would increase Cronbach's alpha score (Kline, 1986). The pilot study of the survey also included an open-ended question for the participants, who were HCPs practicing in MOH hospitals, to write their feedback and opinions about the questionnaire items. Following the pilot stage, the survey was adjusted. The adjustments were discussed and approved by the supervisory team and are presented in section 5.3.2 in this chapter's results.

5.2.2.6 Survey distribution

Survey distribution started 7th of February 2021 to 22nd of June 2021. All 7 secondary hospitals and 18 tertiary governmental hospitals in Kuwait were included in the study, while one tertiary

hospital was not included (the director of this hospital refused to participate as they did not have a pharmacy department). Based on an agreement with the targeted hospitals, the survey link was sent by the researcher (by WhatsApp messages or emails) to a staff member/member to be distributed via WhatsApp messages or emails to their staff members (in all departments that provide patient care). An invitation to the survey was also printed including the link and the QR code and was distributed as an alternative method in some departments. To increase the sample size, the following methods of distribution were utilised: snowball sampling (sending to HCPs and asking them to send the link to HCPs that they know), social media (dr_conference Instagram account, an academic and pharmacists twitter account), and the link was sent by three professional organisations (Kuwait Pharmacy Technicians Union, Kuwait Pharmaceutical Association, and Kuwait Medical Association) to their members. Other methods were tried by the researcher but were not successful due to none response from the aimed organisation (organisations related to nursing association and neurology league). Another method was approaching a third party (a private company) that had connection and experience in disseminating surveys in MOH hospitals. Concerns related to bias and a perceived lack of details in the contract agreement.

5.2.2.7 Survey data analysis

Descriptive statistics, including frequency and percentile were used. Moreover, the principal component analysis (PCA) was performed to reduce the set of variables in certain questions into smaller sets of dimensions or components (Field, 2018). By transforming original variables into linear components, PCA technique attempts to explain the maximum amount of total variance in a correlation matrix (Field, 2018). Furthermore, Kaiser-Meyer-Olkin (KMO) was utilised as a measure for sampling adequacy with a minimum acceptable value of 0.5 (Kaiser & Rice, 1974), and a significant Barlett's test of sphericity ($p < 0.05$ [Field, 2018]).

The researcher considered the number of components to be included after carefully examining variables with total initial eigenvalues greater than 1 in the "Total Variance Explained" table following a Varimax rotation (Field, 2018; Kaiser, 1960). Kanyongo (2005, pp122) explained eigenvalue as *" the amount of variance that a particular variable or component contributes to the*

total variance. This corresponds to the equivalent number of variables that the component represents". Furthermore, items loading was considered acceptable if they scored 0.4 or higher. In case of cross-loading, someone could either remove the item with overloading to avoid complexity, exclude items that have similar high loading (cross-loading) on 2 or more component (Nathai-Balkissoon & Pun, 2016), or include the item with the component that had a higher loading (Sandsdalen et al., 2015). In the case of an item removal, the researcher repeated the PCA procedure as the removal of a variable could affect KMO (Field, 2018).

Three statistical tests were used to assess the hypotheses of this study including the Kruskal-Willis H test, Fisher-Freeman-Halton Exact Test and Mann-Whitney U Test. The study's hypotheses and the statistical tests used are presented in Table 5.5.

Table 5.5: Hypotheses and statistical techniques used to test them

Domain	Subdomain	Null Hypothesis (H_0) Alternative Hypothesis (H_A)	Test used
Knowledge about medication safety communications.	**Knowledge of the responsible bodies for issuing medication safety communications in Kuwait.** Is there a difference in total knowledge scores of the four HCP groups in accurately identifying correct and incorrect statements regarding who is responsible for issuing recommendations related to medication safety to HCPs in Kuwait?	H_0: There is no significant difference among the four HCPs groups in their knowledge about the bodies responsible for issuing medication safety communications in Kuwait. H_A: There is a significant difference among the four HCPs groups in their knowledge about the bodies responsible for issuing medication safety communications in Kuwait.	Kruskal-Willis H test
	Knowledge of the medications' life cycle stages at which medication safety assessments occur. Is there a difference in the total knowledge scores of the four HCP groups in accurately identifying correct and incorrect statements regarding when medication safety assessment occurs?	H_0: There is no significant difference among the four HCPs' groups in their knowledge about medications' life cycle stages at which medication safety assessments occur. H_A: There is a significant difference among the four HCPs groups in their knowledge about medications' life cycle stages at which medication safety assessments occur.	Kruskal-Willis H test
	Familiarity with medication safety communication tools used by KDFC. Is there a difference in the total familiarity scores of the four HCP groups in being familiar with the different forms of medication safety communications?	H_0: There is no significant difference among the four HCPs groups in their familiarity with medication safety communication tools used by KDFC. H_A: There is a significant difference among the four HCPs groups in their familiarity with medication safety communication tools used by KDFC.	Kruskal-Willis H test

HCPs' practices to update their knowledge about medication safety.	**Frequency of checking for medication safety updates.** Is there a difference between the four HCPs groups on whether they check for updates about medication safety even if they don't receive an alert about it?	H_0: There is no significant difference among the four HCPs groups in their practices to check for updates about medication safety. H_A: There is a significant difference among the four HCPs groups in their practices to check for updates about medication safety.	Kruskal-Willis H test
	Frequency of using the listed different sources for medication safety updates. Is there a difference among the professional groups in using the different types of sources in updating their knowledge about medication safety?	H_0: There is no significant difference among the four HCPs groups in their practices in using the different types of sources in updating their knowledge about medication safety. H_A: H_0: There is a significant difference among the four HCPs groups in their practices in using the different types of sources in updating their knowledge about medication safety.	Kruskal-Willis H test
HCPs' attitudes towards medications safety communications.	**HCPs' attitudes towards the possible receivers of medication safety communications.** Is there a difference between the four HCPs groups in terms of their attitudes towards who should receive medication safety communication?	H_0: There is no significant difference among the four HCPs groups in their attitudes towards the possible receivers of medication safety communications. H_A: There is a significant difference among the four HCPs groups in their attitudes towards the possible receivers of medication safety communications.	Kruskal-Willis H test
	HCPs' attitudes towards the importance of medication safety information. Is there a difference between the four HCPs groups in how strongly they agree or disagree with the statement "Information about medication safety is important for my practice"?	H_0: There is no significant difference among the four HCPs groups in their attitudes towards the importance of medication safety information. H_A: There is a significant difference among the four HCPs groups in their attitudes towards the importance of medication safety information.	Kruskal-Willis H test

	Healthcare professionals' attitudes towards the sources of medication safety communications. Is there a difference between the four HCPs groups in terms of their attitudes towards the trustworthiness of the sources of medication safety information	H_0: There is no significant difference among the four HCPs groups in their attitudes towards the trustworthiness of the sources of medication safety information. H_A: There is a significant difference among the four HCPs groups in their attitudes towards the trustworthiness of the sources of medication safety information.	Kruskal-Willis H test
HCPs' preferences for future medication safety communications.	**Format preferences for future medications safety communications** Is there a difference between the four HCPs groups in terms of their preferences for the format for future medication safety communications?	H_0: There is no significant difference among the four HCPs groups in their preferences of the format to be used for future medication safety communications. H_A: There is a significant difference among the four HCPs groups in their preferences of the format to be used for future medication safety communications.	Fisher-Freeman-Halton Exact Test.
	Future communications channels preferences of HCPs Is there a difference between the four HCPs groups in terms of their preferences for the channels for future medication safety communications?	H_0: There is no significant difference among the four HCPs groups in their preferences of the channels to be used for future medication safety communications. H_A: There is a significant difference among the four HCPs groups in their preferences of the channels to be used for future medication safety communications.	Fisher-Freeman-Halton Exact Test.
HCPs' perceived barriers to implementing medication safety recommendations.	**Healthcare professionals' perceived barriers to implementing medication safety recommendations** Is there a difference between the four HCP groups in identifying the different types of barriers as barriers that hinder them from implementing recommendations required	H_0: There is no significant difference among the four HCPs groups in their perceived barriers to implementing medication safety recommendations. H_A: There is a significant difference among the four HCPs groups in their perceived barriers to implementing medication safety recommendations.	Kruskal-Willis H test

	by emerging information related to medication safety?		
HCPs' knowledge of valproate teratogenicity and DHCP	**HCPs awareness about the valproate teratogenicity.** Is there a difference in the total awareness scores of the four HCP groups in terms of being aware of valproate teratogenicity?	H_0: There is no significant difference among the four HCPs groups in their awareness of valproate teratogenicity. H_A: There is a significant difference among the four HCPs groups in their awareness of valproate teratogenicity.	Fisher-Freeman-Halton Exact Test.
	HCPs' knowledge of KDFC recommendations in response to valproate teratogenicity. Is there a difference in the total knowledge scores of the four HCP groups in accurately identifying correct and incorrect statements regarding when KDFC's recommendations related to valproate teratogenicity?	H_0: There is no significant difference among the four HCPs groups in their knowledge of KDFC recommendations in response to valproate teratogenicity. H_A: There is a significant difference among the four HCPs groups in their knowledge of KDFC recommendations in response to valproate teratogenicity.	Kruskal-Willis H test
Sources by which they became aware of valproate teratogenicity	**Sources by which HCPs became aware of valproate teratogenicity** Is there a difference in sources from which HCPs knew about valproate teratogenicity?	H_0: There is no significant difference among the four HCPs' groups in their sources from which they knew about valproate teratogenicity. H_A: There is a significant difference among the four HCPs groups in their sources from which they knew about valproate teratogenicity.	Fisher-Freeman-Halton Exact Test.
Self-reported impact of valproate safety communication	**Self-reported impact of valproate safety communication** Is there a difference between the four HCP groups in their total intended impact scores in response to valproate safety communication?	H_0: There is no significant difference among the four HCPs' groups in reporting applying the intended impacts of valproate safety communication. H_A: There is a significant difference among the four HCPs' groups in reporting applying the intended impacts of valproate safety communication.	Kruskal-Willis H test

Perceived barriers to implementing valproate safety recommendations	**Perceived barriers to implementing valproate safety recommendations.** Is there a difference in the means of the four HCP groups in identifying the different types of barriers as barriers that hinders them from implementing recommendations related to valproate teratogenicity information?	H_0: There is no significant difference among the four HCPs groups in their perceived barriers to implementing valproate safety recommendations. H_A: There is no significant difference among the four HCPs groups in their perceived barriers to implementing valproate safety recommendations.	Kruskal-Willis H test
	Perceived barriers to implementing valproate safety recommendations. Is there a difference between males and females in identifying a lack of confidence in talking to female patients about pregnancy issues as a barrier to implementing valproate safety recommendations?	H_0: There is no significant difference between males and females identifying lack of confidence in talking to female patients about pregnancy issues as a barrier to implementing valproate safety recommendations. H_A: There is a significant difference between males and females identifying a lack of confidence in talking to female patients about pregnancy issues as a barrier to implementing valproate safety recommendations.	Mann-Whitney U Test

HCP: Healthcare professionals; **KDFC**: Kuwait Drug and Food Control; **DHCP**: Dear Healthcare professional communication

To find if there were significant difference between the four HCP groups “nurses”, “pharmacists”, “pharmacy technicians” and “physicians,” Kruskal-Wallis H test was used to identify if there was differences in the professional groups in terms of: (1) their use of the different sources to update their knowledge; (2) identification of different barriers that hinders them from implementing recommendations required by emergent information related to medication safety; (3) as well as their total knowledge and familiarity scores. Kruskal-Wallis H test was also performed in the ordinal data to identify the difference among the four healthcare professionals’ groups in terms of their practice of updating their knowledge about medication safety even if they do not receive an alert, and in terms of their attitudes towards medication safety communications. Kruskal-Wallis H test is a nonparametric test that is used to find if there are statically significant differences between two or more groups of an independent variables (healthcare professionals) on a continues or ordinal variable (Dunn, 1964; Laerd Statistics, 2015a; Vargha & Delaney, 1998).

The following steps were taken for the Kruskal-Wallis H test:

a. The researcher tested whether the distribution of scores/means had the same shape or different shapes by visually examining boxplots. In case the distribution was similar the medians were compared, while the mean ranks were compared in case of different distributions.
b. The “Hypothesis test summary” table in the output was reviewed for the asymptotic significance to decide whether to accept or reject the null hypothesis.
c. Null hypothesis would be retained if $p \geq 0.05$ (CI 95%). The equation below was reported:

   X2 (3) = (test statistic value), p (asymptotic sig value); (3 is the degree of freedom).

d. A post-hoc analysis was conducted on variables that had significant results. In the post-hoc analysis, the adjusted (Adj) significance (corrected by SPSS using a Bonferroni correction) was considered to avoid type-1 error (which might occur when only considering the significance of the pair being compared and not the whole data).
e. The results were reported on whether a significant (Adj significance) difference was presented between each two types of healthcare professionals in terms of their mean ranks or medians.

Mann-Whitney U Test was used to detect if there was a difference between males and females and identifying lack of confidence in talking to female patients about pregnancy issues (Hart, 2001; Laerd Statistics, 2015b). Fisher's exact test was used to detected if there was a difference between the four healthcare professionals' groups in terms of their preferences towards future medications safety communications (format and channels), their general knowledge of valproate teratogenicity and the sources by which they learnt about valproate teratogenicity (Field, 2018; Laerd Statistics, 2016). This test was used instead of Chi-square because not all cells in the four questions had values greater than 5 (Field, 2018). Moreover, multivariate regression analysis was performed to detect predictors for implementing the intended recommendations specified in KDFC's valproate-related DHCP. The participants' answer in the *others, please specify* options were analysed descriptively. However, the answer to the opened-ended general barriers and valproate were analysed using conventional content (Hsieh & Shannon, 2005). The following steps were applied:

1. Read data repeatedly.
2. Data read word by word to derive codes by first highlighting key thoughts or concepts.
3. Make thoughts of first impressions, thoughts, and initial analysis.
4. As this process continues, labels for codes emerge that are reflective of more than one key thought, which becomes the initial coding scheme.
5. Codes stored into categories based on how different codes are related and linked.
6. These emergent categories are used to organise and group codes into meaningful clusters.

This results in identifying the cluster and subclusters of the general barriers (initially coding and refinements of codes resulted in 155 codes, which were categorised into 10 categories, then reduced to 6 categories, and to 4 clusters and finally 3 clusters) and the valproate specific barriers (initially 41 codes, which were categorised into 7 categories, reduced to 6 , and reduced to 4 clusters, then to 3 clusters).This was followed by discussions with supervisors to assess the suitability of the cluster-subclusters to the participant quotes.

5.2 Results

The results section includes of the focus group discussion (5.3.1), the results of piloting the online survey (5.3.2), the results of the survey relating to medication safety communications in general (5.3.3) and the results of valproate section of the survey (5.3.4).

The results of the focus group discussion included four themes and nine subthemes.

5.3.1 Results of the focus group discussions

In total four focus group discussions were conducted. Each focus group included a unique HCP group. This included nurses, pharmacists, pharmacy technicians and physicians. A summary of the themes and subthemes relating to this study are presented in table 5.6.

Table 5.6: Summary of the focus groups' derived themes and subthemes

Theme	Subthemes
Perceptions about medication safety communications and familiarity with their sources	- Perceptions about medication safety communications. - Familiarity with the sources of medications safety information.
Experiences with the sources of medication safety communication	- Preferred sources of medication safety information. - Challenges with medication safety information sources.
Attitudes to responsibilities and the implementation of medication safety communications	- Attitudes towards implementing medication safety recommendations. - Attitudes towards the roles of HCPs in implementing medication safety recommendations.
HCPs experiences with the valproate-related KDFC's safety communication	- HCPs' familiarly with the valproate related safety communication. - HCPs' implementation of the valproate related recommendations. - Perceived barriers and suggestions for improvements.

HCP: Healthcare professionals; **KDFC**: Kuwait Drug and Food Control

5.3.1.1 Perceptions about medication safety communications and familiarity with their sources

The participants were asked about their perceptions of the concept of medication safety communications and their familiarity with the tools used in disseminating emergent medication safety information. Interestingly, none of the participants in the four focus groups had correctly defined the concept of medication safety communication. Physicians mentioned that they were aware of medication safety because they had lectures about them, but not medication safety communications in particular. However, all HCPs groups had different perceptions of concept. Of medication safety communications. These perceptions are presented in subtheme 5.3.1.1.1.

All HCPs' group mentioned the sources by which they learn about medication safety information. The researcher asked about the sources that were not mentioned by the HCPs to explore the relevancy of these sources to the HCPs' groups. In total, eight types of sources were discussed, and these are presented in 5.3.1.1.2. While mentioning the sources of medications safety, HCPs mentioned examples of medications safety communications they had previously received from the different sources. These are illustrated in Table 5.6. These examples were mentioned while discussing the sources, asked directly by the researcher to provide examples and opportunistic examples mentioned by the participants throughout the discussion.

5.3.1.1.1 Perceptions about medication safety communications

HCPs discussed the concept of medication safety communications from five viewpoints. These included their perception about: (1) the type of information included in such communications (by nurses and physicians), (2) the type of people whom the communications aim to improve their safety (by pharmacists, pharmacy technicians and physicians), (3) the measures that are required to be taken to improve patients safety (by nurses), (4) the type of medication use process involved (by pharmacists and pharmacy technicians), (5) and the type of HCPs who are involved in such communications (by pharmacists and pharmacy technicians). The type of information included in medication safety communications reported by nurses included Look Like and Sound A Like

(LASA) medications, high-risk medication groups and the right standards of medication administration. The physicians, however, perceived that medication safety communications include information related to dosage adjustments with comorbidities, drug-drug interactions, information regarding medication concentrations, contraindications and common side effects, as described in the following quote:

> *"Contraindications common side effects … and interaction now mainly for warfarin"* (Physician).

The type of people whom the communications aim to improve their safety from the perception of physicians included high-risk individuals, such as pregnant and lactating patients. On the other hand, both the pharmacists' group and pharmacy technicians' groups perceived that medication safety communication is an umbrella term concerned with the safety of the patients and the HCPs working in the hospital.

> *"This is the first time I hear the term itself but I guess it is about for example the safety of the patients the safety of the workers inside the hospital I guess it is this"* (Pharmacy technician).

The measures that are required to be taken to improve patients' safety by the nurses include confirming patients' identity through the patient identification (ID) card. Nurses also perceived that it included using colour coding of medications' labels based on the therapeutic group of the medication.

> *"and we have sound a like look a like like some variety you know safety words are there regarding medicines and a how to you know this anticoagulants are we are here labelling with red a circle and antibiotics notify with green with green pen …"*(Nurse).

The type of medication use process involved was mentioned by both the pharmacy technicians' group and the pharmacists' group. Pharmacy technicians mentioned that medication safety communication focuses on the patient while dispensing. They also added that it aims to reduce

dispensing errors. The pharmacists added a different point, which is providing good counselling for the patients.

> *"a to reduce the errors like a dispensing for [patients]"* (Pharmacy technician).

Finally, both pharmacists and pharmacy technicians reported their perceptions about the type of HCPs who are involved. Pharmacy technicians reported that the concept of medication safety communication focuses on the actions of physicians and the pharmacy department, including pharmacists. Pharmacists, on the other hand, mentioned that it involves the communications between HCPs and the procedures employed by them to improve patients' safety, without specifying a certain group of HCPs.

> *"I think this is communications aa between the all members of healthcare to to use more safety procedures to our patients"* (Pharmacist).

The familiarity of HCPs with the sources medications safety information were also discussed. These are presented in the subtheme 5.3.1.1.2.

5.3.1.1.2 Familiarity with the sources of medications safety information

A variety of sources were stated by the HCPs as the sources through which they learn about medication safety information. Generally, these sources were related to (1) KDFC and/or the MOH, (2) pharmaceutical companies, (3) international drug regulatory agencies, (4) scientific journal articles, formularies, books and conferences, (5) local sources in the hospital (where they practised), (6) applications and software, (7) the internet and websites, (8) the media and social media.

MOH circulars were mentioned as sources by physicians, pharmacy technicians, and pharmacists. The physicians reported that they receive MOH circulars, similar to the KDFC DHCP presented

to them by the researcher. However, they do not receive these circulars regularly. On the other hand, a discrepancy in the pharmacy technicians' focus group was noted at two points. Firstly, while the MOH and KDFC circulars were mentioned to be frequently received in certain situations, such as urgent situations and medication recalls due to impurities, were voiced, other pharmacy technicians reported not receiving MOH circulars. These pharmacy technicians were not fluent in Arabic (communicated in English). However, they believed that it was received by the in-charge pharmacist. Secondly, when the pharmacy technicians were presented with a sample of a KDFC DHCP letter by the researcher, all pharmacy technicians reported never seeing a similar letter before. On the other hand, pharmacists reported searching MOH's Twitter and Instagram accounts for medication-related updates. Pharmacists also reported receiving medication safety information from the Inspection Administration. In addition, pharmacists mentioned receiving circulars from the CMS, as described in the following quotation:

> *"we we receive from medical store about some medication or a so it will it will be like a circular distributed to our head of department and they will give us …"*(Pharmacist).

The KUFDA newsletter was reported to be received by the physicians and pharmacists, but not by all participants in these two group discussions. In the physicians' focus group, the KUFDA newsletter was reported as either not previously received, or received but infrequently. Similarly, not all pharmacists were aware of this tool of communication. Those pharmacists who were familiar with the KuFDA newsletter reported either hearing about it but did not receive it before, or that they have seen this tool before. One pharmacist reported finding the KuFDA newsletter opportunistically while searching online for information related to Ciprobay (ciprofloxacin). Both pharmacy technicians and nurses reported not being familiar with KuFDA newsletters. However, a belief that it must have been received by the central pharmacy and sent to other pharmacies was voiced in the pharmacy technician focus group.

Pharmaceutical companies were mentioned as sources of information by pharmacists, pharmacy technicians and physicians. Nurses, however, reported that they have no contact with pharmaceutical company representatives. Both pharmacists and pharmacy technicians' focus groups reported receiving information from pharmaceutical companies if the medication was

newly available in Kuwait. They both added a medication-related issue as another situation where pharmaceutical companies provide them with information. In particular pharmacy technicians reported receiving information from pharmaceutical companies in the case of an error related to medication manufacturing, in which the pharmaceutical company would recall the medication of concern. Similarly, having a problem with the medication, such as an expiry issue related to injections, would lead the pharmacist to contact the pharmaceutical company for information confirmation. Pharmacy technicians had also specified that pharmaceutical company representatives would conduct lectures in the pharmacy department. In the physicians' focus groups, hesitancy was expressed regarding whether they received information related to medication warnings from pharmaceutical company representatives or not. Nevertheless, they indicated that pharmaceutical company representatives inform them about updates in medication indications. Physicians also reported that pharmaceutical company representatives would ask them about their medication-related experiences. In addition, these representatives meet with physicians to ask them whether they knew about certain information (the type of information was not specified). Furthermore, some people (physicians did not specify who) approach physicians to ask them whether the representative had delivered information to them. From a physician's perspective, these individuals are checking whether the pharmaceutical companies have done their job properly or not, as expressed in the following quote:

> *"I have seen some people coming to us doctors and a they are asking whether the representative told you about this what is this drug and how it is used and they are talk they're checking that watching the representatives a whether they are doing their job properly or not this has been some representatives are coming to us about they asked to meet us and they ask us are you aware of this are you aware of this"* (Physician).

Besides learning information from pharmaceutical company representatives, both pharmacists and pharmacy technicians reported reading medication leaflets. Pharmacy technicians, however, specified that they have never seen a DHCP letter or a circular from pharmaceutical companies.

Both physicians and pharmacists use international drug regulatory agencies to be updated with medication safety information. Only pharmacists reported using UK MHRA. Both pharmacists

and physicians mentioned learning about new information from US FDA. This is described by a physician in the following extract:

> *"FDA warnings usually … so we are become aware especially doctors here we are more careful whenever there is any update about a warning from FDA we look into it the normal which we are referring every day like Medscape medicine UpToDate BMJ and this new journal of medicine all this we look for the what is happening"* (Physician).

Interestingly, pharmacy technicians reported they do not use the US FDA as a source of information despite their awareness of its availability. This is because they perceived that the MOH would send a circular about any information updated by the US FDA.

Scientific journal articles, formularies, books and conferences were reported as sources of medication safety-related information. Physicians, pharmacists and pharmacy technicians reported reading journal articles. Pharmacy technicians reported reading articles in medical journals, such as American drug journals, as well as reading the Pharmacist Journal published by Kuwait Pharmaceutical Association. Physicians mentioned reading recent articles and cited both the British Medical Journal (BMJ) and the New England Journal of Medicine. Whereas, pharmacists did not cite a specific journal. Pharmacists also mentioned using books and textbooks without specifying their titles. However, physicians reported previously using books, but not currently as described in the following quote:

> *"we used to use books but now I think it's it's too too regressive we cannot rely on books anymore"* (Physician).

In the physicians' group discussion, one physician stated previously used the BNF during his University study in Ireland. This led to the discussion about the lack of existence of a similar medication information source that is based on medications available locally in Kuwait. One physician indicated a book that includes the most common drugs in Kuwait, but he was not sure if it was a MOH publication or not. A more senior physician (i.e., had more years of experience than the other physicians) mentioned that Kuwait Drug Index (KDI) is a useful source for quick

reference of information on medications that are registered in Kuwait. KDI was used as a source of information by this physician, but he mentioned it was discontinued without knowing the reason for its discontinuation. The British National Formulary (BNF), was reported to be used by both pharmacists and pharmacy technicians. This is described by a pharmacist in the following quotation:

> *"mainly UpToDate Lexicomp Epocrates because I heard that they use it in Canada and BNF"* (Pharmacist).

Pharmacists had also added conferences as a source of medication safety information.

Local sources in the hospital, where the HCPs practised, were revealed by all HCPs groups. Generally, these included information from the administration, colleagues, local publications by staff members, lectures being conducted by staff members, or visual prints (without specifying the source of the print). Only pharmacists mentioned hospital administration as a source of medication safety information. This included administration distribution of paper-based materials or posting information on their Twitter or Instagram accounts. Colleagues being a source of information were mentioned by all groups. The pharmacy technicians mentioned the in-charge-pharmacist and senior colleagues as sources of information. Similarly, physicians reported MOH circulars are being shared by their new head of department through a WhatsApp group (specific for physicians in their department).This was stated in the following excerpt:

> *"Actually we have very good group in our medicine department you know it's called … group were our head actually she is very active and she is publishing everything what ever comes from the Ministry of Health information it is being distributed to all the doctors"* (Physician).

Pharmacists mentioned colleagues from the central pharmacy as sources of information, whether new information or information about a new medication. After searching for the information, these colleagues would conduct lectures and prepare a brief sheet containing information about a new medication, if requested by other pharmacists. Likewise, nurses had mentioned colleagues,

but from other professional backgrounds, including physicians and pharmacists. Nurses stated that the pharmacists would provide them with information in case of an issue had occurred (the type of issue was not specified); and when the nurses request medication from the pharmacy (such as ward nurses requesting medication for inpatients or stocks). Moreover, nurses reported receiving information from pharmacists regarding medication storage. Nurses also mentioned receiving local publications that are developed by pharmacists. These included circulars from the pharmacy department regarding new medications. These also included protocols and policies developed by the pharmacy accreditation team for nurses to follow, such as the drug calculation book. Before being distributed to nurses, nurses reported that policies developed and/or updated by the pharmacy accreditation team are approved by the director of the hospital. A local source that was only mentioned by the nurses was a visual print of LASA medications, which was hung in the wards near nurses. Nurses also reported attending classes in the hospital to improve their knowledge. These included weekly classes conducted by the Staff Development Unit (SD [specific for nurses]) and the Quality Control department to teach nurses about protocols. Additionally, the nurses mentioned that these include special classes for medication. According to the nurses, they also have weekly rounds, at which they check medication-related information through the internet. Besides the weekly lectures and rounds, nurses are required to attend an annual assignments class and seminars to upgrade their knowledge. Nurses' weekly round are explained in the following quote:

> *Weekly we are arranging for Saturday one nursing round class and checking one diagnosis and what all medication we are using and we are checking this one through internet and we are checking side effect when to contain what intra this one contraindication indication and everything regarding medication* (Nurse).

All HCPs groups cited applications and software as sources for updating their knowledge of medication safety. Pharmacists, pharmacy technicians and physicians mentioned UpToDate as an example of an application they use to update their knowledge; and, Medscape was cited by physicians and pharmacists. Medscape was mentioned in the physician group to be the source for reading about the ranitidine safety issue (regarding ranitidine impurity with NDMA) and a source for dosing adjustments. In addition, physicians reported using RxList, and LactMed. The latter was

used for information related to pregnancy and lactation. On the other hand, pharmacy technicians cited using an application named INVOICE for medical information; they, also reported using medicine feds. When discussing sources, nurses mentioned Google Play and applications to update their medication-related knowledge. An offline mobile application was specified as an example by nurses, which was BUDMUD. Pharmacists, on the other hand, had also reported using Lexicomp and Epocrates.

Using websites and/or the internet to obtain medication related information was reported by nurses, pharmacy technicians and the pharmacists. Google was mentioned by pharmacy technicians and nurses, and google scholar was mentioned by nurses, without specifying a website. However, not all pharmacy technicians agreed on using google as a source of medication safety information. Pharmacists and pharmacy technicians mentioned using the internet without specifying a website. Similarly, nurses did not specify a certain website for learning about medication safety updates, as explained in the following quotation:

> *"we don't have special website but but we are typing the medication by medicine name it will come it will be so many website but when we update and we will go our research by this way"* (Nurse).

The final sources of medication safety information were media and social media (other than MOH official accounts). Social media was recognised as a source by physicians, pharmacists and pharmacy technicians. Social media was considered a method for alarming physicians about medication safety information in case they were not updated through scientific sources. In addition, information posted on social media was reported to make physicians invest time in reading about the topic. Another point of view was voiced in the physicians' focus group discussion. This included viewing social media favourably and considering it the best source of information. This physician stated following updates from another specialised experienced physician, who regularly posts information on social media related to medication or internal medicine, whether from studies or approved medications from the FDA. Similarly, pharmacy technicians reported receiving notifications from Instagram accounts regarding new medications and their ADRs. This is stated in the following extract:

> *I use internet only but mostly I'm using Instagram [page] there are pages like pharmacy life and pharmacy related pages they will give you information if any new drug releasing they will give … notification about drug … reactions and adverse reactions* (Pharmacy technician).

The pharmacist also mentioned Twitter as a platform for knowing about medication information. On the other hand, the media was recognised as a source by pharmacy technicians and pharmacists. Examples of using media by pharmacy technicians included reading newspaper articles and the news. Pharmacists reported situations where media is used. These include knowing about information related to conferences and knowing about medication-related complain.

Table 5.7 Illustrates examples that were stated while discussing the sources, asked by the researcher to provide examples, or opportunistic examples mentioned by the HCPs during the discussion.

Table 5.7: Examples of previously received medications communication

Medication involved	Nurses	Pharmacy technicians	Pharmacists	Physicians	*Illustrative quotations*
Zantac (ranitidine) (Pharmacists: social media before it was sent by the MOH; received official MOH circular regarding ranitidine injection; Physicians: circular from the MOH was mentioned in the physicians focus group; Pharmacy technicians: first from social media, it was considered that the MOH was very late (estimated one week late) in delivering the circular to them. One pharmacy technician thought they had not received the safety information from the MOH, another thought they might have received an official circular. A third pharmacy technician mentioned that they had received the MOH circular but after they already knew about it from social media; two pharmacy technicians (not fluent in Arabic) who did not receive the MOH circulate regarding ranitidine safety information said their in-charge staff might have received it or that it was written in Arabic. They learned this information from their in-charge staff, who asked them to remove ranitidine from the pharmacy).	-	√	√	√	*"aa yes sometimes if there is any complain for example what haapened for the ranitidine it was first distributed in the media then there was a reaction from the ministry of health this is what we heared about" (Pharmacist).* *"Yeah yeah we we see official Ministry circular about … Ranitidine [in] circulate came" (Physician).* *"I saw it in Arabic [ranitidine- related from the MOH] but because we already knew about this issue so no one read it we all had seen the circular on the Internet I saw it on the MOH Instagram all the girls had already seen it so directly we put it in the file no one had read it" (Pharmacy technician).*
Diovan (valsartan) (Physicians first learned of it through social media).	-	-	-	√	*"… for example diovan we were scared [at the beginning] then we relised … it's chineese aa manfacture that had the carsinogeneic not the European which is used in Kuwait so it's not applicable concern here in our unit … so it does situmulate you to read more we get the information but it's not as you said it's definitely not a source … physicians or healthcare woekers reliy on social media that's a disaster" (Physician).*
Fluoroquinolone; Ciprobay (ciprofloxacin) (Pharmacists: learned about fluoroquinolones alert from US FDA and did not receive it from the KDFC; Ciprofloxacin: a pharmacist learned its safety issue from KuFDA newsletter). **Antibiotics' drug-drug interactions:** this was also mentioned in the pharmacists' focus group, which was thought to be received locally form the department (the source of the original information was not specified).	-	√	√	√	*"I would like to add something not just valproic acid there is recent FDA warning regarding fluoroquinolones use in epliptic patents and patients with tendinitis I see this daily doctors are prescribing fluoroqunilones in epliptic a but personal I haven't received any warning from Kuwait regarding the safety use of fluroquinolone …" (Pharmacist)*

Also mentioned Augmentin (Amoxicillin / Clavulanic acid) (Pharmacist, the source of information was not specified). **Klacid (Clarithromycin):** this was mentioned in the pharmacy technician group, the source of information was the clinical pharmacist.					*"other Zantac and for Klacid also when they when the clinical pharmacist came specific for Klacid they said a for medical wards they are not using a mostly Klacid and so they checking two three times with them you have to check with doctors" (Pharmacy technician).* *"It depends no no I mean like certain things we already know for instance when the fluoroquinolones blok Black box warning or a you know the tavanic We already know about its nothing knew that tavanic will prolong the QTa and rupture the tendon this is old news for some reason became ... up and I think here no one really followed you know it didn't affect our prescription because we give it when it's indicated so once the medication is indicated I think we are already careful about prescribe you know so side effects like those they are nothing new to you and we didn't experience ... (Physician).*
Diltiazem (a pharmacist learned its safety issue from KuFDA newsletter).	-	-	√	-	*"From KuFDA [newsletter] I find the black box indication for ciprobay and talizem [diltiazem]" (Pharmacist).*
Proscar (Finasteride) (pharmacist learned the information from drug leaflet or a book, but not from KDFC or the MOH).	-	-	√	-	*"That the pregnant even they should not touch this a proscar [we give] and we are not telling that patient they are not doing counsling it's very important for proscar also there are so many drug vary harmful for the collegues also or the person who is giving medication to their parents or family member ..." (Pharmacist)* When asked why are they not informing the patients about Proscar's teratogenicity, a pharmacist responded*:* *"No not we ... I'm telling general from the government from the safety a authority they didn't give us any information about this whatever we are*

					taking from information from leaflet or book we are writing" (Pharmacist).
Ezipect (Bromhexine Hydrochloride) syrup (pharmacy technician, source of information: in-charge staff member).	-	√	-	-	*"Last year maybe [hear] we removed ezipect syrup mucolyte there is some particles"* (Pharmacy technician). *"When the pharmacy technician was asked who told him about this information he responded: "like some in-charge they send us … to remove the pharmacy"* (Pharmacy technician*).*
Roaccutane (Isotretinoin) (pharmacy technician, the source of information was not specified).	-	√	-	-	*"not necessarily Depakine for example in the dermatology [pharmacy] they have Roaccutane of course the doctor will talk to [the patient] about Roaccutane"* (Pharmacy technician).
Neurontin (Gabapentin); Lyrica (Pregabalin) (pharmacist, the source of information was not specified).	-	-	√	-	*"For example the Neurontin and the Lyrica they have more restriction like [they] should be like different prescription anticoagulant"* (Pharmacist).
Anticoagulant (pharmacist, the source of information was not specified).	-	-	√	-	*"For example the Neurontin and the Lyrica they have more restriction like [they] should be like different prescription anticoagulant"* (Pharmacist).
Electrolyte	√	-	-	-	*"Electrolyte we are not mixing with the other medicines we are keeping it separate cabanit and there is a a special register also aa [senior] stamp and you will realease the one aa handling this one and a record also we have a updating if we are using it we we are not keeping in stock according to the patient needs we are getting from the pharmacy"* (Nurse).
High-risk medications/ high toxic medications	√	-	√	-	*"high risk medication in a now high-risk medication they removed form the medical department make only for the special areas is more safety [now] and the there is strict order the doctor should write in aa MR you know brother's note on the treatment sheet without that we can we are not able to and also there*

					should be two staff nurses to be noted before we are giving the medication this .." (Nurse).
Look A Like and Sound A Like (LASA) medications.	√				*"and also there for the LASA medicat medication"* (Nurse).
Manging broken Ampules		√			*"A recent last year they make one yellow box to broken ampules to put in yellow box"* (Pharmacy technician).
Warfarin	-	-	-	√	*"... really like rarely one of them will have a major major side effect but the one I can think of that have like we mentioned earlier warfarin maybe that's the one little bet concern"* (Physician). *When asked concern about what the participant answered: "With the safety wise because patient has to be cooperative and we do try explain to the patient but we don't let them sign ..."* (Physician).
Chemotherapy	-	-	√	-	*"So many drugs we which we are dealing here like cancer drugs like ... injection it is very harmful for the person who is diluting so we have to give good information to the sisters and doctors as a pharmacist from the pharmacy"*(Pharmacist).
Adenuric (Febuxostat)	-	-	√	-	*"Yeah there is a recent warning regarding the the use of the I don't know if I'm pronouncing the brand name Adenuric for hyperuricemia aa that cannot should be avoided or caution in patient with am a cardiovascular disease but I see a lot of prescription its prescribed a lot for a patient with heart failure with ischemic heart disease a and no one is doing anything about it"* (Pharmacist).

Following this, the HCPs mentioned their experiences with using medications safety sources, which is presented in the following theme (5.3.1.2).

5.3.1.2 Experiences with the sources of medication safety communication

This theme presents the experiences of HCPs using different sources of medication safety information. It includes two subthemes that reflect HCPs' preferred sources and the challenges of using sources of medication safety information.

5.3.1.2.1 Preferred sources of medication safety information

All HCP groups cited their preferred sources of medication safety information. Preferred sources by physicians included UpToDate and Medscape. UpToDate was perceived to be faster in releasing updates than Medscape by one or two months. However, Medscape was considered to be more summarised than UpToDate and to be useful for dosage adjustments. Physicians' preference for using UpToDate and Medscape is illustrated in the following quotation:

> *"More most commonly we are using as he said Medscape and UpToDate these are standard any doctor uses"* (Physicians).

LactMed was also preferred by one physician in the case of pregnancy or lactation. Another preferred source in this group of HCPs included the US FDA. On the other hand, nurses favoured updates and protocols from the pharmacy department and pharmacy-quality accreditation team, as well as circulars. Nurses emphasised that they are not against other sources, such as Google, but they prefer the use of circulars due to different reasons. These reasons included that circular- are official and considered to be proof, and they could be handed from one staff member to another, between the in-charge nurses, and from one ward to another. Moreover, nurses explained that circulars are available for the staff to read without missing information as seen with verbal communication. Similarly, nurses preferred communication and updates from the pharmacy department as they considered them to be official since they are approved by the hospital director.

Generally, pharmacy technicians expressed that this is the internet age, and they preferred general sources, such as the Internet, websites and software. They also considered these sources as an easy option for all staff members to use. The sources preferred by pharmacy technicians also included MOH circulars, BNF, and medication-related applications like Epocrates. A pharmacy technician differentiated between websites and circulars. This included noticing that websites target all HCPs, but circulars are for the pharmacy department. Moreover, Instagram pages and notifications were also considered to be easy to use and were cited as preferred sources, as clarified in the quote that follows:

> *"there are pages like pharmacy life and pharmacy related pages they will give you information if any new drug releasing they will give notification about drug ...reactions and adverse reactions"* (Pharmacy technician).

The sources that were cited by pharmacists as sources they prefer included applications, BNF (book and application), Lexicomp and original studies. They mentioned that applications are fast and information could be taken from them immediately. It was also stated that both books and applications are easy to read. Medication leaflets were also reported to be sometimes used, as the pharmaceutical company would explain how to use a medication. Comparisons between the different sources were made by pharmacists. The BNF, for example, was described as easy to read, but not detailed. Therefore, original (primary) studies were used to compare the strengths of the evidence. Primary studies were also mentioned as having updated information compared to the BNF, guidelines and textbooks; and Lexicomp and primary studies were perceived to have more detailed information than the BNF. Pharmacists also mentioned that the source they prefer to use depends on how urgently the information is needed (an example given for urgent need is when a medical colleague asks about medication), the type of information they need, and the question they need to answer. If the information is needed urgently, websites would be used. Regarding the type of information, it was mentioned that if the question was about a medication, then Lexicomp and Epocrates would be utilised. However, a preference for Lexicomp over Epocrates was voiced because the former is more focused on medication problems, thus relevant to pharmacists.

UpToDate was also mentioned to be used if the question is disease-focused. This was explained in the excerpt that follows:

> *"it depends on the question I'm facing if I face the question that is related to a disease or a condition I might actually use UpToDate if I was find the question that was related to medications manily I would use Lexicomp and Epocrates but preferably I would use Lexicomp because a as pharmacists our main focus is aimed at the medication problems"* (Pharmacist).

5.3.1.2.2 Challenges with medication safety information sources and suggestions for overcoming these challenges.

These challenges included (1) not trusting the source of the medication safety information, (2) information not based on medications locally available in Kuwait, (3) medication safety communication not being effective in attracting HCPs' attention, and (4) sources' delays in publishing new information. Not trusting the source of information was reported by physicians and pharmacists. On the one hand, physicians reported not trusting information from social media or pharmaceutical companies. According to the physicians, both sources might introduce bias, thus they double-check information from these sources. On the other hand, not trusting the MOH to be a source of medication safety information was mentioned in the pharmacy focus group discussion. Although, one participant reported they cannot judge KDFC's tools as they have not received them previously. The reasons for not trusting the MOH with medication safety information included not trusting resources used by the MOH, as pharmacists reported they do not specify the sources. Another reason was feeling that the MOH is not an authentic source and they need an authentic source to use such as the BNF or Lexicomp.

> *"I have an opinion but it might be taken as slightly as radical opinion the thing is as total I do not trust the like the Ministry with such papers I would prefer using an application such as Lexicomp it already has a special alert section for warnings or anything that's related to medication a problems for these I don't know even for the sources they do not like specify the sources like I I have some trust issues with"* (Pharmacist).

Medication safety communication is not effective in attracting HCPs' attention was reported by the pharmacy technicians. Nevertheless, different opinions regarding this matter were expressed in this focus group. Although KDFC tools were considered by some pharmacy technicians to be good, paper-based medicines safety communications were reported to be ineffective at attracting their attention because they can be forgotten as a result of the workload. Thus, a pharmacy technician perceived that it would be better to combine them with a lecture, as described in the following quotation:

> *"okay for example if we are going to distribute it for every pharmacist or we had a load in our work in the pharmacy I will not pay attention to it I will not give it a lot of importance it is not that I will not give it (the importance) I will ask a colleague who will tell me for example what is (written) in it"* (Pharmacy technician).

An opposite opinion was voiced in the pharmacy technician group discussion considering it (paper-based) the most effective method of disseminating information in an emergency situation. Such a method would attract their attention to the safety issue as they would see it (the paper-based communication) in front of them on a board.

> *"by media we receive we don't know but it is most commonly used by the paper only because they can stick like notice boards anywhere we can focus on that"* (Pharmacy technician).

Sources' delays in publishing new information were mentioned by both the pharmacy technicians and the pharmacists. Despite the Pharmacist Journal being mentioned as a source of medication safety information by a pharmacy technician, it was expressed that they mostly published information about meetings, and rarely about medications or research. Similarly, the MOH website was criticised for not publishing such information all the time, while they might publish it sometimes.

Finally, sources used for medication safety information not being based on medications that are locally available in Kuwait were expressed by physicians as a challenge. A need for locally based sources was voiced as clarified in the following quote:

> *"because sometimes you look at the reference and they tell you the dosage and it's like here for gabba albumin here is in milli fluid mL and we have to calculate it and it's a bit tricky but if we have a local reference I don't think anyone would mind because microbiology they introduced booklet for [XX] for common infections so we do look it up"* (Physician).

After presenting HCPs' experiences with medication safety information, the following theme (5.3.1.3) focuses on HCPs' attitudes towards the implementation of medication safety communications.

5.3.1.3 Attitudes to responsibilities and the implementation of medication safety communications

HCPs mostly expressed positive attitudes towards implementing medication safety recommendations. These are stated in 5.3.1.3.1. However, all HCPs commented on the responsibilities of other healthcare professionals in implementing these recommendations. HCPs attitudes towards the roles of other HCPs in implementing medication safety recommendations are presented in 5.3.1.3.2.

5.3.1.3.1 Attitudes towards implementing medication safety recommendations

Except for physicians, all HCPs groups mentioned they always follow the medication safety recommendations. All HCPs groups mentioned the reasons for following medication safety recommendations. These included protecting patient safety and providing the patient with appropriate care and the right therapy. Protecting staff from committing errors was another reason provided by nurses, pharmacy technicians and pharmacists. This is demonstrated in the following quotations:

> *"actually for our own also because sometimes if you do some errors or somethings you will the one who will be in troubles they're always following whatever rules we have the regulators"* (Nurse).

> *"I'm telling not only for them for colleagues for ourselves also"* (Pharmacist).

The physicians, however, were the only group who provided situations where they did not follow such recommendations. Among these were situations where they felt the evidence supporting the recommendation was weak. One physician mentioned that MOH not providing information about a certain issue reflects that its evidence was not strong, as explained by the physician:

> *"I think the only medicine … we were sceptical about it for me was a Plavix and losec clopedogril … combination interaction I never followed I didn't think it was a strong evidence that's wasn't even like strongly you know it wasn't here locally it wasn't here locally the Ministry against or opposing the combination so"* (Physician).

Physicians also questioned the changes that occurred to the recommendations. In addition, they questioned the evidence in some situations. This is because they have or know patients who used the medication of concern for years before the recommendation was issued without any harm to the patients. The following quotes explain these two previous points:

> *"renal arteries stenocis In ACE and ARB like now they're treatment they used to be contraindication now so sometimes I think at the end of the days medicine change it's not constant what you know then might change now"* (Physician).

> *"how strong is the recommendation because ranitidine I have seen for many people are using for 15 years many people we know have used and nothing happened so this thing discovery now [laugh] this we are not using anymore ranitidine but how strong is the evidence we don't know" (Physician).*

They clarified, however, that if an alternative medication was available, the alternative might be prescribed until the issue is confirmed, as described in the quote that follows:

> *"I think that's the thing like Diovan if you were not sure just go with the other ARBs until you double check the like how consistent how how strong this indication"* (Physician).

Another described instance of not following a medication safety recommendation involved believing they are prescribing the medication because it is indicated while they are already aware of the safety issue. A point brought up in the physicians' focus group is that the patients' privacies should be maintained while implementing medication safety recommendations.

5.3.1.3.2 Attitudes towards the roles of HCPs in implementing medication safety recommendations

Interestingly, all HCPs commented on the roles of other professional groups in discussing the implementation of medication safety communications. This included nurses, pharmacy technicians and pharmacists describing the roles of physicians in implementing medication safety communications and physicians commenting on the roles of nurses. The roles other pharmacists have in not implementing medication safety communication were also described in the pharmacists' focus group.

Nurses highlighted perceived malpractices in physicians' prescribing, such as not writing that medication is discontinued on the treatment sheet and giving antibiotics for a long duration. Nurses also mentioned that they talked about this issue with the head of the department. This person informed junior physicians about it. However, the issue was not resolved according to the nurses.

> *"You know Tazocin they started today tomorrow they will change to Rocephin there is no gap to start … nothing to do I don't know… so many hour so that they will start Tazocin then they will start Rocephin then evening Klacid"* (Nurse).

> *"Because we have the main problem in the medical department never their doctor are prescribing on prescription sheet there never … are … medicine on the treatment sheet"* (Nurse).

Nurses had also described physicians not accepting to be informed or questioned by nurses was also reported.

> *"Staff nurses we were telling the doctor we were not accept they will ask you you are staff nurse who...are to teach me you know but we are facing and we are the one administrating"* (Nurse).

Nurses in the OPD reported a positive experience of nurse-physician collaboration for improving patient education. Following training in diabetes, nurses discussed collaborating and having close contact with physicians and patients in an initiative that was perceived as coming from a physician. The types of activities they performed included providing diabetes health education to hospitalised and OPD patients. This education involved information about diabetes mellitus, its medications, signs and symptoms; and, the patient could contact these nurses by their phone number. They also reported that they were being trained to deliver the same service to patients attending neurology clinics. The nurses expressed that this was a positive experience for them and the patients, as the patients appreciated the information provided. In the inpatient wards, nurses reported providing education to the discharged patient. This information includes drug and food interactions, as well as simple health education.

Physicians stated that the nurses in the inpatient setting might jeopardise patient safety. This is because, unlike in the OPDs, pharmacists are not involved in counselling the patients, as they only dispense the medications, and the pharmacists in the OPD check the prescription for duplicate

therapies. It was also mentioned in the physicians' focus group that nurses might be distracted or busy. It was also indicated that they do not know if the message was delivered appropriately to the patients or not if counselled by a nurse. They explained that any person that would counsel the patients should be checked that he/she has the right information. They also suggested that nurses should not explain to the patients if they (the nurses) were not aware of the information or if they were not focused. It was also mentioned that physicians are not aware if nurses are doing their job properly or not.

> *"I think maybe an important safety point is to make sure the patient gets the information correctly from the like to desi designate who's the person that should provide the information to the patient because what happens here is you go you talk to the patient you explain everything you want to explain then the nurse comes you know because the pharmacists just dispense to the in-patient discharge in-patient and then the patient gets the information from the nurse so the nursing staff will be like just saying whatever you know maybe they're busy maybe they're not annoyed aware and this is a problem in the like"* (Physician).

Interestingly, it was suggested in the physicians' focus group to conduct the medication safety communications focus group with the nurses. While nurses also suggested giving the example used as a DHCP letter from KDFC (valproate rated) to the physicians.

Initially, the pharmacy technicians indicated that they would implement medication safety recommendations without any barriers. One provided example was drug-drug interactions. However, during the valproate discussion, one pharmacy technician perceived that it is the physicians' role to implement such recommendations. This included providing information to the patients. It was also revealed during this group discussion that the pharmacy department could give extra information if the patient asked about a medication's safety during pregnancy, however, the primary and most important source is the prescribing physician, as described in the quotation that follows:

> *"we as [the] pharmacy [department] we can give to the patient extra information what I know for example the physician when he wants to prescribe a medication for sure he will ask her [the patient] about her condition or for example he will tell her that she could not take it [the medication] we can [the pharmacy department] for example give her [information] as an information only"* (Pharmacy technicians).

Pharmacists reported that physicians insist on their opinions, which might contradict the safety recommendations. As perceived by pharmacists, physicians might refuse to change a wrong dose of medication if it was a home medication. This is explained in the following quotation,

> *"…sometimes when we are telling about this that to this does must not for example Xarelto they are not taking 20mg they are taking 15mg they are telling this not this is home medication the patient is taking it since long"* (Pharmacist).

However, information not being passed to physicians was also reported in the pharmacy focus group discussion as a reason for the perceived lack of physician implementation. Pharmacists not taking responsibility for implementing medication safety recommendations while blaming physicians were also highlighted. A pharmacist described this thought as follows:

> *"I think a major barrier is am not I I really sure of this not every pharmacist is willing to participate reading such papers or such articles and changing their practice not everyone a lot of them they just think it's going it's going to be like the doctors' fault for writing such a mistake like some of them they are not willing to take the responsibility for the approval for such a prescription"* (Pharmacist).

HCPs' experiences with the valproate-related KDFC's safety communication were also explored. These are presented in 5.3.1.4.

5.3.1.4 HCPs experiences with the valproate-related KDFC's safety communication

This theme demonstrates the experiences of the HCPs with valproate-related medication safety communication. It included HCPs' both HCPs familiarity with the valproate-related safety communication (5.3.1.4.1), and implementation of the valproate-related recommendations (5.3.1.4.2). This theme also included HCPs' perceived barriers and suggestions for improvements, both related to the valproate-DHCP and for medication safety communications generally (5.3.1.4.3).

5.3.1.4.1 HCPs' familiarly with the valproate related safety communication

All HCPs in the four groups, except one pharmacist, were not familiar with KDFC's valproate-related DHCP letter. This pharmacist described receiving the valproate DHCP letter while working in another secondary MOH hospital. On that occasion, the pharmacist indicated the DHCP letter was sent from the director of the hospital to the pharmacy department. While other pharmacists participating in the focus group discussion reported not receiving this DHCP letter, the possibility of receiving it while not remembering was expressed. This is clarified in the following quote:

> *"the date of this circular is 2016 so it's more than three years ago maybe it was distributed nobody will remember that so I have an issue with the date of the circular"* (Pharmacist).

Despite a lack of familiarity with KDFC's valproate-related DHCP letter, some HCP groups knew about the teratogenic risks of valproate. In particular, neither pharmacy technicians nor nurses were aware of this risk. As a result, nurses felt that they should have known about this information as they are responsible for medication administration to patients. However, paediatric ward nurses initially perceived that their patients were not targeted as they were younger than 12 years old, as stated in the following quotation:

> *"yeah because we are in the paediatric side and 12 years old and below we are giving for some patient male or female so maybe that's why we don't have this information regarding this"* (Nurse).

Nevertheless, their perception of their patients' irrelevance changed after reading the DHCP demonstrated by the researcher, which also included female children. On the other hand, awareness of the teratogenicity risk was demonstrated in the pharmacy and physicians' groups. Sources for knowing about this risk cited by the pharmacists included US FDA and MHRA. None of the pharmacists reported learning about this information from local sources in Kuwait, as reported in the following quote:

> *"yes it should be avoided in childbearing females unless there's no other options but I haven't received this in Kuwait [I mean] I have read this outside"* (Pharmacist).

However, not all pharmacists were aware of valproate's teratogenicity even if previously dispensed this medication to female patients. In contrast, all physicians were aware of this risk as they reported studying at the university was their source of knowledge. Similar to pharmacists, physicians were not informed about this risk through KDFC, as explained by a physician:

> *"we know it but nobody has told us but we know it birth defects and those things are common with valproic acid we should not use in pregnancy unless you give folic acid or you warn the patient and this"* (Physician).

Although physicians were aware of the valproate-related risks without receiving the DHCP letters, concerns were voiced that there might be other DHCP letters with safety issues that they did not know about.

5.3.1.4.2 HCPs' implementation of the valproate related recommendations

The physicians reported that their previous knowledge about valproate teratogenicity had affected their practice. This is specifically in terms of prescribing valproate for females. However, different situations were stated concerning whether they do or do not prescribe it. On the one hand, they reported that they do not use valproate in female patients. As all physicians participating in the focus group were from internal medicine, they expressed that physicians in their speciality rarely prescribe complicated medications or medications with major side effects, except warfarin. They explained that valproate is initiated by neurologists as some patients might be resistant to treatment. Even if they encounter a female patient on valproate, they would confirm with the prescribing physician or neurologist regarding their choice of treatment, as demonstrated in the excerpt that follows:

> *"we we question mark this situation because we have to know why now like in this day and age we still going to valproic acid when you have different safer options so we already like know this but again it's nothing new that it's harmful for female and childbearing age and teratogenic effects so we already know but sometimes you patients very resistance they're like on two three drug already by neurologists that's the only scenario when we are not really we ask them again the neurologist are you sure you want to continue this they decide but personally I I never give*" (Physician).

Physicians reported that they were not obligated to prescribe valproate as it has alternatives. For example, the majority of physicians indicated that they would initiate levetiracetam, as an anti-epileptic, instead of valproate. When it comes to medications that have no alternatives, however, they stated that they would consider the benefit-to-risk ratio.

> *"usually valproic acid is from the medications that have many alternatives ... unlike for example there are medications that [you are] compelled [to prescribe] that has no alternative in this case we have to see the benefit and the hazard relationship"* (Physician).

On the other hand, they also reported that they would prescribe valproate in resistant cases. Physicians clarified that they are trained to counsel patients about teratogenic medications in such situations. They would also be cautious, explain the side effects to the patients and inform the patient to avoid pregnancy while on valproate. Nevertheless, they stated that if the patient was planning for pregnancy, they would advise her to delay her pregnancy for some time. This is so they could replace valproate with a safer alternative, as described in the following quote:

> *"if the patient is really dependant on it if the time-frame we advised them against pregnancy while on it because it's teratogenic and if they are planning to get pregnant maybe they can delay it for a while and then substitute the drug withdraw it and introduce the safer option l like it's a it's a it's a long communication process with the patient ... we already trained in our way but not like a formal letter saying how to communicate it no like but we already been trained during our study in medical school in post-grad school education how to communicate teratogenic medication to childbearing age women but again even if I have a scenario where I have to give a patient teratogenic medication we have to explain to them"* (Physician).

Physicians were not aware of KDFC's valproate-related recommendation related to asking patients to sign a consent form to indicate their acknowledgement of valproate teratogenicity. It was perceived that they were not required to ask their patients to consent as mostly they do not prescribe complicated medications. Despite not encountering such a form, physicians were not sure whether prescribers of complicated medications have a special form or not for their patients to sign.

As nurses were not previously aware of KDFC's valproate-related DHCP or its teratogenicity, they did not implement any of the recommendations. However, a discussion was generated by the participants regarding the targeted population. After reading the valproate-related DHCP, nurses concluded that since the valproate-related DHCP targeted the paediatric population, consent from their parents should be obtained. This is demonstrated in the following quotation:

> *"just a question only doctor we are here not complaining … you just ask yeah …we didn't give this one to the children they mean … they need the consent of the parents the parents they agree …"* (Nurse).

They explained that even if these paediatric female patients were not affected immediately, they would get married in the future. This discussion also raised two questions. The first was how common this safety concern is. The second question was why valproate was not restricted by the pharmacy department, which is reported in the following quote:

> *"drug leaflet contraindication means there why they are not band this medicine pharmacy why they are supply still we use to get this medicine from the pharmacy how"* (Nurse).

Even after knowing about the valproate-related safety issues and recommendations, some nurses believed that knowing this information would not affect their practice as it is the physician's responsibility to implement such recommendations. This is demonstrated in the following quotation:

> *"it will not affect our practice … because doctor are prescribing you know…we will follow the doctors orders only"* (Nurse).

Nurses reported that they would notify physicians after learning about this information. In addition, nurses in outpatient clinics indicated that knowing about valproate-related DHCP would affect their practice in terms of providing information to patients.

None of the pharmacy technicians had dispensed valproate directly to a female patient within the last three years of conducting the focus group. Pharmacy technicians from the inpatient pharmacy reported providing valproate to the medical wards, while not knowing if it was given to female patients or not. The pharmacy technician who had dispensed valproate to female patients reported that she never asked patients to consent. However, this was five years before the focus group discussions (before the release of KDFC's valproate-related DHCP). After knowing about KDFC's DHCP, some changes to practice were indicated by the pharmacy technicians. These changes

included reading more about the DHCP and not dispensing valproate to pregnant patients. Similar to the nurses' group, two questions arose from the pharmacy technicians during the discussion. These questions were whether the recommendations are applied locally in their hospital, and second whether the DHCP instructs that patients' consent should be specifically taken by the pharmacy department. Another form of practice change after knowing about the valproate-related DHCP includes asking the patient directly whether the physician informed her about this information or not, so the pharmacy technician could further confirm the information for the patient.

The implementation of the valproate-related DHCP was only reported by one pharmacist, who noted receiving this medication safety communication while working in another MOH hospital. According to this participant, not all pharmacists in the other MOH hospital were interested in reading the valproate DHCP letter as it was perceived as being lengthy. However, they distributed the patient cards to patients who were using a valproate-related medication, as stated by this pharmacist:

> *"yes as I told you there was a circular we … a circular for that but sometimes … its the all the people do not read it … they will not be interested in reading actually it was … too long so I think what what was done that we distributed the card for the patient okay to be aware of it that all what was done"* (Pharmacist).

This participant clarified that patients' consent was not taken by the pharmacists in that hospital. Moreover, she did not know whether the prescribing physicians discussed the issue with the patients and obtained their consent or not. This participant perceived that the valproate-related DHCP letter and any information related to medication were only distributed to the pharmacy department. This according to the participant was a barrier to implementing the recommendations as they were not disseminated to other HCPs, such as physicians. This participant perceived that the valproate-related DHCP should have been shared with other HCPs so they could work as a team.

After knowing about the valproate- related DHCP, the other pharmacists reported their practice would be affected. An example provided for changing their practice included paying attention to the patient gender while dispensing a valproate related medication. Another form of change included appointing a pharmacy staff member for monitoring and applying new medication safety recommendations.

> *"for me I think we need to to have special personal regarding monitoring of safety and and apply new protocols for any new warnings for specific medication that we recive"* (Pharmacist).

It was also mentioned that the development of such protocols should take into account attracting the pharmacists' attention to the safety recommendations, as explained by a pharmacist:

> *"I can say one example of that protocol high toxic medication we are putting we triangle or high alert medication red circle I think it should be like this so all of the staff they … to be attention"* (Pharmacist).

5.3.1.4.3 Perceived barriers and suggestions for improvements.

Barriers to receiving medication safety communications were discussed in the four HCP groups. These perceived barriers were either common between the HCPs or specific to a certain group (i.e. mentioned by one group of HCPs). The shared barriers were either related to the current method of manual dissemination, miscommunication, information not being shared with the HCP group, or perceived irrelevancy. Whereas, barriers unique to the HCP group included information being masked by random messages, lack of medication updates-focused lectures, and lack of internet connections in the wards. Moreover, MOH not monitoring the implementation of DHCPs and not developing a protocol for this purpose was another barrier unique to the HCP group. The final unique barrier involved HCPs not having a WhatsApp application or not joining the department's WhatsApp group.

The first barrier was related to the current way of disseminating medication safety information, which is manual distribution. From the pharmacists' point of view through this method of dissemination, safety communication might fail to reach the HCPs. This is because it could mistakenly reach a different place. Moreover, HCPs who are on annual leave or sick leave might miss the opportunity to receive the distributed communication. Among the pharmacy technicians' group, despite valproate being available in their pharmacy stock, one pharmacy technician attributed being a new staff member (employed within the last three months of the focus group), as the reason for not knowing whether the valproate DHCP was received or not in their pharmacy.

Physicians also shared perceiving the current KDFC's manual dissemination of medication safety communication as a barrier to receiving these communications. The current way of sending such letters to the head of the department, who would verbally ask physicians to read the letter was considered to be inadequate. They also questioned using hard copies (paper-based) letters while there is a shortage of papers in the hospital, as expressed in the following quote.

> *"It's not enough it's old style who send letters nowadays you don't [have] paper to print for patients request you want to send the notification from the head and verbally the head will say read this and this"* (Physicians).

From the pharmacists' perspective, using papers slows down the dissemination process, as explained by one pharmacist:

> *"yeah this papers are these paper already slow they have to change"* (Pharmacist).

Nurses described administrative delays in approving the circular (or a medication safety communication) before its dissemination as a reason for delays in receiving information. From their standpoint, during the time the administration is approving a circular, the medication of concern is being used. Physicians, on the other hand, reported that the hospital administration does not intentionally stop the dissemination of medication safety communications as they are already conducting lectures and workshops related to medication safety for the accreditation process. They

suggested, however, that medication safety communications may file up unintentionally in administration.

Nurses had generally cited miscommunication as a barrier to receiving the valproate-related DHCP letter. According to pharmacists, miscommunication specifically between the MOH, KDFC, and other departments was a barrier to receiving medication safety communications.

Another barrier was mentioned across three HCP groups, which was the perception that information was not shared with HCPs. For instance, pharmacy technicians believed that the valproate DHCP letter might have reached the head of the pharmacy department, who they thought was responsible for distributing such letters to staff members, but it was only delivered to the inpatient pharmacy and not the outpatient pharmacies. Similarly, it was suggested in the physicians' focus group that the valproate-related DHCP might have reached the head of department or the unit head, but not delivered to the physicians at the ground level, as described in the quote that follows:

> *"I believe that usually these [letters] are delivered to the head of department or to the head of unit and then they reach a dead end I do not think that we are receiving anything directly or that we [have been] directly informed of any new [information about drug safety]"* (Physician).

Nurses, however, believed that the valproate-related DHCP was not sent to the nurses' representative on the risk management team of their hospital. Otherwise, this member would have passed this information on to other nurses. On the other hand, nurses expressed their feeling of being excluded from invitations to medication-focused lectures and conferences conducted by pharmaceutical companies. Additionally, nurses reported being excluded from receiving circulars. They believe that medication-related circulars are directed to physicians as they are the prescribers of medications.

> *"already doctor they give why the nurse should know why the staff should know from the other one who is writing"* (Nurse).

Nurses indicated that such information regarding medication safety is not shared with them by physicians or by the pharmacy department unless they request it, where they may receive an answer or not. Thus, nurses perceived that they were making an effort to search for medication information. Nurses believed in particular that physicians were required to pass such information on to them. Interestingly, nurses expressed two contrasting points of view regarding physicians' knowledge about valproate-related safety communication but not sharing it with nurses. Before reading the valproate-related DHCP (illustrated in the focus group by the researcher), nurses voiced that physician knew about this information but did not share it with the nurses, as expressed in the following quotation:

> *"Maybe reach for doctor and doctor not tell us"* (Nurse).

Another point of view was expressed regarding this matter after viewing the DHCP letter. This relates to obtaining the patient's consent before prescribing a valproate-related medication. As they did not see physicians asking patients for such consent, nurses believed, although not all agreed, that physicians were not aware of the valproate-related DHCP letter. Nurses also thought that they would have known about the information if they saw physicians taking patients' consent, as explained in the quote that follows:

> *"then we ask why you are taking consent at least we can ask that"* (Nurse).

Pharmacy technicians who were not native speakers of Arabic (communicating in English because they were neither from Kuwait nor from another Arab country) perceived reasons for not receiving circulars related to medication safety as their perception that such circulars are written in Arabic.

The irrelevancy of medication safety information to the HCPs' work was also expressed. For example, one physician indicated that the DHCP related to valproate was irrelevant to him since he does not prescribe it, but another antiepileptic. Similarly, no longer having valproate within

their pharmacy stock (which includes different specialities, such as obstetrics and gynaecology) was a perceived reason for not receiving the valproate DHCP by a pharmacy technician. The same pharmacy technician stated that they currently have levetiracetam in their pharmacy stock.

Other barriers were unique to one group of HCPs. One of these included random messages obscuring important information as expressed by a physician in the following quotation:

> *"but I think when it's send as paper even with me personally when I read the notification like you read this very important piece of information about a very common drug we all know about then you read something about a random like I can't even give you an example now because so random it's so totally different like workshop for a nominate three people to travel abroad for you know that what happens in the groups so sometimes the message gets lost even electronic but if you as an individual you know where is the source from"* (Physician).

Other barriers reported by the nurses included a lack of lectures focusing on medication safety updates. Nurses also mentioned that no Internet connection on the ward was a barrier to accessing medication safety information.

Pharmacists also provided other reasons for not receiving the valproate-related DHCP. These were mainly related to two levels, the MOH level and the pharmacist level. The MOH-related reasons included not following up and monitoring the application of the DHCP by HCPs. This included the MOH never developing a protocol after the dissemination of the DHCP to address the recommendations as expressed in the following quotation:

> *"so a protocol should be developed after 2016 for the certan childbearing mother so it never developed and never followed up by the Ministry this is the I think the problem"* (Pharmacist).

At the pharmacists' level, on the other hand, not having a WhatsApp application or not joining the pharmacists' WhatsApp group were reported as barriers to receiving medication safety

information. This is because these individuals would be unaware of the information shared in the pharmacy WhatsApp group.

All groups suggested methods to improve the dissemination and implementation of medication safety communications. One pharmacist was not familiar with the ADR online reporting system provided by KDFC, thus suggested to implement online reporting, as explained in the following quote:

> *"I think you are familiar with the yellow card scheme in UK right why we don't have something similar in Kuwait"* (Pharmacist).

While another pharmacist indicated that any change or suggestion to improve communication would take a long time as they are already facing problems related to patients visiting more than one polyclinic, while there is no unified system to know about what other medications is the patient is using. This is explained in the following quotation:

> *"if the problem was mainly about the communication process why are these papers not arriving us I think it's going to take a long time to ... to to solve it because we already facing this problem with the communication with the patient patients who are visiting more than a polyclinic ...we have a problem in knowing every single ... step we don't have a unified system so I think this is going to be harder ... we have to do it ... manually ..."* (Pharmacist).

However, a variety of suggestions were stated by HCPs participating in the four focus groups. These suggestions are presented in Table 5.8.

Table 5.8: Healthcare professionals' suggestions for future medications safety communication

Suggestion	Nurses	Pharmacy technicians	Pharmacists	Physicians	Illustrative quotations
Increase involvement and referral to clinical pharmacists (had previously positive experience with the role of clinical pharmacists, they had referral to clinical pharmacists but not all units are aware of it, they have an important role in patient education, physicians' rounds, appropriate selection of patients' medications, polypharmacy, physicians might forget; clinical pharmacists might do a better if received medication consultation requests instead of internal medicine physicians; supervision by clinical pharmacist will help in avoiding mistakes by pharmacy technicians).	-	√	-	√	Today they are advising the patient by mistake maybe the doctor is busy … is forget to tell the side effects or or anything warnings signs I think it's the duty of the the pharmacists also to help this matter I feel like this (Physician). "*Through the clinical pharmacist they have to a … this one like [like our charge ward] they have to they make so this we do do do not this one ma make mistake"* (Pharmacy technician).
Post medication safety communications on MOH/ KDFC website (This is so they could find the communication in the website; better to post the information in an official website that waiting for the paper-based letter to arrive; HCPs should not depend on receiving letters as they might get lost, better to know where to find them)	-	-	√	√	"*It's better if you have certain website for committee every one healthcare professional we can enter and see what the news what's up today better for waiting for circular come from many circular year to year"* (Pharmacist).
Use a formal electronic source/email for sending letters (the MOH should send emails to all HCPs at once; the staff members should have emails that are known by the MOH so the MOH could send alerts to them; questioned the use of paper-based circulars in favour of emails; the use of emails was suggested to overcome the barrier of not receiving the safety information due to sick leave/on-leave or circulars mistakenly not reaching to HCPs; the method chosen should be unified for all staff members).	-	-	√	√	*"Formal electronic source or don't bother sending letters that we waist"* (Physician). *… even if we get it not all people would be aware of it because sometimes because sometimes [those] people [take] sick leaves or they're not on duty so it's better aa it's better I think to … let say a there should be an email for all of us from the Ministry of Health to send these circulars but that's not happing sometimes even it's by mistake it doesn't go to the certain place or certain hospital so they're not all [aware] all these things* (Pharmacist).

Have a local drug index source (This should be as the BNF, but based on medications that are available in Kuwait; Kuwait Drug Index (discontinued source) used to be useful for quick referencing; they will not need to calculate the dose of some medicines if they had a local drug index/formulary).	-	-		√	" *but if we have a local reference I don't think anyone would mind because microbiology they introduced booklet for [XX] for common infections so we do look it up"* (Physician).
Send text-messages/ WhatsApp messages	-	-	-	√	*"Because now we are in media age its better to just to send messages to doctors" (Physician).*
Increase the involvement of the MOH and/or the KDFC in explanting the safety issue, checking that it has been received, and in monitoring the implementation of the recommendations (Ask HCPs if they had received the safety communications letters; MOH should dedicate a person to follow-up the safety communication and monitor its implementation (not following-up from the MOH was a barrier for not receiving VRM DHCP); Meetings groups from MOH (designate five people from the MOH to explain the issue to the staff)	-	√	√	√	*"They [KDFC] have to check also they have to meet the doctors and ask them nobody ever asked us nobody"* (Physician). *"Pharmacy technician: Some like groups ... like meeting groups from the ministry of health* *Moderator: meeting groups like* *Pharmacy technician: like a should maintain like some five members to explain about the what we have problem"* *"there is no follow up from the Ministry regarding this and develop a protocol and a way aa people aa follow through for this kind of information and apply it in their aa work setting a they will not do it so you need to monitor and a apply this from Ministry and a and I think there should be a dedicated person or personal from the Ministry to follow up with these monitoring"* (Pharmacist).
If an inpatient prescription contains a medication with a safety concern, physicians should put their stamp next to the medication name (To increase the sense of responsibility, This is to alert nurses, notify the pharmacy to check the patient information and check with prescriber, and nurses can explain to the patients).	√	-	-	-	*"at least doctor if we are dispensing from the pharmacy pharmacy can notify the patient age everything is mentioned all that so at least they can ... counsel or how we are who is prescribing medicine or you know antibiotics we have to put the doctor stamp while this medicine we have to put a stamp on the prescription same hospital they can do to risk to medicine the doctors they should stamp on it so we are responsible and we are the*

					one who… give so the pharmacy ask the doctor how you give it and … counsel we know explain to the patient this all (Nurse).
The information should be sent to heads of departments (This is to overcome administration delays, ensure the information will reachable to the staff members, and nurses will be able to disseminate the information through nurses' systems (thus wards and special areas will receive the information early), this was given as an example for proper communication).	√	-	-	-	"*for better they can handover to each department head of the department it's better that is we will get the information soon not delay administration they will approve and they will take maybe six months like that time we are using this medicine some other medication also come like this"* (Nurse).
To put the original copy of the information in the wards (This is because if only one nurse attended a lecture (where the information is shared), other nurses could still know about the safety issue; all staff would be able to read the information and sign next to it as a proof that it was read; a copy of the safety information could be placed in an information book as nurses already have one, after reading the information the staff member could sign next to it in the information book).	√	-	-	-	*"Maybe original copy in our ward all staff will read sign next... all knows if I am the one attended the class other ward all staff will see this information"* (Nurse). *"Once we received this message we used to write information book..."* (Nurse).
Regular lectures/ lectures with the circular (lectures suggested to be conducted by the Staff Development Unit (SDU, it involves quality nurses), the quality control department, or by pharmacists; outside lectures, such as those presented at pharmaceutical companies' conferences; a nurse suggested that doctors; from the pharmacy technicians focus group, lectures following a medication safety circular would help them to focus on the issue, remember it, increase the importance of the issue to them, as well as it will be a facilitator for them to implement the recommendation.	√	√	√	-	*"Regular class … and circular and class also for the doctors…"* (Nurse). *"Regular class or lecture"* (Nurse). *"This we need like this lectures and discussions like this it will improve our safety [information]"* (Pharmacy technicians). *"If I am going to distribute it to every pharmacist and we have workload in the pharmacy I would not pay attention to it that means I wouldn't give it a big importance it doesn't mean that I wouldn't give it [the importance] I would ask a colleague to tell me for example what is written in it on the opposite if there was a circular and we did a lecture it will be kept in your mind that there was a lecture that you attended and saw sometimes*

					here for example they would do outside for any medication celebrations [exhibitions] or something it will be kept [in the mind] the opposite if it was for example a paper for example sometimes I put it in my pocket [and] I forget about it" (Pharmacy technician).
All staff should continually be updated by good communication (examples mentioned through pharmacy or the administration; circulars were also mentioned; the administration should distribute the papers locally in the hospital and post the information in their official Instagram or twitter accounts).	√	-	-	-	*"Good communication any updation for any information regarding any medicine same thing to send to all our staff "*(Nurse). *"Already pharmacy is getting this information they can give copy to each ward yeah we will we will be aware of it"* (Nurse).
To take the patients phone numbers before their discharge (This is to facilitate the communication with patients after their discharge, pharmacists would be also able to contact the patients regarding their medications; a positive example that was applied by the OPD nurses (perceived to be a physician's initiative), which included having a close contact between the nurses, physicians and patients, was mentioned. This included nurses being trained to provide diabetic patients with education (disease and medication), answer their questions (the patient also has the nurses' numbers). These nurses also provide education for inpatients. At the time of the focus group OPD nurses were being trained to provide the same service for neurology clinics).	√	-	-	-	*"Better to take the patient phone number if any thing if patient discharge from our hospital you can contact also by pharmacist about this medication because now we are following in the hospital after discharge at least there is something"* (Nurse).
Include the medication safety information in a leaflet for discharged patients (This was suggested to guarantee that the patient would have the appropriate awareness about his medication safety as currently inpatient do not have contact with patients such as in the OPD example; nurses can give the patient this leaflet while providing them with health education; such leaflet would be clearer if it was written in both Arabic and English).	√	-	-	-	*"No we don't because you know better to provide this on leaflet during discharge from us patient we can give to them on discharge because usually they have … patient have …[medication] you have no contact with them so better to provide this risk …risk medicine provide leaflet together … so at least they can …what are the contraindications but for …stop medicine this all information should be in the leaflet we can handle it discharge"* (Nurse).

					"During… all the patient will be during discharge we have to give health education so this is our role nurses role they will give health education so during health education we can hand this one it will be more clear… it will be more clear in Arabic and English we can make it" (Nurse).
Discussion with a colleague (Discussion with a colleague even for 5 to 10 minutes regarding the content, and one pharmacy technician mentioned giving the pharmacy technician an idea about the content will help her to focus more about the safety issue; however, she will not focus if she was only given a paper without discussion especially due to the workload; described as similar to a meeting).	-	√	-	-	*"If there is a circular do not give me a paper and leave me while I do not know anything about it you should give an idea about the issue so I could give it the importance"* (Pharmacy technician).
Visual representation of the information (Examples included small figures, charts, and diagrams)	-	√	-	-	*"Not like this photo colour photo I mean like small figures we can use if you want to use diagrams … charts"* (Pharmacy technician).
Use social media, software and local applications (The MOH should put medication alerts in their official social media accounts, examples Instagram, Twitter, and Facebook, use local applications in Kuwait, If alters posted MOH Twitter and Instagram accounts, the information could be read with focus at the staff's free time).	-	√	-	-	"*I think if you post it on Instagram or Twitter I can't focus on it and read it for example at any time I am free to me this is better than this is [paper-based circulars"* (Pharmacy technician).
Use the internet (KDFC should improve their dissemination by using the internet, this is because people these days are focusing on the internet; information is easily spread through websites, and they are faster and then paper-based circulars; circulars only focus on the pharmacy departments, but websites would include information for the different departments; though positively that circulars are issued periodically but preferred to see them on the internet; in emergency situations using the internet could aid in spreading the information to everyone).	-	√	-	-	*"This is good but they have to improve themself and through the internet also they"* (Pharmacy technician).
Designate staff members to learn, distribute, and monitor the implementation of medication safety information (could be one group in the hospital, could disseminate in any effective way such as classless and seminars; there is now a quality control unit in each	-	√	√	-	*"Yeah I have one though if any hospital use hospital any hospital knew one group to a aware of this medications … they will conduct classes*

pharmacy department in the hospital. They should follow and monitor updates regarding safety communications, as well as follow its implementation. A "down to up" approach also was suggested to be applied in each hospital. This includes a staff member who are responsible for medication safety (i.e., the pharmacy department) should be proactive and initiate communication with the MOH to check if there is update in a regular bases (e.g., weekly or monthly). This person should then send the information via WhatsApp or emails to the rest of departments and staff members. Thus, not waiting for the information to arrive form the MOH; In addition to monitoring the safety updates, a designated staff member (one suggestion included quality control in the pharmacy) was suggested to monitor the recommendations; it was also suggested take one or two individuals from each department to make a committee).					*seminars and … they can distribute any easy way effective way"* (Pharmacy technician). *" in each department in each pharmacy department in the hospital is now there is quality control a unit I think they need to to follow up and monitor any updates regarding safety communication and a follow through to implement any aa news* (Pharmacist). *I think one of the facilitators a am for improvement is the one that my colleague have just pointed out I think a pharmacist maybe one or two could be assigned with the am objective to inform other pharmacists about these medication safety aam problems they they should the people be the who are responsible for taking these papers from the Ministry and then trying to a just d decode them or encode them again inside the computer and send them by email also or something like that this is a facilitator for the barriers* (Pharmacist).
Introduce a local information centre to regularly send updates (this centre should send information at least monthly through emails; it should focus on patient safety; any medication safety information should pass through this centre; it should send information about new medications, drug-drug interactions, or medications safety or alerts; these centres should also operate 24-hours and answer questions from HCPs and the public; their hospital had previously a positive experience in introducing a quality centre where they could call and have answers; it was suggested that it should be a separate centre not KDFC; the suggested centre should be connected with hospitals in both the governmental and the private sectors; it should be a national centre not inside a hospital).	-	-	√	-	They should do some centers also not only for the professionals also for the patients sometime they need some help for example my son if I don't know the dose of paracetamol at night I should call have to call somebody to whom I will ask so there must be some centers to give the information about the medications (Pharmacist).

To put programme that include medication alerts through the hospital's software/computer programme (This is the system for registering prescriptions, dispensing, laboratory orders, etc.; a mentioned example was HIS computer programme; not all participants agreed as different hospitals use different computer programmes and these should be unified).	-	-	√	-	*"Or sometimes put the programme in the HIS [HIS programme] programme in the HIS better for easy for all all pharmacists"* (Pharmacist). *"Yeah but the problem it's not unified for the all hospitals according some hospitals are using HIS some hospitals are using another aa sorry according to a programme we have so it's not unified for all hospitals"* (Pharmacist).

The following section (5.3.2) involves the results of the pilot survey focusing on those that led to changes in the survey, and the reliability of the survey.

5.3.2 Results of the pilot survey

This section presents the result from the pilot survey, specifically those that led to changes in the survey and the reliability tests.

The survey was administered twice to the same sample (same individuals) with at least two weeks difference. Fifty participants answered at the first survey administration (test sample), and forty-six participants completed the survey at the second time (re-test sample). The answers of those who completed the survey at the two administration times were joined in one data set, resulting in a third data set consisted of 92 participants (test and re-test).

The survey had a good reliability in the test data set (n =50, Cronbach's alpha = 0.798). Spearman's correlation coefficient ranged from 0.30 to 0.853. In nine items, Spearman's correlation coefficient was at least 0.7. The details of Spearman's correlation coefficient for each item are presented in Table 5.9. The ICC values ranged from -0.088 to 0.855. Of the 68 items, 7.4% (n=5) had good reliability, 39.7% (n=27) had moderate reliability and 52.9% (n=36) had poor reliability. Details of the ICC results are presented in Table 5.10.

Table 5.9: Spearman's correlation of the survey ordinal items

Survey question (item)	Correlation Coefficient (r)	p-value (2-tailed)
Do you check for updates about medications safety even if you do not receive an alert about it?	.432	.003
How often do you use the following sources to check updates on medications safety information?		
MOH	.422	.003
KDFC	.609	<.001
Pharmaceutical companies	.510	<.001
Professional organisations	.477	<.001
International regulatory agencies	.422	.003
Books	.300	.043
Medical software/websites	.586	<.001
Medical journals	.155	.305
Colleagues	.567	<.001
Patients	.462	.001
Media	.492	<.001
Social media	.699	<.001
Conferences	.352	.016
Lectures conducted by hospital staff	.030	.841
Hospital circulates	.571	<.001
Diseases/ medical guidelines	.468	.001
Who do you think should know about emergent medications safety information?		
Physicians	.526	<.001
Pharmacists	.330	.025
Pharmacy technicians	.261	.080
Nurses	.513	<.001
Patients	.345	.019
Family members	.264	.077
Legal guardian	.288	.052
Administrators	.606	<.001
Carers	.298	.044
How strongly do you agree or disagree with the following statement " I think that information about medication safety is important" ?	.386	.008
From the following sources of medication safety information, please indicate which sources in your opinion provide trustworthy information.		
Professional organisations	.394	.007
MOH	.587	<.001
KDFC	.376	.010
Pharmaceutical Companies	.694	<.001
Media	.280	.059
Social Media	.404	.005
International regulatory agencies	.372	.011
Please indicate the barriers to you implementing recommendations required by emerging information related to medications safety.		
Lack of guidance or training is a barrier for implementing medication safety recommendations.	.272	.068
Lack of space for consultation is a barrier for implementing medication safety recommendations.	.578	<.001

Lack of hospital organisational support is a barrier for implementing medication safety recommendations.	.424	.003
Lack of cooperation between different professionals is a barrier for implementing medication safety recommendations.	.521	<.001
When I think the medication safety recommendations will negatively affect the patient compliance.	.405	.005
When I do not agree with the medication safety recommendations.	.619	<.001
When I think the medication safety recommendations are not evidence-based.	.496	<.001
When I have other work to do that has higher priority.	.463	.001
I do not consider medication safety information in my clinical practice.	.491	<.001
I do not have the necessary skills or knowledge to implement medication safety recommendations.	.749	<.001
I do not think it is my role to implement medication safety recommendations.	.546	<.001
Other professionals do not think it is my role to implement medication safety recommendations.	.419	.004
Patient resistant or refusal to accept medication safety recommendations.	.609	<.001
How did the safety information related to the teratogenic effects of Depakine (valproate) and Depakine Chrono (valproic acid and valproate) affect your practice ?		
I decreased prescribing Depakine/Depakine Chrono to female patients.	.371	.047
I stopped prescribing Depakine/Depakine Chrono to all patients.	.638	<.001
I stopped prescribing Depakine/Depakine Chrono to female patients.	.546	.002
I prescribe Depakine/Depakine Chrono to female patients only if other treatments fail.	.628	<.001
I counsel female patients at childbearing age about contraceptive use.	.370	.048
I ask adult female patients to sign an acknowledgment that they know about the risks of Depakine/Depakine Chrono	.255	.182
I provide female patients a written information about the risks of using Depakine/Depakine Chrono during pregnancy	.320	.091
It did not affect my practice.	.657	<.001
Please indicate the barriers to you implementing recommendations related to the teratogenic effects of Depakine (valproate) and Depakine Chrono (valproic acid and valproate)		
I do not think the recommendations are useful.	.530	.003
I think the recommendations will negatively affect the patient compliance	.744	<.001
When I have other work to do that has higher priority.	.822	<.001
I am not familiar on how to implement the recommendations.	.853	<.001
I do not think it is my role to implement the recommendations.	.709	<.001
I think the recommendations are not evidence-based.	.697	<.001
Other professionals do not think it is my role to implement the recommendations.	.593	<.001
I am not confident in talking about pregnancy issues with female patients.	.408	.028
I do not agree with the recommendations.	.796	<.001
I do not have the space to implement the recommendations.	.781	<.001
I do not consider medication safety information in my clinical practice.	.727	<.001
I do not work in a cooperative environment between different professionals' teams.	.742	<.001
My hospital policies do not encourage me to implement the recommendations.	.558	.002

MOH: Ministry of Health (in Kuwait). **KDFC**: Kuwait Drug and Food Control.

Table 5.10: ICC of the survey ordinal items

Survey question (item)	Intraclass Correlation (a) (b)	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)	p-value
Do you check for updates about medications safety even if you don't receive an alert about it?	.380	.101	.602	.005
How often do you use the following sources to check updates on medications safety information?				
MOH	.436	.167	.644	.001
KDFC	.644	.437	.787	<.001
Pharmaceutical companies	.550	.315	.722	<.001
Professional organisations	.484	.234	.675	<.001
International regulatory agencies	.403	.129	.619	.003
Books	.245	-.043	.496	.048
Medical softwares/websites	.491	.240	.682	<.001
Medical journals	.128	-.149	.393	.185
Colleagues	.469	.207	.667	<.001
Patients	.402	.135	.616	.002
Media	.471	.209	.669	<.001
Social media	.731	.562	.841	<.001
Conferences	.294	.014	.534	.021
Lectures conducted by hospital staff	-.088	-.350	.195	.731
Hospital circulates	.546	.310	.719	<.001
Diseases/ medical guidelines	.411	.137	.625	.002
Who do you think should know about emergent medications safety information?				
Physicians	.606	.386	.760	<.001
Pharmacists	.564	.329	.733	<.001
Pharmacy technicians	.214	-.074	.470	.073
Nurses	.365	.092	.589	.005
Patients	.319	.035	.556	.015
Family members	.240	-.053	.495	.054
legal guardian	.220	-.053	.469	.058
Administrators	.542	.269	.727	<.001

Carers	.274	-.019	.523	.033
How strongly do you agree or disagree with the following statement " I think that information about medication safety is important" ?	.296	.022	.533	.018
From the following sources of medication safety information, please indicate which sources in your opinion provide trustworthy information.				
Professional organisations.	.419	.146	.632	.002
MOH.	.287	-.004	.533	.027
KDFC.	.286	-.006	.532	.027
Pharmaceutical Companies.	.526	.279	.707	<.001
Media.	.255	-.041	.508	.045
Social Media.	.370	.090	.595	.006
International regulatory agencies.	.543	.304	.718	<.001
Please indicate the barriers to you implementing recommendations required by emerging information related to medications safety.				
Lack of guidance or training is a barrier for implementing medication safety recommendations.	.400	.129	.616	.003
Lack of space for consultation is a barrier for implementing medication safety recommendations.	.656	.453	.794	<.001
Lack of hospital organisational support is a barrier for implementing medication safety recommendations.	.400	.126	.618	.003
Lack of cooperation between different professionals is a barrier for implementing medication safety recommendations.	.520	.273	.703	<.001
When I think the medication safety recommendations will negatively affect the patient compliance.	.464	.201	.664	<.001
When I don't agree with the medication safety recommendations.	.620	.407	.769	<.001
When I think the medication safety recommendations are not evidence-based.	.520	.279	.701	<.001
When I have other work to do that has higher priority.	.453	.195	.653	<.001
I don't consider medication safety information in my clinical practice.	.322	.033	.560	.015
I don't have the necessary skills or knowledge to implement medication safety recommendations.	.707	.528	.826	<.001
I don't think it is my role to implement medication safety recommendations.	.501	.252	.688	<.001
Other professionals don't think it is my role to implement medication safety recommendations.	.408	.145	.619	.001
Patient resistant or refusal to accept medication safety recommendations.	.619	.405	.769	<.001

How did the safety information related to the teratogenic effects of Depakine (valproate) and Depakine Chrono (valproic acid and valproate) affect your practice ?				
I decreased prescribing Depakine/Depakine Chrono to female patients.	.390	.048	.654	.014
I stopped prescribing Depakine/Depakine Chrono to all patients.	.647	.371	.817	<.001
I stopped prescribing Depakine/Depakine Chrono to female patients.	.537	.216	.752	.001
I prescribe Depakine/Depakine Chrono to female patients only if other treatments fail.	.616	.330	.799	<.001
I counsel female patients at childbearing age about contraceptive use.	.341	-.009	.621	.029
I ask adult female patients to sign an acknowledgment that they know about the risks of Depakine/Depakine Chrono	.221	-.133	.532	.112
I provide female patients a written information about the risks of using Depakine/Depakine Chrono during pregnancy	.302	-.076	.601	.057
It did not affect my practice.	.689	.442	.840	<.001
Please indicate the barriers to you implementing recommendations related to the teratogenic effects of Depakine (valproate) and Depakine Chrono (valproic acid and valproate)				
I don’t think the recommendations are useful.	.585	.285	.781	<.001
I think the recommendations will negatively affect the patient compliance	.704	.465	.848	<.001
When I have other work to do that has higher priority.	.855	.715	.929	<.001
I am not familiar on how to implement the recommendations.	.855	.713	.930	<.001
I don't think it is my role to implement the recommendations.	.674	.418	.831	<.001
I think the recommendations are not evidence-based.	.646	.372	.816	<.001
Other professionals don't think it is my role to implement the recommendations.	.605	.315	.792	<.001
I am not confident in talking about pregnancy issues with female patients.	.450	.101	.699	.007
I don’t agree with the recommendations.	.828	.664	.915	<.001
I don't have the space to implement the recommendations.	.789	.599	.895	<.001
I don't consider medication safety information in my clinical practice.	.776	.574	.888	<.001
I don’t work in a cooperative environment between different professionals teams.	.748	.528	.873	<.001
My hospital policies doesn’t encourage me to implement the recommendations.	.561	.259	.765	<.001

MOH: Ministry of Health (in Kuwait). **KDFC:** Kuwait Drug and Food Control.

Following the pilot stage, some changes were made to the survey questions due to three main reasons, which were either technical, clarity or statistical, which are further described below.

5.3.2.1 Technical related changes

Technical related changes were made due to the identified technical issues. Firstly, wrong coding, within Qualtrics, of the answer options was detected in three questions. This was resolved by replacing code values to sequential numbers. Secondly, the answer of one question was mistakenly excluded from the analysis. Thus, the "exclude" option in the analysis box was unchecked. Thirdly, the pilot survey had two questions about the participants' feedback: at the end of the general and the valproate specific sections. These two questions were removed from the survey.

5.3.2.2 Clarity related changes

Few participants misdescribed their workplace in the demographic question: "how do you describe your workplace" specifically in relation to secondary and tertiary governmental hospitals. Thus, the terms "secondary hospital" and "tertiary hospital" were replaced by "general hospital" and "specialised hospital", respectively. Moreover, the names of the seven general governmental hospitals in Kuwait were added to this option.

5.3.2.3 Statistical related changes

Minor changes on some questions and/or variables were made after examining the corrected item-to-total correlation of the variables in the test sample (n= 50), retest sample (n=46), and the test and retest sample (n=92), along with Cronbach's alpha score possible change if the variable would be removed. Variables were considered problematic if total correlation of the corrected item was less than 0.2, and its removal would increase Cronbach's alpha score.

The following section (5.3.3) describes the results survey relating to the general objectives.

5.3.3 Results of the survey: the general objectives

This section presents the results of the general questions of the online survey. Table 5.11 indicates the presentation of the results in this section.

Table 5.11: Summary of the general survey results arrangements

Domain	Subdomain
Participants' characteristics	-
Knowledge about medications safety communications.	- Knowledge of the responsible bodies for issuing medications safety communications in Kuwait. - Knowledge of the medications' life cycle stages at which medications safety assessments occur. - Familiarity with medications safety communication tools used by KDFC.
HCPs' practices to update their knowledge about medication safety.	- Frequency of checking for medication safety updates. - Frequency of using the listed different sources for medication safety updates.
HCPs' attitudes towards medications safety communications.	- HCPs' attitudes towards the possible receivers of medication safety communications. - HCPs' attitudes towards the importance of medication safety information. - Healthcare professionals' attitudes towards the sources of medication safety communications
HCPs' perceived barriers to implementing medication safety recommendations.	- Barriers from the closed-ended questions - Barriers from the open-ended question
HCPs' preferences for future medication safety communications.	- Preferred format (i.e., paper - based or electronic). - Preferred channels for dissemination.

HCPs: Healthcare professionals. **KDFC**: Kuwait Drug and Food Control.

5.3.3.1 Participants' characteristics

A total number of 380 healthcare professionals were aimed, and 395 of the targeted participants answered the survey (Figure 5.1). About two-thirds of the participants were females (n=251, 63.5%) and non-Kuwaitis (n=257, 65.1%). Nearly, half of the participants were nurses (n= 199,

50.4%), and the rest were physicians (n=101, 25.6%), pharmacists (n=81, 20.5%) and pharmacy technicians (n=14, 3.5%). Most of the participants were younger than 41 years of age (n=247, 62.5%), while only (n=13) 3.3% of the participants aged between 61 to less than 71 years old. The most common years of experience was reported to be 10 years to less than 15 years (n=89, 22.5%), followed by 5 years to less than 10 years (n=83, 21%). About 41% (n=162) of the participants had a postgraduate education level, and 36.2% (n=143) had an undergraduate degree. The details of participants' characteristics are presented in table 5.12.

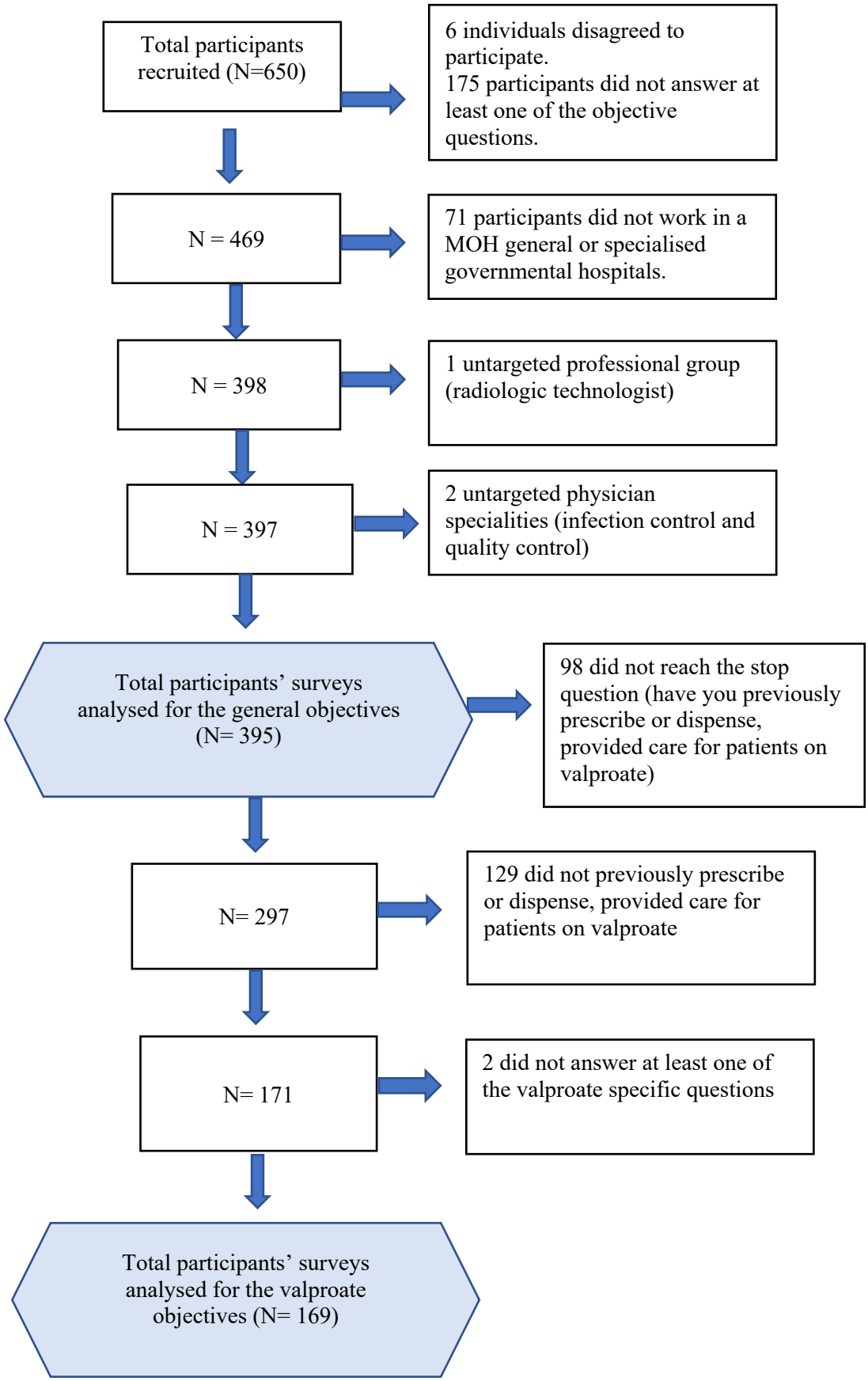


Figure 5.1: Flowchart of participants' inclusion and exclusion in both the general and the valproate-related questions

Table 5.12: Details of the participates characteristics (general objectives)

Category	Subcategory	N (%)
Gender (N=395, 100%)	Male	144 (36.5%)
	Female	251(63.5%)
Nationality (N=395, 100%)	Kuwaiti	138 (34.9%)
	Non-Kuwaiti[a]	257(65.1%)
Age (N=395, 100%)	21 to less than 31 years	81 (20.5%)
	31 to less than 41 years	166 (42%)
	41 to less than 51 years	104 (26.3%)
	51 to less than 61 years	31 (7.8%)
	61 to less than 71 years	13 (3.3%)
	71 years or more	0 (0%)
Education (N=395, 100%)	High school degree	15 (3.8%)
	Undergraduate degree	143 (36.2%)
	Postgraduate degree	162 (41%)
	Other[b]	75 (19%)
Professional background (N=395, 100%)	Nurse	199 (50.4%)
	Pharmacist	81 (20.5%)
	Pharmacy technician	14 (3.5%)
	Physician	101(25.6%)
Workplace description (N= 426, 107.8%)[c,d]	Primary care governmental centres	0(0%)
	General governmental hospital	250 (63.3%)
	Specialized governmental hospital	161 (40.8%)
	Private clinic or hospital	4 (1%)
	Other[e]	11(2.8%)
Health area administration (N=410, 103.8%) [c,d]	Ahmadi	45 (11.4%)
	Asimah (Capital)	23 (5.8%)
	Farwanyia	38 (9.6%)
	Hawali	39 (9.9%)
	Jahra	81(20.5%)
	Mubarak	18 (4.6%)
	Sabah	165 (41.8%)
	Other[f]	1(0.3%)
Work experience (N=395, 100%)	less than 5 years	57 (14.4%)
	5 years to less than 10 years	83 (21%)
	10 years to less than 15 years	89 (22.5%)
	15 years to less than 20 years	61 (15.4%)
	20 years to less than 25 years	48 (12.2%)
	25 years to less than 30 years	32 (8.1%)
	30 years or more	25 (6.3%)
Nurses' job title (N=199, 100%)	Assistant nurse	13 (6.5%)
	Nurse	96 (48.2%)
	Senior nurse	43 (21.6%)
	Specialist nurse	16 (8%)
	Senior specialist nurse	22 (11.1%)
	Head of nursing specialist	2 (1%)
	Other[g]	7 (3.5%)
Pharmacists' job title (N=81, 100%)	Beginner pharmacist	15 (18.5%)
	Pharmacist	15 (18.5%)

	Senior pharmacist	25 (30.9%)
	Pharmacy specialist	12 (14.8%)
	Senior pharmacy specialist	4 (4.9%)
	Head of pharmacy specialist	10 (12.3%)
	Other	0 (0%)
Pharmacy technicians' job title (N=14, 100%)	Assistant pharmacy technician	3 (21.4%)
	Pharmacy technician	2 (14.3%)
	Senior pharmacy technician	9 (64.3%)
	Other	0 (0%)
Physicians' job title (N=101, 100%)	Trainee	6 (5.9%)
	Resident	4 (4%)
	Assistant registrar	12 (11.9%)
	Registrar	9 (8.9%)
	Senior registrar	13 (12.9%)
	Senior general practitioner (B)	10 (9.9%)
	Senior general practitioner (A)	12 (11.9%)
	Specialist	6 (5.9%)
	Senior specialist	6 (5.9%)
	Consultant	23 (22.8%)
	Other	0 (0%)
Physicians' specialities	Anaesthesiology and intensive care (or critical care)	4
	Audio-Vestibular medicine/Audiology medicine	5
	Chest physician	1
	Clinical molecular genetics/ Genetics	2
	Dermatology	5
	Diabetes	1
	Ear, nose, and throat	2
	Family medicine	2
	Gastroenterology	1
	Haematology/ internal medicine and haematology	3
	Infectious diseases	1
	Internal medicine and rheumatism	1
	Kidney transplant surgeon	1
	Medical imaging	1
	Medicine and therapeutic nutrition	1
	Medicine/ internal medicine	15
	Nephrology	1
	Neuro otology	1
	Obstetrics and gynaecology/ Obstetrics and gynaecology, Reproductive endocrinology, and infertility	2
	Ophthalmology	4
	Orthopaedic surgery	4
	Orthopaedics	1
	Oto-Rhino-Laryngology	3

	Paediatric surgery	1
	Paediatrics	5
	Paediatrics, paediatric infectious diseases	1
	Physical medicine and rehabilitation/ physiatrist	8
	Plastics	1
	Psychiatry	3
	Pulmonology	3
	Radiology	2
	Surgery/ General Surgery	11
	Trainee/ not specialised yet/ trainee medicine rotation	3
	Preferred not to say (due to fear that it would not be anonymous)	1

[a] 195 participants specified their nationalities, this included India (105), Egypt (42), Jordan (11), Philippines (9), Pakistan (6), Saudi (5), Syria (4), Indonesia (3), Iran (2), Stateless (2), and one participant from each Argentina, Liberia, Palestine, Somalia, UK and Yemen.

[b] 72 of those selecting "other" specified their highest educational degrees. 32 participants (included 26 nurses and 6 pharmacy technicians) stated having a diploma. 22 Nurses reported having a bachelor's degree. One of these nurses reported also having an MBA (hospital management) degree. 4 other participants (2 nurses and 2 physicians) reported having a postgraduate degree. 3 physicians specified their degrees as the following Kuwait board general surgery (one physician), MRCP MD SCE nephrology (one physician), MRCP (UK) and Kuwait board of internal medicine (one physician). Other nurses stated the following without specifying their educational level: general nursing and midwifery (n=3), institute (health technician) nursing division after high school (n=1), nursing institute (n=1), collage (n=2), degree (n= 1), graduate (n=2), graduate degree (n=1), graduation (n=2).

[c] Participants could choose more than one answer.

[d] Percentages presented by percent of cases (number of participants).

[e] 10 of those specifying "others" worked in either general or specialised MOH hospitals (also counted in the general or specialised hospitals options). One physician wrote "hospital administration" without specifying his/her workplace as a general or specialised hospital.

[f] The participant did not specify the health area administration that his/her workplace follows.

[g] Nurses that chose "other" for their job title wrote the following: Anaesthesia technician (n=1), Clinical instructor (n=4), Nurse specialist (n=1) and Technician (n=1).

5.3.3.2 Knowledge about medications safety communications

5.3.3.2.1 Knowledge about the responsible bodies for issuing safety recommendations for medicines in Kuwait

Only seven participants (1.8%) had complete knowledge about the responsible parties for issuing medication safety recommendations in Kuwait, while 34 participants (8.6%) had no knowledge at all (Table 5.13 and Table 5.14). Out of 395 healthcare professionals, 118 (30.1%) correctly identified KDFC and Drug Companies as the responsible bodies for issuing medication safety recommendations.

Table 5.13: Healthcare professionals total scores of each of the knowledge questions

Total scores	N (%)
Knowledge about the entities responsible for issuing safety recommendations for medicines in Kuwait	
0	34 (8.6%)
1	108 (27.3%)
2	133 (33.7%)
3	70 (17.7%)
4	43 (10.9%)
5	7 (1.8%)
Total	395 (100%)
Knowledge about the medicines' life cycle stages at which medicines' safety assessments occurs	
0	40 (10.1%)
1	158 (40%)
2	105 (26.6%)
3	92 (23.3%)
Total	395 (100%)
Familiarity with medicines safety communications tools used by KDFC	
0	186 (48.9%)
1	133 (35%)
2	61 (16.1%)
Total[1]	380 (100%)

[1] Total less than 395 due to missing answers. **KDFC**: Kuwait Drug and Food Control.

Table 5.14: Details of the healthcare professionals' answers to each of the knowledge questions

		Nurse		Pharmacist		Pharmacy technician		Physician		Total	
		N	%	N	%	N	%	N	%	N	%
Knowledge about the entities responsible for issuing safety recommendations for medicines in Kuwait											
Central Medical Stores (Ministry of Health).	No	56	28.1%	43	53.1%	7	50.0%	60	59.4%	166	42.0%
	Not sure	54	27.1%	20	24.7%	3	21.4%	24	23.8%	101	25.6%
	Yes	89	44.7%	18	22.2%	4	28.6%	17	16.8%	128	32.4%
Drug and Food Control (Ministry of Health).	No	37	18.6%	4	4.9%	0	0.0%	5	5.0%	46	11.6%
	Not sure	32	16.1%	6	7.4%	1	7.1%	24	23.8%	63	15.9%
	Yes	130	65.3%	71	87.7%	13	92.9%	72	71.3%	286	72.4%
Pharmaceutical Services Administration (Ministry of Health).	No	19	9.5%	38	46.9%	4	28.6%	22	21.8%	83	21.0%
	Not sure	42	21.1%	23	28.4%	2	14.3%	40	39.6%	107	27.1%
	Yes	138	69.3%	20	24.7%	8	57.1%	39	38.6%	205	51.9%
Inspection Administration Department (Ministry of Health).	No	46	23.1%	28	34.6%	7	50.0%	33	32.7%	114	28.9%
	Not sure	58	29.1%	13	16.0%	2	14.3%	34	33.7%	107	27.1%
	Yes	95	47.7%	40	49.4%	5	35.7%	34	33.7%	174	44.1%
Drug Companies.	No	75	37.7%	27	33.3%	5	35.7%	54	53.5%	161	40.8%
	Not sure	56	28.1%	15	18.5%	2	14.3%	19	18.8%	92	23.3%
	Yes	68	34.2%	39	48.1%	7	50.0%	28	27.7%	142	35.9%
Knowledge about the medicines' life cycle stages at which medicines' safety assessments occurs											
Before the clinical trials stage.	No	42	21.1%	29	35.8%	6	42.9%	41	40.6%	118	29.9%
	Not sure	38	19.1%	15	18.5%	1	7.1%	16	15.8%	70	17.7%
	Yes	119	59.8%	37	45.7%	7	50.0%	44	43.6%	207	52.4%
During the clinical trials stage.	No	58	29.1%	12	14.8%	4	28.6%	27	26.7%	101	25.6%
	Not sure	50	25.1%	11	13.6%	4	28.6%	15	14.9%	80	20.3%
	Yes	91	45.7%	58	71.6%	6	42.9%	59	58.4%	214	54.2%
After the medication grants approval to be used by patients.	No	63	31.7%	23	28.4%	5	35.7%	31	30.7%	122	30.9%
	Not sure	27	13.6%	10	12.3%	1	7.1%	12	11.9%	50	12.7%
	Yes	109	54.8%	48	59.3%	8	57.1%	58	57.4%	223	56.5%
Familiarity with medicines safety communications tools used KDFC											
KuFDA newsletter.	No	103	53.9%	55	68.8%	2	15.4%	75	78.1%	235	61.8%
	Not sure	43	22.5%	6	7.5%	4	30.8%	6	6.3%	59	15.5%
	Yes	45	23.6%	19	23.8%	7	53.8%	15	15.6%	86	22.6%
Letters to Healthcare professionals.	No	57	29.8%	25	31.3%	1	7.7%	45	46.9%	128	33.7%
	Not sure	53	27.7%	7	8.8%	6	46.2%	17	17.7%	83	21.8%
	Yes	81	42.4%	48	60.0%	6	46.2%	34	35.4%	169	44.5%

Column N %

Using the Kruskal-Willis H test, the distribution of the total score was different between the four healthcare professional groups detected by boxplot. Pharmacy technicians (n= 14, mean rank = 267.29) had the highest knowledge levels followed by pharmacists (n=81, mean rank = 262.04), physicians (n=101, mean rank =209.85) and nurses (n=199, mean rank =161.05). The total scores were statistically significantly different between the four healthcare professionals' groups, X^2 (3) =56.293, $p <$ 0.001 [Asymptotic derived p-value (2-sided test)]. Post-hoc analysis, which included pairwise comparisons using Dunn's (1964) procedure with Bonferroni's correction for multiple comparisons (Adjusted p-values are presented), revealed statistically significantly differences between nurses and physicians (p=.002), between nurses and pharmacists (p <0.001), between nurses and pharmacy technicians (p = 0.003), and between physicians and pharmacists (p =.009). No statistically significant differences were found between any other groups' comparisons.

5.3.3.2.2 Knowledge about the medicines' life cycle stages at which medicines' safety assessments occurs

Over one-fifth of the participants (n=92, 23.3%) were able to correctly identify all stages of the medicines' life cycle at which safety assessment occurs (Table 5.10). Participants, however, most commonly identified just one stage (n=158, 40%). A similar proportion of participants identified each stage, with 52.4% (n=207) identifying "before clinical trials", 54.2% (n=214) identifying "during clinical trials", and 56.5% (n=223) identifying "after medication grants approval to be used by patients". Details in table 5.11.

Kruskal-Wallis's test was conducted to detect if there were statistically significant differences between the four healthcare professionals' groups in terms of their total knowledge about the medicines' life cycle stages at which medicines' safety assessments occurs. Distributions of the scores of the four groups were similar as visually detected using boxplot. Median scores (nurses' median =1; pharmacists' median=2; pharmacy technicians' median=1; physicians' median=1) were not statistically significantly different between the four HCPs' groups, $X^2(3)=2.480$, p=0.479 [Asymptotic derived p-value (2-sided test)].

5.3.3.2.3 Familiarity with medicines safety communications tools used by the KDFC

Of the total of 380 participants who answered these questions, 16.1% (n=61) were familiar with both tools of communication used by KDFC (Table 5.10). Almost half of the of 380 participants (n=186, 48.9%) were not familiar with neither communication tools. Eighty-six (22.6%) of the 380 participants were familiar with KuFDA newsletter, while 169 participants (44.5%) were familiar with DHPLs. Details in Table 5.11.

In the Kruskal-Willis H test, distribution of the total score was different between the four healthcare professional groups detected by boxplot. Pharmacy technicians (n=13, mean rank = 228.96) were more familiar with KDFC's medicines safety communication tools, followed by pharmacists (n=80, mean rank = 216.93), nurses (n= 191, mean rank= 187.59) and physicians (n=96, mean rank = 169.05). The total scores were statistically significantly different between the four healthcare professionals' groups, X^2 (3) = 11.987, p = .007 [Asymptotic derived p-value (2-sided test)].

In the post-hoc analysis, which included pairwise comparisons using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons, statistically significantly difference between physicians and pharmacist (p = .010, adjusted p-value) were detected. No statistically significantly difference was found between any other groups' comparisons.

5.3.3.3 Healthcare professionals' practices to update their knowledge about medicines safety communications

5.3.3.3.1 Frequency of checking for medication safety update, even if they do not receive alert about it

A total of 353 participants reported the frequencies by which they check for medication safety updates. Almost half of these participants (n= 166, 47%) frequently or always check for updates even if they do not receive an alert about it. Of the 351, 129 participants (36.5%) reported that

they check for updates sometimes. On the other hand, 16.4% (n = 58) of participants reported that they never or rarely check updates about medications safety.

Using the Kruskal-Willis H test distribution of means was different between the four healthcare professional groups detected by boxplot. Pharmacy technicians (n=12, mean rank = 206.46) checked for medicines' safety update more than nurses (n=172, mean rank = 193.78), pharmacists (n=77, mean rank=162.61) and physicians (n=92, mean rank = 153.83). The mean ranks of HCPs updating their knowledge on medication safety was statistically significantly different between the four healthcare professionals' groups, X^2 (3) = 12.920, p = .005 [Asymptotic derived p-value (2-sided test)]. The post-hoc analysis including pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons revealed statistically significantly difference between physicians and nurses (p = .010, adjusted p-value). No statistically significantly difference was found between any other groups' comparisons.

5.3.3.3.2 Frequency of using the different sources for medication safety updates

A total of 353 participants answered this question. A similar number of participants reported rarely or never (n=124, 35.1%), and always or frequently (n=119, 33.7%) receiving medicines safety information from KDFC. Interestingly more participants reported frequently or always (n=152, 43.1%) learning about safety updates from international drug regulatory agencies (e.g., FDA). However, 116 (32.9%) participants reported rarely or never learning about safety updates from international drug regulatory agencies.

The minority of participants reported frequently or always (n=80, 22.7%) knowing about safety updates from drug companies, whereas more participants reported that they never (n=149,42.2%) or rarely learned about an update from drug companies. Most of the participants (n=189, 53.5%) frequently or always received updates about medicines' safety information from medical programs, applications, or websites (e.g., UpToDate). This was followed by 169 (47.9%) participants being informed about new safety information from Kuwait MOH and 164 (46.5%) from hospital circulates. The least cited sources by which HCPs learn about medicines

safety updates were professional organisations (n=63, 17.8%), media (n=46, 13%) and patients (n=32, 9.1%). Further details are presented in Figure 5.2.

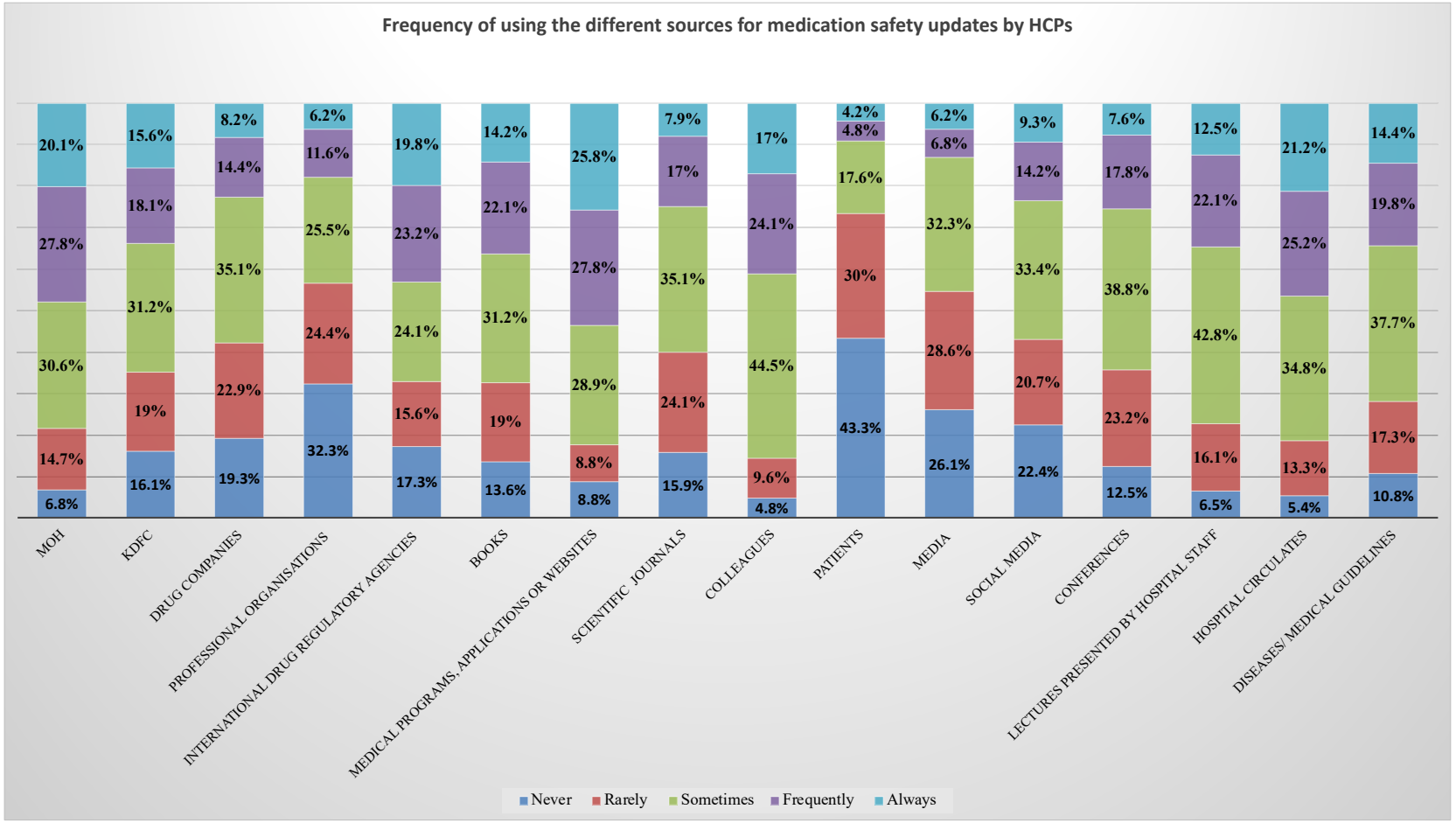


Figure 5.2: Frequencies of using the different sources for medication safety updates

MOH: Ministry of Health (in Kuwait). **KDFC:** Kuwait Drug and Food Control. **HCPs**: healthcare professionals

Four iterations of PCA were conducted by removing one item each time due to cross-loading with two components (i.e., the item scored 0.4 or above in two components). The three removed items were drug companies, disease/medical guidelines, and hospital circulars. In the fourth iteration, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy revealed that the sample size was adequate (KMO = 0.796), and the Bartlett's test of sphericity was significant ($P < 0.001$), and all items had at least one variable that is greater than 0.3 detected by the correlation matrix (Appendix 29).

Three components had eigenvalues above 1, which was above Kaiser's criterion (Appendix 30). Interpretations of the items loaded within the three components resulted in labelling these component to: (1) scientific0 sources (scientific journals, medical programs, applications or websites, books, international drug regulatory agencies, and conferences); (2) other people sources (social media, media, colleagues, lectures presented by hospital staff, and patients); (3) organisational sources (KDFC, Kuwait MOH, professional organisations; table 5.15.

Table 5.15: Rotated component matrix of perceived valproate-related barriers (4th iteration)

Frequency of using the different sources for medication safety updates	Component		
	Component1: Scientific Sources	Component 2: Other-people sources	Component 3: Organisational sources
Medical programs, applications or websites	.786	.157	-.044
Scientific journals.	.784	.122	.049
Books	.660	.266	.001
International Drug regulatory agencies	.637	-.159	.372
Conferences.	.588	.175	.283
Social media.	-.006	.841	.129
Media	.036	.801	.216
Colleagues.	.358	.591	.100
Lectures presented by hospital staff.	.234	.488	.223
Patients.	.190	.482	.259
KDFC	.116	.149	.842
MOH	.049	.267	.773
Professional organisations	.106	.327	.661

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.[a]
a. Rotation converged in 5 iterations.

For all three types of sources, differences in shapes of distributions among the four HCPs groups were detected using boxplots. Physician (n=92; mean rank=230.40) were significantly more frequently than both nurses (n=172; mean rank=143.15) and pharmacists (n=77; mean rank= 178.23) in using scientific sources. Pharmacy technicians (n=12; mean rank=261.08) were more significantly likely to report using other people sources than both physicians (n=92; mean rank= 131.39) and pharmacists (n=77; mean rank =171.31). Nurses (n=172; mean rank=198.08) were also more significantly likely to use these sources than physicians. On the other hand, physicians (n=92; mean rank=130.51) were significantly less frequently using organisational sources than pharmacists (n=77; mean rank=178.74), nurses (n=172; mean rank=197.26) and pharmacy technicians (n=12, mean rank=231.92; more details are presented in Table 5.16).

Table 5.16: Differences between healthcare professionals' groups and their use of the sources in updating their medication safety knowledge

Who do you think should know about emergent medications safety information?	Independent-Samples Kruskal-Wallis Test	Asymptotic significance (p-value)	Post-hoc analysis (pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.	Adjusted p-value
Scientific Sources	$X^2(3) = 49.688$	<.001	Nurse-Physician	<.001
			Nurse -Pharmacy technician	0.005
			Pharmacist-physician	0.005
Organisational sources	$X^2(3) = 29.686$	<.001	Physician-nurse	<.001
			Physician-pharmacy technician	<.001
			Pharmacist-pharmacy technician	0.027
Other-people sources	$X^2(3) = 34.346$	<.001	Physician-pharmacist	.013
			Physician-nurse	<.001
			Physician-pharmacy technician	.007

5.3.3.4 Healthcare professionals' attitudes towards medicines safety communications

5.3.3.4.1 Healthcare professionals' attitudes towards the possible receivers of medicines safety information

The majority of 334 participants answering these questions agreed that healthcare professionals, including pharmacists (n=315, 94.3%), physicians (n=307, 91.9%), nurses (n=292, 87.4%) and pharmacy technicians (n=281, 84.1%), should receive updates about medicines safety. This was followed by 242 (72.5%) participants agreeing that carers should receive updates. A similar percent of participants agreed that patients (n= 205, 61.4%), legal guardians (n=203, 60.8%) and family members (n=195, 58.4%) should receive updates. Whereas 49 (14.7%), 53 (15.9%), and 58 (17.4%) participants thought that patients, family members and legal guardians should not receive medicine safety updates, respectively. A total of 124 (37.1%) participants agreed that administrators should receive medicines' safety updates, while 97 (29%) disagreed.

Using Kruskal-Wallis test, similar shapes of distribution for family members, legal guardians and administrators were detected among the HCPs' groups using boxplots, while the rest had different shapes of distributions. A statistically significantly difference between the four HCPs'

groups were detected in perceiving pharmacists and administrators as receivers of medications safety communications (Table 5.17).

Table 5.17: Differences between healthcare professionals' groups and their attitudes towards who should receive medication safety communications

Who do you think should know about emergent medications safety information?	Independent-Samples Kruskal-Wallis Test	Asymptotic significance (p-value)	Post-hoc analysis (pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.	Adjusted p-value
Doctors (physicians)	$X^2(3) = 4.118$	0.249	-	-
Pharmacists	$X^2(3) = 15.254$	0.002	Nurses and physicians	0.002
Pharmacy technicians	$X^2(3) = 4.454$	0.216	-	-
Nurses	$X^2(3) = 7.338$	0.062	-	-
Patients	$X^2(3) = 3.178$	0.365	-	-
Family members	$X^2(3) = 1.510$	0.680	-	-
legal guardian	$X^2(3) = 0.183$	0.980	-	-
Administrators	$X^2(3) = 48.299$	<.001	Pharmacists and Nurses	< 0.001
			Physicians and Nurses	< 0.001
Carers	$X^2(3) = 5.072$	0.167	-	-

Physicians (n=90, mean rank= 185.68) were significantly more likely to perceive that pharmacist should receive medication safety communications than nurses (n=161, mean rank =152.44). In addition, nurses (n=161, median=4) were significantly more likely to perceive that administrator should receive medication safety communications than both physicians (n=90, median=3), and pharmacists (n=72, median=3).

5.3.3.4.2 Healthcare professionals' attitudes towards the importance of medicines safety information

The majority of 334 participants answering this question agreed that medicines safety information is important for their practice (n=315, 94.3%). The remaining participants had either disagreed (n=13, 3.9%) or were neutral (n=6, 1.8%) about the statement.

A Kruskal-Wallis test was conducted to determine if there were differences between the four healthcare professionals' attitudes towards the presented statement regarding the importance of medication safety information. Distribution of their agreements had different shapes as detected visually by the boxplot. Pharmacists (n=72, mean rank = 182.69) were more likely to agree that medicine safety information is important to their practice than pharmacy technicians (n=11, mean rank = 173.55), physicians (n=90, mean rank = 167.72), and nurses (n=161, mean rank = 160.17). However, agreements scores were not statistically significantly different between the four healthcare professionals' groups $X^2(3) = 5.208$, $p = 0.157$ [Asymptotic derived p-value (2-sided test)].

5.3.3.4.3 Healthcare professionals' attitudes towards the sources of medicines safety information

Most of the 334 participants answering this question thought that Kuwait MOH (n=298, 89.2%), KDFC (n=287, 85.9%), and international drug regulatory agencies, such as US FDA, (n=285, 85.3%) provide trustworthy information. Totally, 217 (65%) participants trusted information from professional organisations (e.g., Kuwait Medical Association). Nearly one-fourth of responding participants (n=75, 22.5%) were neutral, and 42 (12.6%) participants did not trust information provided by professional organisations. More than half of the participants (n=205, 61.4%) trusted information from drug companies, while 44(13.2%) participants did not trust information from drug companies, and 85 (25.4%) participants were neutral. While 103 (30.8%) participants did not trust information from the media, 131 (39.2%) participants thought that medicine safety updates provided by the media were trustworthy, and 100 (29.9%) were neutral. One hundred and twenty-six participants (37.7%) did not trust information on medicines safety provided by social media, 119 (35.6%) did, and 89 (26.6%) remained neutral.

Using Kruskal-Wallis Test, similar shapes of distribution for KDFC were detected among the HCPs' groups using boxplots, while the rest had different shapes of distributions. A statistically significantly difference between the four HCPs' groups were detected in trusting professional organisations, drug companies, media, social media, and international drug regulatory agencies as sources of medications safety information (Table 5.18).

Table 5.18: Differences between healthcare professionals' groups and their attitudes towards the trustworthiness of the different sources of medications safety information

Please indicate which sources in your opinion provide trustworthy information	Independent-Samples Kruskal-Wallis Test	Asymptotic significance (p-value)	Post-hoc analysis (pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.	Adjusted p-value
Professional organisations	$X^2(3) = 14.959$	0.002	Physicians and Nurses	0.002
MOH	$X^2(3) = 8.162$	0.043	-*	-
KDFC	$X^2(3) = 2.544$	0.467	-	-
Drug companies	$X^2(3) = 28.417$	<.001	Physicians and Nurses	<0.001
			Pharmacists and Nurses	0.024
Media	$X^2(3) = 53.518$	<.001	Physicians and Nurses	<0.001
			Pharmacists and Nurses	<0.001
Social media	$X^2(3) = 47.554$	<.001	Physicians and Nurses	<0.001
			Pharmacists and Nurses	<0.001
International drug regulatory agencies	$X^2(3) = 20.459$	<.001	Physicians and Nurses	0.016
			Pharmacists and Nurses	0.001

MOH: Ministry of Health. **KDFC:** Kuwait Drug and Food Control. * Post-hoc analysis revealed significant difference between pharmacists and nurses (p=0.015), and between physicians and nurses (p=.041), but the adjusted p-value revealed unsignificant differences between these groups, (p=0.92, and p=0.248, respectively).

Nurses (n= 161, mean rank=185.90) trusted professional organisations as sources of medication safety information more significantly than physicians (n=90, mean rank=143.02). In addition, drug companies were perceived to be trustworthy among nurses (n=161, mean rank=192.64) more significantly than both physicians (n=90, mean rank=130.36) and pharmacists (n= 72, mean rank=155.04). Similarly, nurses (n= 161, mean rank=206) trusted media more significantly than both physicians (n=90, mean rank=126.90) and pharmacists (n=72, mean rank=137.31). likewise, nurses also reported trusting social medica (n= 161, mean rank=203.24) more significantly than both physicians (n=90, mean rank=124.44) and pharmacists (n=72, mean rank=147.47). However, with regards to trusting international drug regulatorily agencies as sources of medications safety information, nurses (n=161, mean

rank=145.59) were significantly less likely to trust such agencies than physicians (n=90, mean rank=180.67) and pharmacists (n= 72, mean rank=194.13).

5.3.3.5 Healthcare professionals' perceived barriers to implementing medicine safety recommendations

5.3.3.5.1 Barriers from the closed-ended questions

Overall, 297 participants responded to these questions. The three most frequently identified barriers by these participants were lack of guidance (n=228, 76.8%), lack of space for consultation (n= 201, 67.7%), and lack of a cooperative teamwork environment (n=180, 60.6%). Following that, 138 (46.5%) participants reported when recommendations are not evidence-based, 130 (43.8%) respondents reported patients' resistance or refusal to accept medication safety recommendations, and 124 (41.8%) reported that informing patients about the recommendation might make them stop taking their medicine. Not prioritising the implementation of medicines safety recommendations by hospital management was identified as a barrier by 85 (28.6%) participants; however, 139 (46.8%) participants disagreed with this statement. Participants' disagreement with medicines' safety recommendations was identified as a barrier by 65 (21.9%) participants, while 116 (39.1%) participants did not perceive this as a barrier.

Half of the respondents (n=148, 49.8%) did not believe having other work with higher priorities was a barrier, while 78 (26.3%) did, and 71 (23.9%) were neutral. Similarly, 159 (53.5%) participants did not consider the perception of other professionals that it is not the participants' roles to implement medicines safety recommendations was a barrier, while 71 (23.9%) participants did, and 67 (22.6%) were neutral.

Two statements were most often not perceived by the participants as barriers to implementing the recommendations: thinking it is not their role to implement the recommendations (n=228, 76.8%), and not having the necessary skills or knowledge to implement the recommendations (n=204, 68.7%). Further details are provided in Figures 5.3, 5.4 and 5.5.

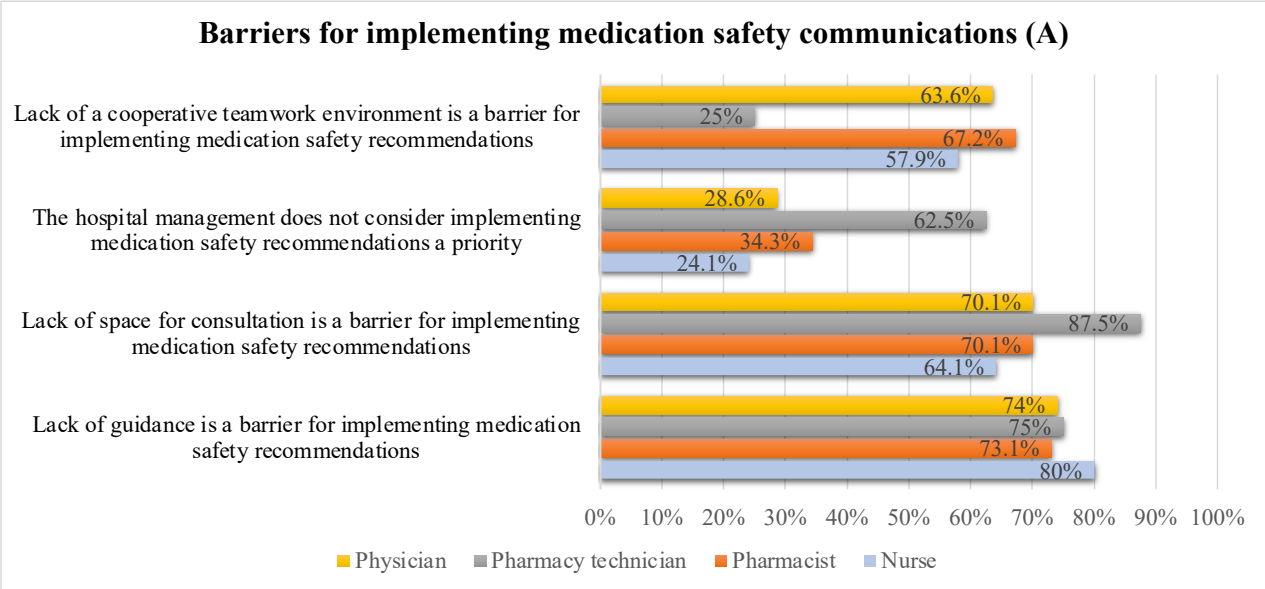


Figure 5.3: Barriers for implementing medications safety communication (A)

Figure 5.3 presents each of the HCPs' groups' agreements on four barriers statements.

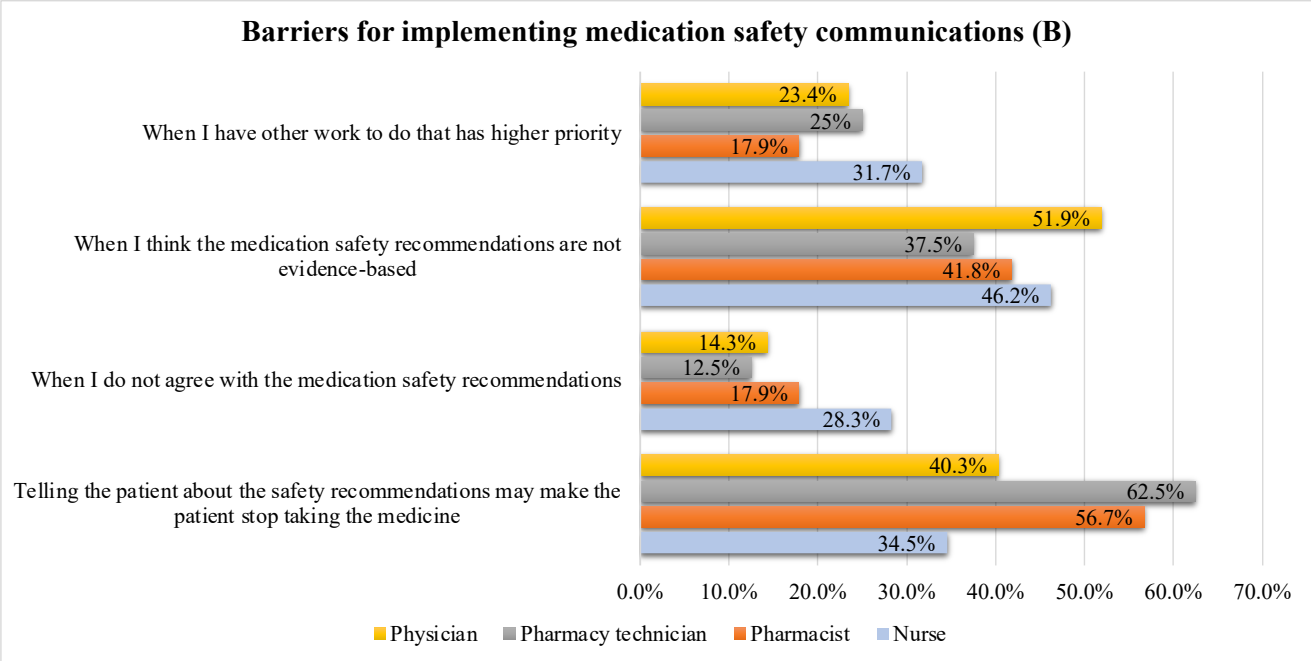


Figure 5.4: Barriers for implementing medications safety communication (B)
Figure 5.4 presents each of the HCPs' groups' agreements on four barriers statements.

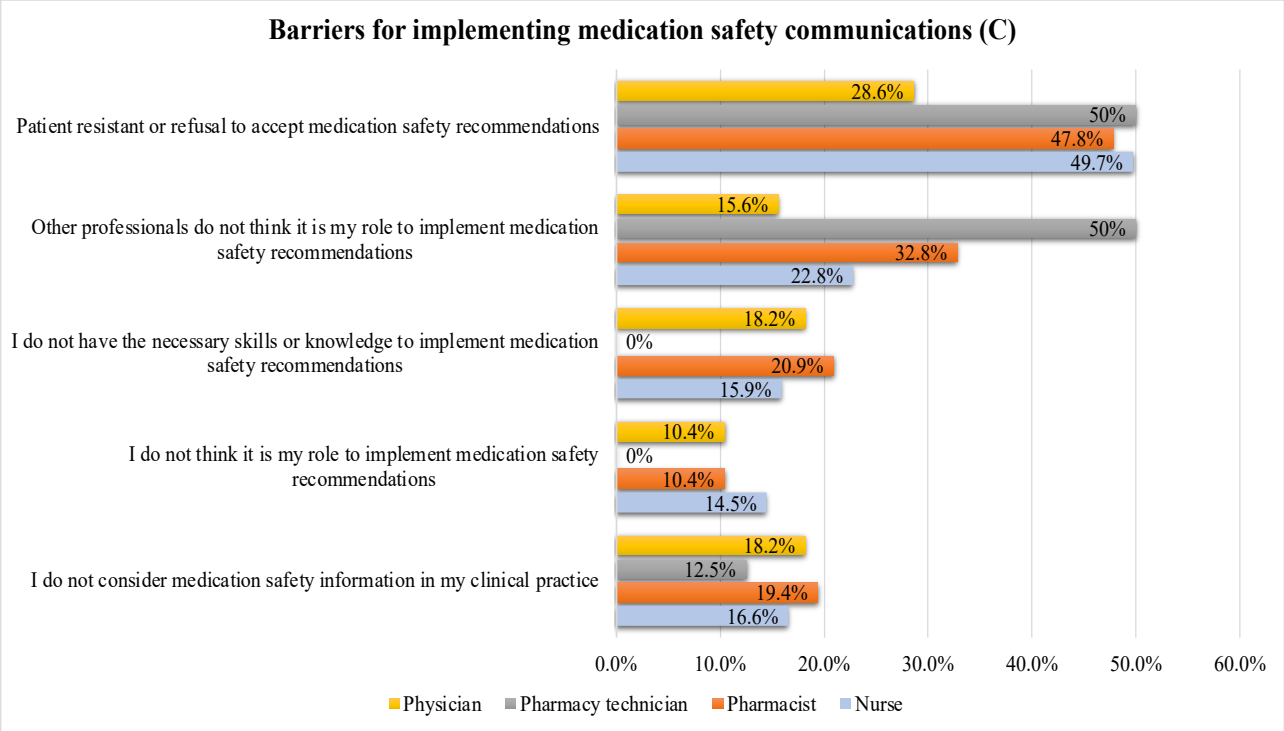


Figure 5.5: Barriers for implementing medications safety communication (C)
Figure 5.5 presents each of the HCPs' groups' agreements on five barriers statements.

Two iterations of PCA were conducted by removing one item due to cross-loading with two components (i.e., the item scored 0.4 or above in two components). The removed item was patient resistance or refusal to accept medication safety recommendations. In the second iteration, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy revealed that the sample size was adequate (KMO =.814), the Bartlett's test of sphericity was significant ($p <$ 0.001), and all items had at least one variable that is greater than 0.3 detected by the correlation matrix (Appendix 31). Three components had eigenvalues above 1, which was above Kaiser's criterion (Appendix 32). Interpretations of the items loaded within the two components resulted in labelling these component to: (1) Professionals' related barriers, (2) External-related barriers, and (3) Situational-related barriers. Details about the items within each component are presented in Table 5.19.

Table 5.19: Rotated component matrix of perceived general barriers (2nd iteration)

Please indicate the perceived barriers to you implementing recommendations required by emerging information related to medications safety.	Component		
	Professionals' related barriers	External barriers	Situational-related barriers
I do not have the necessary skills or knowledge to implement medication safety recommendations.	.816	.193	.065
I do not think it is my role to implement medication safety recommendations.	.806	-.023	.218
I do not consider medication safety information in my clinical practice.	.719	-.032	.090
Other professionals do not think it is my role to implement medication safety recommendations.	.659	.224	.190
Lack of space for consultation is a barrier for implementing medication safety recommendations.	.031	.814	.126
Lack of guidance is a barrier for implementing medication safety recommendations.	.062	.775	.003
Lack of a cooperative teamwork environment is a barrier for implementing medication safety recommendations.	.010	.750	.181
The hospital management does not consider implementing medication safety recommendations a priority.	.262	.590	.212
When I do not agree with the medication safety recommendations.	.210	.029	.756
When I think the medication safety recommendations are not evidence-based.	.090	.154	.675
Telling the patient about the safety recommendations may make the patient stop taking the medicine.	.018	.207	.590
When I have other work to do that has higher priority.	.394	.053	.584

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization[a].
a. Rotation converged in 5 iterations.

Using the Independent-Samples Kruskal-Wallis Test, no significant differences were detected between the four HCPs' groups in identifying professionals' related barriers, external barriers or situational-related barriers as the barriers preventing them from implementing medications safety communications (Table 5.20).

Table 5.20: Differences between healthcare professionals' groups and their perceived barriers for implementing medications safety communications

	Independent-Samples Kruskal-Wallis Test	Asymptotic significance (p-value)	Post-hoc analysis (pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.	Adjusted p-value
Professionals' related barriers	$X^2(3) = 1.843$	.606	-	-
External Barriers	$X^2(3) = 6.671$	.083	-	-
Situational-related barriers	$X^2(3) = 0.756$	.860	-	-

5.3.3.5.2 Barriers from the open-ended question

The barriers from the open-ended survey included three clusters: (1) Definiens in HCPs knowledge and work system (subclusters: work pressure and staff shortage; lack of awareness, knowledge or guidance and unmet information needs; lack of physical resources; lack of confidence or skills; lack of none physical resources); (2) Perception of responsibilities (subclusters: perceptions about HCPs' related responsibilities; perceptions about patients-related responsibilities; perception of system-related responsibilities; roles of rumours and erroneous sources); (3) Communication challenges (subclusters: organisational communications; patient-facing communications).

5.3.3.5.2.1 Deficiencies in HCPs knowledge and work system

5.3.3.5.2.1.2 Work pressure and staff shortage

Nine HCPs reported work overload as a barrier to implementing medication safety communications recommendations, one of which specified a shortage of staff compared to the number of patients treated.

5.3.3.5.2.1.3 Lack of awareness, knowledge or guidance and unmet information needs

This subcluster was reported by 21 HCPs, while one physician reported a facilitator, which is mandatory regular updates. Those who contributed to this subcluster either reported general statements, like lack of awareness, awareness spreading or information, or stated specific statements. The more specific statements included a lack of awareness about the standards of medication safety and its importance and a lack of health awareness among staff. This subcluster also included a lack of awareness of emerging side effects and a lack of staff education. Moreover, one nurse indicated a lack of awareness about medication and a lack of awareness of the importance of nurses' roles in medication management as barriers. Lack of safety information about unlicensed medication use was also reported. Two physicians reported not receiving medication safety recommendations. One of these physicians suggested that governmental institutions should have a dedicated team for informing HCPs of such information. Moreover, a HCP recommended increasing lectures to identify and define barriers. Furthermore, one HCP suggested that the shared information should be clear and communicated to all HCPs involved in patient care.

5.3.3.5.2.1.4 Lack of physical resources

Nine HCPs reported a lack of physical resources. These included a shortage of gloves and a lack of digital links between hospital and MOH departments. Furthermore, the absence of electronic connections between hospital departments and the pharmacy department, as well as the inability to send information electronically to all HCPs due to the lack of such systems, were also reported. The lack of modern means of communication, such as WhatsApp, has been noted by one physician.

Insufficient free information resources were also highlighted. Similarly, a lack of information resources as it is time-consuming to check every medication was reported by one physician. One physician also reported medication non-availability as a barrier to implementing medication safety recommendations. Moreover, a physician stated lack of blood test levels (vancomycin trough levels) was a barrier to implementing medication safety recommendations.

5.3.3.5.2.1.5 Lack of confidence or skills

Lack of confidence was reported by three HCPs. One of which indicated a lack of confidence in his/her experience in determining the strength of the source of information as a barrier to implementation. One HCP reported a lack of communication skills as a barrier.

5.3.3.5.2.1.6 Lack of none physical resources

Lack of time was reported by three HCPs.

5.3.3.5.2.2 Perception of responsibilities

5.3.3.5.2.2.1 Perceptions about HCPs' related responsibilities

This subcluster was reported by 11 HCPs. The answers are either related to staff negligence, resistance to change, and failure to take the recommendations seriously by the HCPs. Hierarchy issues and solo decision processes were also highlighted as barriers. These included Hierarchy issues among clinical pharmacists (reported by a clinical pharmacist), nurses are exposed to pressure by physicians (stated by one nurse, if a nurse refuses a decision due to medication safety concerns, the physician might complain against her/him), and lack of a multidisciplinary team in decision making.

Responsibility transfer to other HCPs was noted in the statements of five HCPs. One nurse reported that medication safety-related explanations should be performed by pharmacists and physicians and not by nurses. Moreover, three HCPs (two nurses and one physician) indicated that pharmacists should share information about medication safety. These two nurses stated sharing information through lectures, and one of these nurses' specified pharmacists with

KDFC professionals for conducting such lectures. Furthermore, a lack of clinical pharmacists in the wards and internal medicine units was identified as a barrier to implementation.

5.3.3.5.2.2.2 Perceptions about patients-related responsibilities

This subcluster was reported by seven HCPs. These included a lack of patients' knowledge and awareness about medication, standards of medication safety and the importance of medication safety. Other HCPs reported more general statements such as a lack of knowledge among patients, and knowledge levels of patients. A lack of patient cooperation was also mentioned.

One nurse reported patients' relatives as the barrier without further clarification. Further, lack of public awareness was also reported by a nurse as a barrier.

5.3.3.5.2.2.3 Perception of system-related responsibilities

These were internal to the hospital and external (e.g. MOH) responsibilities, and they were reported by 13 HCPs. The barriers included differentiation and segregation between HCPs, lack of cooperation between the authorities authorised to deliver medication safety information, and lack of communication between administration hierarchies. Perceiving that the MOH is not concerned about the implementation of medication safety communications, medication information is not regularly and continually updated were reported. In addition, dereliction of authorities to spread the information was also noted. An insignificant role of the drug control and not trusting the qualification of its staff, and communication issues between those who issued the recommendation and those who are supposed to implement it (lack of feedback acceptance) were both reported. Hospital management was reported as a barrier by one HPC but without clarification. Moreover, a lack of community health promotion and a lack of standardisation was also stated. Lack of standardisation included HCPs differ on drug efficacy and safety, drug safety being a continuously changing field, and what is true for one patient is not true for another, nothing is absolute, everything is relative, and information inconsistencies.

5.3.3.5.2.2.4 Roles of rumours and erroneous sources

Roles of rumours and erroneous information about the medication were reported by two HCPs. One pharmacist reported that such information might lead to patients' lack of confidence in the healthcare system.

5.3.3.5.2.3 Communication challenges

5.3.3.5.2.3.1 Organisational communications

This subcluster was reported by seven HCPs. This included a lack of open communication with the pharmacy department (by one nurse), poor communication with other HCPs, lack of professionalism and respect for others' opinions among the HCPs and condescension between them, and a need for communication between all parties was also noted. Moreover, one nurse cited a language barrier between HCPs as a barrier. Two general answers were given without clarification. These included communication and lack of communication

5.3.3.5.2.3.2 Patient-facing communications

This subcluster was reported by one nurse and included a language barrier between the HCPs and the patients.

5.3.3.6 Healthcare professionals' preferences for future medicines safety communications

5.3.3.6.1 Preferred format

A total of 326 participants indicated their preferences for future communications regarding medicines safety. Of these respondents, 67.8% (n=221) preferred to receive both hardcopies and softcopies, whereas 26.1% (n=85) preferred softcopies alone, and 6.1% (n=20) preferred hardcopies alone. There was a statistically significant association between professional group and their preferences for format of future medications safety communications assessed by Fisher's exact test, $p<0.001$ (Table 5.21).

Table 5.21: Differences in future communications format preferences of HCPs

		Nurse (n=158)		Pharmacist (n=70)		Pharmacy technician (n=9)		Physician (n=89)		P[b] (Exact Sig. (2-sided)
		N	%[a]	N	%[a]	N	%[a]	N	%[a]	
Format preferences for future medications safety communications	Hard copies (i.e., paper-based).	16	10.1%	2	2.9%	0	0.0%	2	2.2%	<0.001 *
	Soft copies (i.e., electronic-based).	21	13.3%	25	35.7%	1	11.1%	38	42.7%	
	Both hard and soft copies.	121	76.6%	43	61.4%	8	88.9%	49	55.1%	

[a] Column N%.
[b] All based on Fisher-Freeman-Halton Exact Test.

5.3.3.6.2 Preferred channels

In the multiple-response question, where participants could choose more than one answer, lectures (n=245, 27.1% of chosen channels) were the most preferred channel for disseminating medicines safety information, followed by emails (n=192, 21.2% of chosen channels), meetings (n=160, 17.7% of chosen channels), verbal communications (n=120, 13.3% of chosen channels), text messages (n= 113, 12.5% of chosen channels), posted letters or mails (n=53, 5.9% of chosen channels), and others (n=22, 2.4% of chosen channels).

Twenty-one participants wrote their preferences for other channels. The details of their preferences are presented in Table 5.22.

Table 5.22: HCPs preferred other channels for future communications

Preferences for future safety communications	Nurses	Pharmacists	Pharmacy technicians	Physicians
Social media (social media platforms; social media accredited accounts; infographic posts on social media with reliable sources; pharmacist twitter accounts; official social media, like MOH, Kuwait Medical Association; WhatsApp/ WhatsApp group; any official social media group for staff update with the head of departments or experts, and departments in charge that understand and communicate to their departments).	4	4	-	4
Circulars (official circular; official circular signed by all medical personnel without exception).	2	-	-	2
Printed format.	1	-	-	-
Videos.	-	-	-	1
Updated medicines policy/guidelines.	1	-	-	-
Approved/trusted webpage that notifies HCPs of any updates.	-	-	-	1
Media (television advertisements, commercial magazines, and newspapers).	1	-	-	-

There was a statistically significant association between professional group and their preferences for using emails as channels for disseminating future medications safety communications assessed by Fisher's exact test, $p<0.001$ (Table 5.23).

Table 5.23: Differences in future communications channels preferences of HCPs

		Nurse (n=158)		Pharmacist (n=70)		Pharmacy technician (n=9)		Physician (n=89)		P[b] (Exact Sig. (2-sided)
		N	%[a]	N	%[a]	N	%[a]	N	%[a]	
Emails	No	87	55.1%	23	32.9%	4	44.4%	20	22.5%	<0.001*
	Yes	71	44.9%	47	67.1%	5	55.6%	69	77.5%	
Text messages	No	107	67.7%	43	61.4%	6	66.7%	57	64%	0.796
	Yes	51	32.3%	27	38.6%	3	33.3%	32	36%	
Posted letters/mails	No	126	79.7%	58	82.9%	9	100%	80	89.9%	0.118
	Yes	32	20.3%	12	17.1%	0	0%	9	10.1%	
lectures	No	32	20.3%	21	30%	1	11.1%	27	30.3%	0.170
	Yes	126	79.7%	49	70%	8	88.9%	62	69.7%	
Verbal communications	No	95	60.1%	47	67.1%	5	55.6%	59	66.3%	0.632
	Yes	63	39.9%	23	32.9%	4	44.4%	30	33.7%	
Meetings	No	79	50%	41	58.6%	4	44.4%	42	47.2%	0.507
	Yes	79	50%	29	41.4%	5	55.6%	47	52.8%	

[a] Column N %
[b] All based on Fisher-Freeman-Halton Exact Test

5.3.4 Results of the survey: the valproate-specific objectives

This section presents the results of the valproate-specific objectives of the online survey. This section included the following domains: (1) Participants' characteristics; (2) HCPs knowledge of valproate teratogenicity and DHCP; (3) Sources by which they became aware of valproate teratogenicity; (4) Self-reported impact of valproate safety communication; (5) Perceived barriers to implementing valproate safety recommendations (results from closed-ended questions and open-ended question).

5.3.4.1 Particpants' charasteristics

A total of 169 particpants answerd thise section, represnting 42.8% of particpants in the prevoius section. More than two-thirds of particpants in this sample were females (n= 118, 69.8%) and non-kuwaities (n= 103, 60.9%). This sample was composed of 78 nurses (46.2%), 56 pharmacists (33.1%) 28 physicians (16.6%), and 7 pharmacy technicians (4.1%).

The age ranges of 44.4% (n=75) of respondents were 31 to less than 41 years. One-fourth of particpants in this sample (n=42, 24.9%) had an experince of five to less than ten years. A total of 73 (43.2%) particpants had an undergraduate degree, and 62 (36.7%) had a postgraduate degree. The demographic detalis of the respondents are provided in Table (5.24).

Table 5.24: Participants' characteristics

Category	Subcategory	N (%)
Gender (N= 169, 100%)	Male	51 (30.2%)
	Female	118(69.8%)
Nationality (N= 169, 100%)	Kuwaiti	66 (39.1%)
	Non-Kuwaiti[a]	103 (60.9%)
Age (N= 169, 100%)	21 to less than 31 years	38 (22.5%)
	31 to less than 41 years	75 (44.4%)
	41 to less than 51 years	42 (24.9)
	51 to less than 61 years	10 (5.9)
	61 to less than 71 years	4 (2.4%)
	71 years or more	0 (0%)
Education (N= 169, 100%)	High school degree	3 (1.8%)
	Undergraduate degree	73(43.2%)
	Postgraduate degree	62(36.7%)
	Other[b]	31(18.3%)
Professional background (N= 169, 100%)	Nurse	78 (46.2%)
	Pharmacist	56(33.1%)
	Pharmacy technician	7(4.1%)
	Physician	28(16.6%)
Workplace description (N=180, 106.5%)[c,d]	Primary care governmental centres	0 (0%)
	General governmental hospital	119 (70.4%)
	Specialized governmental hospital	58 (34.3%)
	Private clinic or hospital	2 (1.2%)
	Other[e]	1(0.6%)
Health area administration (N=179, 105.9%) [c,d]	Ahmadi	19 (11.2%)
	Asimah (Capital)	13(7.7%)
	Farwanyia	20 (11.8%)
	Hawali	23 (13.6%)
	Jahra	39 (23.1%)
	Mubarak	9 (5.3%)
	Sabah	56 (33.1%)
	Other	0 (0%)
Work experience (N)	less than 5 years	27 (16%)
	5 years to less than 10 years	42 (24.9%)
	10 years to less than 15 years	38 (22.5%)
	15 years to less than 20 years	26 (15.4%)
	20 years to less than 25 years	17 (10.1%)
	25 years to less than 30 years	10 (5.9%)
	30 years or more	9 (5.3%)
Nurses' job title (N= 78, 100%)	Assistant nurse	4 (5.1%)
	Nurse	39 (50%)
	Senior nurse	18 (23.1%)
	Specialist nurse	8 (10.3%)
	Senior specialist nurse	7 (9%)
	Head of nursing specialist	0 (0%)
	Other[f]	2 (2.6%)
Pharmacists' job title (N= 56, 100%)	Beginner pharmacist	10 (17.9%)
	Pharmacist	9 (16.1%)
	Senior pharmacist	19 (33.9%)
	Pharmacy specialist	8 (14.3%)

	Senior pharmacy specialist	2 (3.6%)
	Head of pharmacy specialist	8 (14.3%)
	Other	0 (0%)
Pharmacy technicians' job title (N=7, 100%)	Assistant pharmacy technician	0 (0%)
	Pharmacy technician	0 (0%)
	Senior pharmacy technician	7 (100%)
	Other	0 (0%)
Physicians' job title (N=28,100%)	Trainee	3 (10.7%)
	Resident	2 (7.1%)
	Assistant registrar	2 (7.1%)
	Registrar	4 (14.3%)
	Senior registrar	7 (25%)
	Senior general practitioner (B)	1 (3.6%)
	Senior general practitioner (A)	1 (3.6%)
	Specialist	1 (3.6%)
	Senior specialist	1 (3.6%)
	Consultant	6 (21.4%)
	Other	0 (0%)
Physicians' specialities	Anaesthesiology and intensive care (or critical care)	4
	Audio-Vestibular medicine/Audiology medicine	2
	Gastroenterology	1
	Haematology/ internal medicine and haematology	1
	Medicine/ internal medicine	8
	Nephrology	1
	Ophthalmology	2
	Paediatrics	3
	Physical medicine and rehabilitation/ physiatrist	1
	Psychiatry	1
	Surgery/ General Surgery	3
	Trainee/ not specialised yet/ trainee medicine rotation	1

[a] 80 participants specified their nationalities, this included India (44), Egypt (19), Jordan (4), Pakistan (4), Philippines (2),
and one for each Indonesia, Iran, Palestine, Somalia, Stateless, Syria, and the UK.
[b] 29 of those selecting "other" specified their highest educational degrees. 9 participants (included 5 nurses and 4 pharmacy technicians) stated having a diploma.10 Nurses reported having a bachelor's degree. 2 other participants (1 nurse and 1 physician) reported having a postgraduate degree.2 physicians specified their degrees as the following MRCP MD SCE nephrology (one physician), MRCP (UK) and Kuwait board of internal medicine (one physician). Other nurses stated the following without specifying their educational level: general nursing and midwifery (n=2), degree (n= 1), graduate (n=1), graduate degree (n=1), and graduation (n=1).
[c] Participants could choose more than one answer.
[d] Percentages presented by percent of cases (number of participants).
[e] One participant selected "others" worked in a general MOH hospital (also counted in the general hospitals options).
[f] Nurses that chose "other" for their job title wrote the following: Clinical instructor (n=2).

5.3.4.2 HCPs' knowledge related to valproate teratogenicity and DHCP

HCPs' general knowledge about valproate teratogenicity, as well as their specific knowledge about KDFC recommendations regarding this issue were measured. Most of the 169 participants answering this question were aware about valproate teratogenic effects (n= 110, 65.1%), while the remaining participants were either unaware (n=26, 15.4%) or not sure whether they knew this information previously or not (n=33, 19.5%). A significant association was detected between being aware of valproate teratogenicity and the participants' professional group (p=0.003; Table 5.25)

Table 5.25: HCPs' general knowledge of valproate teratogenicity

		Nurse (n=78)		Pharmacist (n=56)		Pharmacy technician (n=7)		Physician (n=28)		p[b] (Exact Sig. (2-sided)
		N	%[a]	N	%[a]	N	%[a]	N	%[a]	
General awareness about valproate teratogenicity	Not Aware	37	47.4%	12	21.4%	4	57.1%	6	21.4%	0.003*
	Aware	41	52.6%	44	78.6%	3	42.9%	22	78.6%	

[a] Column N %
[b] All based on Fisher-Freeman-Halton Exact Test
Not aware: (those who answered no or not sure)

A total of 156 participants answered questions about the accuracy of seven statements related to KDFC recommendations. No participants had correctly answered all statements, and only four participants (2.6%) had accurately answered six of the seven statements. Table 5.26 presents the details of healthcare professionals' answers to each of the seven statements. Kruskal-Wallis test was conducted to detect if there were statistically significant differences between the four healthcare professionals' groups in terms of their knowledge of KDFC's recommendations related to valproate teratogenicity. Distributions of the scores of the four groups' total knowledge were different as visually detected using a boxplot. The differences among the four groups, however, were not statistically significantly different, X2(3) = 5.165, p=.160 [Asymptotic derived p-value (2-sided test)].

Table 5.26: Healthcare professionals answers of the accuracy of the statements representing KDFC recommendations in response to valproate teratogenicity

Category	Subcategory	Frequency (%) N= 156[1] (100%)
VRMs should not be prescribed to female patients unless other treatments are not effective or not tolerated	No	30 (19.2%)
	Not sure	88 (56.4%)
	Yes	38 (24.4%)
Avoid VRMs in all patients unless other treatments fail	No	53 (34%)
	Not sure	81 (51.9%)
	Yes	22 (14.1%)
Inform all female patients about the risk of VRMs in pregnancy	No	11 (7.1%)
	Not sure	48 (30.8%)
	Yes	97 (62.2%)
Inform female patients to use effective contraceptives	No	19 (12.2%)
	Not sure	69 (44.2%)
	Yes	68 (43.6%)
Provide female patients with a patient information booklet	No	22 (14.1%)
	Not sure	49 (31.4%)
	Yes	85 (54.5%)
Ask female patients to sign an acknowledgment about the risks of VRMs	No	41 (26.3%)
	Not sure	70 (44.9%)
	Yes	45 (28.8%)
Avoid using VRMs with other medications used in epilepsy or bipolar disorder	No	36 (23.1%)
	Not sure	74 (47.4%)
	Yes	46 (29.5%)
Sum having accurate knowledge about the specific KDFC VRM recommendation	Answered all seven statements correctly (scored 7/7)	0 (0%)
	Answered six of the seven statements correctly (scored 6/7)	4 (2.6%)
	Answered five of the seven statements correctly (scored 5/7)	29 (18.6%)
	Answered four of the seven statements correctly (scored 4/7)	23 (14.7%)
	Answered three of the seven statements correctly (scored 3/7)	29 (18.6%)
	Answered two of the seven statements correctly (scored 2/7)	25 (16%)
	Answered one of the seven statements correctly (scored 1/7)	24 (15.4%)
	Did not answer any of the seven statements correctly (scored 0/7)	22 (14.1%)

[1]Less than 169 due to missing answers. **VRM**: Valproate related medication

5.3.4.3: Sources by which HCPs became aware about valproate teratogenicity

A total of 131 participants answered this multiple-response question, where participants could choose more than one answer, regarding the sources by which they became aware about valproate safety issue. The most cited source by the HCPs were scientific journals (n=53, 40.5% of 131 participants). This was followed by drug companies (n=43, 32.8%), international drug regulatory agencies (n=42, 32.1%), and colleagues (n=38, 29%).

Almost one-fourth of the participants cited 'circular' from Kuwait MOH (n=32, 24.4% of the 131 participants) as the main source by which they became aware of the valproate safety issue, and 19.8% (n=26) selected circular from KDFC. On the other hand, social media, and media were selected by 21.4%(n=28) and 11.5% (n=15) of respondents to this question, respectively. Seven participants (5.3%) selected patients as the source of knowing valproate teratogenicity. While thirteen participants (9.9%) did not remember the source, twenty-six participants (19.8%) reported other sources.

Figure 5.6 represents HCPs' reported sources in accordance with the total options selected in this question. Other sources written by healthcare professionals the text areas are presented in Table 5.27.

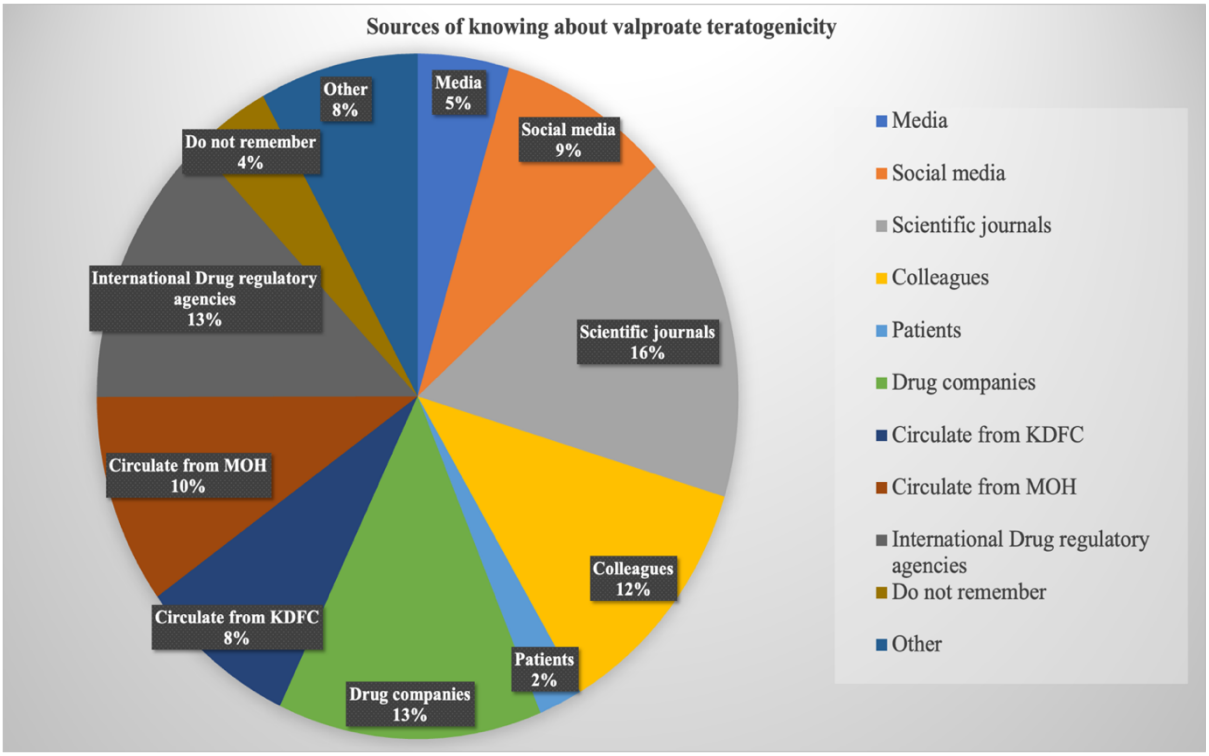


Figure 5.6: Sources from which healthcare professionals became aware about valproate teratogenicity

Table 5.27: Other sources by which HCPs became aware about valproate teratogenicity

Other sources[1,2]	Nurses	Pharmacists	Pharmacy technicians	Physicians	Total
Books (Books/ books and medical references/ Rn Exam books/ scientific books/ studying and keeping up to date with scientific publications and books / drug books CIMS)	2	1	1	3	7
Studies/ Learning/educations (during MPharm studies, study curriculum, university, medical school lectures, studying during bachelor's degree, education years, studying years, participants' education, learned pharmacology, studying in general, through study in the field of specialisation and through medical sources)	3	9	0	3	15
Websites (medical websites, medical sites (UpToDate[3]))	0	0	0	2	2
Medical references/scientific publications	0	0	1	2	3
Apps or programmes (Medscape App, UpToDate[3], Medscape (without specifying if app or website)	0	1	0	1	2
Product packaging (Warning on the product packaging)	0	1	0	0	1

[1]26 participants answered, 30 answers above because four participants wrote two methods by, she or he become aware of valproate safety information. [2] This column includes the different alternative sources stated by healthcare professionals. [3] UpToDate was mentioned twice, one as an of websites, and another without specifying whether as an app, programme or website.

By Fisher's exact test, a significant association was detected between the type of the professional group, and whether they learnt about the valproate teratogenicity from the media ($p=.001$), social media ($p<0.001$), scientific journals ($p=0.041$) or from international drug regulatory agencies ($p=0.009$). On the other hand, no significant association was found between the professional group variable with each of colleagues, patients, circulate from MOH, circulate from KDFC, and drug companies (details in Table 5.28).

Table 5.28: Differences in sources from which HCPs knew about valproate teratogenicity

		Nurse (n=57)		Pharmacist (n=46)		Pharmacy technician (n=6)		Physician (n=22)		P[b] (Exact Sig. (2-sided)
		N	%[a]	N	%[a]	N	%[a]	N	%[a]	
Media	No	44	77.2%	46	100.0%	6	100.0%	20	90.9%	.001*
	Yes	13	22.8%	0	0.0%	0	0.0%	2	9.1%	
Social media	No	35	61.4%	44	95.7%	5	83.3%	19	86.4%	<0.001*
	Yes	22	38.6%	2	4.3%	1	16.7%	3	13.6%	
Scientific journals	No	34	59.6%	33	71.7%	3	50.0%	8	36.4%	0.041*
	Yes	23	40.4%	13	28.3%	3	50.0%	14	63.6%	
Colleagues	No	42	73.7%	34	73.9%	2	33.3%	15	68.2%	0.216
	Yes	15	26.3%	12	26.1%	4	66.7%	7	31.8%	
Patients	No	52	91.2%	46	100.0%	6	100.0%	20	90.9%	0.119
	Yes	5	8.8%	0	0.0%	0	0.0%	2	9.1%	
International drug regulatory agencies	No	45	78.9%	32	69.6%	3	50.0%	9	40.9%	0.009*
	Yes	12	21.1%	14	30.4%	3	50.0%	13	59.1%	
Circulate from MOH	No	37	64.9%	40	87.0%	5	83.3%	17	77.3%	0.066
	Yes	20	35.1%	6	13.0%	1	16.7%	5	22.7%	
Circulate from KDFC	No	44	77.2%	39	84.8%	4	66.7%	18	81.8%	0.569
	Yes	13	22.8%	7	15.2%	2	33.3%	4	18.2%	
Drug companies	No	35	61.4%	34	73.9%	2	33.3%	17	77.3%	0.116
	Yes	22	38.6%	12	26.1%	4	66.7%	5	22.7%	

[a] Column N %

[b] All based on Fisher-Freeman-Halton Exact Test

5.3.4.4: Self-reported impact of valproate safety communication

A total of 156 participants reported the impact of valproate safety information on their practice. The most reported changes in practice were providing female patients with written information about valproate risks during pregnancy (n= 58, 37.2%), and counselling female patients at childbearing age about contraceptive use (n= 58, 37.2%). Following this, 45 participants (28.8%) reported asking adult female patients to sign an acknowledgment that they knew about the risks of valproate. Thirty-five participants (22.4%) decreased prescribing valproate to female patients, and thirty-four participants prescribed valproate only if other treatments fail (21.8%). Healthcare professionals reported the unintended impact less commonly, as twelve participants (7.7%) stopped prescribing valproate to female patients. Spill-over effect was also less commonly seen with only seven participants (4.5%) stopped prescribing valproate to all patients. Slightly more than one-fifth of participants (n=35, 22.4%) answering these questions reported that the valproate safety issue did not affect their practice. More details about the each of the HCPs' groups self-reported impact are presented in Figures 5.7, 5.8, 5.9 and 5.10.

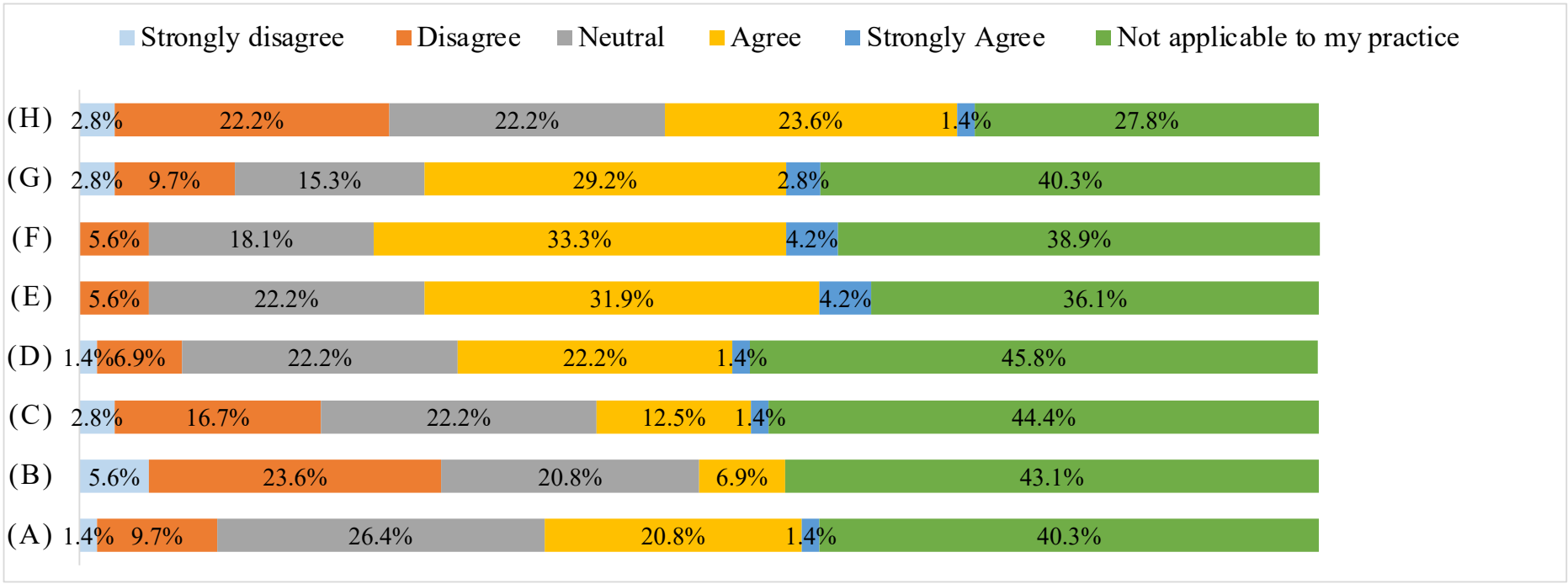


Figure 5.7: Nurses' self-reported impact of the valproate- safety recommendations

Figure 5.7: Nurses' self-reported impact, including:

(A) I decreased prescribing valproate to female patients

(B) I stopped prescribing valproate to all patients

(C) I stopped prescribing valproate to female patients

(D) I prescribe valproate to female patients only if other treatments fail

(E) I counsel female patients at childbearing age about contraceptive use

(F) I ask adult female patients to sign an acknowledgment that they know about the risks of valproate

(G) I provide female patients a written information about the risks of using valproate during pregnancy

(H) It did not affect my practice

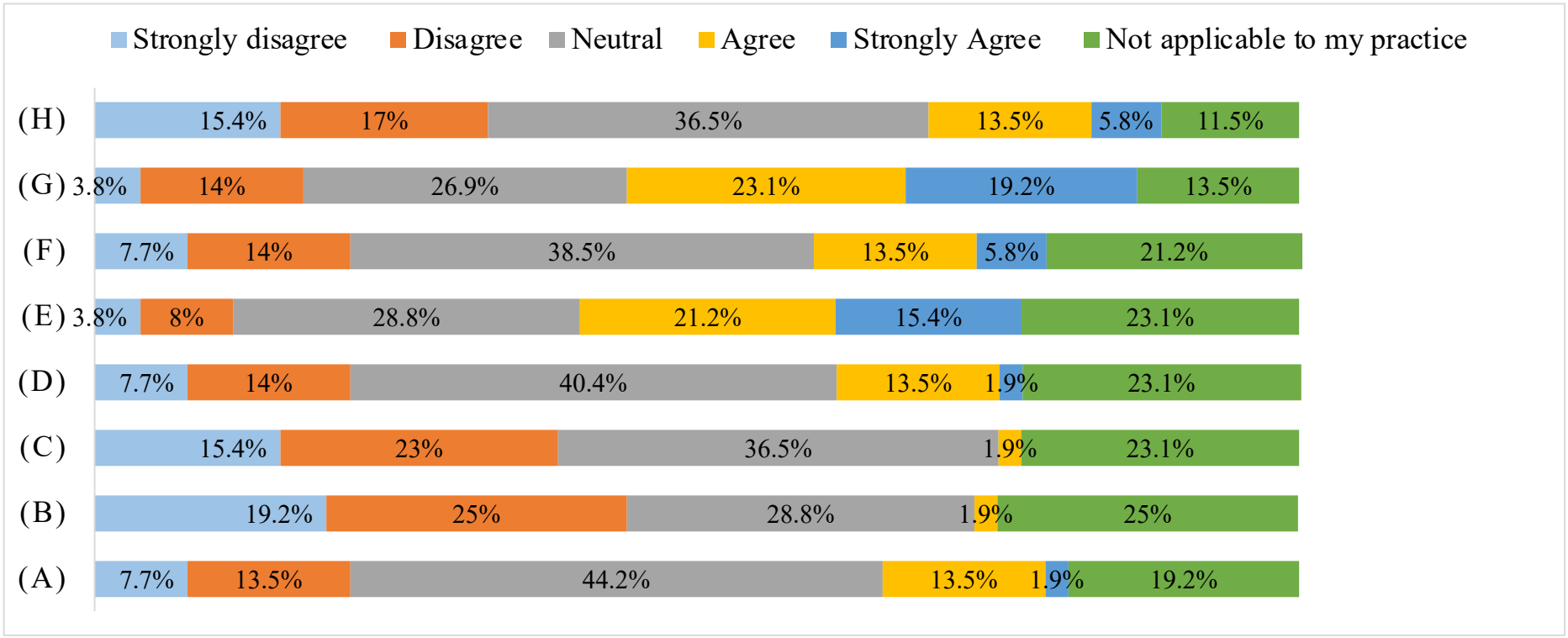


Figure 5.8: Pharmacists' self-reported impact of the valproate-safety recommendations

Figure 5.8: Pharmacists' self-reported impact, including:

(A) I decreased prescribing valproate to female patients

(B) I stopped prescribing valproate to all patients

(C) I stopped prescribing valproate to female patients

(D) I prescribe valproate to female patients only if other treatments fail

(E) I counsel female patients at childbearing age about contraceptive use

(F) I ask adult female patients to sign an acknowledgment that they know about the risks of valproate

(G) I provide female patients a written information about the risks of using valproate during pregnancy

(H) It did not affect my practice

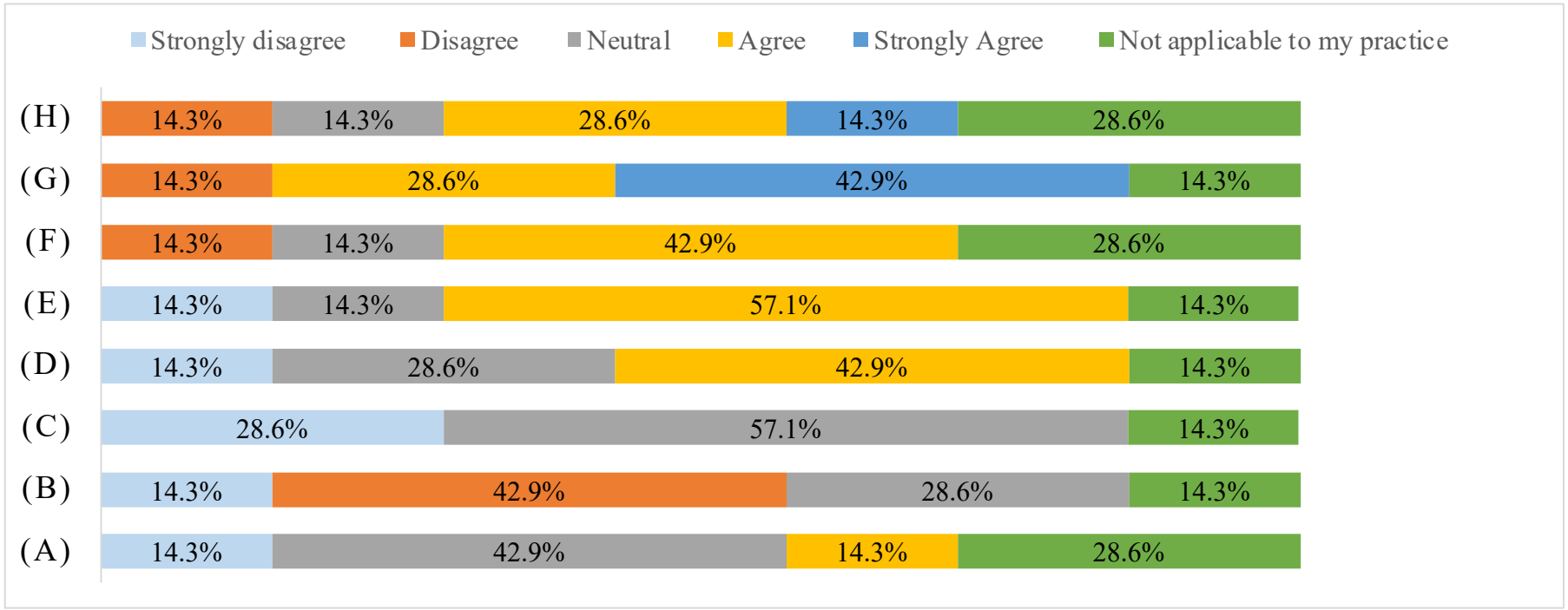


Figure 5.9: Pharmacy technicians' self-reported impact of the valproate-safety recommendations

Figure 5.9: Pharmacy technicians' self-reported impact, including

(A) I decreased prescribing valproate to female patients

(B) I stopped prescribing valproate to all patients

(C) I stopped prescribing valproate to female patients

(D) I prescribe valproate to female patients only if other treatments fail

(E) I counsel female patients at childbearing age about contraceptive use

(F) I ask adult female patients to sign an acknowledgment that they know about the risks of valproate

(G) I provide female patients a written information about the risks of using valproate during pregnancy

(H) It did not affect my practice

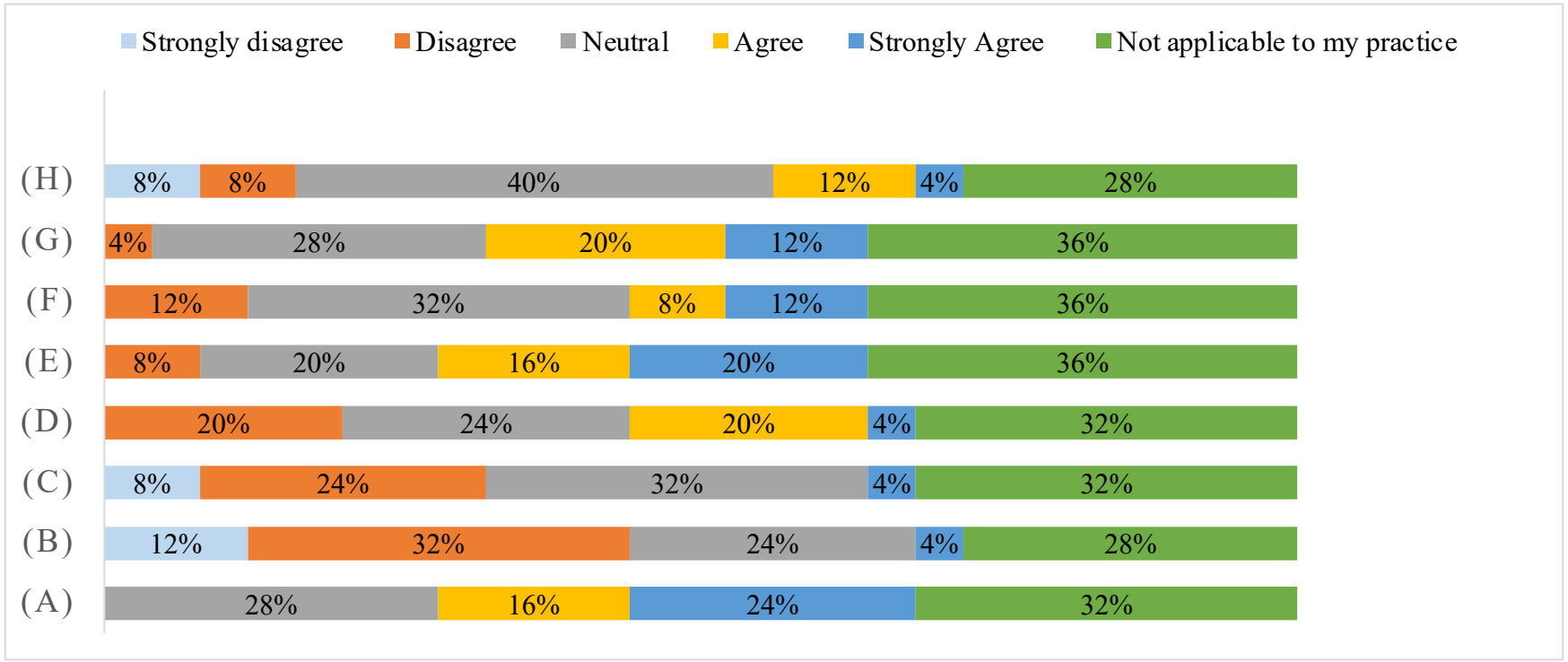


Figure 5.10: Physicians' self-reported impact of the valproate-safety recommendations

Figure 5.10: Physicians' self-reported impact

(A) I decreased prescribing valproate to female patients

(B) I stopped prescribing valproate to all patients

(C) I stopped prescribing valproate to female patients

(D) I prescribe valproate to female patients only if other treatments fail

(E) I counsel female patients at childbearing age about contraceptive use

(F) I ask adult female patients to sign an acknowledgment that they know about the risks of valproate

(G) I provide female patients a written information about the risks of using valproate during pregnancy

(H) It did not affect my practice

Four of the changes to practice statements were reported in KDFC's valproate safety letter. These included prescribing valproate to female patients only if other treatments fail, counselling female patients at childbearing age about contraceptive use, asking adult female patients to sign an acknowledgment that they know about the risks of valproate use in pregnancy, and providing female patients a written information about the risks of using valproate in pregnancy. From the 156 participants answering these questions, 89 participants (57%) had reported changing their practice to at least one of the intended actions in the valproate safety letter. More specifically, thirty (19.2%), twenty-five (16%), and, twenty-one (13.5%) had reported one, two and three intended changes, respectively. Thirteen participants (8.3%) reported changing their practice to the four intended actions specified by the letters. Kruskal-Wallis's test was also conducted to detect if there were statistically significant differences between the four healthcare professionals' groups in terms of their total intended impacts scores. Distributions of the scores of the four groups were different as visually detected using boxplot. The differences among the four groups, however, were not statistically significantly different, $X2(3) = 3.526$, $p=0.317$ [Asymptotic derived p-value (2-sided test)].

A multivariate Regression (General Linear Model) was employed to detect whether the participants characteristics had an effect on their implementation of KDFC's valproate-related recommendations. The multivariate test Table 5.29 shows a significant effect of the professional background on HCPs' implementation of KDFC's valproate-related intended recommendations (Pillai's Trace= 0.193, F= 2.08, P=.040). However, all other demographic factors had no significant effect on HCPs' implementation of KDFC's valproate-related intended recommendations. The parameter estimates table (Table 5.30) indicates only one significant interaction effect on one type of indented impact. Specifically, being a male pharmacist had a negative significant effect on counselling female patients at childbearing age about the use of contraceptives (β=-2.175, P=.040).

Table 5.29: Multivariate tests

Multivariate tests[a]							
Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	.494	18.830[b]	4.000	77.000	<.001	.494
	Wilks' Lambda	.506	18.830[b]	4.000	77.000	<.001	.494
	Hotelling's Trace	.978	18.830[b]	4.000	77.000	<.001	.494
	Roy's Largest Root	.978	18.830[b]	4.000	77.000	<.001	.494
Age	Pillai's Trace	.033	.663[b]	4.000	77.000	.619	.033
	Wilks' Lambda	.967	.663[b]	4.000	77.000	.619	.033
	Hotelling's Trace	.034	.663[b]	4.000	77.000	.619	.033
	Roy's Largest Root	.034	.663[b]	4.000	77.000	.619	.033
Education	Pillai's Trace	.027	.528[b]	4.000	77.000	.716	.027
	Wilks' Lambda	.973	.528[b]	4.000	77.000	.716	.027
	Hotelling's Trace	.027	.528[b]	4.000	77.000	.716	.027
	Roy's Largest Root	.027	.528[b]	4.000	77.000	.716	.027
Experience	Pillai's Trace	.043	.856[b]	4.000	77.000	.494	.043
	Wilks' Lambda	.957	.856[b]	4.000	77.000	.494	.043
	Hotelling's Trace	.044	.856[b]	4.000	77.000	.494	.043
	Roy's Largest Root	.044	.856[b]	4.000	77.000	.494	.043
Professional background	Pillai's Trace	.160	1.115	12.000	237.000	.349	.053
	Wilks' Lambda	.846	1.109	12.000	204.014	.354	.054
	Hotelling's Trace	.175	1.101	12.000	227.000	.360	.055
	Roy's Largest Root	.115	2.264[c]	4.000	79.000	.070	.103
Gender	Pillai's Trace	.036	.718[b]	4.000	77.000	.582	.036
	Wilks' Lambda	.964	.718[b]	4.000	77.000	.582	.036
	Hotelling's Trace	.037	.718[b]	4.000	77.000	.582	.036
	Roy's Largest Root	.037	.718[b]	4.000	77.000	.582	.036
Nationality	Pillai's Trace	.007	.138[b]	4.000	77.000	.968	.007
	Wilks' Lambda	.993	.138[b]	4.000	77.000	.968	.007
	Hotelling's Trace	.007	.138[b]	4.000	77.000	.968	.007

	Roy's Largest Root	.007	.138[b]	4.000	77.000	.968	.007
Professional background * gender	Pillai's Trace	.193	2.087	8.000	156.000	.040	.097
	Wilks' Lambda	.810	2.135[b]	8.000	154.000	.036	.100
	Hotelling's Trace	.230	2.180	8.000	152.000	.032	.103
	Roy's Largest Root	.207	4.046[c]	4.000	78.000	.005	.172
Professional background * nationality	Pillai's Trace	.104	1.074	8.000	156.000	.384	.052
	Wilks' Lambda	.898	1.062[b]	8.000	154.000	.393	.052
	Hotelling's Trace	.110	1.050	8.000	152.000	.402	.052
	Roy's Largest Root	.068	1.333[c]	4.000	78.000	.265	.064
Gender * nationality	Pillai's Trace	.058	1.180[b]	4.000	77.000	.326	.058
	Wilks' Lambda	.942	1.180[b]	4.000	77.000	.326	.058
	Hotelling's Trace	.061	1.180[b]	4.000	77.000	.326	.058
	Roy's Largest Root	.061	1.180[b]	4.000	77.000	.326	.058
Professional background * gender * nationality	Pillai's Trace	.027	.527[b]	4.000	77.000	.716	.027
	Wilks' Lambda	.973	.527[b]	4.000	77.000	.716	.027
	Hotelling's Trace	.027	.527[b]	4.000	77.000	.716	.027
	Roy's Largest Root	.027	.527[b]	4.000	77.000	.716	.027

a. Design: intercept + age + education + experience + professional background + gender + nationality + professional background * gender + professional background * nationality + gender * nationality + professional background * gender * nationality

b. Exact statistic

c. The statistic is an upper bound on f that yields a lower bound on the significance level.

Table 5.30: Parameters estimates

Parameter estimates								
Dependent variable	Parameter	β	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
						Lower Bound	Upper Bound	
I prescribe Depakine/Depakine Chrono to female patients only if other treatments fail.	Intercept	1.979	1.028	1.925	.058	-.067	4.025	.044
	Age	.036	.216	.169	.866	-.393	.466	.000
	Education	-.011	.150	-.072	.942	-.308	.287	.000
	Experience	-.010	.117	-.083	.934	-.242	.222	.000
	Nurse	1.403	.904	1.551	.125	-.397	3.203	.029
	Pharmacist	.612	.946	.647	.519	-1.270	2.495	.005
	Pharmacy Technician	-.029	.811	-.035	.972	-1.643	1.586	.000
	Physician	0[a]	.	.	.	.	.	.
	Male	1.378	.982	1.403	.164	-.576	3.333	.024
	Female	0[a]	.	.	.	.	.	.
	Kuwaiti	1.516	1.097	1.382	.171	-.667	3.699	.023
	Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male	-1.395	1.051	-1.328	.188	-3.486	.696	.022
	Nurse * Female	0[a]	.	.	.	.	.	.
	Pharmacist * Male	-1.009	1.079	-.935	.353	-3.156	1.138	.011
	Pharmacist * Female	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female	0[a]	.	.	.	.	.	.
	Physician * Male	0[a]	.	.	.	.	.	.
	Physician * Female	0[a]	.	.	.	.	.	.
	Nurse * Kuwaiti	-2.285	1.235	-1.850	.068	-4.742	.173	.041
	Nurse * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Kuwaiti	-1.069	1.158	-.922	.359	-3.374	1.237	.011
	Pharmacist * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Male * Kuwaiti	-2.021	1.196	-1.690	.095	-4.400	.359	.034
	Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.

	Nurse * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Male * Kuwaiti	1.102	1.380	.799	.427	-1.643	3.848	.008
	Pharmacist * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
I counsel female patients at childbearing age about contraceptive use.	Intercept	1.518	.994	1.527	.131	-.460	3.495	.028
	Age	.097	.208	.463	.644	-.318	.511	.003
	Education	.157	.145	1.086	.281	-.131	.445	.015
	Experience	-.091	.113	-.807	.422	-.315	.133	.008
	Nurse	1.497	.874	1.712	.091	-.243	3.236	.035
	Pharmacist	1.701	.914	1.860	.066	-.119	3.521	.041
	Pharmacy Technician	1.342	.784	1.711	.091	-.219	2.902	.035
	Physician	0[a]	.	.	.	.	.	.
	Male	1.888	.949	1.989	.050	-.001	3.777	.047
	Female	0[a]	.	.	.	.	.	.
	Kuwaiti	.663	1.060	.625	.534	-1.447	2.772	.005
	Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male	-1.719	1.016	-1.693	.094	-3.740	.302	.035
	Nurse * Female	0[a]	.	.	.	.	.	.
	Pharmacist * Male	-2.175	1.043	-2.086	.040	-4.250	-.100	.052
	Pharmacist * Female	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female	0[a]	.	.	.	.	.	.
	Physician * Male	0[a]	.	.	.	.	.	.
	Physician * Female	0[a]	.	.	.	.	.	.
	Nurse * Kuwaiti	-.954	1.193	-.799	.427	-3.329	1.421	.008
	Nurse * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Kuwaiti	-.505	1.119	-.451	.653	-2.733	1.723	.003
	Pharmacist * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Kuwaiti	0[a]	.	.	.	.	.	.

	Physician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Male * Kuwaiti	-.223	1.156	-.193	.847	-2.523	2.077	.000
	Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Male * Kuwaiti	-.866	1.333	-.649	.518	-3.519	1.788	.005
	Pharmacist * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
I ask adult female patients to sign an acknowledgment that they know about the risks of Depakine/Depakine Chrono	Intercept	2.250	1.000	2.250	.027	.260	4.241	.060
	Age	.340	.210	1.619	.109	-.078	.757	.032
	Education	.154	.145	1.062	.292	-.135	.444	.014
	Experience	-.197	.113	-1.733	.087	-.422	.029	.036
	Nurse	.812	.880	.923	.359	-.938	2.563	.011
	Pharmacist	-.158	.920	-.172	.864	-1.989	1.673	.000
	Pharmacy Technician	.280	.789	.354	.724	-1.291	1.850	.002
	Physician	0[a]	.	.	.	.	.	.
	Male	.644	.955	.674	.502	-1.257	2.545	.006
	Female	0[a]	.	.	.	.	.	.
	Kuwaiti	.298	1.067	.279	.781	-1.825	2.421	.001
	Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male	-.698	1.022	-.683	.497	-2.732	1.336	.006
	Nurse * Female	0[a]	.	.	.	.	.	.
	Pharmacist * Male	-.714	1.050	-.681	.498	-2.803	1.374	.006
	Pharmacist * Female	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female	0[a]	.	.	.	.	.	.
	Physician * Male	0[a]	.	.	.	.	.	.

	Physician * Female	0[a]	.	.	.	.	.	.
	Nurse * Kuwaiti	-.999	1.201	-.832	.408	-3.390	1.391	.009
	Nurse * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Kuwaiti	.320	1.127	.284	.777	-1.922	2.562	.001
	Pharmacist * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Male * Kuwaiti	-.573	1.163	-.493	.624	-2.888	1.741	.003
	Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Male * Kuwaiti	-.418	1.342	-.312	.756	-3.089	2.252	.001
	Pharmacist * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
I provide female patients a written information about the risks of using Depakine/Depakine Chrono during pregnancy	Intercept	2.897	1.196	2.423	.018	.517	5.277	.068
	Age	.165	.251	.658	.512	-.334	.664	.005
	Education	.029	.174	.165	.870	-.317	.375	.000
	Experience	-.157	.136	-1.154	.252	-.426	.113	.016
	Nurse	.487	1.052	.463	.645	-1.606	2.579	.003
	Pharmacist	.980	1.100	.891	.376	-1.210	3.169	.010
	Pharmacy Technician	1.282	.944	1.358	.178	-.596	3.159	.023
	Physician	0[a]	.	.	.	.	.	.
	Male	.801	1.142	.702	.485	-1.471	3.074	.006
	Female	0[a]	.	.	.	.	.	.
	Kuwaiti	.537	1.276	.421	.675	-2.001	3.076	.002
	Non-Kuwaiti	0[a]	.	.	.	.	.	.

	Nurse * Male	-1.033	1.222	-.846	.400	-3.465	1.399	.009
	Nurse * Female	0[a]	.	.	.	.	.	.
	Pharmacist * Male	-1.389	1.255	-1.107	.272	-3.886	1.108	.015
	Pharmacist * Female	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female	0[a]	.	.	.	.	.	.
	Physician * Male	0[a]	.	.	.	.	.	.
	Physician * Female	0[a]	.	.	.	.	.	.
	Nurse * Kuwaiti	-.991	1.436	-.690	.492	-3.849	1.866	.006
	Nurse * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Kuwaiti	-.883	1.347	-.656	.514	-3.564	1.798	.005
	Pharmacist * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Male * Kuwaiti	-.455	1.391	-.327	.744	-3.222	2.313	.001
	Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Nurse * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Male * Kuwaiti	.628	1.604	.391	.696	-2.565	3.821	.002
	Pharmacist * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacist * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Pharmacy Technician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Male * Non-Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Kuwaiti	0[a]	.	.	.	.	.	.
	Physician * Female * Non-Kuwaiti	0[a]	.	.	.	.	.	.

a. This parameter is set to zero because it is redundant.

5.3.4.5: Perceived barriers to implementing valproate safety recommendations

5.3.4.5.1: Barriers from the closed-ended questions

Totally,151 participants reported their perceived barriers to implementing valproate safety recommendations. Nearly one-third of the participants (n=51, 33.8%) reported not having the space to implement the recommendations. Forty-six participants (30.5%) reported that other professionals do not think it is the participants role to implement the recommendation. Moreover, forty-five participants (29.8%) were not familiar on how to implement the recommendations; and forty-three (28.5%) were not confident in talking about pregnancy issues with female patients. A similar proportion of participants reported that they do not work in a cooperative environment between different professionals' teams (n=35, 23.2%), they do not think it is their roles to implement the recommendations (n=35, 23.2%), and they think the recommendations will negatively affect the patient compliance (n=32, 21.2%). However, slightly more than half of the participants disagreed that the previous three statements were barriers to them implementing valproate safety recommendations. Although eighty-five participants (56.3%) disagreed, twenty-seven (17.9%) reported their hospital policies do not encourage them to implement the recommendations. Twenty-two participants (14.6%) participants did not think the recommendations were useful, the same number of participants reported not considering medicine safety information in their clinical practice (n=22, 14.6%), and twenty-one (13.9%) reported having other work to do with higher priority. A few participants reported they disagree with the recommendations (n=16, 10.6%), and they think the recommendations are not evidence-based (n=15, 9.9%). More details are provided in Figures 5.11, 5.12 and 5.13.

A Mann-Whitney U test was run to determine if there were differences in identifying lack of confidence in discussing pregnancy issues with female patients among the males (n=47) and females (n=104) HCPs. Distribution s of identifying this barrier was different between males and females, as assessed by visual inspection. Identifying lack of confidence in discussing pregnancy issues with female patients among males (mean rank 75.78) and females (76.10) was not statistically significantly different, U=2454.5, z=043, p=0.965 [Asymptotic derived p-value (2-sided test)].

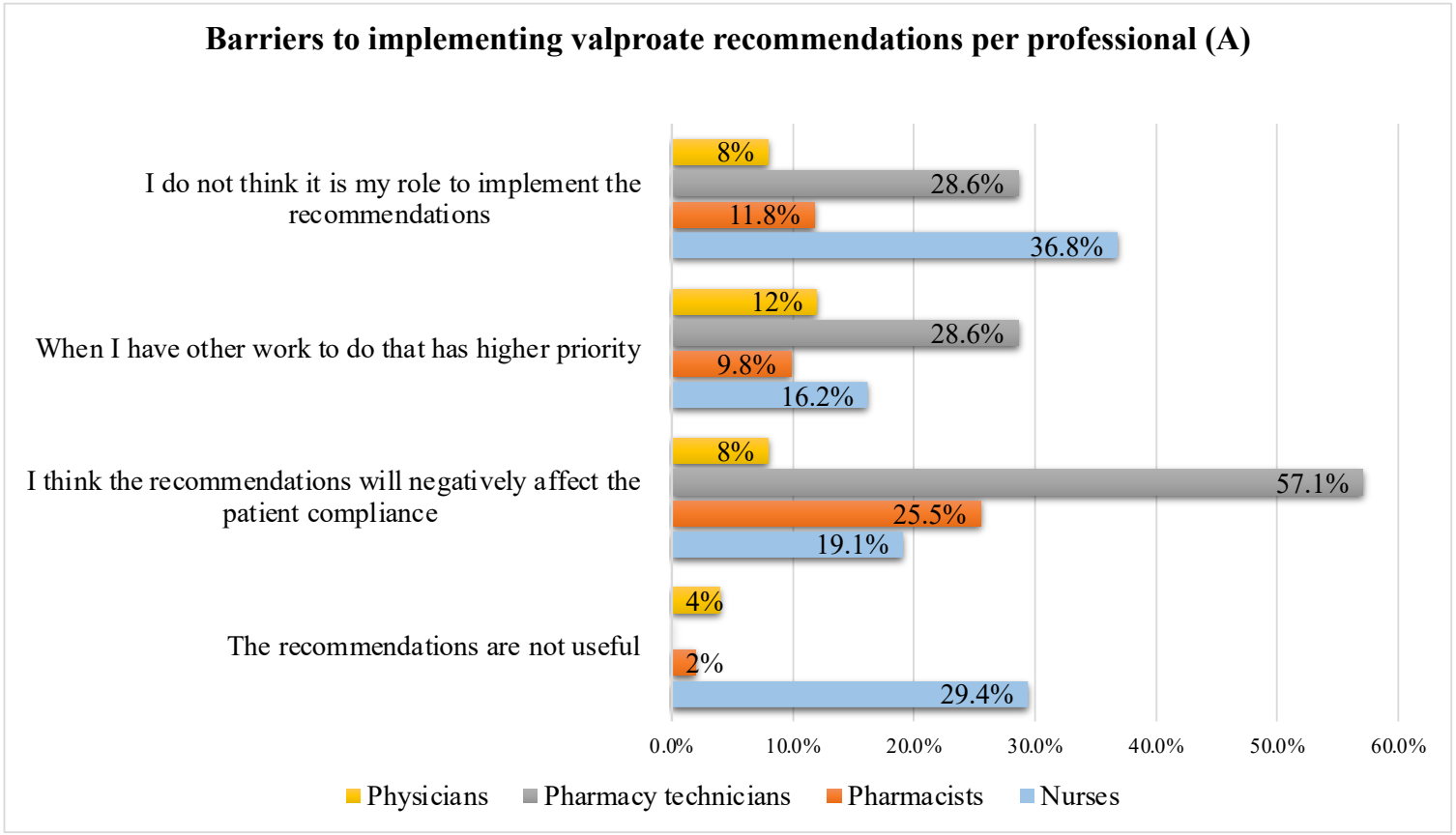


Figure 5.11: Barriers to implementing valproate recommendations per professional group (A)

Figure 5.11 presents each of the HCPs' groups' agreements on four barriers statements.

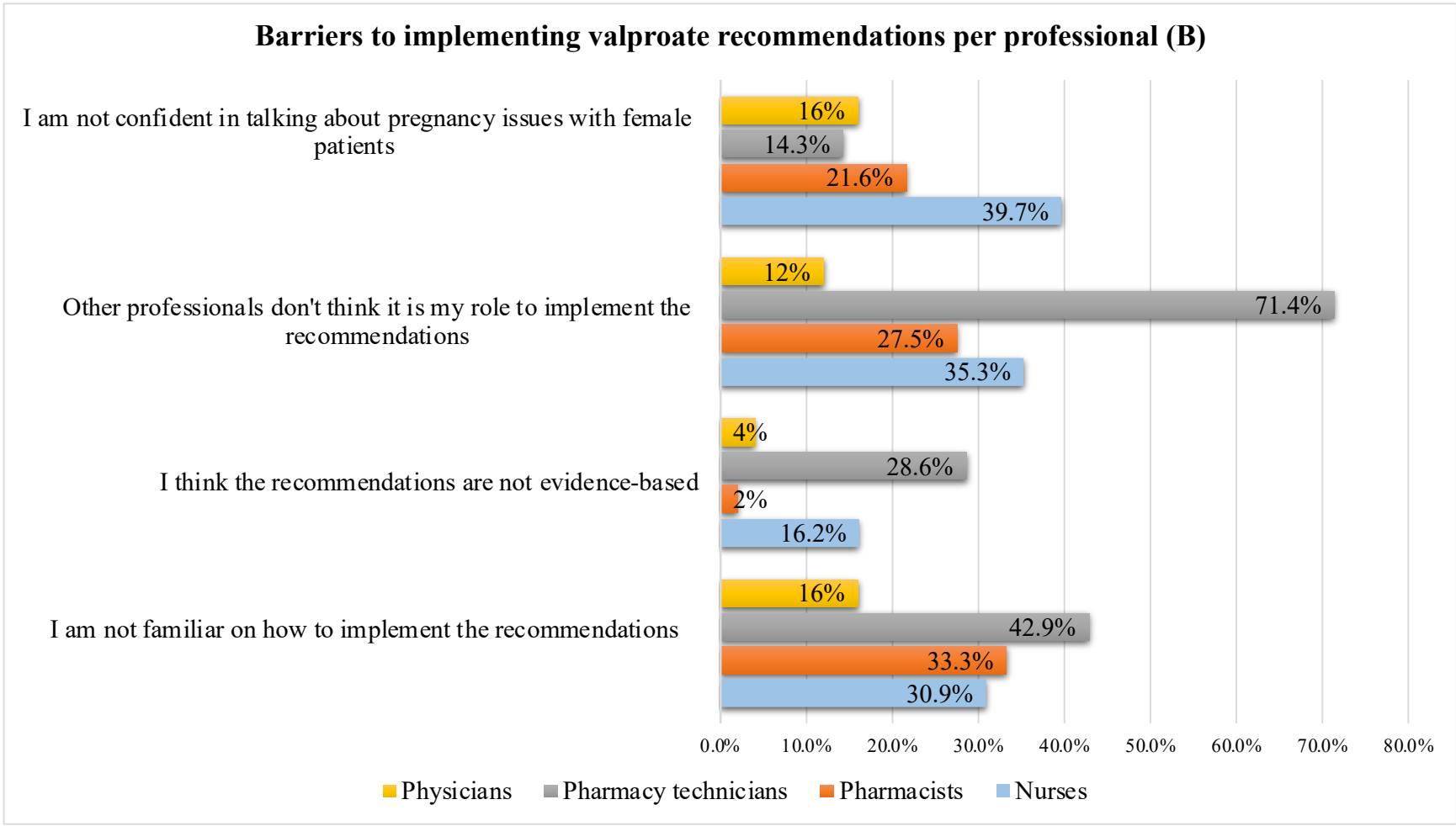


Figure 5.12: Barriers to implementing valproate recommendations per professional group (B)

Figure 5.12 presents each of the HCPs' groups' agreements on four barriers statements.

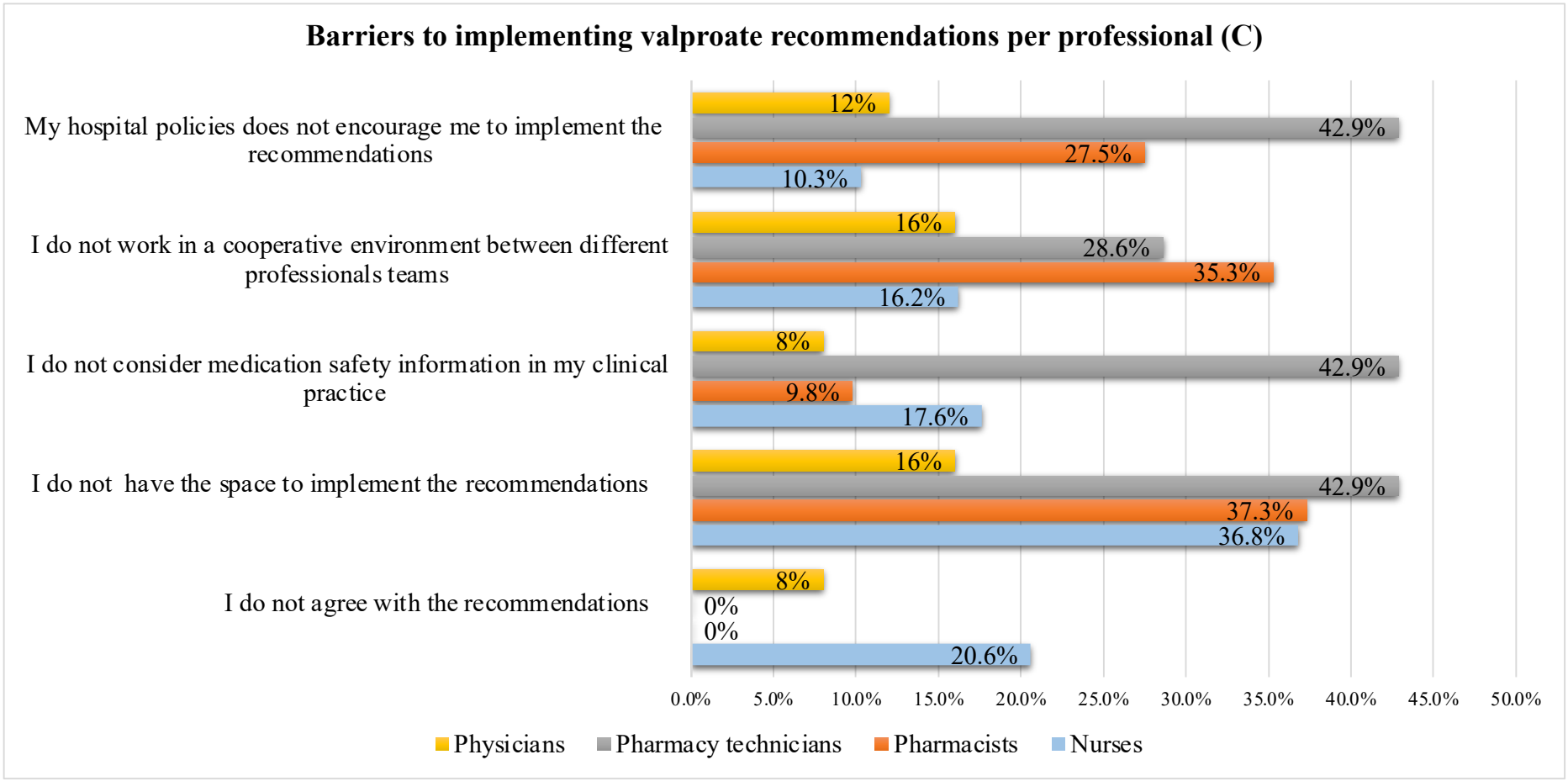


Figure 5.13: Barriers to implementing valproate recommendations per professional group (C)

Figure 5.13 presents each of the HCPs' groups' agreements on four barriers statements.

Two iterations of PCA were conducted by removing one item due to cross-loading with two components (i.e., the item scored 0.4 or above in two components). The removed item was "Other professionals do not think it is my role to implement the recommendations." In the second iteration, the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy revealed that the sample size was adequate (KMO =.887), the Bartlett's test of sphericity was significant ($p < 0.001$), and all items had at least one variable that is greater than 0.3 detected by the correlation matrix (Appendix 33). Two components had eigenvalues above 1, which was above Kaiser's criterion (Appendix 34). Interpretations of the items loaded within the two components resulted in labelling these component to: (1) Individuals-related barriers, and (2) External-related barriers. Details about the items within each component are presented in Table 5.31.

Table 5.31: Rotated component matrix of perceived valproate-related barriers (2nd iteration)

Rotated Component Matrix[a]		
	Component	
Barriers statements	Individual-related barriers	External-related barriers
I think the recommendations are not evidence based	0.841	0.159
I don't agree with the recommendations	0.828	0.175
I don't think the recommendations are useful	0.735	-0.085
I don't think it's my role to implement the recommendations	0.702	0.228
I am not confident in talking about pregnancy issues with female patients	0.679	0.322
I am not familiar on how to implement the recommendations	0.586	0.382
I think the recommendations will negatively affect the patient compliance	0.573	0.385
When I have other work to do that has higher priority	0.568	0.174
I don't consider medication safety information in my clinical practice	0.560	0.344
I don't work in a cooperative environment between different professionals	0.027	0.890
My hospital polices doesn't encourage me to implement the recommendations	0.210	0.848
I don't have the space to implement the recommendations	0.349	0.700

Extraction Method: Principal Component Analysis.
[a]Rotation Method: Varimax with Kaiser Normalization; Rotation converged in 3 iterations.

A Kruskal-Wallis's test was conducted to determine if there were differences between the four healthcare professionals' groups identification of "individual-related barriers", and "external-related barriers", for implementing medication safety recommendations. Distribution of means visually detected by boxplots were different in the two types of barriers.

The mean ranks differences of identifying "individuals-related barriers" and "external-related barriers" as barriers to implementing valproate safety recommendations were significant between the four healthcare professionals' groups (individual-related barriers, $X^2(3) = 29.639$, $p < 0.001$; external-related variables $X2(3) = 12.745$, $p = .005$), thus null hypothesis rejected in both cases. A post-hoc analysis including pairwise comparisons were conducted using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons.

Individual-related barriers were more likely to be reported by pharmacy technicians (n=7, mean rank = 101.21), than nurses (n= 68, mean rank = 94.05), pharmacists (n= 51, mean rank = 62.61), and physicians (n= 25, mean rank = 47.16). Post-hoc analysis revealed significant difference between physicians and nurses, $p<0.001$; between physicians and pharmacy technicians, $p=0.23$, and between pharmacists and nurses ($p = 0.001$) in identifying "personal barriers" as barriers that hinders them from implementing recommendations related to valproate teratogenicity. No significant differences were detected between other combinations.

In the case of "external-related barriers, pharmacy technicians (n= 7, mean rank 99.36) tended to report this type of barrier more frequently than pharmacists (n=51, mean rank = 85.95), nurses (n= 68, mean rank 75.18) and physicians (n= 25, mean rank = 51.38). Post-hoc analysis revealed significant difference between physicians and pharmacists in identifying "external-related barriers" as barriers that hinders them from implementing recommendations related to valproate teratogenicity ($p=0.007$). No significant differences were detected between other combinations.

5.3.4.5.2 Barriers from the open-ended question

The content analysis of the open-ended answers revealed three clusters and six subclusters. These clusters included: (1) Deficiencies in knowledge and work system (subclusters: lack of awareness, knowledge or guidance; lack of physical resources); (2) Perception about responsibilities (subclusters: perceptions about healthcare professionals-related responsibilities; perceptions about patients-related responsibilities); and, (3) Communication challenges (subclusters: organisational communications; patient-facing communications).

5.3.4.5.2.1: Deficiencies in knowledge and work system

The first cluster is further explained, and it included two main subclusters: lack of awareness, knowledge or guidance, and the lack of physical resources.

5.3.4.5.2.1.1 Lack of awareness, knowledge or guidance

This subcluster was identified from the comments of five HCPs (one nurse and four pharmacists). This subcluster revealed that healthcare professionals might lack information about the exact risk, or might be not aware about the prevalence of the exact risk (one nurse). Unawareness about the recommendations concerning a safety issue was also reported (one pharmacist). A need for guidelines to address new safety recommendations (one pharmacist), and the need for continuous professional education and development (two pharmacists) were also reported.

5.3.4.5.2.1.2 Lack of physical resources

The second subcluster was reflected by the absence of counselling areas as indicated by one pharmacist.

5.3.4.5.2.2 Perception about responsibilities

The second cluster, which is perception about responsibilities, is explained by two subclusters, perceptions about healthcare professionals-related responsibilities, and perception about patients-related responsibilities.

5.3.4.5.2.2.1 Perceptions about healthcare professionals-related responsibilities

This cluster was generated by the answers of eight healthcare professionals including two physicians, three nurses and three pharmacists. This subcluster included perception about self-responsibilities shaped by hierarchy issues, including nurses' defining self-roles is to follow the physician orders (3 nurses), and controlled by lack of regulations to give the pharmacist authority for suggesting alternative treatments or to give their recommendations in terms of patients' treatments (one pharmacist). Defer responsibilities to physician of implementing recommendations as they are the prescribers of medicines was also noted (one nurse). The absence of pharmacist responsibility of applying recommendation was justified by physicians' insistence on their decision whether due to their past practice or their evaluation of a medicines risk to benefit balance (one pharmacist). One physician reported it was the specialists (neurologists) role to discuss and apply valproate safety-related recommendations as it is their role (and not the general interests' role) to prescribe and adjust the medications (one physician). Another barrier against applying to the recommendation is the age of the patient being under the age of 12 (i.e., not in the childbearing age) this was reported by one physician. The last barrier provided in this subcluster was antagonism against non-Kuwaiti HCPs that might lead a person to withhold such information as a form of revenge to the society (one pharmacist).

5.3.4.5.2.2.2 Perceptions about patients-related responsibilities

This cluster was identified from the comments of five healthcare professionals (three nurses and two pharmacists). This included describing barriers related to patients and/ or their families, without detailing the exact barrier. Such barriers included the parents of the patients (one pharmacist), patient ignorance (one nurse), patients with mental challenges (one nurse), and patients' poor understanding (one nurse). One pharmacist cited patients' psychological

reaction in accepting that this medicine might affect the pregnancy as a barrier towards implementing valproate related safety recommendations.

5.3.4.5.2.3 Communication challenges

Communication challenges were described at two levels that are presented into subclusters. This includes organizational communications, and patient-facing communications.

5.3.4.5.2.3.1 Organisational communications

This subcluster was identified from the comments of two healthcare professionals, including a nurse and a pharmacist. It included lack of collaboration between a different department (one nurse). A need to improve communication between all healthcare professionals was also expressed (one pharmacist).

5.3.4.5.2.3.2 Patient-facing communications

This involved gender-barrier as a male nurse indicated that discussions with female patients should be contacted by a female nurse (one nurse).

5.4 Discussion

Evidence from the focus group revealed that the majority of the HCPs were not familiar with KDFC's tools for disseminating medication safety communications. Additionally, all HCPs were not familiar with the concept of medication safety communications in the pharmacovigilance context. Similarly, evidence from the quantitative survey revealed that HCPs were mostly not familiar with the stages of medication safety assessment that occurs during the medication life-cycle (only 23.3% of the respondents knew all three stages). Moreover, the minority of the participants (30.1%) were aware that KDFC and drug companies are responsible for sending medication safety communications; and only 16.1% were familiar with both tools used by KDFC. Results obtained in the current study are lower than a study based in Netherland, where the majority of the HCPs were familiar with DHCPs, and only 16% were not familiar (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In a different study conducted across nine European countries, awareness of DHCPs and national competent authorities' communication tools was high among GPs, which were 94% and 89%, respectively (de Vries et al., 2017). This could be explained by current efforts focusing on training and educating HCPs on reporting ADRs, rather than medication safety communications, as pharmacovigilance is relatively new in Kuwait (Chapter 4).

From the focus groups discussion, all groups mentioned using mobile applications and sources locally in the hospital. International drug regulatory agencies were reported by physicians and pharmacists, drug companies were mainly mentioned by the pharmacists and the pharmacy technicians. The media was mentioned as a source that attracts the attention of HCPs to new medication safety alerts.

In the quantitative evidence, almost half of the respondents used medical applications or websites to update their knowledge. The MOH and hospital circulars were identified by almost half of the participants. While, 43.1% use international drug regulatory agencies, 33.7% learn from KDFC, and 22.7% learn from drug companies. Both professional organisations (17.8%) and the media (13%) were among the least cited sources. Except for international drug regulatory agencies, sources including national regulatory agencies' communications, drug

companies, medical applications, media, and clinical practices were all previously reported as sources by which HCPs learn about new medication safety information (Alharbi et al., 2023).

One of the possible factors that might affect HCPs' knowledge is whether they take actions in order to be updated with medication safety information (Alharbi et al., 2023). In the current research, the majority of the HCPs (83.6%) check for medication safety updates. In other studies, HCPs reported different forms of actions in order to be updated, such as reading the letters or the relevant letters they receive (Morrato et al., 2008; Piening, Haaijer-Ruskamp, de Graeff et al., 2012), visiting regulatory agencies websites (Piening, Haaijer-Ruskamp, de Graeff et al., 2012), and subscribing to journals to be updated with such information (Morrato et al., 2008). Other studies had also reported that HCPs might not be actively searching for information (Barker et al., 2019) or did not update their knowledge about medication safety information (Smollin et al., 2016).

Barriers for receiving medication safety communications were mentioned by HCPs in the focus groups discussions in the current research. These included manual distributions of the letters, which might result in the letters not reaching HCPs especially in cases HCPs being on-leave or not on duty. Other barriers included medication safety communications being obscured by other random information. Moreover, administration delays in distributing medication safety communications, as well as delays in MOH websites in posting information, were also reported. Other barriers included excluding nurses from receiving MOH circulars and invitations to lectures conducted by pharmaceutical companies. Another barrier included lack of internet connection within the ward.

Barriers identified from the literature include time consuming to search for medication safety information (Barker et al., 2019; Kesselheim et al., 2017; Piening, Haaijer-Ruskamp, de Graeff et al., 2012). Delays in receiving the letters (Morrato et al., 2008; Sabblah et al., 2016), letters not seen by HCPs were also reported (Kesselheim et al., 2017; Morrato et al., 2008), or receiving overwhelming amount of information (Barker et al., 2019; Kesselheim et al., 2017).

The majority of HCPs (94.3%) reporting their attitudes in the current survey perceived that medication safety information is important. The majority of HCPs participating in a Netherland

based study had also perceived that medication safety information to be important (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). In the current survey, the majority of the respondents to attitude questions trusted information from the MOH, KDFC and international drug regulatory agencies. In addition, 65% trusted information from professional organisation and 61% trusted information from drug companies. Media and social media, on the other hand, were trusted by 39.2% and 35.6%, respectively. Findings from the focus groups discussions revealed that social media and media were not trusted by physicians, thus they doubled-checked information from these sources. Some pharmacists, however, reported not trusting the resources used by the MOH. Whereas, they trusted Lexicomp and the BNF as they considered them as authentic sources.

Faied et al., (2019) had also found lack of trust in the sources of the alerts, as well as busy schedules as barriers that precluded HCPs from reading DHCP letters in Egypt. Reasons for lack of HCPs' trust towards the senders were found in a previous systematic review to be related to lack of evidence that supports the senders' recommendations, and perceiving that sender of medications safety communications are biased towards the industry (Alharbi et al., 2023).

It was also reported by physicians participating in the focus groups that sources used by them do not focus on medications that are locally available in Kuwait. There were discrepancies specifically in the pharmacy technician focus groups on whether paper-based communications are useful in delivering medication safety communications to HCPs or not. In the quantitative survey in the current research the majority of the participants (76.6%) preferred to receive both paper-based copies and electronic copies. The most commonly preferred channels for dissemination included lectures (27.1%) and emails (21.1%). More suggestions for increasing HCPs awareness of emergent medication safety communications were proposed in the focus groups discussions. Five of these suggestions were reported by at least two of the focus groups. These were mostly related to KDFC and the MOH, including: to use formal email or electronic sources; post the communications in their website in order to be found by any HCP; conduct lectures along with distributing the circulars; and, to be directly involved in insuring that the communications have been received by the HCPs, explain the recommendations to the HCPs, and, monitor the implementations. One suggestion was related to clinical practice, as the participants suggested that staff members from the hospitals should be designated to

proactively check for any updated medication safety communication, disseminate them among other staff members, and monitor their implementation within the hospital.

These results indicate a combination of communications suggested by HCPs, including paper-based, verbal (lectures and meetings). The combination of these methods could lead to repetition of information, and risk the development of alert fatigue (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). As the current method of disseminating information manually was criticised by the HCPs as failing to reach all intended HCPs in a timely manner, the use of MOH staff-members official emails needs to be considered. A lead multidisciplinary team member from each hospital could be responsible for receiving paper-based information from KDFC. Holding monthly meetings or conducting lectures within the hospitals to share and discuss emergent medication safety information could be considered to emergent safety information. Such periodic medication safety lectures to discuss emergent medication safety information was discussed among the pharmacists after the pharmacists focus group discussion. Prioritisation of information to be discussed could be considered to avoid the overwhelming amount of information.

Rapid and automatic communications was also suggested by physicians from the US (Morrato et al., 2008). Emails were also suggested as preferred channels for disseminations by HCPs in two US based studies (Bell et al., 2013; Morrato et al., 2008). In another study conducted among nine European countries, overall, 63% preferred electronic format (de Vries et al., 2017). In the same study, the most preferred alternative sources included point of care alerts and emails (de Vries et al., 2017). In a study based in Ghana, 33.4% of the HCPs preferred professional meetings for disseminating medication safety information (Sabblah et al., 2016). HCPs in a study based in the Netherlands rated simultaneous sources as moderately useful (6.3 $\pm$ 2.4 out of 10); the most common preferred combinations reported by participants in this study included paper based DHCPs and emails (Piening, Haaijer-Ruskamp, de Graeff et al., 2012). On the other hand, Théophile et al., (2011) reported that 42% of their respondents preferred postal letters, while 25% preferred emails in a study based in France. In another study based in Canada, reasons for preferring medication safety information sent by fax included easier to sign and avoids overwhelming amounts of emails (Barker et al., 2019).

Drivers for implementing the recommendations of medication safety communications reported by HCPs in the focus group discussions included protecting patients, providing them with an appropriate care, and to protect HCPs from errors. On the other hand, only physicians in the focus group discussions mentioned reasons for previously not implementing medication safety communications, including: perceiving the evidence leading to the recommendation as week; questioning changes occurring in safety information relating to the same product; prescribing the medication of concern for a long time without noticing safety issues with their patients.

All the focus group discussions revealed HCPs' transfer of responsibility to other HCP groups. Nurses, for example, indicated that physicians are not documenting changes in medications for admitted patients. On the other hand, physicians perceived that nurses might not be providing appropriate information to patients on discharge, where pharmacists role in counselling such patients are lacking. Pharmacy technicians, however, revealed that it is the physicians' roles to implement such recommendations. Two opposing ideas were stated by the pharmacists. On the one hand they indicated that physicians insist on their opinions, and information is not being passed to them. On the other hand, it was reported in the pharmacists' focus group that pharmacists might not take the responsibility to implement the recommendations while only blaming physicians for not implementing them. Transferring responsibility for not implementing the recommendations to other key players were also mentioned in the open-ended survey answers. This included perception by a nurse that it is the role of pharmacists and physicians to implement the recommendations and not nurses. Considering the roles of other HCP groups was also identified in the literature. For example, Richardson et al., (2007) reported that some paediatric primary care providers might provide the additional follow-ups recommended by the FDA BW regarding suicidality and antidepressants in youth in coordination with a psychologist. In addition, in a prospective cohort study conducted Kloet et al. (2017), some physicians whom patients' medications were found to include BW nonadherence, deferred intervention until communicating with the primary care provider. This was also identified as one reason for BW nonadherence in the inpatient setting. Specifying each HCPs' groups roles in the sent medication safety communications might be needed to aid HCPs in understanding their roles and the interaction of their roles with other HCP groups.

In the close-ended survey question, the most commonly reported perceived barriers by HCPs included lack of guidance (76.8%), lack of space for consultations (67.7%), and lack of a

cooperative teamwork environment (60.6%). Both lack of guidance and lack of space for consultations were identified as either the most common or the second most common barriers among each of the professional groups individually. In a US-based study, Saad et al., (2010) reported that lack of guidance was the reason for geriatric practitioners not considering a medication safety communication in their practices. They highlighted the need for guideline development to address the US FDA BW related to the use of antipsychotics in patients with dementia (Saad et al., 2010). Richardson et al., (2007) reported that lack of space, although not expressed as physical or temporal, was a reason primary care providers viewed the FDA's recommendations regarding antidepressants in youth negatively.

In the focus group discussion conducted with nurses, work cultural issues related to nurses were expressed. This information not being shared with nurses by other HCPs, feeling excluded from receiving medication safety communications and from receiving invitations to lectures conducted by pharmaceutical companies, and fear from being blamed.

In his doctoral thesis focusing on patient safety culture in Kuwait, Al Salem (2018) conducted interviews with two physicians and four nurses practicing in three governmental hospitals in Kuwait. The interviewees were either Egyptians (3) or Indians (3). Nurses in this study expressed that they suffer from lack of respect and lack of empowerment when communicating with physicians. They also reported that physicians have an ego that they could never be wrong. This study helped to identify that there is a sense of job insecurity among the different nationalities. It was revealed in this study that staff members who were not Kuwaitis were hesitant to report errors because they were afraid from losing their jobs. A similar qualitative study was recently conducted in one Kuwaiti governmental hospital (Al Hamid, Malik & Alyatama, 2019). Participants in this study reported a good level of communication between professionals within the same department, yet the form of this communication varies across different professionals. Nurses reported using written communications among each other, which physicians and members of safety committee reported the use of both written and verbal communication. Participants in this study reported barriers to communication such as hierarchy between professions and differences in educational levels.

Although VRM DHCP was distributed by KDFC to MOH hospitals in 2016, almost all participants (expect one pharmacist) stated that they have not seen this DHCP. The pharmacist who saw this DHCP indicated that they received this letter while working in another MOH

secondary hospital. A recall bias might be present as sent three years prior to the focus groups discussions. However, this finding might reflect a variability in terms of receiving medication safety information by HCPs working in different MOH hospitals.

The physicians were the only group that were fully aware of the VRM teratogenicity. While, not all pharmacists participating in the focus group discussions were aware of this information. Moreover, none of the pharmacy technicians or nurses were aware of this information. As a result, both VRM teratogenicity and KDFC's VRM DHCP had no impact on pharmacy technicians or nurses' practices. In the pharmacists' focus group discussions, the pharmacist who previously received the DHCP stated that patient cards were distributed to female patients. However, this was practiced in the participant's previous hospital, and not the hospital where the focus group took place. This might indicate that patients in different MOH hospitals might not receive the same updated information regarding their treatment. In the physicians focus groups, however, physicians reported the impact of knowing of the VRM teratogenicity that aligned with some of KDFC's recommendations. These included counselling female patients about VRM teratogenicity and not prescribing VRM to female patients unless other treatments fail.

In the survey, although the majority of HCPs responding were aware of the teratogenicity of VRM (65.1%), only 2.6% had correctly answered the statements to the VRM KDFC recommendations. This could be explained by HCPs' cited sources for knowing about VRM teratogenicity, as KDFC and MOH were only cited as sources by 19.8% and 24.4%, respectively. While the most cited sources were scientific journals (40.5%), pharmaceutical companies (32.8%), and international drug regulatory agencies (32.1%). More than half of the participants (57%) reported changing their practice into at least one intended KDFC's recommendations. Providing female patients with written information (37.2%), counselling female patients about contraceptive use (37.2%), and asking female patients to sign acknowledgment consents (28.8%) were the most reported intended changes in practice. The suboptimal levels of implementation could have resulted from KDFC's DHCP not reaching all HCPs.

Poor knowledge levels related to VRM – related birth defects were previously reported by Bell et al., (2013), where this information was known by 33.5% of their participants. Toussi et al. (2021) evaluated the effectiveness of VRM – related RMMs through a cross sectional survey

sent by physicians in five European countries, including France, Germany, Spain, Sweden and the UK. In this study, 84.5% of the participants answered correctly that VRM should not be prescribed to pregnant patients unless other treatments fail. In this study, they found that 92.1% of the physicians always inform patients about the risks of valproate before prescribing it to females at childbearing age. While, 94.4% advised their female patients on effectives contraceptives during their treatment with a VRM. Totally, 25.8% of the participating physicians in this study reported receiving both educational materials and dear healthcare professional communications related to the RMM. Whereas, 57.9% received dear healthcare professional communications only, and 27.7% received educational materials.

In the focus group discussions, HCPs highlighted different points that could be barriers for not receiving and/or implementing the valproate related recommendations. These included not remembering whether the DHCP was received or not because it was issued three years earlier. This was attributed to the MOH never developing a protocol to address and follow up these recommendations; neither it monitored the implementation of these recommendations. Another raised point that even in the other hospital were the DHCP was delivered to pharmacists, it was not disseminated to other HCPs' groups, such as physicians, thus they were not aware of recommendations. Perceiving that the valproate-related DHCP was too long, was a reported reason for it not being read by pharmacists in the other hospital. Thus, the opportunity for a letter to be read by an HCP might be reduced due to its length. However, in another study conducted in the US by Mazor et al. (2005), no association was found between the length of the medication safety communication and primary care physicians rating of the letters' influence on their perception of the importance of the information and the likelihood that they would change their practice as a result of the information. However, the use of special format in the letter was associated with higher ratings (Mazor et al., 2005). In a more recent study conducted in Egypt, the majority for their participants (60.2%) identified the length of the letter as one factor that could affect their reading DHCP letters.

The most commonly perceived barriers to implementing the VRM-related recommendations identified from the survey included: not having space in relation to time and/ or infrastructure to implement the recommendations (33.8%). Lack of consultation area for pharmacists was also reported in the open-ended barriers- related answers. These barriers related to the psychological capability of the HCP, and could be modified through training and enablement (Michie et al., 2011). The second most common barrier reported in the closed-ended question

was other professional groups do not consider it is the participant's role to implement the recommendation (30.5%). Such a barrier aligns with the TDF's professional role and identity (Cane et al., 2012), which was also identified in the open-ended answers (e.g., nurses perceiving their roles is to follow physicians' orders). Lack of confidence when talking to female patients about pregnancy issues was identified by 28.5% of the participants. Although, only a male nurse identified gender as a barrier for comminating with female patients, no significant difference was found between the males and females in identifying lack of confident as a barrier. The source of barriers relating to lack of confidence and professional role and identity is reflective motivation, which could be mitigated through education, persuasion, incentivisation, and coercion (Michie et al., 2011). Another reported barrier included not knowing how to implement the recommendation (29.8%). This barrier is related to the procedural knowledge in the TDF, in which the source of the barrier is psychological capability (Cane et al., 2012). The need of guidance and lack of knowledge were also identified in the open-ended answers. Training and enablement are two methods to overcome these barriers (Michie et al., 2011).

5.6 Strengths and limitations

The strengths of this study included that it answered the research objective through triangulation of different methods. The focus groups included the main types of HCPs involved the patient care, namely nurses, pharmacists, pharmacy technicians and physicians, thus provided insights that were useful for the explorative purpose of this study that aided in the development of the next study (surveys to HCPs). The survey also provided insight to HCPs professionals experiences. Open-ended questions were used in the survey to ensure the capturing of answers that were not included in the structured questions. Both the focus group discussions and the survey included the VRM DHCP as an example of KDFC's medication safety communications to provide relevancy of the topic to the participants.

Most MOH hospitals were included in this study and were approached by the researcher, thus providing an opportunity for all targeted HCPs to participate. Additional methods were used to increase the response to the survey including utilisation social media platforms.

5.6.1 Limitations focus groups

All focus groups were conducted with HCPs working in one hospital, which was chosen based on convenience sampling. The participation in the focus group was limited by self-selection, as it could be that only those who were interested in patient safety were more motivated to participate. Self-motivation to participate might also had led to the variability of the numbers of participants participating across the four professional groups. Despite being targeted, none of the participants from the physician groups were gynaecologists, neurologists or psychiatrics.

Thus, generalisability was not aimed. In addition, the chosen medication "valproate-related medications" does not reflect all HCPs' practices in relation to other medication safety communications. Furthermore, recall bias might be present as the valproate KDFC DHCP was disseminated three years prior to the focus groups discussions.

5.6.2 Limitations of the survey

Survey administration was limited by self-selection; thus, it could be that only those who were interested in medication safety were motivated to answer and complete the survey. The online nature of the survey could had excluded potential participants who are not familiar on answering online questionnaires.

Despite being targeted, none of the participants were neurologists, thus results of the valproate section cannot be generalised to this group of HCPs. In addition, the chosen medication "valproate-related medications" does not reflect all HCPs' practices in relation to other medication safety communications. As well as recall bias might be present as the as the valproate KDFC DHCP was disseminated five years prior to the end of the survey dissemination. Furthermore, not all ordinal items in the questionnaire had good test-retest reliability using Spearman's correlation coefficient and the ICC.

5.7 Summary of Chapter 5

The objective of this chapter was to explore healthcare professionals' knowledge, attitude and experiences of medication safety-related communications. This chapter presented the methods, results and discussion of phase 2. The results of this chapter are presented in four sections, including 5.4.1 (the results of the focus group discussions), 5.4.2 (including the results of the piloting the online survey), section 5.4.3 (the results of the survey relating to medication safety communications in general), and section 5.4.4 (the results of valproate section of the survey). The results of sections 5.4.1, 5.4.3 and 5.4.4 are triangulated in the discussion of this chapter.

The next chapter presents the experiences of female patients on valproate with its DHCP using an interpretive phenomenological approach.

Chapter 6: Patients' experiences with medication safety communications: An Interpretive Phenomenological Approach

6.1. Introduction

Objective: To explore patients 'experiences and views of medication safety communications. This chapter presents the methods, results and discussion of phase 3, which included the experiences of female patients who used or were using valproate-related medication.

6.2. Methods

6.2.1 Study design

This is an interpretive phenomenology study based on Smith and Osborn (2008) and Smith et al. (2009) that was applied using semi-structured interviews with female patients of childbearing age who were using valproate or a valproate-related medication.

6.2.2 Setting

The setting initially included an outpatient general secondary hospital. However, due to a lack of responses during the study period (due to the COVID-19 pandemic, lack of documentation or un-updated documentation of patients' contact numbers, and patients' lack of capacity to consent), the setting expanded to include all secondary hospitals (n=6) (except one that was specified for COVID-cases during the data collection period), and a neurology specialised hospital (n=1) within the MOH hospitals.

6.2.3 Data collection

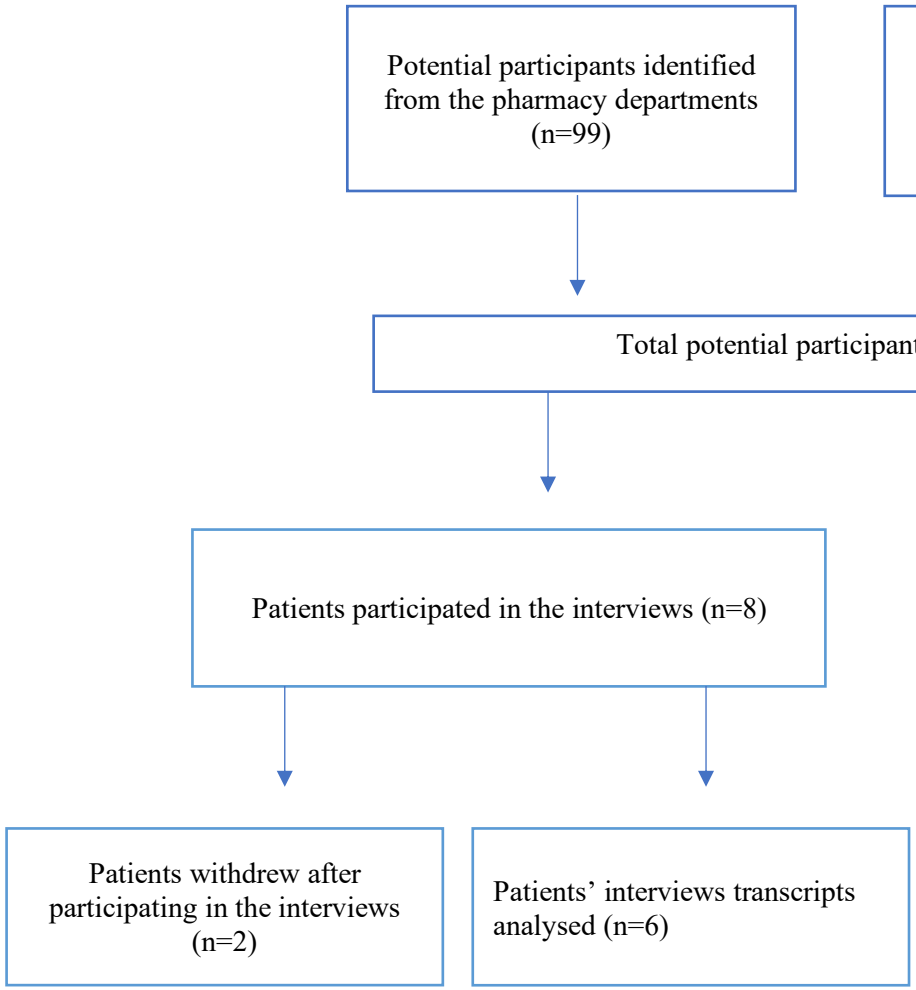
6.2.3.1 Participants' invitation

Initially, participants were invited through an invitation letter that was distributed to outpatient pharmacists and nurses in neurology outpatient clinics in one hospital. The pharmacists and nurses were asked by the researcher to distribute these invitations to eligible patients during their visits to the outpatient clinic. At this stage, no patients were identified (the number of invitations distributed to patients was not recorded). Then, the researcher approached the pharmacy departments in the included hospitals to identify the eligible patients. The pharmacy departments in five of the seven participating hospitals used their dispensing records to identify eligible patients. While two hospitals did not have an electronic system to retrieve the dispensing history of valproate, thus their approach was to invite patients opportunistically while dispensing. However, only one patient was identified in one of these hospitals, who was excluded by the researcher as she was older than 49 years of age.

The pharmacy departments that used their dispensing records had two approaches in terms of contacting patients. In the first approach, the pharmacists attempted to contact the identified patients to seek their initial approval before giving their contact information to the researcher. This was the chosen approach of two hospitals. Using this approach one hospital identified 48 potential participants, however, the contact information of nine participants was provided to the researcher. This is because of the 48 patients, 30 did not have a registered contact number, the contact numbers of 2 patients were wrong, 1 did not pick up the phone, 1 was not available, 1 refused, 1 the registered number was not in-service and the inclusion criteria were not applicable on three (1 male, 2 were on psychiatric medications). The pharmacist in the second hospital identified 32 potential participants. The pharmacist attempted to contact these patients. Then, the pharmacist provided the researcher with the contact numbers of 10 patients who approved their contact numbers to be shared with the researcher. The same pharmacist had then provided the researcher with four additional potential participants (3 from the dispensing records and one opportunistically while dispensing) whom was contacted by the pharmacist and approved to be contacted by the researcher. The second approach was conducted by the pharmacy department in three hospitals. This included providing the list of potential

participants to the researcher without initially being contacted by the pharmacists. The total number of potential participants provided to the researcher using this approach was 75 patients. To increase the number of potential participants the researcher also attempted to approach neurology outpatient clinics (nurses and physicians). However, only four patients were identified from the clinics and their contact information was provided to the researcher. In the end, the researcher had a list of a total of 103 potential participants. Contacting the patients by the researcher was done using their registered phone numbers through phone calls, WhatsApp messages or SMS messages. The inclusion and exclusion of these patients are clarified in Figure 6.1.

All interviews were aimed to be face-to-face, however, telephone interviews were conducted due to the COVID-19 pandemic. Telephone interviews were chosen as all initially contacted patients preferred it over online meetings. Before conducting the interviews, all participants were provided with a participant information sheet and consent form. These forms were developed by the researcher using the University of Hertfordshire ethics templates. Then, these forms were translated via a translation service into Arabic and reviewed by the researcher and one of the supervisors who was fluent in both languages.



- No response from the patient at initial contact (n=29).
- Patient not reachable:
  - The phone call ends without ringing (n=8).
  - Wrong phone number (n=5).
  - Phone number not in service (n=5).
  - The phone number cannot receive calls (n=2).
  - An automated message indicating the person being called is not available (n=1).
  - The patient was not available and a relative responded that the patient would call back, but did not call back (n=2)
  - No registered numbers for the patient in the hospital (n=3).
  - Mobile switched off (n=1).
- No response after sending the consent form (n=11).
- The patient does not have the medical capacity to consent (n=14).
- Refused to participate (n=7).
- The patient died after initial contact (n=1).
- Excluded patients:
  - The patient was a male (n=1).
  - The patient does not take a valproate-related medication (n=1).
  - The valproate was for the son and not the potential participant (n=1).
  - The patient's age was younger or older than the inclusion criteria (n=2).
  - The patient was hospitalised (n=1).

Figure 6.1: Patients' interviews inclusion flowchart

6.2.3.2 Tool development

The interview guide (Appendix 35), was developed based on the objectives of the study, KDFC DHCP communication related to valproic acid and previous literature. An English version was originally developed and piloted and translated with the same principles applied in Chapter 4. The Arabic version was also piloted with three females in the same age group as the participants. Table 6.1 presents the changes made as a result of the transition process.

Table 6.1: Comparison of the original and the backward translated English version of the interview (focusing on errors)

Original interview guide in English	Back-translated interview guide (1)	Translation error
Item **3:** Have there been any changes in the **dose** since you started taking it?	Item 3: Has the **dosage** changed since you started taking it?	Error in the back translation. No action was required both are appropriate for the question, which aims at identifying any changes in the patient's prescription of this medication.
Item 4: Do you have **all the information** you need about your valproic acid?	Item 4: Do you have **sufficient information** on valproic acid?	The Arabic translation used what is equivalent to "all the information that you need", which is also in the original English version. The word sufficient reflects this statement.
Item 6: Did your **doctor**, pharmacist or nurse, explain the benefits and risks to you?	Item 6: Did the **GP**, pharmacist or nurse explain the benefits and risks pertaining to taking it?	Error in the English back translation. It could be because the translation process happened in the UK, where the word GP is utilised. Since the word and the practice of a patient being cared for by one GP is not a common practice in Kuwait, and since the setting of the research is a secondary general hospital, while GPs would be expected to be practising in primary care, the word doctors would be used instead of GP. No further action is required.
Item 9 & 11: healthcare provider	Item 9 & 11: care giver	Error in English back translation. No action was required.
Item 10: Have you previously signed an acknowledgment of knowing the **risk** of valproic acid to the foetus?	Item 10: Have you singed acknowledgement indicating awareness of valproic acid on the foetus?	Missing word "risk" in the English back translation. No action was required.

6.2.4 Data analysis

The data analysis technique was adapted from Smith et al. (2009). All interviews were verbatim transcribed by the researcher (Appendix 36). A supervisor (Dr Fatemah AlSaleh) reviewed one transcript for accuracy, and no corrections were required. The following steps were then followed by the researcher:

1. The researcher listened to the recording while reading the transcript.
2. She wrote in a notebook everything that came across the researcher's mind regarding the interview to focus later on the words themselves.
3. Re-read the transcript and took three types of exploratory comments:
    a. Descriptive comments: focus on describing the content of what the participant had said, the subject of the talk within the transcript.
    b. linguistic comments focused on the specific use of the language by the participant.
    c. Conceptual comments: focused on engaging at a more interrogative and conceptual level (the interpretive part).
4. Deconstruction (the same as the steps above but from reading the transcript backwards).

6. She wrote the emerging themes based on the exploratory comments.
7. To bring it together, the researcher listed the emerging themes in chronological order, printed them, and cut them. Then, she rearranged them by putting like-with-like "abstraction".

Steps 1 to 7 were repeated for all transcripts. A supervisor (Dr. Nada Shebl) recoded one transcript independently, and this resulted in minor changes, such as in the re-organisation of the themes differentiating between the patient's diagnosis and her perception of the diagnosis, moving the names of the medications stated by the patient to her knowledge of her medication. The researcher then compared all the resulting sub-themes, resulting in the overarching themes. The analysis process was conducted in Arabic and the resulting themes and subthemes were translated by the researcher. The translation of the initial themes and subthemes was reviewed by Dr. Nada Shebl. The quotations were translated by a local translator in Kuwait who is

familiar with the use of language and expressions there. The researcher reviewed the translated quotations and Dr Shebl was consulted in one case of uncertainty. Examples from the analysis process are in Appendix 37.

6.3. Results

A summary of the organisation of the results section is provided in Table 6.2. A total of six patients contributed to the findings of this chapter. The researcher used pseudomonas names in the presentation of the result section, which is presented in Table 6.3. The patients' age ranged from 20 years to 48 years of age at the time of the interviews. Four of the patients were employed, while two did not work. Their educational level ranged from the first year of high school to pursuing a postgraduate degree.

Table 6.2: Summary of the themes and subthemes

Theme	Subtheme
Timeline of patient's experience	Diagnosis and the use of medication at a young age
	Participants' marital status and experience of pregnancy
Varied knowledge and perception with valproate use	Disease and medication description and information
	Patient perceptions to their medication
	Perceived own information sufficiency and information seeking behaviour
Patient's expectations from HCPs	Healthcare professionals as a source of information
	Communication and miscommunication
	Satisfaction with the provided healthcare
Patients' experiences and preferences towards medication safety communications	Patients experiences with the valproate-related recommendations
	Patients' pregnancy management experiences
	Patients' views towards improving patients' medicines safety-related information

Table 6.3: Patient's pseudomonas names

Pseudomonas name used by the researcher	Patient interview order[1]
Amena	Patient 1
Bushra	Patient 2
Doaa	Patient 3
Ethar	Patient 6
Farah	Patient 7
Hanan	Patient 8

[1] Patient 4 and Patient 5 withdrew after conducting the interview.

6.3.1 Timeline of patient's experience

6.3.1.1 Diagnosis and the use of medication at a young age

All participating patients were diagnosed at a young age. Most were diagnosed with epilepsy and one with migraine. Most patients have used valproate for more than 20 years, and one patient was using it for about 10 years. For example, Doaa, who was 42 at the time of the interview indicated taking a VRM for around 29 years, as she states:

> *"I don't know exactly when, but I used the regular Depakine at the beginning, around 1991"* (Doaa).

Two patients described changing from Depakine to Depakine Chrono. Moreover, one patient described adding another antiepileptic, Keppra (levetiracetam), to her treatment plan. Two patients described changing their VRM. In one case, the patient changed her medication by herself at a certain point, and re-took it after being involved in a car accident. In the second case, the patient stated that valproate was changed by an alternative physician practising in the private sector that she visited. This change was made about three months prior to conducting the interview. Changes that occurred to the VRM dose, dosage form, and frequency were described by most of the participants. Bushra, who was 20 years old at the time of the interview indicated in the following quotation changing her VRM dosage form:

> *"When I was little, I used to take it as a syrup but when I started with the pills, I became better".*

Two patients, namely Ethar and Hanan mentioned changing their healthcare clinic. Hanan mentioned going to the private sector due to the progression of her disease and her desire to get pregnant. While Ethar explained that she registered herself in a Kuwaiti hospital 10 years prior to the interview after moving from Riyadh. The patients have also described their following up with the medical appointments. Amena explained that she currently does not have a specific physician unlike her experience with appointments in her childhood as she used to have a stable physician. Three patients, including Amena, Farah and Ethar, stated that they had a long period of not following up on their medical visits. Farah described the period of time that she was not adhering to her medical appointments as self-negligent. However, Farah explained she currently follows up online with her physician. She specified needing a medication to be prescribed as a reason for re-adhering to her follow-ups, as she explained in the following:

> *"Didn't go to a doctor, but later I found myself needing to do, otherwise, how to get medication"* (Farah).

And, Ethar explained that she recently visited the clinic after 10 years of not following up on her medical appointments. Ethar's reasons for not following up on her medical appointments included being busy with her children, as explained in the following quote:

> *"I didn't go, because I had my babies one after the other, so I was busy"* (Ethar).

6.3.1.2 Participants' marital status and experience of pregnancy

At the time of the interview, four patients were married and two were single. Both Doaa and Bushra stated being single. While Amena, Ethar, Farah and Hanan were married. Three patients, namely Amena, Ethar and Farah have been previously pregnant, while Hanan was pregnant for the first time at the time of the interview. Bushra and Doaa, however, did not have previous experience with pregnancy at the time of the interview. Amena mentioned that her last pregnancy was two years prior to the interview.

The patients demonstrated various knowledge and perception related to their diagnosis and medication use. This is reflected in the following theme.

6.3.2 Varied knowledge and familiarity with Valproate use

6.3.2.1 Disease and medication description and information

While Hanan described her condition by its name (migraine), the other participants either referred to epilepsy by its name (Doaa, Ethar, Farah) or used the terms seizures or seizures episodes (Amena), or described the condition as electricity in the brain (Bushra). Farah also referred negatively to her disease describing it as "this bad thing" in another point which reflects the lifelong burden that epilepsy imposed on her. A genetic nature of the disease was mentioned by both Amena and Hanan, but in different ways. Amena voiced a concern that her epilepsy might pass on to her children. She questioned whether would it be possible to know in advance before conceiving or during her pregnancy whether or not would it be possible for the next fetus would she/he be carrying epilepsy. This was provoked by her two-year-old child being diagnosed with epilepsy, although she mentioned being relieved by his healthcare team that he would outgrow his condition due to being diagnosed in his early childhood, unlike her case. Whereas, Hanan perceived that her migraine was a progressive inherited disease, as she describes in the following quotation:

> *"I have this inherited from my grandfather, the headache went down to his eye, and he couldn't see. Then there was my aunt, suddenly she became deaf"* (Hanan).

All patients used the medication name, whether brand or generic, to refer to their medications, which included Depakine or Depakine Chrono (all patients), Keppra (Bushra), Folic acid (Ethar), omega 3 and vitamin D (Farah), migraleve pink and BOTOX (Hanan, although she pronounced migraleve differently). Two patients mentioned the medication's strength (Amena and Ethar), two mentioned the dosage forms including tables (Bushra and Hanan), syrup (Bushra), and injection (Hanan), and one patient (Hanan) specified the frequency of taking the medication, and another (Doaa) specified her dose. Additionally, two patients mentioned the class of medications (Ethar, vitamin; Hanan antidepressant). One patient had also identified

her medication by its expected outcome (pregnancy stabilizer, Hanan). Hanan also described her medication by its shape, site of administration, and colour (long injection administered to the head; purple; white strip with a yellow line). For example, she described a medication that she perceived to be an antidepressant as the following:

> *"It's a white strip with a yellow line. It's to all who have a depression"* (Hanan).

6.3.2.2 Patient perceptions of their medication

Ethar's perception was focused on its potential harms, while the other five patients mentioned both its benefits and side effects. The influence of the patients' experiences appeared in four of the patient's accounts, namely Bushra, Doaa, Farah and Hanan. Amena voiced her reassurance after reading about VRM that it is not harmful to discontinue using it, and it is used in another disease (she mentioned depression but was not sure about it). Interestingly, Amena stated that VRM had side effects but it is not a harmful medication for most patients. Ethar's perception, however, was based on lab requests before her medical appointment thus she concluded that it might have a harmful effect on the liver. Bushra, Doaa, Farah and Hanan expressed the negative effects of VRM in light of their personal experiences. Bushra listed the side effects that she suffered from which were confirmed as expected side effects by her physician. This included oversleeping, laziness, hair fall, and fatigue. Doaa mentioned that VRM caused the yellowing of her teeth, which is a side-effect that she explained was not listed in the medication leaflet but detected by her dentist. She perceived, however, that VRM is the safest medication and the best medication for epilepsy worldwide. As she explained that it has no or mild side effects that are not problematic once. She supported this by stating that she had been using VRM for at least 20 years without any problems. Farah has also stated that VRM does not have any side effects. This is contradicting her point that it is harmful to the foetus and results in little increase in weight. This contradiction might reflect the exclusion of harmful effects that she had tried to reduce, whether by using alternative medications (alternative antiepileptics) initially and being on a diet and supplements to control the weight gain or by stopping VRM during pregnancy, which was her way in preventing its teratogenicity. It is also notable that she considered its benefits in stopping seizures when reporting that it does not have any side effects.

Hanan, however, considered VRM to be a harmful medication. She was not specific in her description clarifying that she is interested only in taking the right medication, and not interested in knowing about its details. When asked to describe the harm, she did not provide a specific answer, described it as something that resembles addiction, and that she does not know what is the matter with it. She expressed, however, that she only recently learned that it is harmful from her alternative physician in the private sector. Her experience had not only solidified perceiving VRM negatively, but it also led her to generalise its harm to any female patient. She reflected this in her choice of words when explaining VRM harms as follows:

> *"It's not good for pregnancy, not good for you personally as a body, all this is not good"* (Hanan).

She also, based on her alternative physician, confirms that VRM lacks benefits in her case, as well as it is harmful to her. The influence of her physician (in the private sector) in terms of throwing her medication in the dustbin was apparent in her VRM-related perception. However, the most impactful experience on her perception of VRM as a harmful medication was the temporal occurrence of VRM discontinuation during her pregnancy. Thus, Hanan concluded that the use of VRM along with the other two medications she used (Migraleve pink, and Sumatriptan) had prevented her from conceiving, as she expressed in the following quote:

> *"So he gave me Botox, we stopped the medicines, I got pregnant after the Botox after I stopped the medications- I swear- one month and I became pregnant, I'm pregnant now"* (Hanan).

Although, when Hanan was asked whether she had an experience of pregnancy while using a VRM she responded that she was not married. Regarding her current medications, she perceived that she was prescribed injections because oral medications are not suitable for pregnant patients.

Most patients (Amena, Bushra, Doaa, Farah, and Hanan) reflected on their perception of VRM benefits or lack of benefits. Bushra stated that she is aware that it has benefits, but she does not know them specifically as they were not explained by her physician. Amena, on the other hand, stated that while she was searching for VRM harm she remembers coming across its benefits but does not remember them. Doaa stated that VRM is the best medication in the world for epilepsy, but she did not specify its benefits. Farah indicated that its benefits relate to its ability

to stop epilepsy episodes while emphasising that it is not curative, as observed in the following quotation:

> *"It's helpful, that I'm not facing the condition, that's it, it didn't cure it; it only stopped the condition"* (Farah).

Hanan indicated that VRM (along with her other two medications) are analgesics and not curative. She also perceived that these medications were not appropriate for her progressive stage of disease in justifying the reason for her alternative physician's action of throwing VRM in the dustbin.

Two patients expressed their attitudes towards medicine use. Farah was challenged by the perceived weight gain caused by VRM. Thus, she stopped VRM and used an alternative medication (she did not specify the medication name) without consulting with her healthcare providers. Consequently, epilepsy episodes returned to her and she was involved in a car accident. A change in her attitudes towards adhering to valproate and to the medical appointments resulted from the accident. Now, she expresses being content with both adhering to valproate and being on diet.

Hanan had a different experience with her attitude towards medication use. Although she confirmed her awareness of using valproate daily, she stated that she only used it during an intense migraine attack. Although she did not provide a direct reason for not using it as required, she later expressed her belief that VRM (along with her other medications) are analgesics and not curative. This reflects that she was not aware of the preventive role of VRM in her condition. In a second situation, Hanan reported that she was prescribed a new medication by her prescribing physician in the governmental sector. She stated that she did not use this medication as she read that it is an antidepressant and she does not have depression. She added that this medicine also causes addiction, as it is required that it would be tapered before being stopped.

6.3.2.3 Perceived own information sufficiency and information seeking behaviour

The participants differed in the perception of their information sufficiency, and in their information-seeking behaviour. Two patients (Doaa and Farah) stated that they had sufficient information regarding their VRM benefits and side effects. Bushra, on the other hand, considered that she lacked information related to her VRM benefits. According to her, this was related to her physician focusing only on informing her about the side effects. Both Hanan and Ethar considered that they did not have sufficient information related to VRM. Hanan stressed that she recently (just) learnt that VRM is harmful from her alternative physician in the private sector. Despite this, she indicated on a different occasion that she was not interested in learning information about her medication. While Ethar did not prefer to learn about valproate-related information. Fear of identifying negative information was revealed specifically when she referred to searching the Internet and not to information provided by her physician. Ethar explained at different points that she does not prefer to read about the medication, specifically the side effects. However, she indicated that she had read about it a long time ago on the internet. She stated being busy with her children and reading would consume time as reasons for not reading about her medication, yet she also described on different occasions during the interview that she does not like to read even if she had time about her VRM as expressed in the following excerpt:

> *"See, I'm occupied with my house and kids, so; I don't have time for example to check, and I don't like to do so even"* (Ethar).

Ether also stated that reading about her VRM upset her. This is further reflected in her choice of words. In one instance she described searching for information as digging for information She also stated that she does not like to open the Internet to read about it, where different websites have different information, which was another reason for her not preferring to read about her medication.

Amena stated that her mother was more informed than her about the VRM-related information. This was explained by her mother's involvement in discussions and asking physicians about valproate-related information during her childhood. Amena stated that she currently does not remember the information that was provided to her mother during counselling in her childhood.

She gave two reasons for not remembering this information. First, her mother was responsible for her healthcare. Second, the patient after a seizure episode does not remember. There is a difference in how Amena described her mother's involvement versus her own involvement in her healthcare. As she described her mother's involvement as complete involvement, while she was barely taking control a little bit as well as she does not trust that she has enough information currently. Amena also indicated that she searched Google for information about VRMs after using one for years. Her aim was to check whether it was harmful or not, so she could decide whether to discontinue her medication or not.

Both Farah and Doaa reported reading the medication leaflet. Doaa specifically stated comparing her reading from the internet to what is written in the medication leaflet, as she explained in the following quotation:

> *"Never, never. All my knowledge was based on my readings – external reading, I used to survey the internet and compare with the medication leaflet"* (Doaa).

Amena, Ether, and Doaa also reported asking their physicians about certain information related to their VRM. The perceived roles of HCPs in providing medication-related information to the participants are discussed in 6.3.3.

6.3.3 Patient's expectations from HCPs

6.3.3.1 Healthcare professionals as a source of information

HCPs, specifically physicians, were mentioned as sources of medication safety information. Bushra reported that her prescribing physician explained to her the expected side effects, which she also suffered from. She did not specify who initiated this discussion. Despite that Farrah denied that her prescribing physician informed her about any VRM-related information, she mentioned one exception which was VRM teratogenicity. Ethar mentioned knowing about the possible effects of VRM on the liver as she was requested to perform a new laboratory blood test one week prior to her medical appointments. On the other hand, Doaa coincidentally concluded that the yellowing of her teeth was from using VRM from her dentist. This is because he confronted her that she has been using a medication for a long period of time. Doaa,

however, denied using any medication. She explained not preferring to inform him about using VRM as he has connections with her family. On the other hand, the participating patients had also expressed that the HCPs were not sharing with them their medications- related information. Amena mentioned that currently, her HCPs do not provide her with any medication-related information. She stated that they only emphasise to her that this is her medication. Ethar had also reported not being informed by her physician about the benefits and side effects of VRM. However, Ethar explains that such information must have been given to her parents as she was a child at her early diagnosis, as she explained:

> *"No, not really. See, I was a little girl those days, so definitely they explained to my late parents"* (Ethar).

Scepticism was also voiced when discussing HCPs' roles in patient education. Hanan specified that such practices are not performed in governmental hospitals. In addition, Doaa had a generalised perception that HCPs in Kuwait do not provide their patients with information related to their medications' benefits or side effects. This is described in the quote that follows:

> *"Oh excuse me (laughing) excuse me ... this thing does not happen here in Kuwait, we are not in the US (laughing)"* (Doaa).

6.3.3.2 Communication and miscommunication

The way that physicians communicate VRM-related information to their patients included verbally (Bushra, Hanan, Amena) and by taking action. This action involved throwing Hanan's VRM in the dustbin as described by her in the quote that follows:

> *"Yes, he is… I mean… he… Doctor (X) does understand [he is good] he told me "this medicine is not good, I don't know why they give it to you, this is for …" especially the Depakine, I mean – sorry for the word- I don't know how to say it, he threw it in the dustbin"* (Hanan).

Signs of miscommunication were also found. This included Hanan's experiences as she explained that her physician (in the government sector) only instructed her to use the medication without providing the information. Hanan however had switched to the English

language when she described that her physician used to tell her "*Take this take this"*. Noticeably, she only used the English language when she described the position of her physician in the governmental hospital as the *"head"*, although she was using the Arabic language for the rest of the interview. This was also apparent when she described her experience of being prescribed an antidepressant. A sign of miscommunication was also apparent in Bushra's case as she expressed her need to know about the benefits of VRM, while she did not clarify whether she asked her HCP directly about the benefits or not. Additionally, it was also noticed in Doaa's case as she did not inform her dentist about her medication history due to social influences.

Discussion with the physician we described as either being one-sided or two-sided. A two-sided discussion was noticed in patients using plural tenses when describing the change in their medications, for example, *"we changed"* (Doaa and Farah). However, a one-sided discussion was apparent in both Hanan and Ethar's accounts as both used instructive words in describing physicians' decisions (e.g., "*Take this"*, "*stick to this dose"*).

6.3.3.3 Satisfaction with the provided healthcare

Patients also mentioned their satisfaction with their HCPs-provided care. This included both Farah and Hanan. Hanan described her physician in the private sector to be knowledgeable. Farah expressed her satisfaction with her physician following up on her condition and laboratory blood test results, as she explained in the following quote:

> *"It's good the doctor sees my blood [test results], and liver functions, if I am benefiting from the medication, if my body is absorbing the medication, benefiting from it or not"* (Farah).

However, Farah's perception of the importance of following up with her medical appointments only appeared after her accident. On the other hand, a sense of blaming for HCPs was also described by Hanan and Bushra. Hanan found it unjustifiable to prescribe her an antidepressant. While, Bushra blamed her prescribing physician for not sharing with her information related to VRM benefits, as described in the following quotation:

> *"... that there are benefits, but the Doctor... I used to go to, didn't talk to me about these benefits"* (Bushra).

Farah was the only participant who reflected on the role of the pharmacy. She explained that she had to buy her Omega-3 supplements since they were not available in the public hospital (outpatient clinic pharmacy). She believes that the MOH provides Omega-3 to the outpatient pharmacy, but they distribute it to their connections, so it is no longer available there. Nevertheless, Farah indicated that she used to take her other medication in a similar way (from connections without a prescription) but it no longer works, so she finds herself compelled to follow up with her physician to write a prescription.

6.3.4 Patients' experiences and preferences towards medication safety communications

6.3.4.1 Patients experiences with the valproate-related recommendations

This subtheme includes patients' awareness of VRM teratogenicity, patients' being evaluated by healthcare professionals for the appropriateness of VRM at different points, being received a booklet or being asked to sign a consent acknowledging the risk of VRM to the unborn foetus. Amena mentioned that initially her mother took the initiative to ask the internal medicine physician about the safety of pregnancy in her case. However, Amena does not remember what or how it was discussed. However, she speculates that it must have been directly verbal as her mother used to be a nurse in the same hospital. Both Amena and her mother were careful to ask the physician about the appropriateness of pregnancy while having epilepsy during a regular medical appointment, according to Amena. This had taken place before marriage. At that point, Amena stated that the physician assured her that no harm. However, Amena did not mention being aware of VRM-related teratogenicity. She explained her perception of the safety of using a VRM during pregnancy in the following quote:

> *"No, that won't be harmful; Inshallah (I hope), all my pregnancies and childbirth wer normal with no harm Alhamdulillah (Thank God)"* (Amena).

Bushra had no information related to VRM teratogenicity, neither a discussion was taken place about the safety of pregnancy while being on VRM. However, she reported that her physician only asked her about her period. Doaa has also indicated that no information was given to her

in relation to VRM's teratogenicity. She further explained that the HCPs did not need to provide her with such information as they were aware that she was not married. This is described by Doaa in the following:

> *"They don't need to give me such a thing because- excuse me- I haven't got married They know from my file"* (Doaa).

She further indicated that she did not try to read about this information, neither she asked her physician about such information. She further stated that she does not know if it is safe to use VRM with pregnancy or not as she does not know anyone who uses it, but she does know patients with epilepsy who have kids. Doaa had reported asking her physician specifically about the suitability of marriage and driving to someone with her disease. She described that the physician advised preferably not to do both, as she described in the following quotation:

> *"I was asking him actually if I will be able to marry, he said preferred not to; if I can drive a car, also he said preferred not to; but I do drive, Alhamdulillah (Thank God)"* (Doaa).

Before her marriage, Ethar asked her physician about the safety of valproate in pregnancy about ten years prior to conducting the interview. She stated that her physician provided her with instructions without explanations. Information provided by her physician included that no harm from valproate but she should take folic acid (which was previously prescribed to her) during her pregnancy, use the same dose of valproate, and preferably avoid breastfeeding. Ethar indicated that she was relieved to know that there was no harm from valproate during pregnancy. Despite her visit for a follow-up in 2020, she was also not informed of valproate-related teratogenicity.

Farah was the only participant that is aware of VRM teratogenicity. She indicated that she read the drug leaflet and was informed by her physician about it. She stated that the medication leaflet did not include any details, however, it stated that it is harmful and physicians should be informed before pregnancy. She also explained the options that were instructed for her to do before her pregnancy. This included visiting the physician before her pregnancy. The options that might need to be taken were also explained to her including taking an alternative

antiepileptic, using a medication that prevents teratogenicity, or suspending using valproate for a period of time.

All patients stated that they did not receive an information booklet from their HCP, nor they were asked to sign consent. Amena added that she was not aware whether such things were given to her mother or not. Hanan's perceived reason for not being asked to sign the acknowledgement is that when she became pregnant, she was not on a VRM.

None of the patients reported that HCPs discussed with them the use of contraceptives.

6.3.4.2 Patients' pregnancy management experiences

Amena, Ethar, and Farah had previously been pregnant, while Hanan was recently pregnant at the time of the interview.

Amena's pregnancy management involved careful follow-ups directed by her obstetrician. Amena mentioned her pregnancy experience while being on a VRM. She stated that she currently has four children. She stated that no VRM doses were not changed during her pregnancy. Both her obstetrician and herself were careful about following up on her appointments. She mentioned that her obstetrician asked her if she was tired or if there was any update on her condition. The obstetrician also asked her about the use of her VRM, and she documented her doses. The obstetrician also referred her to the internal medicine appointments and confirmed that she actually adhered to those appointments.

There was no collaboration between Ethar's obstetrician and the neurologist during her pregnancies. She mentioned that she currently has five children. She explained that she did not visit her neurologist during any of her pregnancies as she did not feel tired.

Farah had three children. She explained that she took the action and stops valproate when confirming her pregnancy, as she stated:

> *"So, I used to stop the drug when I'm pregnant once I feel -between you and I-my monthly period is late, I directly checkup. because I'm afraid so I cut the doubt because I'm taking a medication"* (Farah).

Farah explained that she stopped her VRM once pregnant because this was the obvious thing to do as it is a teratogenic medication. This could be related to her belief of a definite negative outcome on the foetus once a VRM is consumed. She also stated not consulting with her physician when stopping the VRM, as she explained:

> *"No, no, no without going back to the doctor. It's common sense as it's not suitable for pregnancy"* (Farah).

She stated that during all her pregnancies she never had a seizure episode, while after one delivery she did have a seizure episode. She also explained that her obstetrician is aware of her epilepsy.

Hanan mentioned that her alternative physician in the private sector asked her to stop using valproate and gave her an alternative, and this was just before her pregnancy. According to Hanan, her obstetrician/gynaecologist reduced the duration of taking the "pregnancy stabilising pills" as these pills trigger her headaches.

6.3.4.3 Patients' views towards improving patients' medicines safety-related information

Bushra indicated that patients should be informed about medications' benefits. She prefers written information, such as books. Doaa stated that patients should read to know about their medicines-related information. She also reported that written information should be handed to the patient while or before medication dispensing. This written material according to Doaa should suit the patient's understanding level. She further states that HCPs should not rely on the medication leaflet as it is difficult to understand by the patients. Farah stated that a patient should be aware before using any medication about its effect on pregnancy, even if she did not read the medication leaflet (the patient's responsibility to be aware). She also stated that a patient should not stop her/his medication from herself/himself. She also referred to her VRM experience as she stated that patients should be aware that weight gain could be controlled by diet.

Ethar indicated that information should be given by the HCP. She explained that such information should include reasons and explanations not only instructions. Hanan further explained that information related to medication should be provided by the physician and not the pharmacist, as society expects such information from physicians. She indicated that patients should receive at least a medication leaflet that includes the mechanism of action/ what is the expected outcome from the medication, and what are its cons and pros. And, this should contain simple points and not narratives so it could be simple and fast for the patient to read. She perceives that physicians should be responsible for providing such leaflets to the patient despite the pharmacist might know more about the medication. She explained that this is because people in this society prefer to hear from the physicians rather than pharmacists. She also perceived that the physician is the one who explains to the patient, and the pharmacist does not have the authority to provide information (the example she used is the pharmacist telling the patient not to take a certain medication) and the pharmacist would be responsible only for dispensing the medication.

Amena stated that patients should adhere to their medical appointments and follow-ups. She further explained that through discussions with the physician, the patient will be reassured that she/he is aware of all relevant information related to their medication. This is explained in the excerpt that follows:

> *"The best best thing is the follow-up visits, where if I – for example- keep following up with the Doctor, I will be aware of everything, the Doctor let me know and see my condition… here I'll be even reassured"* (Amena).

6.4 Discussion

Medication safety communications aim to support patients' safety by providing them with updated and accurate information that supports them in their right to make informed decisions related to their treatment. They also support patients' safety by recommending risk minimisation measures to be applied by patients as well as their HCPs. In Kuwait, KDFC mainly sends such measures to HCPs to pass them on to their patients (Chapter 4). In June 2016, KDFC sent an urgent DHCP to HCPs combined with prescriber and patient guides, and a patient information card from SANOFI. KDFC recommended adequate information to be provided to the female patients, and an acknowledgement consent to be signed by the patient that the risks of VRM during pregnancy were explained to her. Despite this, all except one patient participating in this study reported not being informed about the risks of the use of VRM in pregnancies. Moreover, all patients reported not being requested to sign an acknowledgement consent and were not provided with written information regarding the risks. The six patients had different experiences with regard to their use of a VRM. These experiences revealed influences that could affect patients' optimal care and their right to make informed decisions. These influences included patients not having sufficient information and not being updated about their medication; medication-related information not being retained by the patient; and patients' susceptibility to wrongful perceptions about their medications.

The first influence is patients not having sufficient information and not being updated about their medication-related information. As mentioned previously, most patients in the current study were not aware of the teratogenicity of VRM. Four other studies conducted in other geographical areas also identified inadequate information being provided to patients on valproate. In the study conducted by Beardsley, Dostal, Cole, Gutierrez and Robson, (2021) pregnancy rate decreased from 9.9 per 1000 before the MHRA guidance to 2.8 per 1000 afterwards. The authors found ten pregnancies occurring in the study period to be potentially exposed to VRM. Poor reporting of preconception or contraception advice before these pregnancies were found. Despite this, the general preconception or contraception advice provided to female patients on a VRM increased during the study period by 79% (Beardsley et al., 2021). The second study was a cross-sectional study of two groups of women of childbearing age, 50 women on VRM, and 50 using other antiepileptics, in a neurology department of a large teaching hospital in London, UK (Harris, Lowes & Angus-Leppan,

2020). Each patient undertook a patient questionnaire and a structured telephone interview to assess their understanding of using VRM in pregnancy. About 55% of the patients participating in this study stated that they were not involved in decision-making, and 59% needed more information. More patients in the VRM group were informed and expressed an understanding of the risks involved in treatments than in the control group (64% versus 32%, respectively, $p<0.001$). In an Irish mental health service region, a study was conducted including women who have been receiving a mental health service for more than one year and were on a VRM (Mulryan, McIntyre, McDonald, Feeney & Hallahan, 2018). In this study, 33.3% of the participants had some awareness of the risks of valproate, 19% were aware of specific teratogenic risks, and 16.7% were of the need for folic acid when taking a VRM. A qualitative study including 23 semi-structured interviews with female bipolar patients of childbearing age was conducted in South Africa (Sibanyoni, Joubert & Naidu, 2022). The majority of their participants (n=13) were counselled by an HCP about the teratogenicity of valproate, while 6 knew about the teratogenicity from other sources, and four were not aware of the teratogenicity. Two of the participants learned about the teratogenicity by searching Google as they were interested to know more about the medication driven by other side effects they had experienced. A total of 14 participants were on contraceptives, and only five of them used contraceptives to prevent pregnancy while using valproate. In their study, a lack of knowledge about the benefits and the potential side effects of valproate caused other concerns such as the medication being bad and dangerous, and few participants expressed that being on valproate had prevented them from conceiving more children.

From the current study, different reasons could explain patients' lack of knowledge regarding valproate. One of these reasons is the lack of stable and continuous care. This was found to be resulting from either the patient or the healthcare institution. Patient-related reason includes not adhering to medical visits. For example, one patient in the current study did not follow up on her medical appointments for ten years. In such a situation the patient might miss the opportunity of being informed about the new information that could occur during the time of her non-follow-up. The second reason was related to the healthcare system. This involved not having a stable physician while having different physicians at different healthcare visits. In this scenario, if the physician seeing the patient at the time of the release of the information did not provide her with information, other physicians might assume that she was already informed about the information and consequently not inform her about this information. This situation depends on the level of communication between the patient and the physician on the one hand

(i.e. the physician asking the patient for the information she knows) and between the physicians on the other hand (i.e. the physician documenting and providing the information to the patient in her medical record).

Another reason for patients' lack of information was related to the patient being diagnosed at a young age and healthcare responsibility falling upon the parent. This was apparent in the interviews in the current study, which demonstrated that some of these patients justified their lack of information at this point in their disease by that the information was provided to their parents at earlier stages. This might reveal a lack of healthcare autonomy or health literacy. Healthcare autonomy is "the ability to evaluate options, make decisions and define health-related goals, the confidence to stand by those decisions and to develop strategies to meet those health-related goals" (Beacham & Deatrick, 2013, p. 305); while health literacy is "the degree to which individuals can obtain, process, understand, and communicate about health-related information needed to make informed health decisions" (Berkman, Davis & McCormack, 2010, p.16). However, lack of patient information at this stage of their disease could also result from HCPs assuming that the patient already received sufficient information about their medication in the early stages of their disease without asking the patients about their level of information or information needs.

Patients' attitudes towards information-seeking and their information-seeking behaviour are other reasons that could explain patients' lack of information regarding their medication. Patients' lack of interest in knowing about their medication-related information was observed both directly and indirectly among participants in the current study. The direct lack of interest was revealed by two participants, one related to not preferring to know about her medication-related information in general. While the second patient explained that she does not prefer to search for information related to her medication. She provided multiple reasons including her fear of knowing negative information, finding inconsistent information on different websites, and having a busy lifestyle related to taking care of her children. On the other hand, an indirect lack of interest was observed among some of the participants who expressed positive attitudes with regard to their medication-related information-seeking behaviour. This included perceiving that there was no need to be informed of the teratogenicity of valproate since they were not married. Interestingly, the participants who were married at the time of the interview might have had a similar perception as they indicated that their questioning about the suitability of pregnancy in their condition was triggered by their marriage.

Lack of recall of the information being provided could also explain patients not knowing about their medication-related information. For example, Mulryan et al. (2018) in their study have reported that despite the presence of clinical documentation stating that patients have been informed about the risk of VRM, some patients stated in the interviews that they had no awareness of such discussion (Mulryan et al., 2018). Lack of recall or information not being retained by the patient could also challenge patient-informed decision-making. Notably, in the current study, none of the participants reported being provided with written information. This could challenge the retainability of the information by the patient. Nevertheless, it should be acknowledged that recall bias might be present, i.e., the participants might have been provided with written information but they do not remember.

Patients' susceptibility to wrongful perceptions about their medication could potentially jeopardise the informed decision process. Examples of wrongful perceptions include over or underestimation of risks. Overestimation of the risk in the current study was noted with one participant who expressed that a birth defect occurring due to valproate in pregnancy is inevitable. This led her to stop her medication during pregnancy without consulting with her HCP. Another form of overestimation in the current study included a participant generalising that valproate is harmful to all female patients. Underestimation of risk was additionally observed. This was expressed by participants who thought that there were no risks related to valproate during pregnancy. This could be due to a lack of information, as well as the confirmation approach that was taken by physicians when discussing this issue with the patient. Overestimation or underestimation of the teratogenicity risk is not uncommon. For example, a recent systematic review of risk management of teratogenic medications found that the teratogenic risk of medications tends to be overestimated, while proper estimation or underestimation occurs less frequently among patients and HCPs (Shroukh, Steinke & Willis, 2020). Different factors were derived from the current study that could affect patients' perception of their medication. It includes HCPs' words (such as the words that confirm there is no risk in pregnancy) and actions (such as throwing away the medications). Wrongful perception could also occur from language barriers between the HCP and the patient. It could also result from HCPs not addressing patients' concerns and information needs. This might arise from one-sided communication between the HCP and the patient. Moreover, wrongful perceptions about medications might result from patients' unique perceptions of benefits and risks, and patients' interpretation of the information they read (such as connecting the need to taper a medication with it causing addiction as reflected by one participant).

It is important to overcome the influences that could negatively affect female patients with epilepsy's right to informed decision-making. This necessitates female patients with epilepsy to be adequately informed and educated about their medication. This is due to different reasons, including a complex decision-making process, the consequences of nonadherence to medications, and the possibility of drug-drug interactions. Decision-making about the use of VRM in females of childbearing age could be complex. This is because both deciding to continue or discontinue VRM during pregnancy have documented risks to the foetus and the mother. It also carries ethical challenges as there is no voice of the foetus on the one hand, and the decision is between two patients, the mother and the foetus, on the other hand (Macfarlane & Greenhalgh, 2018). It is also important to be well-informed to avoid the action of nonadherence (as seen with one patient in this interview). This is because nonadherence to antiepileptics, although not fully understood, and discontinuing antiepileptics are modifiable risk factors for sudden unexpected death in epilepsy (Devinsky, Hesdorffer, Thurman, Lhatoo, & Richerson, 2016; Jones & Thomas, 2017). Another challenge is related to possible drug-drug interactions that include the use of contraceptives. The clearance of valproate may be increased when combined hormonal transdermal patches, very low-dose combined hormonal contraceptives, or low-dose combined hormonal contraceptives are used (Gaffield, Culwell & Lee, 2011). This is important as the RMM provided by KDFC to HCPs recommended assessing the need for providing preconception counselling for women using VRM who are not planning pregnancy, including the use of contraceptives. However, no evidence of significant interactions has been found. As a patient with epilepsy might be taking a combination of antiepileptics, based on the type of antiepileptic and the hormonal contraceptive method, interactions may result in decreased contraceptive effectiveness, unplanned pregnancies, and/or increased seizure activity (Davis, Westhoff & Stanczyk, 2011; Gaffield et al., 2011).

One of the challenges for patients to be informed in the current study was the lack of continuous care related to nonadherence to follow-up visits. The use of telemedicine could support the continuity of care (Hincapié et al., 2020). Growth in this field of healthcare was particularly noticed during the COVID-19 pandemic with two technologies being used in outpatient clinic consultations, namely telephone calls and video calls, with positively evaluated experience and usefulness (Hincapié et al., 2020). In Kuwait, a cross-sectional survey targeting the public was conducted between April and May 2021. In this survey, the authors found 73.5% of the respondents were comfortable with using telemedicine, and 65% were likely to accept video call consultations with their HCPs (AlMatar, Al-Haqan, Abdullah & Waheedi, 2022).

However, 41.5% of the respondents were uncomfortable discussing sensitive issues with their HCPs using telemedicine; and only 23.6% perceived that they would receive the same quality of care virtually as in-person visits. It should be highlighted, however, that the majority of the participants (90.5%) had a previous experience with video calls, and the online nature of the survey, could limit the generalisability of the results to the population in Kuwait (AlMatar et al., 2022). This is because those who might be interested in virtual communications might have answered the survey and not those who were not interested or not familiar with these communications. In the case of an emergent alert, dedicated safety alert teams including HCPs and pharmacovigilance officers could be formed to develop protocols for fast notification of patients in response to a certain safety alert. Such teams, operating within the hospital, could be responsible for identifying the patients of concern, training HCPs to contact and counselling patients about the emergent alert. An example of such rapid action was previously published concerning dolutegravir-based regimens' teratogenicity alert (Laker et al., 2020). This was in an infectious diseases institute adult clinic. Three days after the release of the alert, they developed a protocol, which was piloted during the first week following the release of the alert. By using different approaches, this clinic was able to reach most female patients. These included mass rescheduling, group counselling, new clinic flows, and dedicated tracking of the process. To allow the other functions in the clinic to continue, they dedicated some staff to informing the female patients, including a clinical officer to triage, assess for fertility desire, and provide contraceptive information. Two groups comprising a counsellor and a doctor held the talks interchangeably. The clinic manager also supported the talks when needed. The pregnant women were reviewed by the clinic radiographer and a medical doctor who oversees the sexual and reproductive health clinic or an obstetrician when available. However, such an approach might be challenged by the lack of documentation related to patients' contact details. As seen in Chapter 6, the process of identifying patients was challenged by a lack of patients' contact numbers and wrong numbers provided in the patients' files. An alternative approach includes developing a hospital-based screening and intervention protocol to identify and refer women of childbearing age using VRM who might be visiting the hospital due to other reasons to evaluate the possibility of switching VRM to an alternative treatment (Mokni et al., 2022).

Part of providing education to the patient is recognising in which way the information would affect the patient. Lawther, Dolk, Sinclair, and Morrow (2018) conducted interviews with seven female patients with epilepsy that were using valproate preconceptionally in the UK to understand their preconception care experience. The pathways of these women were

characterised by trying to maintain balance. Before their motherhood journey starts, VRM is perceived to provide them with normal life. Moving into motherhood, they realise it is their decision whether to keep or change the medication. They understood they needed to weigh their health against their child's health. Female patients expressed concerns about losing seizure control as their greatest risk after successfully switching to an alternative antiepileptic. They also found that women seek support for pregnancy preparation, and some women were uncertain in regards to who is responsible for delivering such care and how to access such care. Several women described that changing valproate had a serious impact on their mental health, while no specific monitoring was in place. The preconception experience was described as upsetting to the balance a woman is trying to maintain; and, chaining their medication was seen as pulling them away from their stabiliser, which was a source of physical and emotional upset. The authors also reported that the patients' perceived risk-to-benefit balance might change before and after the decision to motherhood by the patient.

Proper communication is an important element in patient care. In complex situations, shared-decision making might be an optimal option for proper communication. This involves interactive communication between the HCPs and the patient, where the patient shares her values and preferences and social roles while the HCP shares the most current evidence-based treatments' benefits and risks and professional experience with the patient. This is expected to be with agreed responsibilities and goals to be achieved (Nakayama, 2018). A web-based survey was held between May and June 2020 on 457 patients with ulcerative colitis aged 20 years and older (Matsuoka et al., 2021). Using a structured equation modelling analysis, it was shown that physician-to-patient and patient-to-physician information significantly affected patients' satisfaction with treatment decision-making and patients' trust in physicians. The greater impact was seen in physician-to-patient information, such as those on disease and treatment. Some elements of patient-to-physician information, including anxiety and distress, intention and desire for treatment, and future expectations of life also affect patient satisfaction with treatment decision-making and patient's trust in physicians. HCP-patient communication should identify patient information needs, concerns and any wrongful perceptions regarding their medications. The form by which information is communicated to the patient is also important. In the current study, patients' preferences for knowing about their medication-related information included written and verbal information, with differences in terms of referring to the responsibility to the patient to read or the HCP to provide the information. Communicating information to the patient should not depend only on verbal communication.

As discussed previously, patients' lack of information could be due to not remembering that the information was given to them. This might highlight the need for written information and repeated information to be provided to patients (Mulryan et al., 2018). Annual review of the patient and counselling of the patient about the risk annually should also be considered (UK MHRA, 2018).

As with other children with chronic conditions, an essential element of developing self-care is developing healthcare autonomy (Beacham & Deatrick, 2013). This should be considered after assessing the readiness of the child and the parent (Beacham & Deatrick, 2013). This is not only for optimising the child's healthcare but also to provide a foundation for the transitioning of care from parental responsibility, as well as the transitioning of care from childhood to early adulthood (Beacham & Deatrick, 2013; Noom, Deković & Meeus, 2001). Noom et al. (2001) examined the concept of adolescent autonomy from different theoretical perspectives and conceptualised a model of autonomy, including attitudinal (cognitive process to identify goals), emotional (affective process to feel confident about one's own decisions), and functional (regulatory process to develop strategies to reach the goals) autonomy. Developing protocols to enhance healthcare autonomy should be considered. This is to avoid situations where patients might not be sufficiently informed about their medications due to being diagnosed at a young age where their healthcare responsibility falls upon their parents as reported in the current study. In addition to healthcare autonomy, health literacy should be promoted in these populations. Health literacy on its own is inadequate for improving patients' adherence to medical recommendations (DeWalt & Hink, 2009). However, health-related knowledge was generally positively associated with literacy (DeWalt, Berkman, Sheridan, Lohr & Pignone, 2004). Health literacy was also found to be positively associated with readiness for the transition of care from child-centred care to adult care, and self-efficacy in youth with chronic diseases (Chisolm et al., 2021; Riemann, Lubasch, Heep & Ansmann, 2021; Zhong, Patel, Ferris & Rak, 2020).

6.5 Strengths and limitations

This study provided insight into the patients' experiences. No limitations were applied in terms of the health area or hospital where the patients were recruited.

Focusing on female patients on valproate does not reflect all patients' experiences with medicines safety communications. A large number of eligible patients were not reachable as their contact information was missing from the hospital system, or their contact number was inaccurate.

Most approached patients were either not eligible due to disability-related reasons or refused to participate, which more insights might have been provided from participants who refused to participate or were not reachable. Recall bias might be present as all of the interviewed patients were using a valproate-related medication for the long term. In addition, this bias might be present as all the participants were interviewed in 2020, about four years following the dissemination of KDFC's valproate-related DHCP. All patients who agreed to participate were native speakers of Arabic.

Phone interviewing had the limitation of budling a rapport and probing questions based on in-person responses to conversation dynamics.

6.6 Summary of Chapter 6

This chapter reported the methods and the results of phase 3, followed by the discussion. This phase involved the experiences of six female patients on a VRM. Only one patient was informed of valproate-related teratogenicity. The following chapter presents the overall discussion, recommendations and conclusions of this research.

Chapter 7: Overall discussion, recommendations and conclusion

7.1 Overall Discussion

This research filled a gap in the literature in terms of evaluating medication safety communications in Kuwait. Evidence from the three key groups including the regulatory agency (KDFC), the HCPs and the patients suggests that despite KDFC's continuity in sending medication safety communications to HCPs, these communications were seldom known by HCPs. Additionally, evidence related to the VRM DHCP suggests suboptimal implementation by HCPs. These were related to different modifiable barriers that are further discussed in this chapter.

A framework should be developed for assessing and creating medication safety communications to avoid the variability observed in these processes (Chapter 4). The variability currently seen in medication safety communications might ultimately lead to different types of information being shared in different situations. As the current capacity of KDFC is limited due to the limited number of staff and a limited number of ADR reports submitted (Chapter 4), continuing reliance on international agencies and pharmaceutical companies for information relating to medication safety might be necessary at this point. However, such a framework might aid in unifying communications sent by KDFC. Information to be added to the content of medication safety communications should also be specified in such a framework. These include describing the risk in the context of benefit and explaining competing risks, such as the risks of nontreatment. Involving this information might help in avoiding unintended effects resulting from therapy discontinuation by the patient. This is especially with patients with epilepsy as the consequences of therapy discontinuation might be fatal, as explained in Chapter 6.

The scientific justifications of the recommendations were only reported in 22.2% of KDFC-sent communications. In a systematic review that was previously conducted, the lack of evidence that supports the regulatory agencies' recommendations was one of the reasons for

not trusting these recommendations by HCPs (Alharbi et al., 2023). In the physician's focus group discussion reviewing the evidence and perceiving it as weak evidence was one of the reasons for not implementing medication safety communications. Similarly, in the survey, 46.5% of HCPs reported believing that the recommendations are not evidence-based as a barrier to implementing them. Disclosing information that led to the regulatory agency's decision could support information transparency and the recipient's trust (Lee & Li, 2021). Unifying information, such as including quantitative information about the ADR, and writing specific recommendations should also be achieved. In the current research, 63% of KDFC's communications included specific recommendations.

Besides unifying the information included in KDFC's medication safety communications, the language of communications should also be evaluated. As noted in Chapter 4, all communications sent to HCPs were in English. As currently, the employment of Kuwaiti HCPs is direct and does not include an evaluation of HCPs' English levels, the understandability and accurate interpretation of medication safety communications should be established before disseminating these communications. The language barrier between HCPs themselves and HCPs and patients was one of the identified barriers to implementing medication safety communications (chapter 5). Language was also a derived barrier from the patients' interviews and the pharmacy technician's focus group discussion. In the later situation, pharmacy technicians who were not fluent in Arabic perceived that the reason for information not being received by them was that it was sent in Arabic. Although none of the safety communications directed at HCPs included in this research were written in Arabic. This could reflect that either another circular was sent by the MOH, or that KDFC had sent other safety communications in Arabic, which were not stored in their archives. As discussed in Chapter 4, sending safety communications in Arabic might be challenging, thus collaborating with other regional pharmacovigilance agencies might be needed to unify future efforts.

It was also indicated in Chapter 4 that current KDFC medication safety communications are not pre-tested. However, it goes through different levels of reviews among staff members in KDFC. As found in a previous systematic review, HCPs and healthcare institutions might interpret the same safety communication differently (Alharbi et al., 2023). Thus, a sample of the intended receivers should evaluate such communications for clarity and understandability. Such practice is currently conducted by other international regulatory agencies, such as EMA.

It was notable that stakeholders outside KDFC's staff members were only involved once in the approval of SGLT-2 inhibitors DHCP. On this occasion, HCPs involved were mainly physicians form a medical counsel. This might not be representative of other groups of HCPs, especially since these physicians were involved in the SGLT-2 inhibitors risks discussions and asked for a DHCP to be developed (chapter 4). The systematic involvement of representatives of different groups, including patients, HCPs, and the industry should be considered. EMA (2016) manages its interactions with the different stakeholders with a set of principles including transparency, independence and integrity, accountability, appropriate interaction, broad representation, effective communication and continuous involvement.

Although KDFC had previously sent medication safety communications to hospitals, with one in particular (KuFDA newsletter) being sent every two months, these tools were seldom known by HCPs. For example, of 380 HCPs participating in the survey, only 22.6% were familiar with KuFDA newsletters, and 48.9% were familiar with DHCP letters. A similar lack of familiarity with these tools was also noted in the focus group discussions. Even when using the VRM DHCP as an example, only one participant among all focus groups saw this DHCP. Among those who provided care for patients on VRM and reported knowing about its teratogenicity, only 19.8% of 131 participants selected KDFC as the source of their information. Although 24.4% of the 131 HCPs chose a circular from MOH, it is not clear if the MOH had sent a different circular or if they had resent KDFC's DHCP.

One of the barriers discussed in the focus groups was delays in receiving medication safety circulars from the MOH compared to the media/social media (chapter 5). Two factors could lead to these delays. First, reliance on international regulatory agencies (chapter 4), where the information might have been spread to the media before being disseminated by KDFC. Moreover, the channels used currently by KDFC to disseminate medication safety communications (manual or by fax) to MOH hospitals might have contributed to HCPs not receiving or delays in receiving the information.

While no electronic sources were used to disseminate information from KDFC to HCPs working in MOH hospitals. Furthermore, although the intended receivers of all DHCPs and KuFDA newsletters were HCPs, none of the evaluated communications were sent directly to HCPs at the ground level. This might also contribute to the delays or failures in receiving these communications by HCPs. The addition of an electronic source for sending medication safety

communications directly to HCPs should be considered. This was suggested by a staff member in KDFC (chapter 4), HCPs in the focus groups (chapter 5) and surveys, where the majority of HCPs preferred receiving both paper-based and electronic format of the medication's safety communications (n=221, 67.8%). This electronic method should be through MOH staff official emails. In such a case, an email could be sent directly from KDFC with a title reflecting the nature of the email and its urgency. Additionally, as the KuFDA newsletter might include different medications, it might be necessary to mention these medications in the email to avoid an overwhelming amount of irrelevant information.

Although WhatsApp is another electronic communication as discussed in Chapter 5, it is not free of challenges. For example, not all HCPs have a WhatsApp app, and important information might be obscured by other random messages or information. While KDFC deals with medication safety information on urgent bases, specifying a deadline for the preparation and dissemination processes might ensure adherence to these timelines and avoid unnecessary delays. This could also unify discrepancies concerning each staff perception of urgency.

Another barrier related to the current way of disseminating medication safety communications by KDFC is that HCPs who were on leave or those who are newly employed staff members might not have a way of identifying a previously disseminated medication safety communication (chapter 5). This is unless this information was archived and shared with other staff members. Thus, the retainability of the information is not guaranteed. At the same time, repeating sending the same information by KDFC might lead to information fatigue. In the focus group discussions, HCPs discussed the importance of knowing where to find medication safety communications by themselves. Although, some of the communications issued by KDFC in Chapter 4 were found on KDFC's website. These communications were removed afterwards. Thus, developing and maintaining a website that includes the medication safety communications issued by both KDFC and pharmaceutical companies is necessary. This website should be user-friendly, include updated information, and allow switching from professional modes to patient modes.

A recurrent barrier that was identified in the current research was professional roles and who is responsible for implementing actionable recommendations. This barrier could be overcome by specifying the roles of the involved HCPs in communications. For example in their guide to HCPs about the risk of VRM on girls and women of childbearing potential, UK MHRA

(2021) specified the roles of GPs, specialist prescribers, pharmacists, and other healthcare professionals including nurses, midwives, obstetricians, and gynaecologists, as well as emergency physicians in different sections of their guide. The current HCP guidance provided by KDFC did not specify the different roles of the HCPs. These roles could be outlined and discussed with stakeholders or representatives from different HCP groups before being included in the DHCP letters.

Another point to be considered is specifying the patients' age groups. This was particularly raised in the nurse's focus group discussion. Currently, KDFC's guide relating to VRM use in female patients divides the patients into female child first prescription, women of childbearing age who are not planning pregnancy, and women of childbearing age who are planning for pregnancy. Specifying the age group, especially when taking the patient's acknowledgement consent, and at which age should the consent be taken by the legal guardian and the patient (in Kuwait from 21 years of age). Including the phrase girls of any age could also be important to avoid being perceived as irrelevant to pediatric patients such as noticed in the nurse's focus group discussion and in the open-ended survey barrier question.

The current research identifies suboptimal information regarding the concept of medication safety within the context of pharmacovigilance, and suboptimal information about the tools used by KDFC among HCPs. Moreover, considering that medication safety information is continually changing as a barrier to implementing medication safety recommendations was reported in chapter 5. As noted in chapter 4 the current efforts in KDFC are focused on delivering training on ADR reporting. Thus, including training and education about the tools and the concepts of the medication safety communications as well as post market drug safety assessment to HCPs is necessary.

The ultimate goal of medication safety communication is to reach the targeted patient whether in the form of actions relating to the intended recommendations or as information provided to patients to make informed decisions. Evidence from chapters 5 and 6 indicated that female patients were not adequately informed about the teratogenicity risks of valproate. Even with the RMMs disseminated by KDFC such as prescribing guides, patients' cards, and patients' consent forms. Barriers to implementing these recommendations arise at different levels including the sender (KDFC), and the intended receivers which include HCPs and patients. The barriers related to KDFC were previously discussed, including delays, not specifying the

recommendations for each HCP group, and not explicitly stating where valproate could or could not be used (chapter 6). Barriers related to the HCPs included a lack of knowledge about the recommendations (chapter 5). Implementing better delivery processes such as electronic pathways might mitigate this barrier. However, even with more established pharmacovigilance systems, a lack of knowledge of the issuance of a medication safety communication in general, and its specific recommendations was regarded as a barrier to implementing medication safety recommendations (Alharbi et al., 2023). Establishing a team locally in the hospitals that is responsible for proactively checking for new updates regarding medication safety with KDFC was suggested in the focus group discussions in Chapter 5. This team could be responsible for monitoring recommendations' implementation, as well as being a channel for feedback between KDFC at the hospital to ensure accurate interpretation of the safety issue and the recommendations.

Other modifiable barriers were also found to preclude professionals from implementing VRM-related recommendations. Lack of confidence when talking to female patients regarding pregnancy issues was one of these barriers. Lack of confidence, as well as lack of knowledge, could be overcome by providing HCPs with adequate training specifically to deliver counselling related to teratogenic medications. Such training could be linked to CME activities. Another barrier was related to time and infrastructure. Training might also be useful in overcoming these barriers in addition to developing alert response teams as discussed earlier. Providing counselling areas for pharmacists (chapter 5) might be required to provide privacy for the patient. It is notable in this research that pharmacist roles and providing care to patients are more valued by other HCPs than in earlier research. For example, Matowe and co-authors conducted a study in 2004 to explore physicians' perceptions and expectations of pharmacists' professional duties in government hospitals in Kuwait (Matowe et al., 2006). In this study, 200 questionnaires were distributed to two governmental hospitals in Kuwait, and 120 questionnaires were answered by physicians. At that time, 33.3% of physicians reported that they never or rarely interact with pharmacists, and 52.5% reported that they interact with pharmacists once a week. Among those who interacted with pharmacists, 78.8% and 54.2% reported that their interactions were to inquire about drug availability, or a drug alternative, respectively. This could be in alignment with the current changes in the roles of pharmacists in Kuwait as discussed in Chapter 1.

Less participation of pharmacy technicians than other HCPs was noticed in this research. The most identified barrier by this group was that other professionals do not think it is the pharmacy

technicians' role to implement recommendations. A clear description of the role of the person who is dispensing medication for the patient whether a pharmacy technician or a pharmacist might be needed in medication safety communications. Alternatively, KDFC could specify that medication of concern should not be dispensed by a pharmacy technician unless reviewed first by a pharmacist. Other barriers were related to the patient. This included not attending follow-ups for long periods of time. A list of the patient with such conditions should be kept in the hospital with complete and updated patient contact information data. These patients should be contacted by a designated staff member to remind them of the follow-up appointments. Flexibility should be offered such as offering telemedicine to the patient to attend the follow-ups without the need to wait in the clinic setting as discussed in Chapter 6. A major barrier to this step is the incomplete and un-updated data documentation of patient communication information. In some situations, a patient might be pregnant and would be in contact with an obstetrician, or might visit the pharmacy for a refill. A screening protocol for female patients with epilepsy should be applied as discussed in Chapter 5.

Female patients with epilepsy should be offered appropriate pre-conception care. This should include a team of professionals as well as a psychologist member to provide patients with the necessary information to make an informed decision, as well as to address patients' concerns. Patients should have a direct line of contact with the team, such as discussed in Chapter 5 by the nurse's focus group. This is to ease the contact of a pregnant patient with HCPs for guidance. Another barrier was autonomy-related issues. This occurred as the patient was diagnosed and treated in their youth, where a parent was responsible for receiving healthcare-related information. It is important to develop a protocol to ensure an appropriate transition of healthcare responsibility, as well as empower patients with the necessary information related to their diseases and treatments. This is specifically important as the legal age for a patient not to be the responsibility of a legal guardian is 21 years of age. At this point, the patient would be at the college level and would have been past childhood and adolescents, where they might most need to be empowered to know how to deal with their chronic diseases, therapies and stigma. A protocol must be developed for guiding HCPs and parents as well as patients for a successful transition of care.

Sending letters directly to the patient by KDFC or the hospital might be the focus of future research. For example, NHS England (2021) sent letters to women between the ages of 12 to 55 who are using valproate-related medication. This letter was sent in multi-languages and

included information regarding safety issues, the use of contraceptives, pregnancy, and the necessity of annual reviews. They also provided information to the patient about the risk of stopping valproate without medical advice, including the risk to the unborn baby (NHS England, 2021).

7.2 Recommendations

7.2.1 Recommendation for healthcare policy

- The MOH should increase PV unit capacity to aid in increasing the functionality of pharmacovigilance activities in Kuwait. It is essential to increase the number of staff and improve the infrastructure to provide such activities.
- In terms of the content of medication safety communications, in addition to risks, medication benefits should be included.
- The safety communications should specify the roles of the different HCP groups.
- A framework should be developed for involving HCPs and patients in the process of developing medication safety communications.
- Including electronic dissemination, such as via MOH emails, of information to HCPs is imperative to increase the reach of medication safety communications to the intended receivers.
- Besides electronic dissemination, medication safety communications should be publicly available on KDFC's website. This approach should not only focus on KDFC's communications but also communications issued by pharmaceutical companies. This is to both increase the reachability of the medication safety communications (e.g. HCPs would know where to find the communications) and for transparency purposes.
- Posting these communications on KDFC's website will provide an opportunity for educational and research purposes, such as initiating impact studies.
- It is important to consider patient-friendly websites for patient information.
- Monitoring the impact of practices should also be incorporated into the MOH's pharmacovigilance function. Before conducting such monitoring, the MOH and KDFC

should be aware of the factors that could affect and impact the implementation of medication safety communications. The different types of impact resulting from safety communication should also be pre-specified.

- Evaluating the effectiveness of risk minimisation measures to be implemented by pharmaceutical companies should also be incorporated into the pharmacovigilance policy. Such evaluation should be followed by evidence-based strategies to improve the impact of medication safety communications.
- Regarding valproate-related safety communication, pregnancy prevention programmes for valproate should be initiated. An audit of valproate prescribing in female patients of childbearing age should also be considered (NHS England, 2022). Currently, the Inspection Administration Department within the MOH is responsible for inspecting pharmacies' adherence to regulations, in terms of checking the legal status of prescriptions and assuring the count of medications. Annually the MOH forms a team of pharmacists to check the stock of dispensary medications (inventory) in all MOH clinics and hospitals. Such teams could be trained and utilised to conduct audits relating to the valproate dispensing and prescribing (through the dispensing and prescribing systems), however, patients' privacy should be maintained.
- Documentation of patient counselling regarding the risks of valproate should be enforced.

7.2.2 Recommendations for practice

- Hospitals should appoint a lead person or implementation team, to aid in the process of implementing medication safety recommendations within the hospital and identify barriers that prevent implementation.
- Such a lead person should also have contact with KDFC to ensure accurate interpretation of medication safety communications.
- HCPs in hospitals should be familiarised with KDFC and the dissemination process of medication safety communications in the hospital setting.
- All patients' contact information should be complete and up to date. Female patients on valproate contact numbers should be recorded and updated.

- A team should be established to contact these patients to remind them of their follow-up visits (e.g., annually).
- The hospital should encourage direct patient contact with their teams. In the event of pregnancy, hospitals should offer direct advice and consultation to women on valproate.
- Hospital teams conducting audits related to valproate use in female patients and related to children with chronic diseases should be established. This is to identify these patients and ensure they receive appropriate information and responsibility for the transition of their care.
- Counselling areas, where it is absent, should be established for patient counselling and privacy.
- Training HCPs to counsel female patients about the teratogenic risk of valproate is necessary. In addition, HCPs should ensure patients understand the competing risks associated with stopping valproate without seeking medical advice and identify their concerns.
- Clear annual information should be provided to patients or their guardians about the risk-benefit balance of valproate use in the patient's case.
- A pre-conception care clinic should be provided for female patients on valproate.
- A protocol should be developed within the hospital to identify eligible patients and refer them to this clinic. At the beginning of treatment, patients and/or their guardians should be informed about the existence of such clinics, in addition to being informed about this clinic while providing them with valproate-related risk information annually.

7.2.3 Recommendations for UPPSALA monitoring centre (UMC)

- The UMC should recognise the maturity of pharmacovigilance centres that have become associate or full members of the UMC to be able to assist them to improve the effectiveness of their medication safety communication strategy.
- It is important for the UMC to evaluate the communication strategy of applicants and member pharmacovigilance centres for its effectiveness in reaching the intended receivers of medication safety messages. This is to avoid situations where the medication safety communication is not sent directly to the intended receivers. An

example of this is found in Chapter 4 where the pathway of medication safety communication involves KDFC sending these communications to directors, but not directly to HCPs at the patient-facing level.

- For regulatory agencies at a similar stage of maturity to KDFC, the UMC could offer support in the following areas:
    - Ensure that the pharmacovigilance centre has a functioning website that includes updated medication safety communications and that this website is accessible to the intended receivers.
    - Offer partnerships or collaborations with more mature pharmacovigilance centres to structure the pharmacovigilance reliance (as explained in 7.1) and provide an opportunity for shared experiences that could be offered in podcasts or webinars.
    - Develop a communication framework with minimum requirements as discussed previously in 7.2.1 that involves utilising different platforms aimed at different receivers. This framework could be adopted by members with a similar maturity to KDFC.
    - Offer training sessions for the pharmacovigilance centres on communicating with different receivers, as well as monitoring the effectiveness of medication safety communications.
    - Offer a framework that can be adapted by members with a similar maturity to KDFC that lists quality control procedures for medication safety communications, and the mechanism for involving stakeholders in the pre-testing processes of medication safety communications.
    - Offer educational sessions to the pharmacovigilance centre staff on the possible barriers that could preclude the effectiveness of the dissemination and implementation of emergent medication safety information. In addition, discuss possible methods to overcome such barriers.
    - The UMC could also develop a list for the pharmacovigilance centre of avoidable barriers. For example, a lack of awareness of the pharmacovigilance centre and its tools for communicating medication safety information was found with other regulatory agencies (Chapter 2), as well as locally in Kuwait (Chapter 5). The UMC could necessitate these pharmacovigilance centres to increase efforts to raise awareness about the centres, their functions, and the tools used to disseminate emergent medication safety information.

7.2.4 Recommendations for future research

Future research should focus on the impact on patient outcomes. In addition, strategies to improve the impact of medication safety communications should be investigated. This should include identifying whether one strategy such as training would be effective in targeting different barriers, like lack of knowledge, lack of time and lack of confidence. Improving communications in Kuwait through electronic means like official MOH email, in improving HCPs' knowledge of issued medications safety communications and familiarity with their content should also be evaluated. In the systematic review (Chapter 2), the patients' related factors were related to refusal and willingness to take the medications and the effect of knowing about the alert before HCPs. The patients' experience in phase 3 revealed other factors, such as non-adherence to follow-ups and communication barriers such as language barriers. This could be related to the systematic review inclusion criteria that only included HCPs. However, language was also perceived as a barrier in the open-ended survey question. Future research in Kuwait should also focus on this aspect of barriers related to medication safety communication, and how this barrier might affect information equity among patients. This is due to the multinational nature of residents in Kuwait, who might have difficulties understanding Arabic and/or English. It also could affect patients whose primary language is Arabic and the HCPs' is English or vice versa.

Furthermore, feasibility studies related to the recommendations of this research on clinical practice (e.g. developing pre-conception clinics for patients) should also be a target for future research. Specific hospitals could apply this service (developing pre-conception clinics for patients), and their success, barriers and facilitators should be explored to be transferred to other clinics. Evaluating the possibility of patients' and HCPs' involvement in the development of medication safety communications in Kuwait should be considered for future research. A framework should further be developed and piloted for involving HCPs and patients in the process of developing medication safety communications. Furthermore, the process of delivering medication safety communications to patients in Kuwait should be explored along with patients' acceptance of such communications.

7.3 Strengths and limitation

In this research, medication safety communications were evaluated from different aspects, including communication, and implementation and included the perspective of the sender (KDFC) and the receivers (HCPs, and patients). An example from KDFC safety communications was utilised in this research, which provided insights into the impact of medication safety communications in Kuwait. This research also included mixed-method approaches to data validity. The included hospitals were from the MOH in Kuwait, which is relevant to all citizens and residents of Kuwait as it is the only public healthcare sector in Kuwait.

The limitations of this research included not involving the perspectives of the pharmaceutical industry, the private healthcare sector, and other healthcare institutions including the Ministry of Interior Affairs, the Ministry of Defence, and hospitals related to the Kuwait oil sector due to limited time. Thus, findings are not generalisable to these sectors. Nevertheless, recommendations related to the content of medication safety communications related to KDFC apply to these healthcare sectors as KDFC is also responsible for sending medication safety communications to them. MOH primary healthcare clinics and polyclinics were not included as well due to the limited time. Generalisability is not claimed for this sector. However, the findings related to KDFC's strategy in terms of creating and disseminating medication safety communications would also reflect the primary sector as part of the MOH. As the strengths of each study add to the overall strength of this research, the limitations of each phase on its might contributes to the limitation of this research. An example of this was the lack of control over the number of documents retrieved. This is because the number of retrieved documents depends on whether the documents were stored or not in KDFC's archives. Thus, medication safety communications retrieved do not reflect the amount of medication safety communications issued by KDFC during the same period.

Limitations related to the focus group discussion included being conducted in one hospital, and self-selection of the participants. In addition, all physicians in the focus group were from internal medicine, thus insight from other physicians that might provide care for female patients

on valproate might have not been reflected. The administration of the survey was limited by self-selection and the online nature of the survey might exclude people who are not familiar with or interested in online surveys. Moreover, the length of the survey might have also led to the increased discontinuation of the participants. Despite being targeted, none of the participants was a neurologist, thus the results of the valproate section cannot be generalised to this group of HCPs. In addition, the chosen medication "valproate-related medications" does not reflect all HCPs' practices in relation to other medicines' safety communications. Recall bias might have been present in the focus groups and the survey as the valproate-related DHCP was issued in 2016, while the focus group discussions were conducted in 2019 and the survey was disseminated in 2021

Patients' interviews were limited by the reachability of the patients. This is because not all hospitals had registered phone numbers of all their patients, or had un-updated telephone numbers of their patients. Most of the identified patients were identified through the pharmacy dispensing system. One secondary governmental hospital did not have an electronic system that could retrieve the dispensed items per patient. Thus, invitations were only distributed through pharmacists, which might be opportunistic depending on patients' appointments for refills. Thus, limiting the possibilities of these patients being reached. Moreover, the findings from the valproate-related DHCP might not reflect the implantation of other medication safety communications in practices. Moreover, patients' phone interviews limited the researcher's capability to view the patient's body langue and expressions. Furthermore, this study does not reflect the experiences of parents/guardians of female children on valproate and further research should be conducted to add to this insight.

7.4 Researcher's reflexivity

The researcher Amal Alharbi worked as a pharmacist in a Kuwaiti MOH-related secondary hospital, and the supervisory team included members with diverse expertise in patient safety, pharmacovigilance, pharmacy practice in the UK and pharmacy practice in Kuwait. The interview and survey questions, interviewing process, and analysis were conducted by the researcher; and all were reviewed and confirmed by the supervisory team. The researcher also had training in different areas including conducting interviews, focus group discussions,

designing surveys, qualitative analysis, SPSS and survey analysis sessions. The following characteristics of the researcher might have influenced the research.

The focus group participants were mostly aware of the researcher's professional background as a pharmacist. In addition, the focus group discussion was conducted in a meeting room belonging to the pharmacy department. These two factors might have affected the data collection, for example having notably more participants participating in the pharmacist's focus group discussion than the other groups. However, less participation was seen in the pharmacy technician group despite working in the same department. Thus, pharmacists' interest in the topic of discussion might have been a driver for their participation. On another angle, recognising that the researcher is a pharmacist might influence the physicians' and nurses' recommendations of increasing the roles of pharmacists to improve the implementation of medication safety communications. With the noted fear of blame culture among nurses, the researcher also acknowledges that the meeting venue (i.e. within the pharmacy department) might be added to their fear of being judged. Thus, the researcher aimed at reducing this fear by ensuring their confidentiality and emphasising on there were no right or wrong answers. Including refreshments within the focus group, and discussion might aid in reducing such fear and establishing rapport.

Data collection for two studies was affected by the COVID-19 pandemic. After initiating data collection for the patients' interviews, it had to be suspended due to restrictions made during that time. This suspension lasted around four months (approximately from the end of February 2020 to June 2020). During this, the researcher and supervisory team had discussions of the contingency plans phase, especially since no patient was recruited at that time. These contingency plans included using registries of female patients using valproate, or patients' entries regarding their experiences on patient groups' websites. The first plan, however, was not achievable as no such registry for female patients existed as confirmed by KDFC and the MAH. A chance for continuing patients' invitations was resumed in June 2020, with one change. This change involved conducting phone interviews with patients rather than face-to-face interviews due to the restrictions and risks related to face-to-face interviews during the pandemic. The initial plan was to invite patients from one secondary public hospital. However, no patients initially agreed to participate. Thus, other hospitals were gradually added, including the only neurology MOH hospital and all secondary-public hospitals in Kuwait, except one hospital which was isolated for COVID-19 cases at that time. This process of identifying and

contacting patients was complicated due to incomplete or un-updated patient records relating to their contact numbers.

Being a female could have facilitated the conduction and the acceptance of the interviews by the patients. This is due to the sensitivity of the topic and the cultural backgrounds of the patients, especially since the patients were contacted by phone by the researcher. It was notable that some patients who initially agreed to participate had withdrawn after the researcher sent the consent form to them. Moreover, two patients had withdrawn after the interviews were conducted after being reminded of the need to send the consent form to the researcher. Although, the patients were not asked directly for the reason for their withdrawal in adherence to the ethics approval form. It could be that the patients and/or their families were concerned about the need to sign a consent form, especially since the researcher is someone that they have never met due to the restrictions of COVID-19.

The researcher was self-conscious while conducting the patient interviews. This is due to the researcher's realisation of the sensitivity along with the complexity of this topic. This is because causing unintentional worrying to the patient might lead to patient discounting of treatment, which might lead to cascading events, including patients stopping treatment, loss of seizure control, and being involved in accidents. Thus, the researcher ensured the evaluation of the research question by the supervisory team, the ethics committee and induvial participating in the pilot study. The researcher also confirmed to the patients at the start of the interviews that the questions are not based on their medical condition, nether the researcher had access to their medical condition. The researcher also explained to the patient that the interview is rather about their experiences to explore what could be improved in the healthcare system.

The survey method was also affected by the COVID-19 pandemic. This is because the healthcare system was occupied by the increasing number of COVID-19 cases. Thus, the pilot study of the survey was only initiated in August 2020, and the launching of the survey was in January 2021. The data collection process of this study was not without challenges. This is because the researcher visited all MOH secondary and tertiary hospitals during this process. This added to the researcher's concern to catch and subsequently pass it to her family members. On the other hand, the researcher was aware of the burden on the HCPs due to months of working during the pandemic. Thus, flexibility in terms of once a survey link was opened by a participant it could be saved for two weeks for the participant to complete at her/his preferred

pace. However, there was a possibility that the participant might forget to continue the survey, thus reminders and snowballing strategies using social were utilised.

To avoid the researcher's previous work affecting the analysis process, supervisors were involved in the analysis process. In addition, the researcher was reflexive during the analysis process by taking notes in a journal throughout the analysis process. In the analysis of the open-ended survey questions, all supervisors were involved. This is because the answers provided by the participants were short, and the researcher was not able to probe the questions due to the nature of the study. Thus, insight from a different perspective including pharmacy practice and pharmacovigilance was required. This process was also necessary to exclude answers that were insufficient to be analysed. In the survey analysis, the researcher ensured the involvement of the statistician in validating the choice of tests to be performed. Despite that the researcher had training in SPSS, she recognised the importance of involving an experienced professional to ensure the appropriateness of the chosen methods to the data set and objective.

7.5 Conclusion

Pharmacovigilance aims at safeguarding patients and one of its dynamic activities is medication safety communications. This is because it does not depend solely on regulators' competence to achieve its outcomes, but rather, it needs to be understood and implemented by HCPs and patients, depending on its recommendations. In Kuwait, a small pharmacovigilance unit within KDFC oversees pharmacovigilance activities, including disseminating such communications. Three main types of medication safety communications were issued by KDFC, including DHCP letters and newsletters targeted at HCPs (KuFDA newsletter) and public releases. No previous research had evaluated medication safety communications in Kuwait, so this research revealed challenges at different levels that could preclude the success of medication safety communications in Kuwait. These challenges occurred at the level of the sender (KDFC), and the intended receivers (HCPs and patients). Recognising these challenges provides opportunities for improving pharmacovigilance-related initiatives to improve patients' safety. Increasing the reach of pharmacovigilance-related medication safety communications in Kuwait should be the main focus of improvement. This could be accomplished by using official electronic methods for disseminating such information to HCPs.

Medication safety communications from KDFC should also be publicly available to increase both the transparency and reach of the medication's safety communications. Involving HCPs at the patient-facing level and using patients' responses to confirm the understandability of KDFC's written materials before their dissemination should be the focus of future research.

References

Abend, G. (2008). The meaning of 'theory'. *Sociological Theory*, *26*(2), 173-199.

Ackroyd-Stolarz, S., Hartnell, N., & MacKinnon, N. J. (2006). Demystifying medication safety: making sense of the terminology. *Research in Social and Administrative Pharmacy, 2*(2), 280-289.

Ahlin, T., Nichter, M., & Pillai, G. (2016). Health insurance in India: what do we know and why is ethnographic research needed. *Anthropology & Medicine*, *23*(1), 102-124.

Al Aqeel, S., Abanmy, N., Aldayel, A., Al-Khalifa, H., Al-Yahya, M., & Diab, M. (2018). Readability of written medicine information materials in Arabic language: expert and consumer evaluation. *BioMed Central Health Services Research*, *18*(1), 1-7.

Al Hamid, A., Malik, A., & Alyatama, S. (2020). An exploration of patient safety culture in Kuwait hospitals: a qualitative study of healthcare professionals' perspectives. *International Journal of Pharmacy Practice*, *28*(6), 617-625.

Al Salem, G. F. (2018). *An assessment of safety climate in Kuwaiti public hospitals.* Doctoral dissertation, University of Glasgow, Glasgow.

Al-Essa, R. K., Al-Rubaie, M., Walker, S., & Salek, S. (2015). The Current Status of Drug Safety and Pharmacovigilance. In R. Al-Essa, M. Al-Rubaie, S. Walker, S. Salek (Eds.), *Pharmaceutical Regulatory Environment*. (pp. 115-140). Springer International Publishing.

Al-Nakib, F. (2016). *Kuwait transformed: a history of oil and urban life*. California: Stanford University Press.

Albu, O. B., & Wehmeier, S. (2014). Organizational Transparency and Sense-Making: The Case of Northern Rock. *Journal of Public Relations Research*, *26*(2), 117–133.

Alghamdi, E. A., Albalawi, O. M., & Alshammari, T. M. (2021). Health outcomes and policy in pharmay curricula among Arab countries: An evaluation of 191 academic institutions. *Saudi Pharmaceutical Journal*, *29*(8), 799-806.

Alhakami, A. S., & Slovic, P. (1994). A psychological study of the inverse relationship between perceived risk and perceived benefit. *Risk analysis, 14*(6), 1085-1096.

Alharbi, A. B., Berrou, I., Umaru, N., Al Hamid, A., & Shebl, N. A. (2023). Factors influencing the uptake of medicine risk communications by healthcare professionals in clinical practice: A systematic review. *Research in Social and Administrative Pharmacy*, 19 (1).

Alharbi, A. B., Berrou, I., Umaru, N., Al Hamid, A., & Shebl, N. A. (2022). Factors influencing the implementation of medicine risk communications by healthcare professionals

in clinical practice: a systematic review using the theoretical domains framework. Unpublished Work.

Alhuwail, D. (2021). Information management practices in public tertiary health-care facilities: an empirical investigation from the state of Kuwait. *Records Management Journal, 31*(1), 60-73.

Aliyu, A. A., Bello, M. U., Kasim, R., & Martin, D. (2014). Positivist and non-positivist paradigm in social science research: Conflicting paradigms or perfect partners?. *Journal of Management and Sustainability*, *4*(3), 79-95.

AlMatar, R., Al-Haqan, A., Abdullah, I., & Waheedi, S. (2022). Population perceptions of health care services provided virtually (telehealth): a cross-sectional study. *Journal of Public Health*.

Alonso-Coello, P., Martínez García, L., Carrasco Gimeno, J. M., Solà, I., Qureshi, S., & Burgers, J. S. (2011). The updating of clinical practice guidelines: Insights from an international survey. *Implementation Science*, *6*(1), 1–8.

Alsaleh, F. M., Alzaid, S. W., Abahussain, E. A., Bayoud, T., & Lemay, J. (2017). Knowledge, attitude and practices of pharmacovigilance and adverse drug reaction reporting among pharmacists working in secondary and tertiary governmental hospitals in Kuwait. *Saudi Pharmaceutical Journal, 25*(6), 830-837.

Alsaleh, F. M., Lemay, J., Al Dhafeeri, R. R., AlAjmi, S., Abahussain, E. A., & Bayoud, T. (2017). Adverse drug reaction reporting among physicians working in private and government hospitals in Kuwait. *Saudi Pharmaceutical Journal*, *25*(8), 1184-1193.

Alshammari, T. M., Alenzi, K. A., & Ata, S. I. (2020). National pharmacovigilance programs in Arab countries: A quantitative assessment study. *Pharmacoepidemiology and Drug Safety*, *29*(9), 1001-1010.

Alshammari, T. M., Mendi, N., Alenzi, K. A., & Alsowaida, Y. (2019). Pharmacovigilance systems in Arab countries: overview of 22 Arab countries. *Drug Safety*, *42*(7), 849-868.

Arlett, P. (2020). Measuring the impact of risk communications: Robust analytical approaches are key. *British Journal of Clinical Pharmacology*, *86*(4), 635-636.

Aronson, J.K. (2012). Adverse drug reactions: history, terminology, classification, causality, frequency, preventability. In J. Talbot & J.K. Aronson (Eds.), *Stephens' detection and evaluation of adverse drug reactions: principles and practice*. (6th ed., pp. 1-119). Wiley-Blackwell.

ASHP. (1998). Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions. *American Journal of Health-System Pharmacy*, *55*(2), 165-6.

Assiri, G. A., Shebl, N. A., Mahmoud, M. A., Aloudah, N., Grant, E., Aljadhey, H., et al. (2018). What is the epidemiology of medication errors, error-related adverse events and risk

factors for errors in adults managed in community care contexts? A systematic review of the international literature. *British Medical Journal Open*, *8*(5), e019101.

Association of Translation Companies. (n.d.). *About the ATC defining standards of excellence*. Last accessed November 28, 2022 from: https://atc.org.uk/about/

Atkins, L., Francis, J., Islam, R., O'Connor, D., Patey, A., Ivers, N., et al. (2017). A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation science*, *12*(1), 1-18.

Badawi, D. A., Alkhamis, Y., Qaddoumi, M., & Behbehani, K. (2015). National transparency assessment of Kuwait's pharmaceutical sector. *Health Policy*, *119*(9), 1275-1283.

Baden, L. R., Solomon, C. G., Greene, M. F., D'Agostino, R. B., & Harrington, D. (2020). The FDA and the Importance of Trust. *New England Journal of Medicine*, *383*(27), e148.

Bahri, P. (2010). Public Pharmacovigilance Communication. *Drug safety*, *33*(12), 1065-1079.

Bahri, P., Dodoo, A. N., Edwards, B. D., Edwards, I. R., Fermont, I., Hagemann, U., et al. (2015). The ISoP CommSIG for improving medicinal product risk communication: A new special interest group of the international society of pharmacovigilance. *Drug Safety*, *38*, 621-627.

Barker, J. R., Boyle, T. C., Tay, L., Bishop, A., Morrison, B., Murphy, A. et al. (2019). Barriers to the use of patient safety information sources by community pharmacies. *Research in Social and Administrative Pharmacy*, *15*(7), 895-901.

Bator, R., & Cialdini, R. (2000). The application of persuasion theory to the development of effective proenvironmental public service announcements. *Journal of Social Issues*, *56*(3), 527-542.

Beacham, B. L., & Deatrick, J. A. (2013). Health care autonomy in children with chronic conditions: implications for self-care and family management. *Nursing Clinics*, *48*(2), 305-317.

Beardsley, S. J., Dostal, I., Cole, J., Gutierrez, A., & Robson, J. (2021). Valproate use in women aged 15–44 years: an observational study in general practice. *British Journal of General Practice open*, *5*(2).

Beaumont, E. (1999). Democracy and public administration reform linked. *The Public Manager: The New Bureaucrat*, *28*(1), 47-51.

Bell, S. G., Matsumoto, M., Shaw, S. J., Brandt, J., & Krauss, G. L. (2013). New antiepileptic drug safety information is not transmitted systematically and accepted by US neurologists. *Epilepsy & Behavior*, *29*(1), 36-40.

Bénard-Laribière, A., Miremont-Salamé, G., Pérault-Pochat, M. C., Noize, P., Haramburu, F., & EMIR Study Group on behalf of the French Network of Pharmacovigilance Centres. (2015). Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. *Fundamental & clinical pharmacology*, *29*(1), 106-111.

Beninger, P. (2017). Risk communication in a pharmacovigilance environment. *Clinical Therapeutics*, *39*(4), 672-674.

Beninger, P. (2018). Pharmacovigilance: an overview. *Clinical therapeutics*, *40*(12), 1991-2004.

Berg, B. L. (2001). *Qualitative research methods for the social sciences*. (4th ed.). Boston: Allyn and Bacon.

Berkman, N. D., Davis, T. C., & McCormack, L. (2010). Health literacy: what is it?. *Journal of Health Communication*, *15*(S2), 9-19.

Bham, B. (2015). The first Eastern Mediterranean region/Arab countries meeting of pharmacovigilance. *Drugs-Real World Outcomes*, *2*(1), 111-115.

Bhatia, S. K., Rezac, A. J., Vitiello, B., Sitorius, M. A., Buehler, B. A., & Kratochvil, C. J. (2008). Antidepressant Prescribing Practices for the Treatment of Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology*, *18*(1), 70–80.

Birch, M., Miller, T., Mauthner, M., & Jessop, J. (2012). Introduction to the second edition. In T. Miller, M. Birch, M. Mauthner & J. Jessop (Eds), *Ethics in qualitative research*. (2nd ed., pp.1-13). SAGE Publications Limited

Bjerre, L. M., Parlow, S., De Launay, D., Hogel, M., Black, C. D., Mattison, D. R., et al. (2018). Comparative, cross-sectional study of the format, content and timing of medication safety letters issued in Canada, the USA and the UK. *British Medical Journal open*, *8*(10), e020150.

Boettger, R. K., & Palmer, L. A. (2010). Quantitative content analysis: Its use in technical communication. *IEEE transactions on professional communication*, *53*(4), 346-357.

Bowling, A. (2014). *Research methods in health: Investigating health and health services*. McGraw-hill Education. Kindle Edition.

Brafield A. (2019). *Martindale the Complete Drug Reference* [online]. https://www.medicinescomplete.com/#/

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology*, *3*(2), 77-101.

Brinkmann, S. & Kvale, Steinar (2015). *Interviews learning the craft of qualitative research interviewing*. (3rd ed.). California: SAGE.

Brislin, R. W. (1986). The wording and translation of research instruments. *Field methods in cross-cultural research*, (8), 137-164.

Broom, A., & Willis, E. (2007). Competing paradigms and health research. In M. Saks & J. Allsop (Eds), *Researching health: qualitative, quantitative and mixed methods*. (pp.16-31). London: SAGE.

Buabbas, A. J., Alsaleh, F. M., Al-Shawaf, H. M., Abdullah, A., & Almajran, A. (2018). The readiness of hospital pharmacists in Kuwait to practise evidence-based medicine: a cross-sectional study. *BioMed Central Medical Informatics and Decision Making*, *18*, 4.

Bunniss, S., & Kelly, D. R. (2010). Research paradigms in medical education research. *Medical Education*, *44*(4), 358-366.

Bürkle, T., Müller, F., Patapovas, A., Sonst, A., Pfistermeister, B., Plank-Kiegele, B., et al. (2013). A new approach to identify, classify and count drug-related events. *British journal of clinical pharmacology*, *76*, 56-68.

Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P.-A. C., et al. (1999). Why don't physicians follow clinical practice guidelines?: A framework for improvement. *Journal of the American Medical Association*, *282*(15), 1458–1465.

Caine, K. J., Davison, C. M., & Stewart, E. J. (2009). Preliminary field-work: Methodological reflections from northern Canadian research. *Qualitative Research*, *9*(4), 489-513.

Calvo Hernaez, B., & Zúñiga, L. (2011). Risk management plan and pharmacovigilance system-biopharmaceuticals: biosimilars. In G. Nota (Ed.), *Risk Management Trends*. (pp. 251-266). Croatia: InTech.

Cane, J., O'Connor, D., & Michie, S. (2012). Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implementation Science*, *7*(1), 37.

Cane, J., Richardson, M., Johnston, M., Ladha, R., & Michie, S. (2015). From lists of behaviour change techniques (BCTs) to structured hierarchies: Comparison of two methods of developing a hierarchy of BCTs. *British Journal of Health Psychology*, *20*, 130-150.

Casey, M. S., Thackeray, F. W., & Findling, J. E. (2007). *The history of Kuwait*. Connecticut: Greenwood Publishing Group.

Chakraborty, S., & Lofstedt, R. (2012). Transparency Initiative by the FDA's Center for Drug Evaluation and Research (CDER): Two qualitative studies of Public Perceptions. *European Journal of Risk Regulation, 3*(1), 57-71.

Cheung, A., Sacks, D., Dewa, C. S., Pong, J., & Levitt, A. (2008). Pediatric prescribing practices and the FDA black-box warning on antidepressants. *Journal of Developmental and Behavioral Pediatrics*, *29*(3), 213–215.

Chisolm, D. J., Keedy, H. E., Hart, L. C., Chavez, L. J., Dolce, M., Morack, J., et al. (2021). Exploring health literacy, transition readiness, and healthcare utilization in medicaid chronically ill youth. *Journal of Adolescent Health*, *69*(4), 622-628.

CIOMS. (2005). *Management of safety information from clinical trials: report of CIOMS Working Group VI*. Geneva: WHO.

CIOMS. (2014). *Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX*. Geneva: CIOMS.

Coplan, P. M., Noel, R. A., Levitan, B. S., Ferguson, J., & Mussen, F. (2011). Development of a framework for enhancing the transparency, reproducibility and communication of the benefit–risk balance of medicines. *Clinical Pharmacology & Therapeutics*, *89*(2), 312-315.

Corbin, J. & Strauss, A. (2014). *Basics of qualitative research: techniques and procedures for developing grounded theory*. (4th ed). SAGE Publications. Kindle Edition.

Corcoran, N. (2007). Theories and models in communicating health messages. In N. Corcoran (Ed.), *Communicating health: Strategies for health promotion*. (pp.5-31). SAGE Publications Ltd.

Cordero, L., Rudd, M. D., Bryan, C. J., & Corso, K. A. (2008). Accuracy of primary care medical providers' understanding of the FDA black box warning label for antidepressants. *Primary Care & Community Psychiatry*, *13*(3), 109–114.

Cotterrell, R. (1999). Transparency, mass media, ideology and community. *Cultural Values*, *3*(4), 414–426.

Craig, L. E., Taylor, N., Grimley, R., Cadilhac, D. A., McInnes, E., Phillips, R., et al. (2017). Development of a theory-informed implementation intervention to improve the triage, treatment and transfer of stroke patients in emergency departments using the Theoretical Domains Framework (TDF): the T3 Trial. *Implementation Science*, *12*,88.

Creswell, J. (2007). *Qualitative inquiry and research design: Choosing among five approaches*. (2nd ed.). California: SAGE Publications, Inc.

Creswell, J. W., & Creswell, J. D. (2017). (5th ed.). *Research design: Qualitative, quantitative, and mixed methods approaches*. California: SAGE.

Creswell, J. W., Plano Clark, V. L., Gutmann, M. L., & Hanson, W. E. (2003). Advanced mixed methods research designs. *Handbook of mixed methods in social and behavioral research*, *209*, 240.

Creswell, J., & Plano Clark, V (2018). *Designing and conducting mixed methods research*. SAGE Publications. Kindle Edition.

Crystal, J. (2016). *Kuwait: The transformation of an oil state*. London: Routledge.

Darzi, A. (2008). Quality and the NHS next stage review. *The Lancet*, *371*(9624), 1563-1564.

Davis, A. R., Westhoff, C. L., & Stanczyk, F. Z. (2011). Carbamazepine coadministration with an oral contraceptive: effects on steroid pharmacokinetics, ovulation, and bleeding. *Epilepsia*, *52*(2), 243-247.

De Koning, R., Egiz, A., Kotecha, J., Ciuculete, A. C., Ooi, S. Z. Y., Bankole, N. D. A. et al. (2021). Survey fatigue during the COVID-19 pandemic: an analysis of neurosurgery survey response rates. *Frontiers in Surgery*, *8*, 690680.

de Vries, S. T., van der Sar, M. J., Coleman, A. M., Escudero, Y., Rodríguez Pascual, A., Maciá Martínez, M. Á., et al. (2018). Safety communication tools and healthcare professionals' awareness of specific drug safety issues in Europe: a survey study. *Drug Safety*, *41*, 713-724.

de Vries, S. T., van der Sar, M. J. M., Coleman, A. M., Escudero, Y., Rodríguez Pascual, A., Maciá Martínez, M. Á., et al. (2020). Correction to: Safety Communication Tools and Healthcare Professionals' Awareness of Specific Drug Safety Issues in Europe: A Survey Study (Drug Safety, (2018), 41, 7, (713-724), 10.1007/s40264-018-0643-5). *Drug Safety*, *43*(8), 827–829.

de Vries, S. T., van der Sar, M. J., Cupelli, A., Baldelli, I., Coleman, A. M., Montero, D., et al. (2017). Communication on safety of medicines in Europe: current practices and general practitioners' awareness and preferences. *Drug Safety*, *40*, 729-742.

DeFrank, J. T., McCormack, L., West, S. L., Lefebvre, C., & Burrus, O. (2019). Unintended effects of communicating about drug safety issues: a critical review of the literature. *Drug Safety*, *42*(10), 1125-1134.

Denzin, N.K. & Lincoln, Y.S. (2018). Introduction: The discipline and practice of qualitative research. In N.K. Denzin & Y. S. Lincoln (Eds.), *The SAGE handbook of qualitative research*. (5th ed., pp.1-26). SAGE Publications. Kindle Edition.

Devinsky, O., Hesdorffer, D. C., Thurman, D. J., Lhatoo, S., & Richerson, G. (2016). Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *The Lancet Neurology*, *15*(10), 1075-1088.

DeVon, H. A., Block, M. E., Moyle-Wright, P., Ernst, D. M., Hayden, S. J., Lazzara, D. J. et al. (2007). A psychometric toolbox for testing validity and reliability. *Journal of Nursing Scholarship*, *39*(2), 155-164.

DeWalt, D. A., & Hink, A. (2009). Health literacy and child health outcomes: a systematic review of the literature. *Pediatrics*, *124*(Supplement_3), S265-S274.

DeWalt, D. A., Berkman, N. D., Sheridan, S., Lohr, K. N., & Pignone, M. P. (2004). Literacy and health outcomes: a systematic review of the literature. *Journal of General Internal Medicine*, *19*(12), 1228-1239.

Dillard, A. J., Ferrer, R. A., Ubel, P. A., & Fagerlin, A. (2012). Risk perception measures' associations with behavior intentions, affect, and cognition following colon cancer screening messages. *Health psychology*, *31*(1), 106.

Dixon-Woods, M., Agarwal, S., Jones, D., Young, B., & Sutton, A. (2005). Synthesising qualitative and quantitative evidence: A review of possible methods. *Journal of Health Services Research and Policy*, *10*(1), 45–53.

Doris, S. F., Lee, D. T., & Woo, J. (2003). Translation of the chronic heart failure questionnaire. *Applied Nursing Research, 16*(4), 278-283.

Drainoni, M. L., Koppelman, E. A., Feldman, J. A., Walley, A. Y., Mitchell, P. M., Ellison, J., & Bernstein, E. (2016). Why is it so hard to implement change? A qualitative examination of barriers and facilitators to distribution of naloxone for overdose prevention in a safety net environment. *BioMed Central Research Notes*, *9*(1), 1–14.

Drolet, B., Rousseau, G., Daleau, P., Cardinal, R., & Turgeon, J. (2000). Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. *Circulation*, *102*(16), 1883-1885.

Dunn, O. J. (1964). Multiple comparisons using rank sums. *Technometrics*, *6*(3), 241-252.

Dusetzina, S. B., Higashi, A. S., Dorsey, E. R., Conti, R., Huskamp, H. A., Zhu, S., et al. (2012). Impact of FDA drug risk communications on health care utilization and health behaviors: A systematic review. *Medical Care*, *50*(6), 466–478.

Eder, J., Herrling, P.L. (2015). Trends in Modern Drug Discovery. In: Nielsch, U., Fuhrmann, U., Jaroch, S. (Eds.), *New Approaches to Drug Discovery. Handbook of Experimental Pharmacology, vol 232*. Cham: Springer.

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*, *356*(9237), 1255-1259.

Ellis, J. (2018). Preliminary fieldwork in Redfern and Waterloo. Last accessed October 11, 2018 from: http://libguides.unitec.ac.nz/apareferencing/webpages.

EMA. (2010). *European Medicines Agency recommends revocation of marketing authorisations for bufexamac.* Last accessed November 9, 2022 from: https://www.ema.europa.eu/en/documents/press-release/european-medicines-agency-recommends-revocation-marketing-authorisations-bufexamac_en.pdf

EMA. (2013). *Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1)*. Last accessed October 31, 2022 from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf

EMA. (2014). *Standard operating procedure*. Last acsessed April 12, 2023 from: https://www.ema.europa.eu/en/documents/sop/standard-operating-procedure-preparation-updates-european-public-assessment-report-summaries-product_en.pdf

EMA. (2016). *European Medicines Agency (EMA) stakeholder relations management framework*. Last access November 30, 2022 from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-ema-stakeholder-relations-management-framework_en.pdf

EMA. (2017a). *Guideline on good pharmacovigilance practices (GVP). Module II – Pharmacovigilance system master file (Rev 2)*. Lasted accessed January 10, 2023 from:

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-ii-pharmacovigilance-system-master-file-rev-2_en.pdf

EMA. (2017b). *Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)*. Last acsessed April 11, 2023 from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

EMA. (2017c). *Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)*. Last accessed October 24, 2022 from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

EMA. (2017d). *Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication (Rev 1)*. Last acsessed April 12, 2023 from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

EMA. (2017e). *Summary of the EMA public hearing on valproate in pregnancy public hearing held on 26 September 2017*. Last acsessed April 24, 2023 from: https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf

EMA. (2018). *Summary of the EMA public hearing on quinolone and fluoroquinolone antibiotics public hearing held on 13 June 2018*. Last acsessed April 24, 2023 from: https://www.ema.europa.eu/en/documents/report/summary-ema-public-hearing-quinolone-fluoroquinolone-antibiotics_en.pdf

EMA. (2021a). *EMA pharmacovigilance system manual version 1.3*. Last acsessed June 7, 2022 from: https://www.ema.europa.eu/en/documents/other/european-medicines-agency-pharmacovigilance-system-manual_en.pdf.

EMA. (2021b). *Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3)*. Last acsessed April 22, 2023 from https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf

EMA. (2022a). *Guidelines on good pharmacovigilance practices (GVP): Introductory cover note, last updated with release of Addendum III of Module XVI on pregnancy prevention programmes for public consultation*. (EMA/95595/2022). Last acsessed April 11, 2023 from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidelines-good-pharmacovigilance-practices-gvp-introductory-cover-note-last-updated-release_en.pdf

EMA. (2022b). *European Medicines Agency post-authorisation procedural advice for users of the centralised procedure*. Last acsessed April 11, 2023 from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-post-authorisation-procedural-advice-users-centralised-procedure_en.pdf

EMA. (n.d.-a). *Pharmacovigilance legislation*. Last acsessed June 7, 2022 from: https://www.ema.europa.eu/en/pharmacovigilance-legislation#:~:text=Pharmacovigilance%20legislation%20was%20developed%20in,per%20year%20in%20the%20EU

EMA. (n.d.-b). Public hearings. Last acsessed April 24, 2023 from: https://www.ema.europa.eu/en/about-us/how-we-work/public-hearings

Esterly, J. S., Steadman, E., & Scheetz, M. H. (2011). Impact of the FDA warning of potential ceftriaxone and calcium interactions on drug use policy in clinical practice. *International Journal of Clinical Pharmacy*, *33*, 537-542.

Evans, D. (2002). Systematic reviews of interpretive research: interpretive data synthesis of processed data. *Australian Journal of Advanced Nursing, The*, *20*(2), 22.

Factor [Def. 1]. (n.d.). In: English Oxford Living Dictionaries. [online] Oxford: Oxford University Press. Accessed from: https://www.lexico.com/en/definition/factor

Faied, M. A., El Wakeel, L., Saad, A. A., & Sabri, N. (2019). Implications of direct healthcare professional communication in Egypt: barriers and preferences of health care professionals. *Archives of Pharmaceutical Sciences Ain Shams University*, *3*(2), 268-276.

Ferrer, R. A., & Klein, W. M. (2015). Risk perceptions and health behavior. *Current opinion in psychology*, *5*, 85-89.

Ferriman, A. (2000). UK licence for cisapride suspended. *British Medical Journal*, *321*(7256), 259-259.

Field, A. (2018). *Discovering statistics using ibm spss statistics*. (5th ed.). SAGE Publications. Kindle Edition.

Finel, B. I., & Lord, K. M. (1999). The surprising logic of transparency. *International Studies Quarterly*, *43*(2), 325–339.

Flood, C., Matthew, L., Marsh, R., Patel, B., Mansaray, M., & Lamont, T. (2015). Reducing risk of overdose with midazolam injection in adults: An evaluation of change in clinical practice to improve patient safety in England. *Journal of Evaluation in Clinical Practice*, *21*(1), 57–66.

Fogler, J., Weber, S., Mahoney, M. R., & Goldschmidt, R. H. (2009). Clinicians' knowledge of 2007 food and drug administration recommendation to discontinue nelfinavir use during pregnancy. *Journal of the International Association of Physicians in AIDS Care*, *8*(4), 249–252.

Francke, A. L., Smit, M. C., de Veer, A. J., & Mistiaen, P. (2008). Factors influencing the implementation of clinical guidelines for health care professionals: A systematic meta-review. *BioMed Central Medical Informatics and Decision Making*, *8*, 1–11.

French, S. D., Green, S. E., O'Connor, D. A., McKenzie, J. E., Francis, J. J., Michie, S., et al. (2012). Developing theory-informed behaviour change interventions to implement evidence

into practice: a systematic approach using the Theoretical Domains Framework. *Implementation Science*, *7*, 38.

Fuller, C., Besser, S., Savage, J., McAteer, J., Stone, S., & Michie, S. (2014). Application of a theoretical framework for behavior change to hospital workers' real-time explanations for noncompliance with hand hygiene guidelines. *American journal of infection control*, *42*(2), 106-110.

Furedi, A. (2000). Social consequences-The public health implications of the 1995'pill scare'. *Human Reproduction Update*, *2*, 59–64.

Gaffield, M. E., Culwell, K. R., & Lee, C. R. (2011). The use of hormonal contraception among women taking anticonvulsant therapy. *Contraception*, *83*(1), 16-29.

Gale, N. K., Heath, G., Cameron, E., Rashid, S., & Redwood, S. (2013). Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BioMed Central Medicine Medical Research Methodology*, *13*(1), 117.

Garashi, H. Y., Steinke, D. T., & Schafheutle, E. I. (2021). A qualitative exploration of pharmacovigilance policy implementation in Jordan, Oman, and Kuwait using Matland's ambiguity-conflict model. *Globalization and Health*, *17*(1), 1-15.

Garashi, H., Steinke, D., & Schafheutle, E. (2022a). Strengths and Weaknesses of the Pharmacovigilance Systems in Three Arab Countries: A Mixed-Methods Study Using the WHO Pharmacovigilance Indicators. *International journal of environmental research and public health*, *19*(5), 2518.

Garashi, H. Y., Steinke, D. T., & Schafheutle, E. I. (2022b). A systematic review of pharmacovigilance systems in developing countries using the WHO pharmacovigilance indicators. *Therapeutic Innovation & Regulatory Science*, 1-27.

Garbutt, J. M., Sterkel, R., Banister, C., Walbert, C., & Strunk, R. C. (2010). Physician and parent response to the FDA advisory about use of over-the-counter cough and cold medications. *Academic pediatrics*, *10*(1), 64-69.

Gibbons, R. D., Brown, C. H., Hur, K., Marcus, S. M., Bhaumik, D. K., Erkens, J. A., et al. (2007). Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *American Journal of Psychiatry, 164*(9), 1356-1363.

Gibson, R., Stacey, N., Drais, E., Wallin, H., Zatorski, W., & Virpi, V. (2012). Risk perception and risk communication with regard to nanomaterials in the workplace. *European Agency for Safety and Health at Work, Luxembourg*.

Glasper, A. (2019). Implementing the NHS patient safety strategy. *British Journal of Nursing*, *28*(15), 1030–1031.

Glessner, M. R., & Heller, D. A. (2002). Changes in related drug class utilization after market withdrawal of cisapride. *The American Journal of Managed Care*, *8*(3), 243-250.

Gliem, J. A., & Gliem, R. R. (2003). Calculating, interpreting, and reporting Cronbach's alpha reliability coefficient for Likert-type scales. *Midwest Research-to-Practice Conference in Adult, Continuing, and Community Education*. (pp.82-88). Ohio: The Ohio State University.

Goedecke, T., Morales, D. R., Pacurariu, A., & Kurz, X. (2018). Measuring the impact of medicines regulatory interventions–systematic review and methodological considerations. *British Journal of Clinical Pharmacology*, *84*(3), 419-433.

Greene, J. C., Caracelli, V. J., & Graham, W. F. (1989). Toward a conceptual framework for mixed-method evaluation designs. *Educational evaluation and policy analysis*, *11*(3), 255-274.

Grigg, S. E., O'Sullivan, J. W., Goldacre, B., & Heneghan, C. (2019). Transparency of the UK medicines regulator: auditing freedom of information requests and reasons for refusal. *British Medical Journal Evidence-Based Medicine*, *24*(1), 20-25.

Grimmelikhuijsen, S., Porumbescu, G., Hong, B., & Im, T. (2013). The effect of transparency on trust in government: A cross-national comparative experiment. *Public Administration Review, 73*(4), 575-586.

Grunig, J. E., & Hunt, T. T. (1984). *Managing public relations*. New York: Holt, Rinehart, and Winston.

Habib, A. S., & Gan, T. J. (2008). The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia. *Journal of Clinical Anesthesia*, *20*(1), 35–39.

Harder, C. K., & Hawboldt, J. J. (2009). Survey of Canadian pharmacists' responses to warnings of potential interactions between ceftriaxone and calcium in IV solutions. *Canadian Journal of Hospital Pharmacy*, *62*(6), 483–489.

Harris, L., Lowes, O., & Angus-Leppan, H. (2020). Treatment decisions in women of childbearing age on valproate. *Acta Neurologica Scandinavica*, *141*(4), 287-293.

Hart, A. (2001). Mann-Whitney test is not just a test of medians: differences in spread can be important. *British Medical Journal* , *323*(7309), 391-393.

Hartford, C. G., Petchel, K. S., Mickail, H., Perez-Gutthann, S., McHale, M., Grana, J. M., et al. (2006). Pharmacovigilance during the pre-approval phases. *Drug Safety*, *29*(8), 657-673.

Hazell, L., & Shakir, S. A. (2006). Under-reporting of adverse drug reactions. *Drug Safety*, *29*(5), 385-396.

Heald, D. A. (2006). Varieties of transparency. In D. H. Christopher Hood (Ed.), *Transparency: The Key to Better Governance?: Proceedings of the British Academy 135.* (pp. 25–43). Oxford: Oxford University Press.

Henney, J. E. (2000). Withdrawal of troglitazone and cisapride. *Journal of the American Medical Association*, *283*(17), 2228-2228.

Hepler, C. D., & Strand, L. M. (1990). Opportunities and responsibilities in pharmaceutical care. *American Journal of Hospital Pharmacy*, *47*(3), 533-543.

Hincapié, M. A., Gallego, J. C., Gempeler, A., Piñeros, J. A., Nasner, D., & Escobar, M. F. (2020). Implementation and usefulness of telemedicine during the COVID-19 pandemic: a scoping review. *Journal of Primary Care & Community Health*, *11*, 2150132720980612.

Hodkinson, A., Tyler, N., Ashcroft, D. M., Keers, R. N., Khan, K., Phipps, D., et al. (2020). Preventable medication harm across health care settings: a systematic review and meta-analysis.
BioMed Central Medicine, *18*(1), 1-13.

Holloway, I. (1997). *Basic concepts for qualitative research*. Oxford: Wiley-Blackwell.

Hong, Q. N., Pluye, P., Bujold, M., & Wassef, M. (2017). Convergent and sequential synthesis designs: implications for conducting and reporting systematic reviews of qualitative and quantitative evidence. *Systematic Reviews*, *6*, 61.

Hong, Q.N, Pluye, P., Fàbregues, S., Bartlett, G., Boardman, F., Cargo, M., et al. (2018). Mixed Methods Appraisal Tool (MMAT), version 2018 user guide. Last accessed April 24, from:
http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127916259/mmat_2018_criteria-manual_2018-08-01_eng.pdf

Hooimeyer, A., Bhasale, A., Perry, L., Fabbri, A., Mohammad, A., McEwin, E., et al. (2020). Regulatory post-market drug safety advisories on cardiac harm: A comparison of four national regulatory agencies. *Pharmacology Research & Perspectives*, *8*(6), e00680.

Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research*, *15*(9), 1277-1288.

Hugman, B. (2006). The Erice Declaration. *Drug safety, 29*(1), 91-93.

Huo, J., Desai, R., Hong, Y. R., Turner, K., Mainous III, A. G., & Bian, J. (2019). Use of social media in health communication: findings from the health information national trends survey 2013, 2014, and 2017. *Cancer Control*, *26*(1), 1073274819841442.

ICH. (1997). *ICH harmonised tripartite guideline testing for carcinogenicity of pharmaceuticals S1B*. last accessed 9 June 2022 from:
https://database.ich.org/sites/default/files/S1B%20Guideline.pdf

ICH. (2003). *ICH harmonised tripartite guideline Stability testing of New drug substances and products Q1A(R2)*. Last accessed April 11, 2023 from:
https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf

ICH. (2004). *ICH Harmonised tripartite guideline–pharmacovigilance planning E2E*. Last accessed April 11, 2023 from: https://database.ich.org/sites/default/files/E2E_Guideline.pdf

ICH. (2005). *ICH harmonised tripartite guideline immunotoxicity studies for human pharmaceuticals S8*. Last accessed October 31, 2022 from: https://database.ich.org/sites/default/files/S8_Guideline_0.pdf

ICH. (2011). *ICH harmonised tripartite guideline guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use S2(R1)*. Last accessed October 31, 2022 from: https://database.ich.org/sites/default/files/S2%28R1%29%20Guideline.pdf

ICH. (2012). *ICH harmonised tripartite guideline periodic benefit-risk evaluation report (pbrer) E2C(R2)*. Last accessed April 13, 2023 from: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

ICH. (2020). *ICH harmonised guideline detection of reproductive and developmental toxicity for human pharmaceuticals S5(R3)*. Last accessed October 31, 2022 from: https://database.ich.org/sites/default/files/S5-R3_Step4_Guideline_2020_0218_1.pdf

Insani, W. N., Whittlesea, C., Alwafi, H., Man, K. K., Chapman, S., & Wei, L. (2021). Prevalence of adverse drug reactions in the primary care setting: A systematic review and meta-analysis. *PLoS One*, *16*(5), e0252161.

International Federation of Pharmaceutical Manufacturers & Associations. (2019). *Considerations for effective regulatory reliance – an Industry perspective*. Last accessed November 30, 2022 from: https://www.ifpma.org/resource-centre/ifpma-position-paper-on-regulatory-reliance/

International Organization for Standardization. (2018). *ISO 18841:2018 Interpreting services — General requirements and recommendations*. Last accessed November 28, 2022 from: https://www.iso.org/standard/63544.html

Ismaile, S. (2014). *Nursing studies: promoters and barriers for adherence to clinical practice guidelines among nurses*. Doctoral dissertation, Durham University, Durham.

Israel, G. D. (1992). *Determining sample size* [Fact sheet PEOD-6]. Last accessed April 19, 2023 from: https://web.archive.org/web/20180423065634id_/http://sociology.soc.uoc.gr/socmedia/papageo/metaptyxiakoi/sample_size/samplesize1.pdf

Japan. Pharmaceuticals and Medical Devices Agency. (n.d.). *The Yellow Letter / Blue Letter*. Last acsessed April 13, 2023 from: https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html

Jha, A. K., Larizgoitia, I., Audera-Lopez, C., Prasopa-Plaizier, N., Waters, H., & Bates, D. W. (2013). The global burden of unsafe medical care: analytic modelling of observational studies. *BRITISH MEDICAL JOURNAL quality & safety*, *22*(10), 809-815.

Johnson, R. B., & Onwuegbuzie, A. J. (2004). Mixed methods research: A research paradigm whose time has come. *Educational Researcher*, *33*(7), 14-26.

Jones, L. A., & Thomas, R. H. (2017). Sudden death in epilepsy: Insights from the last 25 years. *Seizure*, *44*, 232-236.

Jones, P. S., Lee, J. W., Phillips, L. R., Zhang, X. E., & Jaceldo, K. B. (2001). An adaptation of Brislin's translation model for cross-cultural research. *Nursing research, 50*(5), 300-304.

Kaeding, M., Schmälter, J., & Klika, C. (2017). *Pharmacovigilance in the European Union: practical implementation across member states*. Wiesbaden, Germany: Springer Nature.

Kaiser, H. F. (1960). The application of electronic computers to factor analysis. *Educational and Psychological Measurement*, *20*(1), 141-151.

Kaiser, H. F., & Rice, J. (1974). Little jiffy, mark IV. *Educational and Psychological Measurement*, *34*(1), 111-117.

Kaiser, K. (2009). Protecting respondent confidentiality in qualitative research. *Qualitative Health Research*, *19*(11), 1632-1641.

Kanyongo, G. Y. (2005). Determining the correct number of components to extract from a principal components analysis: a Monte Carlo study of the accuracy of the scree plot. *Journal of Modern Applied Statistical Methods*, *4*(1), 13.

Kaplan, A. M., & Haenlein, M. (2010). Users of the world, unite! The challenges and opportunities of Social Media. *Business Horizons*, *53*(1), 59-68.

Karpel, J. P., Peters, J. I., Szema, A. M., Smith, B., & Anderson, P. J. (2009). Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting β-agonists. *Annals of Allergy, Asthma and Immunology*, *103*(4), 304–310.

KDFC (2016). *ADR Reporting Form* [Online]. Kuwait: KDFC. Last accessed November, 1, 2022 from: http://www.emailmeform.com/builder/form/X06afe9fcL8eC0K257Ixmq

Kesselheim, A. S., McGraw, S. A., Dejene, S. Z., Rausch, P., Dal Pan, G. J., Lappin, B. M. et al. (2017). Patient and physician perceptions of drug safety information for sleep aids: a qualitative study. *Drug Safety*, *40*(6), 531-542.

Khan, L. M. (2013). Comparative epidemiology of hospital-acquired adverse drug reactions in adults and children and their impact on cost and hospital stay–a systematic review. *European Journal of Clinical Pharmacology*, *69*(12), 1985-1996.

Kieft,C., Alhmad, F., & Azim, F. (2012). Kuwait health sector report 2012. Last accessed April 7, 2018 from: https://www.tfhc.nl/wp-content/uploads/2016/07/2012-Embassy-Kuwait-Kuwait-Health-Sector-Report.pdf

Kivunja, C., & Kuyini, A. B. (2017). Understanding and Applying Research Paradigms in Educational Contexts. *International Journal of Higher Education*, *6*(5), 26.

Kline, P. (1986). *A handbook of test construction: Introduction to psychometric design*. London: Methuen.

Kloet, M. A., Lohr, B. R., Smithburger, P. L., Seybert, A. L., & Kane-Gill, S. L. (2017). Prospective assessment of inpatient boxed warning prescriber adherence. *Journal of Patient Safety*, *13*(1), 25-30.

Koch, T. (1995). Interpretive approaches in nursing research: The influence of Husserl and Heidegger. *Journal of Advanced Nursing*, *21*, 827-836.

Koo, T. K., & Li, M. Y. (2016). A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *Journal of Chiropractic Medicine*, *15*(2), 155-163.

Kowitt, S. D., Schmidt, A. M., Hannan, A., & Goldstein, A. O. (2017). Awareness and trust of the FDA and CDC: Results from a national sample of US adults and adolescents. *PLOS ONE*, *12*(5), e0177546.

Kraus, C. N., Baldwin, A. T., & McAllister, R. G. (2013). Improving the effect of FDA-mandated drug safety alerts with Internet-based continuing medical education. *Current Drug Safety*, *8*(1), 11–16.

Kroll, T., & Neri, M. (2009). Designs for mixed methods research. *Mixed Methods Research for Nursing and the Health Sciences*, *31*, 31-49.
Krueger, R. A. & Casey, M. A. (2015). *Focus groups a practical guide for applied research*. (5th ed.). California: SAGE.

Kuckartz, U., & Rädiker, S. (2019). *Analyzing qualitative data with MAXQDA Text, Audio, and Video*. Cham: Springer Nature Switzerland AG.

Kuhn, T. S. (1970). *The structure of scientific revolutions*. (2nd ed.). Chicago: Univartsy of Chicago Press.

Kuula, L. S., Backman, J. T., & Blom, M. L. (2022). Healthcare costs and mortality associated with serious fluoroquinolone-related adverse reactions. *Pharmacology Research & Perspectives*, *10*(2), e00931.

Kuwait. CMS. (2018). *Top 20 Items by Quantity (April/2017 to April/2018)*.Unpublished records. Retrieved from the Central Medical Stores on the 7th of April, 2019.

Kuwait. CMS. (2019). *Top 20 Items by Quantity (April/2018 to April/2019).* Unpublished records. Retrieved from the Central Medical Stores on the 7th of April, 2019.

Kuwait. MOH. (2015). *Annual Health Report*. (52nd ed). Kuwait: MOH.

Kuwait. MOH. (2018). *Labour Force Statistics.* (39th ed.). Kuwait: MOH.

Kuwait. MOH. (2022). *Ministerial Decree Number 158 For the Year 2022*. Kuwait: MOH.

Kuwait. MOH. (n.d.). *Drug and Food Control Administration*. Last accessed April 22, 2023 from: https://www.moh.gov.kw/en/pages/DRUGCA.aspx

Kuwait. Public Authority for Civil Information (2022). *Statistics Services System*. Last accessed November 30, 2022 from: https://www.paci.gov.kw/stat/Default.aspx

Laerd Statistics (2015a). *Kruskal-Wallis H test using SPSS statistics*. Last accessed April 19, 2023 from: https://statistics.laerd.com/premium/spss/kwht/kruskal-wallis-test-in-spss.php

Laerd Statistics (2015b). *Mann-Whitney U test using SPSS. statistics*. Last accessed April 19, 2023 from: https://statistics.laerd.com/premium/spss/mwut/mann-whitney-test-in-spss.php

Laerd Statistics (2016). *Test of two proportions using SPSS statistics*. Last accessed April 19, 2023 from: https://statistics.laerd.com/premium/spss/ttp/test-of-two-proportions-in-spss.php

Laker, E. A. O., Arinaitwe, A., Owarwo, N., Onzia, A., Nasasira, B., Wailagala, A., et al. (2020). The potential teratogenicity alert for women conceiving on dolutegravir-based regimens: An assessment of risk communication by an urban HIV clinic in Uganda and choices made by women. *Drug Safety*, *43*(11), 1133-1140.

Lawther, L., Dolk, H., Sinclair, M., & Morrow, J. (2018). The preconception care experiences of women with epilepsy on sodium valproate. *Seizure*, *59*, 82-89.

Lee, Y., & Li, J. Y. Q. (2021). The role of communication transparency and organizational trust in publics' perceptions, attitudes and social distancing behaviour: A case study of the COVID-19 outbreak. *Journal of Contingencies and Crisis Management*, *29*(4), 368-384.

Lemay, J., Alsaleh, F. M., Al-Buresli, L., Al-Mutairi, M., Abahussain, E. A., & Bayoud, T. (2018). Reporting of Adverse Drug Reactions in Primary Care Settings in Kuwait: A Comparative Study of Physicians and Pharmacists. *Medical Principles and Practice*, *27*(1), 30-38.

Leong Wai Yeen, J., Salek, S., & Walker, S. (2014). Strategy for communicating benefit-risk decisions: A comparison of regulatory agencies' publicly available documents. *Frontiers in Pharmacology*, *5*, 269.

Leong, J., Salek, S., & Walker, S. (2015). *Benefit-risk assessment of medicines: the development and application of a universal framework for decision-making and effective communication*. Singapore: Springer International Publishing.

Li, S., Cao, M., & Zhu, X. (2019). Evidence-based practice: Knowledge, attitudes, implementation, facilitators, and barriers among community nurses-systematic review. *Medicine*, *98*(39), e17209–e17209.

Lincoln, Y., & Guba, E. (1985). *Naturalistic inquiry*. California: Sage Publications.

Lipworth, W., Taylor, N., & Braithwaite, J. (2013). Can the theoretical domains framework account for the implementation of clinical quality interventions?. *BioMed Central Health Services Research*, *13*, 530.

Lugtenberg, M., Zegers-van Schaick, J. M., Westert, G. P., & Burgers, J. S. (2009). Why don't physicians adhere to guideline recommendations in practice? An analysis of barriers among Dutch general practitioners. *Implementation Science*, *4*(1), 54

Macfarlane, A., & Greenhalgh, T. (2018). Sodium valproate in pregnancy: what are the risks and should we use a shared decision-making approach?. *BioMed Central Pregnancy and Childbirth*, *18*(1), 1-11.

Mackenzie, N., & Knipe, S. (2006). Research dilemmas: Paradigms, methods and methodology. *Issues in Educational Research*, *16*(2), 193-205.

Madison, T., Donner, B., Mutter, R., Mingrino, R., & Alvaro, G. (2019). Effectiveness of risk minimization measures to prevent pregnancy exposure to mycophenolate-containing medicines in Europe. *Pharmaceutical Medicine*, *33*, 395-406.

Manasse Jr, H. R. (1989). Medication use in an imperfect world: drug misadventuring as an issue of public policy, part 1. *American Journal of Health-System Pharmacy*, *46*(5), 929-944.

Matowe, L., Abahussain, E. A., Al-Saffar, N., Bihzad, S. M., Al-Foraih, A., & Al- Kandery, A. A. (2006). Physicians' perceptions and expectations of pharmacists' professional duties in government hospitals in Kuwait. *Medical Principles and Practice*, *15*(3), 185-189.

Matsuoka, K., Ishikawa, H., Nakayama, T., Honzawa, Y., Maemoto, A., Hirai, F., et al. (2021). Physician–patient communication affects patient satisfaction in treatment decision-making: A structural equation modelling analysis of a web-based survey in patients with ulcerative colitis. *Journal of gastroenterology*, *56*(9), 843-855.

Mays, N., Pope, C., & Popay, J. (2005). Systematically reviewing qualitative and quantitative evidence to inform management and policy-making in the health field. *Journal of Health Services Research & Policy*, *10*(1_suppl), 6–20.

Mazor, K. M., Andrade, S. E., Auger, J., Fish, L., & Gurwitz, J. H. (2005). Communicating safety information to physicians: an examination of dear doctor letters. *Pharmacoepidemiology and Drug Safety*, *14*(12), 869-875.

McGraw, K. O., & Wong, S. P. (1996). Forming inferences about some intraclass correlation coefficients. *Psychological Methods*, *1*(1), 30.

McGuire, W. J. (1984). Public communication as a stratey for inducing health-promoting behaviorial change. *Preventive Medicine*.

Mcilfatrick, S., Sullivan, K., & McKenna, H. (2003). Exploring the patient's experience of a day hospital chemotherapy service: preliminary fieldwork. *European Journal of Oncology Nursing*, *7*(3), 197-199.

McNaughton, R., Huet, G., & Shakir, S. (2014). An investigation into drug products withdrawn from the EU market between 2002 and 2011 for safety reasons and the evidence used to support the decision-making. *British Medical Journal Open*, *4*(1), e004221.

MedDRA (2019). *Introductory guide MedDRA 22.0*. Last accessed August 31, 2019 from: https://www.meddra.org/sites/default/files/guidance/file/intguide_22_0_english.pdf

Medlinskiene, K., Tomlinson, J., Marques, I., Richardson, S., Stirling, K., & Petty, D. (2021). Barriers and facilitators to the uptake of new medicines into clinical practice: a systematic review. *BioMed Central Health Services Research*, *21*(1).

Men, L. R., & Stacks, D. (2014). The Effects of Authentic Leadership on Strategic Internal Communication and Employee-Organization Relationships. *Journal of Public Relations Research*, *26*(4), 301–324.

Metz, ed. (1993). *Persian Gulf States: A Country Study*. Washington: GPO for the Library of Congress.

Meyboom, R. H. B. (1997). Good practice in the postmarketing surveillance of medicines. *Pharmacy World and Science*, *19*, 186-190.

Mheidly, N., & Fares, J. (2020). Leveraging media and health communication strategies to overcome the COVID-19 infodemic. *Journal of Public Health Policy*, *41*(4), 410-420.

Michie, S., Johnston, M., Abraham, C., Lawton, R., Parker, D., & Walker, A. (2005). Making psychological theory useful for implementing evidence based practice: a consensus approach. *British Medical Journal Quality & Safety*, *14*(1), 26-33.

Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., et al. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: Building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine*, *46*(1), 81-95.

Michie, S., Van Stralen, M. M., & West, R. (2011). The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science*, *6*(1), 1-12.

Miller, T., & Bell, L. (2012). Consenting to what? Issues of access, gate-keeping and 'informed'consent. In T. Miller, M. Birch, M. Mauthner & J. Jessop (Eds), *Ethics in qualitative research*. (2nd ed., pp. 53-69). SAGE Publications Ltd.

Mokni, N., Fathi, N., Mupas, M., Moussa, S., Mustafa, A., Abdeljawad, T., et al. (2022). Reproductive Health, Social and Financial Impact of Valproic Acid Withdrawal for Childbearing Epileptic Saudi Woman. *Journal of Neurology and Neuroscience,* 13(2: 413).

Møllebæk, M., Kaae, S., De Bruin, M. L., Callréus, T., Jossan, S., & Hallgreen, C. E. (2019). The effectiveness of direct to healthcare professional communication – A systematic review of communication factor studies. *Research in Social and Administrative Pharmacy*, *15*(5), 475–482.

Moorhead, S. A., Hazlett, D. E., Harrison, L., Carroll, J. K., Irwin, A., & Hoving, C. (2013). A new dimension of health care: Systematic review of the uses, benefits, and limitations of social media for health communication. *Journal of medical Internet research*, *15*(4), e1933.

Moreland, A., & Denham, J. (2019). Disseminating the research findings. *Research Methods in Physical Activity and Health*, 324–329.

Morrato, E. H., Curbow, B., Crum, R. M., Nowels, C., & Feinleib, M. (2008). Communicating drug risk to physicians: challenges and opportunities. *International Journal of Risk & Safety in Medicine*, *20*(3), 143-154.

Morrow, A., Chan, P., Tiernan, G., Steinberg, J., Debono, D., Wolfenden, L., et al. (2022). Building capacity from within: Qualitative evaluation of a training program aimed at upskilling healthcare workers in delivering an evidence-based implementation approach. *Translational Behavioral Medicine*, *12*(1).

Morse, J. M., & Niehaus, L. (2009). *Mixed method design: principles and procedures*. New York: Routledge.

Mossialos, E., Cheatley, J., Reka, H., Alsabah, A., & Patel, N. (2018). *Kuwait Health System Review*. London: LSE.

Moussa, M. A., Bayoumi, A., Al-Khars, A. A., & Thulesius, O. (1985). Adverse drug reaction monitoring in Kuwait (1981–1984). *The Journal of Clinical Pharmacology*, *25*(3), 176-181

Mulrow, C., Langhorne, P., & Grimshaw, J. (1997). Integrating heterogeneous pieces of evidence in systematic reviews. *Annals of Internal Medicine*, *127*(11), 989–995.

Mulryan, D., McIntyre, A., McDonald, C., Feeney, S., & Hallahan, B. (2018). Awareness and documentation of the teratogenic effects of valproate among women of child-bearing potential. *BJPsych Bulletin*, *42*(6), 233-237.

Nabhan, M., Elraiyah, T., Brown, D. R., Dilling, J., LeBlanc, A., Montori, V. M., et al. (2012). What is preventable harm in healthcare? A systematic review of definitions. *BioMed Central Health Services Research*, *12*(1), 1-8.

Nakayama, T. (2018). Evidence-based risk and benefit communication for shared decision making. *Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan*, *138*(3), 331-334.

Nathai-Balkissoon, M., & Pun, K. F. (2016). Factor Analysis of Elements Influencing Occupational Safety and Health Management System Development in Trinidad and Tobago. *West Indian Journal of Engineering*, *38*(2).

National Bureau for Academic & Education Quality Assurance (2019). *Universities List*. Last accessed October 3, 2019 from: http://nbaq.edu.kw/en/category/universities-lists/

Nebeker, J. R., Barach, P., & Samore, M. H. (2004). Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine*, *140*(10), 795-801.

NHS England. (2021). Letter to Women and Girls Taking Sodium Valproate. Last accessed April 19, 2023 from: https://www.england.nhs.uk/publication/letter-to-women-and-girls-taking-sodium-valproate/

NHS England. (2022). 2022/23 Community Pharmacy Contractual Framework National Clinical Audit Reducing the Potential for Harm from Valproate Prescribing in Patients of

Childbearing Age who are Biologically Able to be Pregnant. Last accessed April 19, 2023 from: https://www.england.nhs.uk/wp-content/uploads/2022/11/B2089-22-23-community-pharmacy-contractual-framework-national-clinical-audit.pdf

NHS England. (n.d.). Introducing National Patient Safety Alerts. Last accessed April 24, 2023 from: https://www.england.nhs.uk/patient-safety/national-patient-safety-alerting-committee/

Noom, M. J., Deković, M., & Meeus, W. (2001). Conceptual analysis and measurement of adolescent autonomy. *Journal of Youth and Adolescence*, *30*(5), 577-595.

Nualdaisri, P., Corlett, S. A., & Krska, J. (2021). Provision and need for medicine information in Asia and Africa: a scoping review of the literature. *Drug Safety*, *44*(4), 421-437.

Nunnally, J. C. (1978). An overview of psychological measurement. *Clinical Diagnosis of Mental Disorders*, 97-146.

O'Connor, N. R. (2010). FDA boxed warnings: how to prescribe drugs safely. *American Family Physician, 81*(3), 298-303.

O'Connor, D., Green, S., Higgins, J. P. (Eds). (2008). Defining the review question and developing criteria for including studies. In J. P. Higgins & S. Green (Eds.), *Cochrane handbook for systematic reviews of interventions*. (pp. 83-94). West Sussex: John Wiley & Sons Ltd.

Oliveira, M., Bitencourt, C., Teixeira, E., & Santos, A. C. (2013). Thematic content analysis: Is there a difference between the support provided by the MAXQDA® and NVivo® software packages. In *Proceedings of the 12th European Conference on Research Methods for Business and Management Studies* (pp. 304-314).

Onakpoya, I. J., Heneghan, C. J., & Aronson, J. K. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: A systematic review of the world literature. *BioMed Central Medicine*, *14*(1), 1-11.

Osanloo, A., & Grant, C. (2016). Understanding, selecting, and integrating a theoretical framework in dissertation research: Creating the blueprint for your "house". *Administrative Issues Journal: Connecting Education, Practice, and Research*, *4*(2).

Oscanoa, T. J., Lizaraso, F., & Carvajal, A. (2017). Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. *European Journal of Clinical Pharmacology*, *73*, 759-770.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews*, *10*(1), 1-11.

Paksaite, P., Crosskey, J., Sula, E., West, C., & Watson, M. (2021). A systematic review using the Theoretical Domains Framework to identify barriers and facilitators to the adoption of prescribing guidelines. *International Journal of Pharmacy Practice*, *29*(1), 3-11.

Pal, S. N., Duncombe, C., Falzon, D., & Olsson, S. (2013). WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug Safety*, *36*(2), 75-81.

Panagioti, M., Khan, K., Keers, R. N., Abuzour, A., Phipps, D., Kontopantelis, E., et al. (2019). Prevalence, severity, and nature of preventable patient harm across medical care settings: Systematic review and meta-analysis. *British Medical Journal, 366.*

Pandey, S. C., & Patnaik, S. (2014). Establishing reliability and validity in qualitative inquiry: A critical examination. *Jharkhand Journal of Development and Management Studies*, *12*(1), 5743-5753.

Patel, T. K., & Patel, P. B. (2018). Mortality among patients due to adverse drug reactions that lead to hospitalization: a meta-analysis. *European Journal of Clinical Pharmacology*, *74*(6), 819-832.

Patton, M. Q. (2015). *Qualitative research & evaluation methods*. (4th ed.). SAGE Publications. Kindle Edition.

PCNE. (2020). *Classification for drug related problems*. Last acsessed April 10, 2023 from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf

Perry, L. T., Bhasale, A., Fabbri, A., Lexchin, J., Puil, L., Joarder, M., & et al. (2020). A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States-2007 to 2016. *Pharmacoepidemiology and Drug Safety*, *29*(9), 1054-1063.

Peters, T., Soanes, N., Abbas, M., Ahmad, J., Delumeau, J. C., Herrero-Martinez, E., et al. (2021). Effective pharmacovigilance system development: EFPIA-IPVG consensus recommendations. *Drug Safety*, *44*(1), 17-28.

Piening, S., De Graeff, P. A., Straus, S. M. J. M., Haaijer-Ruskamp, F. M., & Mol, P. G. M. (2013). The additional value of an e-mail to inform healthcare professionals of a drug safety issue: A randomized controlled trial in the Netherlands. *Drug Safety*, *36*(9), 723–731.

Piening, S., Haaijer-Ruskamp, F. M., de Graeff, P. A., Straus, S. M., & Mol, P. G. (2012). Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications. *Drug Safety*, *35*(11), 1061-1072.

Piening, S., Haaijer-Ruskamp, F. M., de Vries, J. T., van der Elst, M. E., de Graeff, P. A., Straus, S. M., & Mol, P. G. (2012). Impact of safety-related regulatory action on clinical practice. *Drug Safety*, *35*(5), 373-385.

Pignatti, F., Ashby, D., Brass, E. P., Eichler, H. G., Frey, P., Hillege, H. L., et al. (2015). Structured frameworks to increase the transparency of the assessment of benefits and risks of medicines: current status and possible future directions. *Clinical Pharmacology & Therapeutics*, *98*(5), 522-533.

Plough, A., & Krimsky, S. (1987). The emergence of risk communication studies: Social and political context. *Science, Technology, & Human Values*, *12*(3/4), 4-10.

Pluye, P., Bengoechea, E.G., Granikov, V., Kaur, N., & Tang, D. L. (2018). A world of possibilities in mixed methods: Review of the combinations of strategies used to integrate qualitative and quantitative phases, results, and data. *International Journal of Multiple Research Approaches*, *10*(1), 41-56.

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., et al. (2006). Guidance on the conduct of narrative synthesis in systematic reviews. *A Product from the ESRC Methods Programme Version*, *1*, b92.

Qato, D. M. (2018). Current state of pharmacovigilance in the Arab and Eastern Mediterranean region: results of a 2015 survey. *International Journal of Pharmacy Practice*, *26*(3), 210-221.

Ralph Edwards, I. (2017). Causality assessment in pharmacovigilance: still a challenge. *Drug Safety*, *40*(5), 365-372.

Raosoft. *Sample Size Calculator*. 2004. Last accessed October 14, 2022 from: http://www.raosoft.com/samplesize.html

Rawlins, B. (2008). Give the emperor a mirror: toward developing a stakeholder measurement of organizational transparency. *Journal of Public Relations Research*, *21*(1), 71–99.

Rawlins, M. D. (1987). Risk-benefit decisions in licensing changes. In S.R. Walker & A.W. Asscher (Eds.), *Medicines and risk/benefit decisions*. (pp. 137-141). Dordrecht: Springer.

Reed, D. B., Gough, J. E., Ho, J. D., & Brown, L. H. (1999). Prehospital consideration of sildenafil-nitrate interactions. *Prehospital Emergency Care*, *3*(4), 306–309.

Research [Def. 1]. (n.d.). In: English Oxford Living Dictionaries. [online] Oxford: Oxford University Press. Last accessed June 29, 2018 from: https://en.oxforddictionaries.com/definition/research

Richards, J. R., Weiss, S. J., Bretz, S. W., Schneir, A. B., Rinetti, D., & Derlet, R. W. (2003). The effects of the FDA warning on the use of droperidol by US emergency physicians. *The California Journal of Emergency Medicine*, *4*(1), 3.

Richardson, L. P., Lewis, C. W., Casey-Goldstein, M., McCauley, E., & Katon, W. (2007). Pediatric primary care providers and adolescent depression: A qualitative study of barriers to treatment and the effect of the black box warning. *Journal of Adolescent Health*, *40*(5), 433–439.

Rick, NG. (2004). Drugs from discovery to approval (second edition). New Jersey: John Wiley & Sons, Inc.

Riemann, L., Lubasch, J. S., Heep, A., & Ansmann, L. (2021). The Role of Health Literacy in Health Behavior, Health Service Use, Health Outcomes, and Empowerment in Pediatric

Patients with Chronic Disease: A Systematic Review. *International Journal of Environmental Research and Public Health*, *18*(23), 12464.

Rothkopf, D. J. (2003). When the buzz bites back. *The Washington Post*, *11*, B1-B5.

Runciman, W., Hibbert, P., Thomson, R., Van Der Schaaf, T., Sherman, H., & Lewalle, P. (2009). Towards an International Classification for Patient Safety: key concepts and terms. *International Journal for Quality in Health Care*, *21*(1), 18-26.

Saad, M., Cassagnol, M., & Ahmed, E. (2010). The impact of FDA's warning on the use of antipsychotics in clinical practice: A survey. *Consultant Pharmacist*, *25*(11), 739–744.

Sabblah, G. T., Darko, D. M., Asamoa-Amoakohene, A., & Ashie, A. (2016). The effectiveness of dear healthcare professional letters as a risk minimization tool in Ghana. *African Journal of Pharmacy and Pharmacology*, *10*(33), 681-689.

Safety. (2022). In *Oxford English Dictionary*. Last acsessed April 10, 2023 from: https://www-oed-com.ezproxy.herts.ac.uk/search?searchType=dictionary&q=safety&_searchBtn=Search

Sandelowski, M. (1994). Focus on qualitative methods. The use of quotes in qualitative research. *Research in Nursing & Health*, *17*(6), 479–482.

Sandsdalen, T., Rystedt, I., Grøndahl, V. A., Hov, R., Høye, S., & Wilde-Larsson, B. (2015). Patients' perceptions of palliative care: adaptation of the Quality from the Patient's Perspective instrument for use in palliative care, and description of patients' perceptions of care received.
BioMed Central Palliative Care, *14*(1), 1-14.

Shneker, B. F., Cios, J. S., & Elliott, J. O. (2009). Suicidality, depression screening, and antiepileptic drugs Reaction to the FDA alert. *Neurology*, *72*(11), 987–991.

Shroukh, W. A., Steinke, D. T., & Willis, S. C. (2020). Risk management of teratogenic medicines: A systematic review. *Birth Defects Research*, *112*(20), 1755-1786.

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420.

Sibanyoni, A. U., Joubert, M., & Naidu, K. (2022). Are female bipolar patients of reproductive age aware of the teratogenic risk of sodium valproate? A qualitative study. *South African Journal of Psychiatry*, *28*, 1719.

Sinclair, M., Ashkanasy, N. M., & Chattopadhyay, P. (2010). Affective antecedents of intuitive decision making. *Journal of Management & Organizatio*n, *16*(3), 382-398.

Skivington, K., Matthews, L., Simpson, S. A., Craig, P., Baird, J., Blazeby, J. M., et al. (2021). A new framework for developing and evaluating complex interventions: Update of Medical Research Council guidance. *British Medical Journal*, *374*, n2061.

Slawomirski, L., Auraaen, A., & Klazinga, N. S. (2017). The economics of patient safety: strengthening a value-based approach to reducing patient harm at national level.

Slovic, P. (1987). *Perception of risk. Science, 236*(4799), 280-285.

Slovic, P. (1993). Perceived risk, trust and democracy. *Risk Analysis*, *13*(6), 675–682.

Slovic, P., & Peters, E. (2006). Risk perception and affect. *Current Directions in Psychological Science, 15*(6), 322-325.

Slovic, P., Finucane, M. L., Peters, E., & MacGregor, D. G. (2004). Risk as analysis and risk as feelings: Some thoughts about affect, reason, risk, and rationality. *Risk Analysis: An International Journal*, 24(2), 311-322.

Smalley, W., Shatin, D., Wysowski, D. K., Gurwitz, J., Andrade, S. E., Goodman, M., et al. (2000). Contraindicated use of cisapride: impact of food and drug administration regulatory action. *Journal of the American Medical Association*, *284*(23), 3036-3039.

Smith, F. (2010). *Conducting your pharmacy practice research project: A step-by-step approach*. London, Chicago: Pharmaceutical press.

Smith, J., & Osborn, M. (2008). Interpretative phenomenological analysis. In J. A. Smith (Ed.), *Qualitative psychology a practical guide to research methods*. (2nd ed., pp. 53-80). London: SAGE.

Smith, JA., Flowers, P. & Larkin, M. (2009). *Interpretative phenomenological analysis* . SAGE Publications. Kindle Edition.

Smollin, C. G., Fu, J., & Levin, R. (2016). Recognition and knowledge of medications with black box warnings among pediatricians and emergency physicians. *Journal of Medical Toxicology, 12*(2), 180-184.

Spicer, N. (2018). Combining qualitative and quantitative methods. In C. Seale (Ed.), *Researching society and culture*. (4th ed.). (pp.305-320). SAGE. Kindle Edition.

Taherdoost, H. (2016). Validity and reliability of the research instrument; how to test the validation of a questionnaire/survey in a research; How to test the validation of a questionnaire/survey in a research. *International Journal of Academic Research in Management*, *5*(3), 28-36.

Teddlie, C., & Tashakkori, A. (2010). Overview of contemporary issues in mixed methods research. In A. Tashakkori & C. Teddlie (Eds.), *Sage handbook of mixed methods in social and behavioral research*. (2nd ed., pp. 1-44). California: SAGE Publications, Inc.

The European Commission. (2012). *Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council*. Brussels. (President JM Barroso).

The European Parliament and the Council of the European Union. (2010). *Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 Amending, as Regards Pharmacovigilance, Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use*. Strasbourg. (Presidents J. Buzek & O. Chastel).

The European Parliament and the Council of the European Union. (2001). *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community Code Relating to Medicinal Products for Human Use*. Last accessed April 11, 2023 from: https://ec.europa.eu/health/system/files/2016-11/dir_2001_83_cons_2012_en_0.pdf

The League of Arab States. (2014). *Guideline on good pharmacovigilance practices (GVP) For Arab Countries*. Last acsessed April 19, 2023 from: https://who-umc.org/media/164038/the-good-pharmacovigilance-practice-for-arab-countries-v3-12-2015.pdf

The National Center for Biomedical Ontology. (2018). *Medical Dictionary for Regulatory Activities Terminology (MedDRA)*. Last accessed August 31, 2019 from: http://bioportal.bioontology.org/ontologies/MEDDRA/?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMEDDRA%2F10043275&jump_to_nav=true

The National Center for Biomedical Ontology. (2022). *Medical Dictionary for Regulatory Activities Terminology (MedDRA)*. Last accessed November 30, 2022 from: https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMEDDRA%2F10018849

Théophile, H., Miremont-Salamé, G., Robinson, P., Moore, N., Bégaud, B., & Haramburu, F. (2011). Relevance of a "dear Doctor letter" to alert healthcare providers to new recommendations for vitamin D administration. *European Journal of Clinical Pharmacology*, *67*(7), 681–686.

Thomas, G. (2016). *How to do your case study*. SAGE Publications. Kindle Edition.

Tolich, M. (2004). Internal confidentiality: When confidentiality assurances fail relational informants. *Qualitative Sociology*, *27*(1), 101-106.

Toussi, M., Isabelle, B., Tcherny-Lessenot, S., de Voogd, H., Dimos, V., & Kaplan, S. (2021). Effectiveness of risk minimisation measures for valproate: A cross-sectional survey among physicians in Europe. *Pharmacoepidemiology and Drug Safety*, *30*(3), 283-291.

UK. MHRA. (2018). *Valproate Pregnancy Prevention Programme: Actions Required Now from GPs, Specialists, and Dispensers*. Last accessed April 19, 2023 from: https://www.gov.uk/drug-safety-update/valproate-pregnancy-prevention-programme-actions-required-now-from-gps-specialists-and-dispensers

UK. MHRA. (2021). *Guide for Healthcare Professionals Information on the Risks of Valproate Use In Girls (of Any Age) and Women of Childbearing Potential (Epilim, Depakote, Convulex, Episenta, Epival, Kentlim, Orlept, Sodium Valproate, Syonell, Valpal, Belvo & Dyzantil)*. Last accessed April 19, 2023 from: https://www.medicines.org.uk/emc/rmm/1203/Document

UK. MHRA. (n.d.). *MHRA Central Alerting System NHS*. Last acsessed April 12, 2023 from: https://www.cas.mhra.gov.uk/Home.aspx

UK. NICE. (2014). *Developing NICE Guidelines: the Manual*. Last accessed March 26, 2022, from: https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

UK. NICE. (2022). *Pneumonia in Adults: Diagnosis and Management*. Last accessed April 24, 2023 from https://www.nice.org.uk/guidance/ng138/resources/pneumonia-communityacquired-antimicrobial-prescribing-pdf-66141726069445

UK. Secretary of State for Health (Ed.). (2008). *High Quality Care for All: NHS Next Stage Review Final Report*. (Vol. 7432). London: The Stationery Office.

UNESCO. (n.d.). *Kuwait*. Last accessed April 3, 2018 from: http://uis.unesco.org/country/KW

United Nations. (2017). *Revision of World Population Prospects*. Last accessed April 2, 2018 from: https://esa.un.org/unpd/wpp/

Uptake [Def. 1]. (n.d.). In: English Oxford Living Dictionaries. [online] Oxford: Oxford University Press. Accessed from: https://www.lexico.com/en/definition/uptake

US pharmacopeia (2010). *〈1066〉 Physical Environments That Promote Safe Medication Use*. Last acsessed April 19, 2023 from: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/c1066.pdf

US. FDA. (2005). *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*. Maryland.

US. FDA. (2007). *Guidance Drug Safety Information – FDA's Communication to the Public*. Last accessed September 4, 2019 from: https://www.fda.gov/media/71668/download

US. FDA. (2009). *Guidance for Industry SPL Standard for Content of Labeling Technical Qs & As DRAFT GUIDANCE*. Last acsessed April 11, 2023 from: https://www.fda.gov/media/71211/download

US. FDA. (2011). *Communicating Risks and Benefits: An Evidence-Based User's Guide*. Maryland: US FDA.

US. FDA. (2015). *CDER's Drug Safety Communications: Ensuring postmarket safety*. Last acsessed April 22, 2023 from: https://www.fda.gov/drugs/news-events-human-drugs/cders-drug-safety-communications-ensuring-postmarket-safety

US. FDA. (2016). *Guidance Outlines How FDA Communicates, Prioritizes Drug Safety Issues*. Last acsessed April 13, 2023 from: https://www.fda.gov/drugs/special-features/guidance-outlines-how-fda-communicates-prioritizes-drug-safety-issues

US. FDA. (2018a). *FDA Drug Safety Communication: Voluntary Market Withdrawal of Xigris [Drotrecogin Alfa (Activated)] due to Failure to Show a Survival Benefit*. Last

acsessed April 11, 2023 from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-voluntary-market-withdrawal-xigris-drotrecogin-alfa-activated-due

US. FDA. (2018b). *Primus Announces a Voluntary Nationwide Recall of All Lots Within Expiry of Prescription Medical Food Limbrel® Due to Rare but Serious and Reversible Adverse Events While Seeking FDA's Cooperation to Restore Access for Patients with Medical Necessity.* Last accessed November 9, 2022 from: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/primus-announces-voluntary-nationwide-recall-all-lots-within-expiry-prescription-medical-food

US. FDA. (2020). *FDA Requests Removal of All Ranitidine Products (Zantac) from the Market*. Last accessed November 9, 2022 from: https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

US. FDA. (2021). *Risk Evaluation and Mitigation Strategies | REMS*. Last acsessed April 11, 2023 from: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems

US. FDA. (2022). *FDA Approval of Lymphoma Medicine Ukoniq (Umbralisib) is Withdrawn due to Safety Concerns*. Last accessed November 9, 2022 from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-approval-lymphoma-medicine-ukoniq-umbralisib-withdrawn-due-safety-concerns

US. Institute for Public Relations. (1999). *Guidelines for Measuring Relationships in Public Relations*. Last acsessed April 25, 2023 from: https://painepublishing.com/measurementadvisor/wp-content/uploads/2014/04/Guidelines_Measuring_Relationships.pdf

US. National Institute on Drug Abuse. (1990). *The Collection and Interpretation of Data from Hidden Populations*. Last accessed April 25, 2023 from: https://www.ojp.gov/pdffiles1/Digitization/128609-128619NCJRS.pdf

US. National Research Council. (1989). *Improving Risk Communication*. Washington DC: National Academies Press.

Vargha, A., & Delaney, H. D. (1998). The Kruskal-Wallis test and stochastic homogeneity. *Journal of Educational and Behavioral Statistics*, *23*(2), 170-192.

Vernooij, R. W. M., Sanabria, A. J., Solà, I., Alonso-Coello, P., & Martínez García, L. (2014). Guidance for updating clinical practice guidelines: A systematic review of methodological handbooks. *Implementation Science*, *9*(1), 1–9.

Weatherburn, C. J., Guthrie, B., Dreischulte, T., & Morales, D. R. (2020). Impact of medicines regulatory risk communications in the UK on prescribing and clinical outcomes: Systematic review, time series analysis and meta-analysis. *British Journal of Clinical Pharmacology*, *86*(4), 698–710.

Welton, D. (Ed.). (1999). *The essential Husserl: Basic writings in transcendental phenomenology*. Indiana: Indiana University Press.

Westland, H., Bos-Touwen, I. D., Trappenburg, J. C. A., Schröder, C. D., de Wit, N. J., & Schuurmans, M. J. (2017). Unravelling effectiveness of a nurse-led behaviour change intervention to enhance physical activity in patients at risk for cardiovascular disease in primary care: Study protocol for a cluster randomised controlled trial. *Trials*, *18*(1).

Wheeler, B. W., Gunnell, D., Metcalfe, C., Stephens, P., & Martin, R. M. (2008). The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. *British Medical Journal , 336*(7643), 542-545.

WHO-UMC. (2017). *Uppsala monitoring centre reports: asocial media project to raise drug safety awareness in Kuwait*. Last accessed April 3, 2018 from: https://www.who-umc.org/archive/a-social-media-project-to-raise- drug-safety-awareness-in-kuwait/

WHO-UMC. (2018). *The use of the WHO-UMC system for standardised case causality assessment*. Last accessed October 30, 2022 from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

WHO-UMC (2022). Signal detection *How UMC detects signals*. Last accessed October 31, 2022 from: https://who-umc.org/signal-work/signal-detection/

WHO-UMC. (2023a). *Members of the WHO Programme for International Drug Monitoring*. Last acsessed April 22, 2023 from: https://who-umc.org/about-the-who-programme-for-international-drug-monitoring/member-countries/

WHO-UMC. (2023b). *Working for a better world*. Last acsessed April 11, 2023 from: https://who-umc.org

WHO. (1964). *EXECUTIVE BOARD Thirty-third Session*. Last acsessed April 10, 2023 from: http://apps.who.int/iris/bitstream/handle/10665/137057/EB33_Min-13_eng.pdf?sequence=1

WHO. (1969). *International drug monitoring: the role of the hospital, report of a WHO meeting.* Last acsessed April 10, 2023 from: https://apps.who.int/iris/bitstream/handle/10665/40747/WHO_TRS_425.pdf?sequence=1&isAllowed=y

WHO. (1972). *International drug monitoring: the role of national centres, report of a WHO meeting [held in Geneva from 20 to 25 September 1971]*. Last acsessed April 10, 2023 from: http://apps.who.int/iris/bitstream/handle/10665/40968/WHO_TRS_498.pdf?sequence=1&isAllowed=y

WHO. (2001). *Pharmaceuticals: restrictions in use and availability*. Last accessed September 2, 2019 from: https://apps.who.int/medicinedocs/pdf/s2203e/s2203e.pdf

WHO. (2002). *The Importance of pharmacovigilance*. Last acsessed April 12, 2023 from: https://apps.who.int/iris/bitstream/handle/10665/42493/a75646.pdf

WHO. (2004). *Pharmacovigilance: ensuring the safe use of medicines*. Last acsessed April 10, 2023 from: http://apps.who.int/iris/bitstream/handle/10665/68782/WHO_EDM_2004.8.pdf?sequence=1

WHO. (2009). *Conceptual framework for the international classification for patient safety version 1.1: final technical report January 2009 (No. WHO/IER/PSP/2010.2).* Last acsessed April 10, 2023 from: https://www.who.int/publications/i/item/WHO-IER-PSP-2010.2

WHO. (2012a). *A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis enhancing the safety of the tb patient.* Last acsessed April 11, 2023 from: https://www.who.int/docs/default-source/documents/tuberculosis/a-practical-handbook-on-the-pharmacovigilance-of-medicines-used-in-the-treatment-of-tuberculosis.pdf?sfvrsn=6e5fc0cf_5

WHO. (2012b). *Pharmaceutical sector country profile questionnaire Kuwait*. Last acsessed April 7 2018 from: http://www.who.int/medicines/areas/coordination/Kuwait_country_profile-questionnaire2012-05-27edited.pdf?ua=1

WHO. (2013). *A practical handbook on the pharmacovigilance of antiretroviral medicines*. Last acsessed April 11, 2023 from: http://apps.who.int/iris/bitstream/handle/10665/44236/9789241547949_eng.pdf?sequence=1

WHO. (2014). *Country cooperation strategy for WHO and Kuwait 2012–2016*. Cairo: WHO Regional Office for the Eastern Mediterranean.

WHO. (2017). *WHO country cooperation strategy at a glance: Kuwait*. Last acsessed April 14, 2023 from: https://apps.who.int/iris/handle/10665/136906

WHO. (2018). *What are the functions of a national pharmacovigilance system?*. Last acsessed April 11, 2023 from: https://whopvresources.org/functions.php

WHO. (2019). *Seventy-second World Health Assembly. Provisional Agenda Item, 12.5.* Last acsessed April 25, 2023 from: https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R6-en.pdf?ua=1

WHO. (2020a). *An ad hoc WHO technical consultation managing the COVID-19 infodemic: call for action, 7-8 April 2020*. Geneva: WHO.

WHO. (2020b). *Quality health services*. Last accessed April 15, 2023 from: https://www.who.int/news-room/fact-sheets/detail/quality-health-services

WHO. (2021a). *Global patient safety action plan 2021–2030: towards eliminating avoidable harm in health care.* Last acsessed April 10, 2023 from: https://www.who.int/teams/integrated-health-services/patient-safety/policy/global-patient-safety-action-plan

WHO. (2021b). *WHO competency framework: Building a response workforce to manage infodemics*. Geneva: WHO.

WHO. (n.d.). *Medicines*. Last accessed May 29, 2022 from: https://www.who.int/health-topics/medicines#tab=tab_1

Wilbur, K. (2013). Pharmacovigilance in the Middle East. *Drug safety*, *36*(1), 25-30.

Williams, D., Kelly, A., Carvalho, M., & Feely, J. (1998). Effect of the British warning on contraceptive use in the General Medical Service in Ireland. *Irish Medical Journal*, *91*(6), 202–203.

World Health Organization Collaboration Centre for Drug Statistics Methodology. (2019). *ATC/DDD Index*. Last accessed November 20, 2022 from: https://www.whocc.no/atc_ddd_index/

Wysowski, D. K., Corken, A., Gallo-Torres, H., Talarico, L., & Rodriguez, E. M. (2001). Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and food and drug administration regulatory actions. *The American Journal of Gastroenterology*, *96*(6), 1698–1703.

Yaghmai, B. F., Cordts, C., Ahlers-Schmidt, C. R., Issa, B. A., & Warren, R. C. (2010). One community's perspective on the withdrawal of cough and cold medications for infants and young children. *Clinical Pediatrics*, *49*(4), 310–315.

Yang, S. U., Kang, M., & Cha, H. (2015). A study on dialogic communication, trust, and distrust: Testing a scale for measuring organization–public dialogic communication (OPDC). *Journal of Public Relations Research*, *27*(2), 175–192.

Yin, R.K. (2018). *Case study research and applications: design and methods*. (6th ed.). SAGE Publications. Kindle Edition.

Zhong, Y., Patel, N., Ferris, M., & Rak, E. (2020). Health literacy, nutrition knowledge, and health care transition readiness in youth with chronic kidney disease or hypertension: a cross-sectional study. *Journal of Child Health Care*, *24*(2), 246-259.

Zijlmans, E. A., Tijmstra, J., Van der Ark, L. A., & Sijtsma, K. (2019). Item-score reliability as a selection tool in test construction. *Frontiers in Psychology, 9*, 2298.

Zuber-Skerritt, O. (2001). Action learning and action research: paradigm, praxis and programs. In S. Sankara, B. Dick & R. Passfield (Eds.), *Effective change management through action research and action learning: concepts, perspectives, processes and applications*. (pp. 1-20). Lismore: Southern Cross University Press.

Appendices

Appendix 1: General search strategy

1 #	("clinical practice" or "clinical setting?" or practice? or "care setting?" or "patient care" or "healthcare system?" or "health care" or "health system?" or "primary care" or "secondary care" or "tertiary care" or "health institution?" or "healthcare institution?" or "health care system?")
2 #	("healthcare provider?" or provider? or "healthcare professional?" or professional? or "healthcare worker?" or worker? or "health practitioner?" or "medical practitioner?" or pharmacist? or physician? or doctor? or "general practitioner?" or "gp" or "gps" or nurse? or dentist? or "health personnel" or midwife or midwives or "health care professional?" or "health care provider?" or "health care worker?" or "health care practitioner?" or prescriber? or "clinical staff" or "health care staff" or dispenser?).
3 #	("regulatory intervention?" or "regulatory action?" or "regulatory advice" or "risk message?" or "risk minimi?ation" or "safety information" or "safety message?" or "safety communication?" or "safety regulation?" or "safety plan?" or "safety issue?" or "risk intervention?" or "pharmacovigilance warning?" or "pharmacovigilance message?" or "black box" or "regulatory response?" or "regulatory intervention?" or "risk communication?" or "risk action?" or "pharmacovigilance report?" or "post-market report?" or "regulatory alert?" or "safety update?" or "regulatory revoke?" or "regulatory revocation?" or "regulatory recommend*" or "regulatory measure?").
4 #	(medicine? or medication? or drug? or medicament? or pharmacon? or pharmaceutical? or "pharmaceutical product?" or treatment or therapy or tablet? or capsule? or "pharmaceutical agent?" or injectable? or injection? or suppository or suppositories or suspension? or syrup? or inhaler? or drop? or lozenge? or "pharmaceutical preparation?" or "therapeutical agent?" or "biological agent?" or cream? or ointment? or solution? or emulsion? or aerosol? or paste? or gel? or powder? or "dosage form?")
5 #	(precaution? or caution? or contraindication? or contra-indication? or withdrawal? or warning? or restriction?)
Combinations used	1 AND 3 2 AND 3 1 AND 4 AND 5 2 AND 4 AND 5

Appendix 2: Search strategy Scopus (four sets of combinations of search terms were used).

Set 1
((TITLE ("healthcare provider" OR provider OR "healthcare professional") OR TITLE (professional OR "healthcare worker" OR worker) OR TITLE ("health practitioner" OR practitioner OR "healthcare practitioner") OR TITLE ("medical practitioner" OR pharmacist OR physician) OR TITLE (doctor OR "general practitioner" OR nurse) OR TITLE (dentist OR "health personnel" OR dispenser) OR TITLE (midwife OR "health care professional" OR "health care provider") OR TITLE ("health care worker" OR "health care practitioner" OR gp) OR TITLE (prescriber OR "clinical staff" OR "health care staff"))) AND ((TITLE ("regulatory intervention" OR "regulatory action" OR "regulatory advice") OR TITLE ("risk message" OR "risk minimisation" OR "risk communication") OR TITLE ("safety information" OR "safety message" OR "safety communication") OR TITLE ("safety regulation" OR "safety plan" OR "safety issue") OR TITLE ("risk intervention" OR "pharmacovigilance warning" OR "pharmacovigilance message") OR TITLE ("black box" OR "regulatory response" OR "safety plan") OR TITLE ("risk action" OR "pharmacovigilance report" OR "post market report") OR TITLE ("regulatory alert" OR "safety update" OR "Regulatory revoke") OR TITLE ("regulatory revocation" OR "regulatory recommend*" OR "regulatory measure")))
Set 2
((TITLE ("clinical practice" OR "clinical setting" OR practice) OR TITLE ("care setting" OR "patient care" OR "healthcare system") OR TITLE ("health care" OR "health system" OR "primary care") OR TITLE ("secondary care" OR "tertiary care" OR "health institution") OR TITLE ("healthcare institution" OR "health care system "))) AND (((TITLE (medicine OR medication OR drug) OR TITLE (medicament OR pharmacon) OR TITLE (treatment OR therapy) OR TITLE (tablet OR capsule) OR TITLE (injectable OR injection OR suppository) OR TITLE (suspension OR syrup OR inhaler) OR TITLE (drop OR lozenge) OR TITLE ("pharmaceutical product" OR "theraputical agent" OR "biological agent") OR TITLE ("pharmaceutical agent" OR "pharmaceutical preparation" OR cream) OR TITLE (ointment OR solution OR emulsion) OR TITLE (aerosol OR paste OR gel) OR TITLE (powder OR "dosage form" OR pharmaceuticals))) AND ((TITLE (precaution OR caution OR "contra indication") OR TITLE (contraindication OR withdrawal OR warning) OR TITLE (restriction))))
Set 3
((TITLE ("healthcare provider" OR provider OR "healthcare professional") OR TITLE (professional OR "healthcare worker" OR worker) OR TITLE ("health practitioner" OR practitioner OR "healthcare practitioner") OR TITLE ("medical practitioner" OR pharmacist OR physician) OR TITLE (doctor OR "general practitioner" OR nurse) OR TITLE (dentist OR "health personnel" OR dispenser) OR TITLE (midwife OR "health care professional" OR "health care provider") OR TITLE ("health care worker" OR "health care practitioner" OR gp) OR TITLE (prescriber OR "clinical staff" OR "health care staff"))) AND (((TITLE (medicine OR medication OR drug) OR TITLE (medicament OR pharmacon OR pharmaceutical) OR TITLE ("pharmaceutical product" OR treatment OR therapy) OR TITLE (tablet OR capsule OR "pharmaceutical agent") OR TITLE (injectable OR injection OR suppository) OR TITLE (suspension OR syrup OR inhaler) OR TITLE (drop OR lozenge OR "pharmaceutical preparation") OR TITLE ("pharmaceutical product" OR "theraputical agent" OR "biological agent") OR TITLE ("pharmaceutical agent" OR "pharmaceutical preparation" OR cream) OR TITLE (ointment OR solution OR emulsion) OR TITLE (aerosol OR paste OR gel) OR TITLE (powder OR "dosage form" OR pharmaceuticals))) AND ((TITLE (precaution OR caution OR "contra indication") OR TITLE (contraindication OR withdrawal OR warning) OR TITLE (restriction))))
Set 4
((TITLE ("clinical practice" OR "clinical setting" OR practice) OR TITLE ("care setting" OR "patient care" OR "healthcare system") OR TITLE ("health care" OR "health system" OR "primary care") OR TITLE ("secondary care" OR "tertiary care" OR "health institution") OR TITLE ("healthcare institution" OR "health care system "))) AND ((TITLE ("regulatory intervention" OR "regulatory action" OR "regulatory advice") OR TITLE ("risk message" OR "risk minimisation" OR "risk communication") OR TITLE ("safety information" OR "safety message" OR "safety communication") OR TITLE ("safety regulation" OR "safety plan" OR "safety issue") OR TITLE ("risk intervention" OR "pharmacovigilance warning" OR "pharmacovigilance message") OR TITLE ("black box" OR "regulatory

response" OR "safety plan") OR TITLE ("risk action" OR "pharmacovigilance report" OR "post market report") OR TITLE ("regulatory alert" OR "safety update" OR "Regulatory revoke") OR TITLE ("regulatory revocation" OR "regulatory recommend*" OR "regulatory measure")))

Appendix 3: Search strategy PubMed (four sets of combinations of search terms were used).

Set 1
Search ((((((((((("health care staff"[Title] OR Dispenser[Title]) OR ((GP[Title] OR prescriber[Title]) OR "clinical staff"[Title])) OR ((("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "provider"[Title]) OR "health care provider"[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "worker"[Title]) OR "health care worker"[Title])) OR health care practitioner[Title])) OR ((("midwifery"[MeSH Terms] OR "midwifery"[Title] OR "midwives"[Title]) OR ("midwifery"[MeSH Terms] OR "midwifery"[Title] OR "midwife"[Title])) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "professional"[Title]) OR "health care professional"[Title]))) OR ((("dentists"[MeSH Terms] OR "dentists"[Title] OR "dentist"[Title]) OR "health personnel"[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title]))) OR ((("physicians"[MeSH Terms] OR "physicians"[Title] OR "doctor"[Title]) OR ("general practitioners"[MeSH Terms] OR ("general"[Title] AND "practitioners"[Title]) OR "general practitioners"[Title] OR ("general"[Title] AND "practitioner"[Title]) OR "general practitioner"[Title])) OR ("nurses"[MeSH Terms] OR "nurses"[Title] OR "nurse"[Title]))) OR ((medical practitioner[Title] OR ("pharmacists"[MeSH Terms] OR "pharmacists"[Title] OR "pharmacist"[Title])) OR ("physicians"[MeSH Terms] OR "physicians"[Title] OR "physician"[Title]))) OR ((health practitioner[Title] OR practitioner?[Title]) OR "healthcare practitioner"[Title])) OR ((professional?[Title] OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "worker"[Title]) OR "healthcare worker"[Title])) OR worker?[Title])) OR ((("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "provider"[Title]) OR "healthcare provider"[Title]) OR provider?[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "professional"[Title]) OR "healthcare professional"[Title]))) AND ((((((((((((("medicine"[MeSH Terms] OR "medicine"[Title]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR "medication"[Title])) OR drug?[Title]) OR ((medicament?[Title] OR pharmacon?[Title]) OR ("pharmacy"[MeSH Terms] OR "pharmacy"[Title] OR "pharmaceutical"[Title] OR "dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title]))) OR ((pharmaceutical product[Title] OR ("therapy"[Subheading] OR "therapy"[Title] OR "treatment"[Title] OR "therapeutics"[MeSH Terms] OR "therapeutics"[Title])) OR ("therapy"[Subheading] OR "therapy"[Title] OR "therapeutics"[MeSH Terms] OR "therapeutics"[Title]))) OR ((("tablets"[MeSH Terms] OR "tablets"[Title] OR "tablet"[Title]) OR ("capsules"[MeSH Terms] OR "capsules"[Title] OR "capsule"[Title])) OR "pharmaceutical agent"[Title])) OR ((("injections"[MeSH Terms] OR "injections"[Title] OR "injectable"[Title]) OR ("injections"[MeSH Terms] OR "injections"[Title] OR "injection"[Title])) OR ("suppositories"[MeSH Terms] OR "suppositories"[Title] OR "suppository"[Title] OR "pessaries"[MeSH Terms] OR "pessaries"[Title]))) OR ((("suppositories"[MeSH Terms] OR "suppositories"[Title] OR "pessaries"[MeSH Terms] OR "pessaries"[Title]) OR ("suspensions"[MeSH Terms] OR "suspensions"[Title] OR "suspension"[Title])) OR Syrup[Title])) OR ((("nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[Title] AND "vaporizers"[Title]) OR "nebulizers and vaporizers"[Title] OR "inhaler"[Title]) OR drop[Title]) OR lozenge[Title])) OR (("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR ("pharmaceutical"[Title] AND "preparation"[Title]) OR "pharmaceutical preparation"[Title]) OR "pharmaceutical product"[Title])) OR (("biological agent"[Title] OR pharmaceutical agent[Title]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR ("pharmaceutical"[Title] AND "preparation"[Title]) OR "pharmaceutical preparation"[Title]))) OR ((cream[Title] OR ("ointments"[MeSH Terms] OR "ointments"[Title] OR "ointment"[Title])) OR ("pharmaceutical solutions"[Pharmacological Action] OR "solutions"[MeSH Terms] OR "solutions"[Title] OR "solution"[Title] OR "pharmaceutical solutions"[MeSH Terms] OR ("pharmaceutical"[Title] AND "solutions"[Title]) OR "pharmaceutical solutions"[Title]))) OR ((("emulsions"[MeSH Terms] OR "emulsions"[Title] OR "emulsion"[Title]) OR ("aerosols"[MeSH Terms] OR "aerosols"[Title] OR "aerosol"[Title])) OR ("ointments"[MeSH Terms] OR "ointments"[Title] OR "paste"[Title]))) OR ((Gel[Title] OR ("powders"[MeSH Terms] OR "powders"[Title] OR "powder"[Title])) OR ("dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title]))) OR ("pharmacy"[MeSH Terms] OR "pharmacy"[Title] OR "pharmaceutical"[Title] OR "dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title]))) AND

(((((precaution[Title] OR caution[Title]) OR contra-indication[Title]) OR ((("contraindications"[MeSH Terms] OR "contraindications"[Title] OR "contraindication"[Title]) OR withdrawal[Title]) OR withdrawals[Title])) OR ((warning[Title] OR warnings[Title]) OR restrictions[Title])) OR restriction[Title]))
Set 2
((((((((((("health care staff"[Title] OR Dispenser[Title]) OR ((GP[Title] OR prescriber[Title]) OR "clinical staff"[Title])) OR ((("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "provider"[Title]) OR "health care provider"[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "worker"[Title]) OR "health care worker"[Title])) OR health care practitioner[Title])) OR ((("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "provider"[Title]) OR "health care provider"[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "worker"[Title]) OR "health care worker"[Title])) OR health care practitioner[Title])) OR ((("midwifery"[MeSH Terms] OR "midwifery"[Title] OR "midwives"[Title]) OR ("midwifery"[MeSH Terms] OR "midwifery"[Title] OR "midwife"[Title])) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("health"[Title] AND "care"[Title] AND "professional"[Title]) OR "health care professional"[Title]))) OR ((("dentists"[MeSH Terms] OR "dentists"[Title] OR "dentist"[Title]) OR "health personnel"[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title]))) OR ((("physicians"[MeSH Terms] OR "physicians"[Title] OR "doctor"[Title]) OR ("general practitioners"[MeSH Terms] OR ("general"[Title] AND "practitioners"[Title]) OR "general practitioners"[Title] OR ("general"[Title] AND "practitioner"[Title]) OR "general practitioner"[Title])) OR ("nurses"[MeSH Terms] OR "nurses"[Title] OR "nurse"[Title]))) OR ((medical practitioner[Title] OR ("pharmacists"[MeSH Terms] OR "pharmacists"[Title] OR "pharmacist"[Title])) OR ("physicians"[MeSH Terms] OR "physicians"[Title] OR "physician"[Title]))) OR ((health practitioner[Title] OR practitioner?[Title]) OR "healthcare practitioner"[Title])) OR ((professional?[Title] OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "worker"[Title]) OR "healthcare worker"[Title])) OR worker?[Title])) OR ((("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "provider"[Title]) OR "healthcare provider"[Title]) OR provider?[Title]) OR ("health personnel"[MeSH Terms] OR ("health"[Title] AND "personnel"[Title]) OR "health personnel"[Title] OR ("healthcare"[Title] AND "professional"[Title]) OR "healthcare professional"[Title]))) AND ((((((((((("regulatory intervention"[Title] OR "regulatory action"[Title]) OR regulatory action[Title]) OR (("regulatory advice"[Title] OR regulatory advice[Title]) OR "risk message"[Title])) OR (risk message[Title] OR "risk minimisation"[Title])) OR (("risk minimization"[Title] OR "risk communication"[Title]) OR "safety information"[Title])) OR (("safety message"[Title] OR "safety communication"[Title]) OR "safety regulation"[Title])) OR (("safety plan"[Title] OR "safety issue"[Title]) OR "risk intervention"[Title])) OR ((("pharmacovigilance"[MeSH Terms] OR "pharmacovigilance"[Title]) AND warning[Title]) OR "black box"[Title])) OR (("regulatory response"[Title] OR risk communication[Title]) OR safety plans[Title])) OR (("risk action"[Title] OR pharmacovigilance report[Title]) OR "pharmacovigilance report"[Title])) OR (((post-market[Title] AND ("research report"[MeSH Terms] OR ("research"[Title] AND "report"[Title]) OR "research report"[Title] OR "report"[Title])) OR "regulatory alert"[Title]) OR "safety update"[Title])) OR (((Regulatory[Title] AND revoke[Title]) OR (regulatory[Title] AND revocation[Title])) OR (regulatory recommendation[Title] OR regulatory recommendations[Title]))) OR ("regulatory measure"[Title] OR "regulatory measures"[Title]))
Set 3
((((((((clinical practice[Title] OR clinical setting[Title]) OR practice[Title]) OR ((care setting[Title] OR ("patient care"[MeSH Terms] OR ("patient"[Title] AND "care"[Title]) OR "patient care"[Title])) OR ("delivery of health care"[MeSH Terms] OR ("delivery"[Title] AND "health"[Title] AND "care"[Title]) OR "delivery of health care"[Title] OR ("healthcare"[Title] AND "system"[Title]) OR "healthcare system"[Title]))) OR ((("secondary care"[MeSH Terms] OR ("secondary"[Title] AND "care"[Title]) OR "secondary care"[Title]) OR ("tertiary healthcare"[MeSH Terms] OR ("tertiary"[Title] AND "healthcare"[Title]) OR "tertiary healthcare"[Title] OR ("tertiary"[Title] AND "care"[Title]) OR "tertiary care"[Title])) OR "health institution"[Title])) OR ("healthcare institution"[Title] OR ("delivery of health care"[MeSH Terms] OR ("delivery"[Title] AND "health"[Title] AND "care"[Title]) OR "delivery of health care"[Title] OR ("health"[Title] AND "care"[Title] AND "system"[Title])

OR "health care system"[Title])) OR ((Care, Health[Full Investigator Name] OR health system[Title]) OR ("primary health care"[MeSH Terms] OR ("primary"[Title] AND "health"[Title] AND "care"[Title]) OR "primary health care"[Title] OR ("primary"[Title] AND "care"[Title]) OR "primary care"[Title])) AND ((((((((((((("medicine"[MeSH Terms] OR "medicine"[Title]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR "medication"[Title])) OR drug?[Title]) OR ((medicament?[Title] OR pharmacon?[Title]) OR ("pharmacy"[MeSH Terms] OR "pharmacy"[Title] OR "pharmaceutical"[Title] OR "dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title])))) OR ((pharmaceutical product[Title] OR ("therapy"[Subheading] OR "therapy"[Title] OR "treatment"[Title] OR "therapeutics"[MeSH Terms] OR "therapeutics"[Title])) OR ("therapy"[Subheading] OR "therapy"[Title] OR "therapeutics"[MeSH Terms] OR "therapeutics"[Title]))) OR ((("tablets"[MeSH Terms] OR "tablets"[Title] OR "tablet"[Title]) OR ("capsules"[MeSH Terms] OR "capsules"[Title] OR "capsule"[Title])) OR "pharmaceutical agent"[Title])) OR ((("injections"[MeSH Terms] OR "injections"[Title] OR "injectable"[Title]) OR ("injections"[MeSH Terms] OR "injections"[Title] OR "injection"[Title])) OR ("suppositories"[MeSH Terms] OR "suppositories"[Title] OR "suppository"[Title] OR "pessaries"[MeSH Terms] OR "pessaries"[Title]))) OR ((("suppositories"[MeSH Terms] OR "suppositories"[Title] OR "pessaries"[MeSH Terms] OR "pessaries"[Title]) OR ("suspensions"[MeSH Terms] OR "suspensions"[Title] OR "suspension"[Title])) OR Syrup[Title])) OR ((("nebulizers and vaporizers"[MeSH Terms] OR ("nebulizers"[Title] AND "vaporizers"[Title]) OR "nebulizers and vaporizers"[Title] OR "inhaler"[Title]) OR drop[Title]) OR lozenge[Title])) OR (("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR ("pharmaceutical"[Title] AND "preparation"[Title]) OR "pharmaceutical preparation"[Title]) OR "pharmaceutical product"[Title])) OR (("biological agent"[Title] OR pharmaceutical agent[Title]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[Title] AND "preparations"[Title]) OR "pharmaceutical preparations"[Title] OR ("pharmaceutical"[Title] AND "preparation"[Title]) OR "pharmaceutical preparation"[Title]))) OR ((cream[Title] OR ("ointments"[MeSH Terms] OR "ointments"[Title] OR "ointment"[Title])) OR ("pharmaceutical solutions"[Pharmacological Action] OR "solutions"[MeSH Terms] OR "solutions"[Title] OR "solution"[Title] OR "pharmaceutical solutions"[MeSH Terms] OR ("pharmaceutical"[Title] AND "solutions"[Title]) OR "pharmaceutical solutions"[Title]))) OR ((("emulsions"[MeSH Terms] OR "emulsions"[Title] OR "emulsion"[Title]) OR ("aerosols"[MeSH Terms] OR "aerosols"[Title] OR "aerosol"[Title])) OR ("ointments"[MeSH Terms] OR "ointments"[Title] OR "paste"[Title]))) OR ((Gel[Title] OR ("powders"[MeSH Terms] OR "powders"[Title] OR "powder"[Title])) OR ("dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title]))) OR ("pharmacy"[MeSH Terms] OR "pharmacy"[Title] OR "pharmaceutical"[Title] OR "dosage forms"[MeSH Terms] OR ("dosage"[Title] AND "forms"[Title]) OR "dosage forms"[Title]))) AND (((((precaution[Title] OR caution[Title]) OR contra-indication[Title]) OR ((("contraindications"[MeSH Terms] OR "contraindications"[Title] OR "contraindication"[Title]) OR withdrawal[Title]) OR withdrawals[Title])) OR ((warning[Title] OR warnings[Title]) OR restrictions[Title])) OR restriction[Title]))

Set 4

((((((clinical practice[Title] OR clinical setting[Title]) OR practice[Title]) OR ((care setting[Title] OR ("patient care"[MeSH Terms] OR ("patient"[Title] AND "care"[Title]) OR "patient care"[Title])) OR ("delivery of health care"[MeSH Terms] OR ("delivery"[Title] AND "health"[Title] AND "care"[Title]) OR "delivery of health care"[Title] OR ("healthcare"[Title] AND "system"[Title]) OR "healthcare system"[Title]))) OR ((("secondary care"[MeSH Terms] OR ("secondary"[Title] AND "care"[Title]) OR "secondary care"[Title]) OR ("tertiary healthcare"[MeSH Terms] OR ("tertiary"[Title] AND "healthcare"[Title]) OR "tertiary healthcare"[Title] OR ("tertiary"[Title] AND "care"[Title]) OR "tertiary care"[Title])) OR "health institution"[Title])) OR ("healthcare institution"[Title] OR ("delivery of health care"[MeSH Terms] OR ("delivery"[Title] AND "health"[Title] AND "care"[Title]) OR "delivery of health care"[Title] OR ("health"[Title] AND "care"[Title] AND "system"[Title]) OR "health care system"[Title]))) OR ((Care, Health[Full Investigator Name] OR health system[Title]) OR ("primary health care"[MeSH Terms] OR ("primary"[Title] AND "health"[Title] AND "care"[Title]) OR "primary health care"[Title] OR ("primary"[Title] AND "care"[Title]) OR "primary care"[Title]))) AND ((((((((((("regulatory intervention"[Title] OR "regulatory action"[Title]) OR regulatory action[Title]) OR (("regulatory advice"[Title] OR regulatory advice[Title]) OR "risk message"[Title])) OR (risk message[Title] OR "risk minimisation"[Title])) OR (("risk minimization"[Title] OR "risk communication"[Title]) OR "safety information"[Title])) OR (("safety message"[Title] OR "safety communication"[Title]) OR "safety regulation"[Title])) OR (("safety plan"[Title] OR "safety issue"[Title]) OR "risk intervention"[Title])) OR ((("pharmacovigilance"[MeSH Terms] OR "pharmacovigilance"[Title]) AND warning[Title]) OR "black box"[Title])) OR (("regulatory response"[Title] OR risk communication[Title]) OR safety plans[Title])) OR (("risk action"[Title] OR pharmacovigilance report[Title]) OR "pharmacovigilance report"[Title])) OR (((post-market[Title] AND ("research report"[MeSH Terms] OR ("research"[Title] AND "report"[Title]) OR "research report"[Title] OR "report"[Title])) OR "regulatory alert"[Title]) OR "safety update"[Title])) OR

(((Regulatory[Title] AND revoke[Title]) OR (regulatory[Title] AND revocation[Title])) OR ((regulatory[Title] AND recommendation[Title]) OR regulatory recommendations[Title]))) OR ("regulatory measure"[Title] OR "regulatory measures"[Title]))

Appendix 4: Search strategy Web of science (four sets of combinations of search terms were used).

Set 1: #30 AND #27 AND #26
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 30
#29 OR #28
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

29
TITLE: (Powder$) OR TITLE: (Solution$) OR TITLE: (Suppositories) OR TITLE: (Suppository) OR TITLE: (Suspension$) OR TITLE: (Syrup$) OR TITLE: (Tablet$) ORTITLE: (therapy) OR TITLE: (treatment$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

28
TITLE: ("biological agent$") OR TITLE: ("pharmaceutical agent$") OR TITLE: ("pharmaceutical product$") OR TITLE: ("theraputical agent$") OR TITLE:("clinical setting$") OR TITLE: ("dosage form$") OR TITLE: ("pharmaceutical preparation$") OR TITLE: (Aerosol$) OR TITLE: (Capsule$) OR TITLE: (Cream$) ORTITLE: (Drop$) OR TITLE: (drug$) OR TITLE: (emulsion$) OR TITLE: (Gel$) OR TITLE: (Inhaler$) OR TITLE: (Injectable$) OR TITLE: (Injection$) OR TITLE:(Lozenge$) OR TITLE: (Medicament$) OR TITLE: (Medication$) OR TITLE: (Medicine$) OR TITLE: (Ointment$) OR TITLE: (Paste$) OR TITLE: (Pharmaceutical$) OR TITLE: (Pharmacon$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 27
TITLE: ("health institution$") OR TITLE: ("healthcare institution$") OR TITLE: ("care setting$") OR TITLE: ("clinical practice$") OR TITLE: ("clinical setting$") ORTITLE: ("health care system$") OR TITLE: ("health care") OR TITLE: ("health system$") OR TITLE: ("healthcare system$") OR TITLE: ("patient care") OR TITLE:("primary care") OR TITLE: ("secondary care") OR TITLE: ("tertiary care") OR TITLE: (Practice$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 26
TITLE: (Caution$) OR TITLE: (Contraindication$) OR TITLE: (contra-indication$) OR TITLE: (precaution$) OR TITLE: (restriction$) OR TITLE: (warning$) ORTITLE: (withdrawal$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years

Search language=Auto

Set 2: #36 AND #30 AND #26
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 36
#35 OR #34
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

35
TITLE: (prescriber$) OR TITLE: (professional$) OR TITLE: (provider$) OR TITLE: (worker$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

34
TITLE: ("clinical staff") OR TITLE: ("health care staff") OR TITLE: ("health personnel") OR TITLE: ("healthcare practitioner$") OR TITLE: ("general practitioner$") OR TITLE: ("health care practitioner$") OR TITLE: ("health care professional$") OR TITLE: ("health care provider$") OR TITLE: ("health care worker$") ORTITLE: ("health practitioner$") OR TITLE: ("healthcare professional$") OR TITLE: ("healthcare provider$") OR TITLE: ("healthcare worker$") OR TITLE:("medical practitioner$") OR TITLE: (Dentist$) OR TITLE: (Dispenser$) OR TITLE: (Doctor$) OR TITLE: (GP) OR TITLE: (GPs) OR TITLE: (midwife) OR TITLE:(midwives) OR TITLE: (nurse$) OR TITLE: (pharmacist$) OR TITLE: (physician$) OR TITLE: (practitioner$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 30
#29 OR #28
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

29
TITLE: (Powder$) OR TITLE: (Solution$) OR TITLE: (Suppositories) OR TITLE: (Suppository) OR TITLE: (Suspension$) OR TITLE: (Syrup$) OR TITLE: (Tablet$) ORTITLE: (therapy) OR TITLE: (treatment$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

28
TITLE: ("biological agent$") OR TITLE: ("pharmaceutical agent$") OR TITLE: ("pharmaceutical product$") OR TITLE: ("theraputical agent$") OR TITLE:("clinical setting$") OR TITLE: ("dosage form$") OR TITLE: ("pharmaceutical preparation$") OR TITLE: (Aerosol$) OR TITLE: (Capsule$) OR TITLE: (Cream$) ORTITLE:

(Drop$) OR TITLE: (drug$) OR TITLE: (emulsion$) OR TITLE: (Gel$) OR TITLE: (Inhaler$) OR TITLE: (Injectable$) OR TITLE: (Injection$) OR TITLE:(Lozenge$) OR TITLE: (Medicament$) OR TITLE: (Medication$) OR TITLE: (Medicine$) OR TITLE: (Ointment$) OR TITLE: (Paste$) OR TITLE: (Pharmaceutical$) OR TITLE: (Pharmacon$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 26
TITLE: (Caution$) OR TITLE: (Contraindication$) OR TITLE: (contra-indication$) OR TITLE: (precaution$) OR TITLE: (restriction$) OR TITLE: (warning$) ORTITLE: (withdrawal$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

Set 3: #36 AND #33
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 36
#35 OR #34
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

35
TITLE: (prescriber$) OR TITLE: (professional$) OR TITLE: (provider$) OR TITLE: (worker$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

34
TITLE: ("clinical staff") OR TITLE: ("health care staff") OR TITLE: ("health personnel") OR TITLE: ("healthcare practitioner$") OR TITLE: ("general practitioner$") OR TITLE: ("health care practitioner$") OR TITLE: ("health care professional$") OR TITLE: ("health care provider$") OR TITLE: ("health care worker$") ORTITLE: ("health practitioner$") OR TITLE: ("healthcare professional$") OR TITLE: ("healthcare provider$") OR TITLE: ("healthcare worker$") OR TITLE:("medical practitioner$") OR TITLE: (Dentist$) OR TITLE: (Dispenser$) OR TITLE: (Doctor$) OR TITLE: (GP) OR TITLE: (GPs) OR TITLE: (midwife) OR TITLE:(midwives) OR TITLE: (nurse$) OR TITLE: (pharmacist$) OR TITLE: (physician$) OR TITLE: (practitioner$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 33 #32 OR #31
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

32
TITLE: ("risk action$") OR TITLE: ("risk message$") OR TITLE: ("safety plan$")

Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

31
TITLE: ("black box") OR TITLE: ("regulatory action$") OR TITLE: ("regulatory alert$") OR TITLE: ("regulatory intervention$") OR TITLE: ("regulatory response$") OR TITLE: ("risk communication$") OR TITLE: ("risk intervention$") OR TITLE: ("risk minimisation$") OR TITLE: ("risk minimization$") OR TITLE:("safety communication$") OR TITLE: ("safety information") OR TITLE: ("safety issue$") OR TITLE: ("safety message$") OR TITLE: ("safety regulation$") ORTITLE: ("safety update$") OR TITLE: ("pharmacovigilance message$") OR TITLE: ("pharmacovigilance report$") OR TITLE: ("pharmacovigilance warning$") ORTITLE: ("post-market report$") OR TITLE: ("regulatory action$") OR TITLE: ("regulatory advice$") OR TITLE: ("regulatory measure$") OR TITLE: ("regulatory recommend*") OR TITLE: ("regulatory revocation$") OR TITLE: ("Regulatory revoke$")
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

Set 4: #33 AND #27
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 33 #32 OR #31
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

32
TITLE: ("risk action$") OR TITLE: ("risk message$") OR TITLE: ("safety plan$")
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

31
TITLE: ("black box") OR TITLE: ("regulatory action$") OR TITLE: ("regulatory alert$") OR TITLE: ("regulatory intervention$") OR TITLE: ("regulatory response$") OR TITLE: ("risk communication$") OR TITLE: ("risk intervention$") OR TITLE: ("risk minimisation$") OR TITLE: ("risk minimization$") OR TITLE:("safety communication$") OR TITLE: ("safety information") OR TITLE: ("safety issue$") OR TITLE: ("safety message$") OR TITLE: ("safety regulation$") ORTITLE: ("safety update$") OR TITLE: ("pharmacovigilance message$") OR TITLE: ("pharmacovigilance report$") OR TITLE: ("pharmacovigilance warning$") ORTITLE: ("post-market report$") OR TITLE: ("regulatory action$") OR TITLE: ("regulatory advice$") OR TITLE: ("regulatory measure$") OR TITLE: ("regulatory recommend*") OR TITLE: ("regulatory revocation$") OR TITLE: ("Regulatory revoke$")
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

 # 27

TITLE: ("health institution$") OR TITLE: ("healthcare institution$") OR TITLE: ("care setting$") OR TITLE: ("clinical practice$") OR TITLE: ("clinical setting$") ORTITLE: ("health care system$") OR TITLE: ("health care") OR TITLE: ("health system$") OR TITLE: ("healthcare system$") OR TITLE: ("patient care") OR TITLE:("primary care") OR TITLE: ("secondary care") OR TITLE: ("tertiary care") OR TITLE: (Practice$)
Databases= BCI, BIOSIS, MEDLINE Timespan=All years
Search language=Auto

Appendix 5: Search strategy CINHAL PLUS (four sets of combinations of search terms were used).

Interface - EBSCOhost Research Databases
Search Screen - Advanced Search
Database - CINAHL Plus

#	Query	Limiters/Expanders
Set 1	S77 AND S122	Expanders - Apply related words Search modes - Boolean/Phrase
Set 2	S122 AND S137	Expanders - Apply related words Search modes - Boolean/Phrase
Set 3	S11 AND S47 AND S137	Expanders - Apply related words Search modes - Boolean/Phrase
Set 4	S11 AND S47 AND S77	Expanders - Apply related words Search modes - Boolean/Phrase
S137	(S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136)	Search modes - Boolean/Phrase
S136	TI tertiary care	Search modes - Boolean/Phrase
S135	TI secondary care	Search modes - Boolean/Phrase
S134	TI primary care	Search modes - Boolean/Phrase

S133	TI practice	Search modes - Boolean/Phrase
S132	TI patient care	Search modes - Boolean/Phrase
S131	TI healthcare system	Search modes - Boolean/Phrase
S130	TI health system	Search modes - Boolean/Phrase
S129	TI health care system	Search modes - Boolean/Phrase
S128	TI health care	Search modes - Boolean/Phrase
S127	TI clinical setting	Expanders - Apply related words Search modes - Boolean/Phrase
S126	TI clinical practice	Expanders - Apply related words Search modes - Boolean/Phrase
S125	TI care setting	Search modes - Boolean/Phrase
S124	TI "healthcare institution"	Search modes - Boolean/Phrase
S123	TI "health institution"	Search modes - Boolean/Phrase
S122	S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S105 OR S106 OR S107 OR S109 OR S111 OR S117 OR S118 OR S119 OR S120 OR S121	Search modes - Boolean/Phrase

S121	TI "safety message"	Search modes - Boolean/Phrase
S120	TI safety plans	Search modes - Boolean/Phrase
S119	TI risk minimi?ation	Search modes - Boolean/Phrase
S118	TI risk message	Search modes - Boolean/Phrase
S117	TI risk communication	Search modes - Boolean/Phrase
S116	TI (regulatory action)	Search modes - Boolean/Phrase
S115	TI (post-market report)	Search modes - SmartText Searching
S114	TI (post-market report)	Search modes - Boolean/Phrase
S113	TI (Regulatory revoke)	Search modes - SmartText Searching
S112	TI (Regulatory revoke)	Search modes - Boolean/Phrase
S111	TI Regulatory revoke	Search modes - SmartText Searching
S110	TI Regulatory revoke	Search modes - Boolean/Phrase
S109	TI regulatory revocation	Search modes - SmartText Searching
S108	TI regulatory revocation	Search modes - Boolean/Phrase

S107	TI regulatory advice	Search modes - Boolean/Phrase
S106	TI regulatory action	Search modes - Boolean/Phrase
S105	TI post-market report	Search modes - SmartText Searching
S104	TI post-market report	Search modes - Boolean/Phrase
S103	TI pharmacovigilance warning	Search modes - Boolean/Phrase
S102	TI pharmacovigilance report	Search modes - Boolean/Phrase
S101	TI "safety plan"	Search modes - Boolean/Phrase
S100	TI "risk message"	Search modes - Boolean/Phrase
S99	TI "risk action"	Search modes - Boolean/Phrase
S98	TI "regulatory measures"	Search modes - Boolean/Phrase
S97	TI "regulatory advice"	Search modes - Boolean/Phrase
S96	TI "pharmacovigilance report"	Search modes - Boolean/Phrase
S95	TI "pharmacovigilance message"	Search modes - SmartText Searching
S94	TI "pharmacovigilance message"	Search modes - Boolean/Phrase

S93	TI "safety update"	Search modes - Boolean/Phrase
S92	TI "safety regulation"	Search modes - Boolean/Phrase
S91	TI "safety issue"	Search modes - Boolean/Phrase
S90	TI "safety information"	Search modes - Boolean/Phrase
S89	TI "safety communication"	Search modes - Boolean/Phrase
S88	TI "risk minimization"	Search modes - Boolean/Phrase
S87	TI "risk minimisation"	Search modes - Boolean/Phrase
S86	TI "risk intervention"	Search modes - Boolean/Phrase
S85	TI "risk communication"	Search modes - Boolean/Phrase
S84	TI "regulatory response"	Search modes - Boolean/Phrase
S83	TI "regulatory measure"	Search modes - Boolean/Phrase
S82	TI "regulatory intervention"	Search modes - Boolean/Phrase
S81	TI "regulatory alert"	Search modes - Boolean/Phrase
S80	TI "regulatory action"	Search modes - Boolean/Phrase

S79	TI "black box"	Search modes - Boolean/Phrase
S78	TI regulatory recommend*	Search modes - Boolean/Phrase
S77	(S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76)	Search modes - Boolean/Phrase
S76	TI practitioner?	Search modes - Boolean/Phrase
S75	TI worker?	Search modes - Boolean/Phrase
S74	TI provider?	Search modes - Boolean/Phrase
S73	TI professional?	Search modes - Boolean/Phrase
S72	TI prescriber	Search modes - Boolean/Phrase
S71	TI physician?	Search modes - Boolean/Phrase
S70	TI pharmacist?	Search modes - Boolean/Phrase
S69	TI nurse	Search modes - Boolean/Phrase
S68	TI midwives	Search modes - Boolean/Phrase
S67	TI midwife	Search modes - Boolean/Phrase
S66	TI medical practitioner	Search modes - Boolean/Phrase

S65	TI healthcare worker	Search modes - Boolean/Phrase
S64	TI healthcare provider	Search modes - Boolean/Phrase
S63	TI healthcare professional	Search modes - Boolean/Phrase
S62	TI health practitioner	Search modes - Boolean/Phrase
S61	TI health personnel	Search modes - Boolean/Phrase
S60	TI health care worker	Search modes - Boolean/Phrase
S59	TI health care provider	Search modes - Boolean/Phrase
S58	TI health care professional	Search modes - Boolean/Phrase
S57	TI health care practitioner	Search modes - Boolean/Phrase
S56	TI GP	Search modes - Boolean/Phrase
S55	TI general practitioner	Search modes - Boolean/Phrase
S54	TI doctor?	Search modes - Boolean/Phrase
S53	TI Dispenser	Search modes - Boolean/Phrase
S52	TI dentist?	Search modes - Boolean/Phrase

S51	TI "healthcare practitioner"	Search modes - Boolean/Phrase
S50	TI "health personnel"	Search modes - Boolean/Phrase
S49	TI "health care staff"	Search modes - Boolean/Phrase
S48	TI "clinical staff"	Search modes - Boolean/Phrase
S47	(S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46)	Search modes - Boolean/Phrase
S46	TI treatment	Search modes - Boolean/Phrase
S45	TI therapy	Search modes - Boolean/Phrase
S44	TI tablet?	Search modes - Boolean/Phrase
S43	TI Syrup	Search modes - Boolean/Phrase
S42	TI suspension?	Search modes - Boolean/Phrase
S41	TI Suppository	Search modes - Boolean/Phrase
S40	TI Suppositories	Search modes - Boolean/Phrase
S39	TI solution?	Search modes - Boolean/Phrase
S38	TI powder?	Search modes - Boolean/Phrase

S37	TI pharmacon?	Search modes - Boolean/Phrase
S36	TI pharmaceutical?	Search modes - Boolean/Phrase
S35	TI pharmaceutical product	Search modes - Boolean/Phrase
S34	TI pharmaceutical preparation	Search modes - Boolean/Phrase
S33	TI pharmaceutical agent	Search modes - Boolean/Phrase
S32	TI paste?	Search modes - Boolean/Phrase
S31	TI ointment	Search modes - Boolean/Phrase
S30	TI medicine?	Search modes - Boolean/Phrase
S29	TI medication?	Search modes - Boolean/Phrase
S28	TI medicament?	Search modes - Boolean/Phrase
S27	TI lozenge	Search modes - Boolean/Phrase
S26	TI injection?	Search modes - Boolean/Phrase
S25	TI injectable?	Search modes - Boolean/Phrase
S24	TI inhaler?	Search modes - Boolean/Phrase

S23	TI Gel	Search modes - Boolean/Phrase
S22	TI emulsion?	Search modes - Boolean/Phrase
S21	TI drug?	Search modes - Boolean/Phrase
S20	TI drop	Search modes - Boolean/Phrase
S19	TI dosage forms	Search modes - Boolean/Phrase
S18	TI cream	Search modes - Boolean/Phrase
S17	TI capsule?	Search modes - Boolean/Phrase
S16	TI aerosol?	Search modes - Boolean/Phrase
S15	TI "theraputical agent"	Search modes - SmartText Searching
S14	TI "pharmaceutical product"	Search modes - Boolean/Phrase
S13	TI "pharmaceutical agent"	Search modes - Boolean/Phrase
S12	TI "biological agent"	Search modes - Boolean/Phrase
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	Search modes - Boolean/Phrase
S10	TI restriction	Search modes - Boolean/Phrase

S9	TI restrictions	Search modes - Boolean/Phrase
S8	TI warnings	Search modes - Boolean/Phrase
S7	TI warning	Search modes - Boolean/Phrase
S6	TI withdrawals	Search modes - Boolean/Phrase
S5	TI withdrawal	Search modes - Boolean/Phrase
S4	TI contraindication	Search modes - Boolean/Phrase
S3	TI contra-indication	Search modes - Boolean/Phrase
S2	TI caution	Search modes - Boolean/Phrase
S1	TI precaution	Search modes - Boolean/Phrase

Appendix 6: Search strategy OVID (four sets of combinations of search terms were used).

Database: AMED (Allied and Complementary Medicine) <1985 to May 2019>, Embase Classic+Embase <1947 to 2019 May 21>, Global Health <1910 to 2019 Week 19>, Health and Psychosocial Instruments <1985 to April 2019>, HMIC Health Management Information Consortium <1979 to April 2019>, International Pharmaceutical Abstracts <1970 to April 2019>, Maternity & Infant Care Database (MIDIRS) <1971 to March 2019>, PsycEXTRA <1908 to April 16, 2019>, PsycINFO <1806 to May Week 2 2019>

Search Terms
1
("clinical practice" or "clinical setting?" or practice? or "care setting?" or "patient care" or "healthcare system?" or "health care" or "health system?" or "primary care" or "secondary care" or "tertiary care" or "health institution?" or "healthcare institution?" or "health care system?").ti.
2
(precaution? or caution? or contraindication? or contra-indication? or withdrawal? or warning? or restriction?).ti.
3
(medicine? or medication? or drug? or medicament? or pharmacon? or pharmaceutical? or "pharmaceutical product?" or treatment or therapy or tablet? or capsule? or "pharmaceutical agent?" or injectable? or injection? or suppository or suppositories or suspension? or syrup? or inhaler? or drop? or lozenge? or "pharmaceutical preparation?" or "therapeutical agent?" or "biological agent?" or cream? or ointment? or solution? or emulsion? or aerosol? or paste? or gel? or powder? or "dosage form?").ti.
4
("regulatory intervention?" or "regulatory action?" or "regulatory advice" or "risk message?" or "risk minimi?ation" or "safety information" or "safety message?" or "safety communication?" or "safety regulation?" or "safety plan?" or "safety issue?" or "risk intervention?" or "pharmacovigilance warning?" or "pharmacovigilance message?" or "black box" or "regulatory response?" or "regulatory intervention?" or "risk communication?" or "risk action?" or "pharmacovigilance report?" or "post-market report?" or "regulatory alert?" or "safety update?" or "regulatory revoke?" or "regulatory revocation?" or "regulatory recommend*" or "regulatory measure?").ti.
5
("healthcare provider?" or provider? or "healthcare professional?" or professional? or "healthcare worker?" or worker? or "health practitioner?" or "medical practitioner?" or pharmacist? or physician? or doctor? or "general practitioner?" or "gp" or "gps" or nurse? or dentist? or "health personnel" or midwife or midwives or "health care professional?" or "health care provider?" or "health care worker?" or "health care practitioner?" or prescriber? or "clinical staff" or "health care staff" or dispenser?).ti.
Sets/ combinations of terms used
Set 1: 4 and 5 Set 2: 2 and 3 and 5 Set 3: 1 and 4 Set 4: 1 and 2 and 3

Appendix 7: Definitions used in the systematic reviews' inclusion and exclusion criteria (based on English Oxford Dictionaries):

Term	Definition
Factor	"A circumstance, fact, or influence that contributes to a result" ([online], n.d.a).
Uptake	"The action of taking up or making use of something that is available" ([online], n.d.b).

Appendix 8: Decisions on quality assessment

AB conducted the quality assessment on all the included papers, and each IB and NU repeated the quality assessment using the MMAT on nine studies (2 of NU checked papers (abstracts) were removed due to not obtaining the full text) for each. Initial disagreements was due to not agreeing initially on the criteria to be used for evaluating each item. This resulted in an agreement of 86.7% with IB and a 71.1% agreement with NU (the percentage was calculated on the level of fulfilling the items of MMAT).

Differences explained

With regard to using the MMAT tool, all the differences were related to questions 4.3 (measurements), 4.4 (risk on non-response bias) or 4.5 (analysis); except for one related to screening question 2. An agreement was reached regarding the criteria for 4.3, 4.4 and 4.5 after the discussion process. Regarding 4.3, the five criteria were reduced to 4 (gold standard was removed) that are related to the following:
1. Measurements are clear and justifiable.
2. Validity.
3. Reliability.
4. Questionnaire was pre-tested.
If the score is 3 out of 4, then the item will be fulfilled. If less than that and most of answers to the above criteria were "no" then the item will not be fulfilled. If most of the above criteria were not reported, then the assessment will be "cannot be determined".
From the criteria item 4.4, the response rate was the measure. Thus, it was if the response rate was low, then there is a risk of nonresponse bias.
4.5 involved considering the general analytical approach as correct, not correct or cannot be determined. In addition, missing information not reported by the authors were captured.

Study	Reviewer	Reviewer's answer	AB answer and reason
Bhatia et al (2008)	NU	4.3 Are the measurements appropriate? Yes 4.4 Is the risk of nonresponse bias low? Yes	4.3 can't tell score 2/4, and those two were not reported (validity and reliability). 4.4 No→ response rate 57.5% from 1521 addressed individuals. There is a noticeable differences among the subpopulation (**(A)**most population are from Urban settings 85.3%, **(B)** 69.9% of the participants are family medicine physicians while only 16% paediatric practitioners and 14.1% psychiatric clinicians and from those only 20 specialised child and adolescents (this 16.4%, 2.3% and 1.3% of the psychiatrics, all respondents and the total population, respectively). These subpopulations are important as the study is about antidepressants in children and adolescents.
Habib et al (2008)	NU	4.3 Are the measurements appropriate? Yes 4.4 Is the risk of nonresponse bias low? Can't tell	4.3 → can't tell score 1/4 (validity, reliability and pretesting the questionnaire were not reported). 4.4→ No, 25% respondent rate (295 out of 1179)
Jacopy et al (2005)*	NU	4.3 Are the measurements appropriate? Yes 4.5 is the statistical analysis appropriate to answer the research question? Yes	4.3→ can't tell score 1/4 (validity, reliability and pretesting the questionnaire were not reported) 4.5 → Can't tell (percentages are appropriate; no enough information on their type of data to judge if using chi-square testing or not).
Smollin et al (2016)	NU	4.3 Are the measurements appropriate? Yes	4.3 can't tell → score 2/4, and those two were not reported (validity and questionnaire tested prior to data collection).
Yaghami et al (2010)	NU	4.4 Is the risk of nonresponse bias low? Yes	4.4 → Can't tell. Response rate for physicians is 71.7% (33 out of 46 individuals) I couldn't determine if this high or not).

West et al (2015)*	NU	S2. Do the data collected allow to address the research question? No	S2→ Yes. They reported using several design research probes during a symposium (with neurologists) without clarifying what are those designs. However, they also reported using telephone interview (with family practice physicians) which is appropriate.
Bell et al (2013)	IB	4.3 Are the measurements appropriate? Yes 4.5 is the statistical analysis appropriate to answer the research question? Yes	4.3→ Can't tell → Score 1/4 (validity, reliability and questionnaire pretested are not reported) 4.5→ Can't tell → reported using chi-square and ANOVA to test for dependence between demographics, practice characteristics, answers to individual questions, and use of each source of information. Not sure why they used ANOVA
Esterly at al (2011)	IB	4.5 is the statistical analysis appropriate to answer the research question? No	4.5→ Yes (I agree with your point on regression analysis, but their method of analysis is appropriate for answering their research question. Thus, I kept it as yes with comments.)
Piening et al (2012)	IB	4.5 is the statistical analysis appropriate to answer the research question? Yes	4.5 → Can't tell, not sure which type of ANOVA they used. I'm also not sure why they used Wilcoxon signed rank test, although it's for pared data.
Shneker et al(2010)	IB	4.3 Are the measurements appropriate? Can't tell.	4.3→ No score 1/4 (they did not assess for validity or reliability; they did not report pre-testing the questionnaire).

* Abstract was excluded from the systematic review after this step as full-text was not obtained.

Appendix 9: Examples of the data analysis process

Code by the researcher	Quotation from the study	Theme (thematic analysis)	TDF domain (construct) matched
Knowledge and remember the content	Majority of the health workers 289 (82.57%) who had knowledge of the letters remembers the content while the rest did not (Sabblah et al., 2016).	Knowledge of alerts (knowledge of the alerts content)	Knowledge (knowledge) Memory, attention and decision process (memory)
Concerns of inadequate sedation as a result of the warning	'I am concerned that this has resulted in more patients having inadequate sedation for what can be very unpleasant and even distressing procedures. We need to learn how to use sedation safely, not just to reduce it. The major recent issue with midazolam is that SpRs (equivalent to a consultant in training) are now terrified of using more than minimal doses of midazolam, leading in many cases to under-sedation of patients for procedures such as colonoscopy.' Another clinician also commented on the risk of using insufficient dosing: 'I have had very experienced patients who have had repeated procedures over many years recently complaining that their latest procedures have been the most unpleasant they have ever experienced, and when I have reviewed the sedation doses, they are much lower than they used to be. An incomplete examination due to patient discomfort is important. When endoscopists are learning, they inevitably need greater doses of sedation than when they are experienced, sometimes just to top up a sedation that is wearing off, and this needs to be taken account of.' (Clinician comment) (Flood et al., 2015).	Attitude and concerns (concerns)	Beliefs about consequences (outcome expectancies)
Agree/not agree with level of adherence to the recommendation	However, only 39 (25.7%) of the 152 respondents agreed that the 48-h window for calcium avoidance described in the Health Canada Notice to Hospitals should be strictly heeded (Figure 2). Of these 39 respondents,	Attitude and concerns (attitudes)	Goals (implementation intention)

	24 (61.5%) agreed and 15 (38.5%) strongly agreed with strict adherence to the 48-h window. In contrast, about half (77 [50.7%]) of the respondents thought that the 48-h window for calcium avoidance did not require strict adherence. The remaining 36 respondents (23.7%) were undecided (Harder & Hawboldt, 2009).		
Use fluoxetine to avoid off-label use	About half of prescribing providers indicated that they now only use Fluoxetine to avoid off-label usage (Richardson et al., 2007).	Self-reported impact	Beliefs about consequences (consequences), due to liability issues
Source of knowing about the warning	The most common method of learning about the new recommendation was from the Pfizer Inc ‘‘Dear Healthcare Professional Letter’’ (Fogler et al., 2009).	Knowledge (possible factors affecting healthcare professionals’’ knowledge)	None
Institution position/interpretation of the warning[48]	Only 21 (14.7%) of 143 respondents described their institution’s official position regarding the administration of ceftriaxone and calcium-containing IV solutions within 48 h of one another as an absolute contraindication. Conversely, 88 (61.5%) participants described their institution’s official position on this scenario as a relative contraindication, where-by the benefit may outweigh the risk in individual cases. Almost one-fourth (32/143 [22.4%]) of respondents indicated that their institutions did not have a clear position on this issue (Harder & Hawboldt, 2009).	Perceptions about the alerts (perceptions about alert recommendations)	Environmental context (organisational culture/climate)

Appendix 10: Tabulation of the results of the included studies

Reference	Relevant results
Richardson et al. (2007)	• Awareness of the existence of antidepressants alerts was 100%. • The authors reported that only a few knew about the recommended frequency of follow-ups. • About 20% of participants were sceptical about the BW believing there was no risk or that the risk was low compared to the benefit. • About two-thirds of the participants (primary care providers) considered the recommended schedule unreasonable. Further concerns expressed included (1) a lack of space (the study did not specify space as physical or time); (2) the recommended frequencies would not be acceptable to patients and their families; (3) felt uncomfortable recommending additional follow-up visits, while not knowing the value of additional follow-ups; and (4) Providers who believed they could see two or three patients with acute complaints in the same amount of time as they could see one depressed young person, raised concerns about financial reimbursement (this study was conducted within the US healthcare system). • Participants in this study expressed concerns about the BW. They were specifically concerned about media attention and liability issues stating that most antidepressants' use by young people is off-label, and no clear guidelines are available for treating depression. • Approximately 20% of the primary care providers were somewhat sceptical about reporting the risk, adjudging it to be minor compared to the potential benefits, or not believing that there was a risk. • About half of providers stated that now they only use fluoxetine to avoid off-label use due to the alert related to the use of antidepressants in young people. • Some providers stated that they may be able to provide follow-up in collaboration with a psychologist. Nevertheless, a lack of communication might be a potential barrier to applying this strategy. • No specific policies or changes were made in any of the participants' practices as a result of the BW. • The authors first investigated factors that affect primary care physicians in treating depression. They found three main influences: a lack of mental health resources in the community, a sense of responsibility to help due to longstanding relationships with patients and their families, and the beliefs and preferences of patients and families. • This study also investigated providers' roles in treating depression. The authors reported that the factors that influenced providers' roles in treating depression were mainly the same factors that shaped providers' responses to the BW, which were access to mental health resources and providers' motivation to treat. Healthcare professionals' responses to the BW were divided into the following: o Those with lower motivation and greater access to mental health resources, who are less comfortable with the treatment of depression, but believe in the efficacy of medicine, especially in communities where mental health speciality care is available but with lengthy waiting times. They provided antidepressants for a limited period until the family could obtain treatment from a mental health specialist. Their response to the BW was described as being hesitant to prescribe and placing more emphasis on referrals. o Those with lower motivation and more access to mental health resources, in which counselling was perceived as more effective than medicines. They offered a few supportive counselling sessions, directed patients to counselling and community resources, and rarely prescribed medicines. Their response to the BW was to report that they had not changed their practices. o Those with higher motivation and more access to mental health resources: they appear to be more comfortable with depression and its treatment. They usually begin treatment with an antidepressant, but occasionally they provide informal counselling or support. These providers refer patients only if necessary. Their responses to the BW were described as being hesitant to prescribe, delaying any prescriptions and emphasising counselling. o Those with more motivation and less access to mental health: they are more comfortable prescribing medications than providing counselling. As a response to the BW, they were likely to be sceptical about the alert. They stated that they had not altered their practices apart from improving patient education and documentation.

	• Those with lower motivation and less access to mental health: they are more comfortable prescribing medications than providing counselling. Their response to the BW was characterised as being more hesitant to prescribe, and a few refused to prescribe unless the patient had an initial prescription from a psychiatrist, or the patient had anxiety as a comorbidity. The majority of these providers still prescribe when no other option is available.
Morrato et al. (2008).	• Among the sources cited by participants, no one source was used by all participants. • Sources were divided into: (1) scientific (medical newsletters, medical journals, colleagues, continuing medical education and medical treatment guidelines), (2) third party (internet services, popular press, drug software/personal digital assistant, Physician Desk Reference, product labelling, US FDA, medical insurance companies electronic medical records/prescribing alerts), and (3) drug company (medical affair [DHCP letter], sales representatives, professional drug advertising, and direct-to-consumer drug advertising). • Sources were divided based on how frequently they are used by physicians: (1) used most often (medical newsletters, medical journals, and colleagues), (2) used often (internet services, popular press, drug software/ personal digital assistant, Physician Reference Desk, Product Labelling, Medical affairs (DHCP letters) and sales representatives), (3) occasionally used (continuing medical education, US FDA, medical insurance companies, and electronic medical records/prescribing alerts), and (4) never used (medical treatment guidelines, professional drug advertising and direct-to-consumer drug advertising). • Participants used sources according to those they considered timely and unbiased and what style of continuing education they preferred. • Different opinions were expressed regarding the sources of medicines safety information in general, some of which included the following: o A participant focuses on what is of interest and importance to the participant themself. o A participant expressed receiving excessive amounts of sources through mail such as journals, brochures, and newsletters. The participant described a lot of them are redundant, but felt it is better to receive a large amount of information than an inadequate amount. o A participant expressed a preference to get information from various sources while ensuring information quality. o A participant indicated reading everything they received. Also, the participant reported trying not to use computers. • Scientific sources are regarded as the most credible and provide in-depth information; however, information might be overlooked or not found by physicians. • Except for journals, the authors reported that there was more variation at the level of individual physicians than between the two groups of physicians (psychiatrists and internists) in terms of their preferences for specific scientific sources. • Third-party sources are considered to be fast, readily accessible electronically, and can be customized according to the physicians' needs. Third-party sources, however, have mixed credibility. Physicians might not be able to assess the information before the patient requests it since the patient could learn the information at the same time as the physician. • Drug companies communicate with physicians through their representatives, explaining what risk means to their clinical practices and answering their questions, thus providing two-way communication. Companies are legally required to provide accurate information in their product labelling, as well as all the information they have about their product. Drug companies, however, are perceived as being the least credible and biased. It is also difficult to distinguish between what is evidence-based and what is simply promotional material. In addition, their targeted audiences may be limited depending on the medicines' indications and a physician's prescribing habits. • The use and the challenges reported regarding the participants' use of the different sources: • A few reported that the FDA website is difficult to use. • The general internists in the study did not know about the service of a free email alert about new medicine warnings. • Taking information from pharmaceutical representatives, while balancing it with clinical practice. • Avoiding pharmaceutical representatives. • HCPs expressed varying reactions towards drug companies' representatives, which ranged from being a source of information, but treating them with scepticism, to completely avoiding them. The reactions were as follows: to consider information from drug companies while balancing that information with their own experiences; representatives from competing companies are regarded as sources of information, talk with representatives for a short period to get samples, while not trusting the information they provide; or avoid drug company representatives. • DHCPs might be missed or discarded thinking they are advertising mail. • DHCP letters were not received. • Delays in receiving DHPCs, as information might have been known from other sources. • Medicine risk information in journals might be missed because of their location in the letters section or shorter articles.

	• Becoming immune to electronic record alerts.
	• Beliefs and opinions about the different sources:
	• Two physicians believed that the FDA was biased towards the industry; and one physician reported not listening to the FDA anymore, believing that the FDA is a bought and sold group.
	• One physician stated that the FDA was much better than a colleague's opinion.
	• Four psychiatrists reported using the safety alert service of the FDA's MedWatch and indicated that the free email of medicines alerts was useful. However, general internists did not know about this service.
	
	• Different attitudes about pharmaceutical representatives were reported, including:
	  o Considered them a source of medicine risk information, but were sceptical of them.
	  o Balance their information with one's own clinical experience.
	  o Avoided them completely.
	• The authors report that DHPCs have been discussed favourably, yet some issues have been identified, including late delivery, not receiving the letters, and difficulty in differentiating them from advertising mail.
	• A participant reported initially not trusting the Physician Desk Reference because it is developed by pharmaceutical companies. However, the same participant believed that pharmaceutical companies would provide all the information regarding the safety issues associated with their product.
	• Medical meetings were not perceived as an efficient source of information because these meetings did not usually address safety-related issues. The credibility of medical meetings was questioned because they were often sponsored by pharmaceutical companies.
	• The popular press was noted to be the first source of medicines' news by several physicians. News reports assist in attracting their attention to medicines risk issues for further reading. They are believed to improve physician-patient dialogue, yet there have been concerns about the public becoming aware of risks first.
	• Pharmacy alert systems have been criticised by physicians for not considering the whole clinical picture.
	• Concerns were expressed regarding becoming immune to electronic medical record alerts due to their frequent appearance.
	• A variety of medical journals and newsletters were mentioned by participants.
	• Several physicians indicated that first case reports of serious adverse events appear in other journals, so they subscribed to those publications to stay updated about medicines.
	• Participants perceived that treatment guidelines focus on medicines' classes, indications, and doses more than medicines' safety profile. Thus, treatment guidelines were not perceived as sources of medicines' safety information.
	• Colleagues as a source of information could be contacted through casual social interactions, patient consultations, or formal journal clubs.
	• Computer-aided and online sources were commonly described as reliable and timely. The authors reported that younger physicians were more likely to use these sources.
	• Specific electronic resources differed across the participants. Examples of software included Epocrates, MicroMedix, and Lexidrugs. Examples of online sources included psychopharmacology discussion groups, monthly drug safety rounds from the University of California San Francisco, WebMD, and searchable resources (e.g. P-450 drug interaction site and Up-to-Date.
	• Electronic patient systems were created by a few physicians to track the medicines used by the patients, assess medicine interactions, and act as an aid in contacting patients easily if necessary.
	• Questioned credibility of meetings if sponsored by a pharmaceutical company.

Kesselheim et al. (2017).	• Awareness about the existence of the Zolpidem and Eszopiclone alert was 100%.
	• Half of the participants (prescribers of zolpidem or eszopiclone if primary care physicians) did not know (or could not remember) that women were more likely to suffer from morning drowsiness from Zolpidem or that the FDA had asked pharmaceutical companies to lower the dose for female patients.
	• Sources of medicines' safety information used by physicians:
	  o Nine physicians used medical journals.
	  o Nine physicians used online medical sources.

	○ Nine physicians mentioned the FDA. ○ Six physicians mentioned news reports. ○ Six physicians mentioned point of care sources (formularies and electronic medical records). ○ Five physicians mentioned colleagues. ○ Five physicians mentioned conferences. ○ Four physicians mentioned a drug company (website, mailed materials and company representatives). ○ Three physicians mentioned advertisements (without specifying the source of advertisement). ○ Two physicians mentioned pharmacy inserts. ○ One physician mentioned social media. • No source mentioned by the respondents satisfied their expressed desire for high-quality information. • Physicians viewed academic sources (e.g. journals) as being third parties that are not directly influenced by financial interests, thus trusted these sources the most. • Online references (e.g. Medscape, MEDLINE, Monthly Prescribing Reference, Epocrates, and DyneMed) were considered reliable by about one-third of the participating physicians. • Concerns over conflicts of interest were expressed regarding sources from drug companies; these sources were considered unreliable due to possible bias. • A total of six physicians reported that drug company representatives were not permitted in their workplaces. • Some physicians reported that they received trustworthy information from drug companies. • Due to time constraints, physicians reported avoiding using online references. • Other physicians reported difficulty using the FDA website, thus they did not use it often. One physician described an information overload that occurs when using the FDA website, where information might pertain to the regulatory aspects of medicine instead of the medicines safety issues that would be relevant to physicians' practice. • Physicians reported using multiple sources of information mostly to confirm information obtained from the lay media or medicine advertisements. • One physician noted that it is easier to read the information published by a drug company and then double-check the evidence after that. • The lay media was the most common source through which participants learned about the alert. Some knew about the alert from professional journals, Medpage, other health newsletters and the FDA website. • One physician described a new safety alert as "hit-or-miss" and expressed that they might not have the time to read the alert in detail. • One physician noted that they have no concerns regarding the accuracy of information as they believe it has been reviewed rigorously and they tend to trust it. However, it was unclear from the quotation whether the participant was referring to sources from journals or other sources in general. • The authors found that most participants welcomed the sleep aid medicines alert. The authors attributed this to participants' reluctance to prescribe these medicines, and the alerts supported their arguments against using them. • Concerns about patient dependence on sleep aids medicines were voiced. • In addition, the same physician noted that it can be challenging to help the patient understand safety issues particularly since they are not sleeping, they are fatigued and not functioning well, and many of the patients are willing to compromise some safety for the sake of getting adequate sleep.
Barker et al. (2019).	• The authors found several matters that may contribute to variations in patient safety information received by pharmacy staff, which were related to the managers' various reactions to the information received, as follows: ○ Filtering the information before sharing it with staff, making it available for employees and assuming it was read, and leaving it on the counter for other staff to read it if it was significant. ○ Reviewing the safety concern when it was relevant information or hospital-related information that was relevant to their population, and then discussing it with the staff at the quarterly meetings. ○ Not always reading the information, discussing the events that occurred in their own pharmacy, rather than events they received by email, and not always reading the email when they received it, but the participant would read it when they had the chance, even if the information did not specifically pertain to their practice, as the information would serve as a reminder.

	○ In one pharmacy, the manager is the only one who reads and shares the information, while both the manager and the associate receive the email. Hence, the email would not be shared if the manager did not share it. This participant usually prints out the bulletin, scans it, and reads its details. The same manager will then discuss it and share it with everyone if it is relevant to their practice. ○ Staff members receive weekly and monthly reminders about quality-related events, and they review the information as soon as they receive it. ○ The participant noted that although the web is supposed to be reviewed daily, it is probably not reviewed every day. • Sources for receiving safety information included: the company owning the community pharmacy. • Type of safety information received: A pharmacy manager explained that they received weekly reminders regarding quality-related events or general information based on the situation (e.g. flu shots). Their company also sends them scenarios about quality incidents, so they can be vigilant (e.g. sound like and look like medicines). • Challenges for using the sources for medicine safety information: ○ Being interrupted can interfere with the completion of reading an article, thus having the article online was advantageous to completing reading it at home ○ Lack of time was a barrier for a certain pharmacy to access and utilise information from external sources, thus, they discussed events occurring within their own pharmacy. Furthermore, the lack of time and the multiple tasks made it difficult to assess, filter, read, reflect, and implement the information. ○ Patient safety information does not get immediate attention due to staffing issues and the nature of pharmacy work. A pharmacy manager has noted it is time-consuming to get into patient safety information and would like access to resources or a guide for using patient safety information tools. ○ There are several barriers to using patient safety information sources, including sources overload (challenging to access, retain, and update information with a large number of sources), content overload, limited time, and complex information systems, making it difficult to navigate and find the relevant information. ○ Managers are concerned that patients' safety information fails to account for the complex and evolving pharmacy environment. ○ Moreover, pharmacy managers reported having to filter the information received since much of it is not relevant to community pharmacists. Consequently, the pharmacists could not understand the overall value of the information they received. • Pharmacy managers reported a range of barriers including sources overload, content overload, lack of information relevancy, source-system complexity, and lack of time, had affected their ability to access, filter, read, reflect, and act on the safety information, despite their desire to use this information in their practice. It was time-consuming to access information from external sources, easier to discuss incidents in their own pharmacy.[65] a. Due to receiving irrelevant information, the overall value of the patient safety information received was not apparent to the pharmacists.[65] 2. Information overload with the volume of emails received (and information getting lost among the many emails received and easier to pick up a fax).[65] 3. One pharmacy manager noted that they are not getting the type of information they are interested to know about, or at least they do not know how to access this information.[65]Complex information systems, making it difficult to navigate and find the relevant information.[65]
Kloet et al. (2017).	A knowledge deficit was one of the reasons for BW non-adherence in both the general medicine floor and intensive care units. • On the general medicine floor, 23 medicines (celecoxib, conjugated estrogens, diclofenac topical, Divalproex ER, emtricitabine-tenofovir, etodolac, indomethacin, ketorolac, medroxyprogesterone, risperidone, ritonavir, 8 cases involved ibuprofen, and 4 naproxen cases) were linked to BW non-adherence, 13 of which were home medicines. • Twenty-one of the BW non-adherence incidents on the general medicine floor were related to drug–disease interactions, one drug–laboratory interaction, and one BW classified as a drug–drug interaction. • The reasons for BW non-adherence in general medicine included acceptable risk-to-benefit ratios, a knowledge deficit, and deferring intervention until communication with the primary care provider. In six cases, the authors were not able to assess the reason for BW non-adherence because the patient was discharged before the research team communicated with the patient care team. • The majority of nonadherent BW medications in general medicine were prescribed by postgraduate year 1 PGY1 residents, followed by PGY2.

	• In the intensive care units, BW non-adherence occurred with11 medicines (6 of which were home medicines). Medicines with BW non-adherence that occurred in the intensive care units included: cyclosporine (3 cases), fentanyl patch, formoterol, gentamicin (2 cases), indomethacin, minoxidil, risperidone, and valganciclovir. • Six of the BW non-adherence incidents occurring in the intensive care units were classified as drug–drug interactions, four were drug–disease interactions, and one was a drug–laboratory interaction. • Reasons for BW non-adherence that occurred in the intensive care units included acceptable risk-to-benefit ratios and knowledge deficit. BW non-adherence was common among critical care fellows (36.3%) and PGY1 medical residents (36.3%).
Reed et al. (1999).	• About 28% of paramedics reported that chest pain medicines administered to patients would not be affected by the use of sildenafil. • About 59% of the participants stated receiving guidelines about the management of chest pain patients who take sildenafil. • Only 17% of participants reported that their chest pain treatment protocols had changed since the introduction of sildenafil.
Richards et al. (2003).	• Awareness about the existence of the droperidol alert was 91%. • The physicians' opinions about the alert were as follows: o 53% (n = 242) felt that the droperidol alert was unjustified. o 0.4% (n = 2) thought that droperidol should be banned entirely. o 4% (n = 20) thought that the alert was completely appropriate. • Only 8% of the participants were not concerned about the potential loss of droperidol from the market as was the case in Europe. • Droperidol was no longer available in 122 (24%) of respondents' emergency departments after the FDA alert. • Around 42% (n=137) of physicians who prescribed droperidol for agitation in the emergency department believed there were no other medicines with greater efficacy. • 28% (n=116) of physicians who used droperidol as an antiemetic in the emergency department believed no other medicines were effective than it. • A significant decrease (P<0.001) was seen in physicians' opinions about droperidol's overall utility in the emergency department following the FDA alert. Droperidol was rated as extremely useful by 200 (44%) physicians before the FDA alert, but by only 69 (15%) physicians afterwards. • 304 physicians (67%) reported that droperidol's alert affected directly their ability to treat patients in the emergency department. However, the nature of this effect was not reported in this article.
Mazor et al (2005).	• Based on the physicians' rating, the authors identified the following areas of deficiencies in the letters: o Deficiencies in clarity of the writing (occurred in about 25% of the letters). o Deficiencies in readability (occurred in about 28% of the letters). o Deficiencies in the ratio of relevant information to supporting information (occurred in about 36% of the letters). o Deficiencies in key information being readily apparent (occurred in about 36% of the letters). o Deficiencies in the overall effectiveness of communication (occurred in about 28% of the letters). • For all letters, the information included was rated as important by the participants. • Physicians stated that they would likely change their practice in response to most of the letters they rated. • Participants rated letters with special formatting higher than letters without. • Ratings of letters' formatting were related to the total presentation quality ratings, perceptions about the criticality of the information included in the letters, and intention to change practice due to the letters. • Length of the letters or placement of key information were not significantly related to the ratings of the letters.

	• The authors reported not evaluating the effect of the content of the letters due to the lack of variation in content characteristics. • Information was seen to be important in all letters. • Primary care physicians (internists) stated that they would likely change their practice in response to most of the letters they rated.

Habib et al. (2007).	• 92% of 284 respondents felt that the droperidol alert was unjustified.
	• The 123 individuals who stated that they currently never use droperidol reported the following reasons:
	  o Medicolegal reasons due to the FDA BW (39%).
	  o Droperidol is not available (30%).
	  o Other medicines are perceived by respondents to be more effective (15%).
	  o Droperidol is dangerous (1.5%).
	  o The authors reported that other reasons were given (14%), but they did not specify these reasons.
	• Ff 292 respondents, 33 (11%) reported that droperidol was available before the FDA black box warning but not afterwards, although it was not specified if it was as a result of the alert or not.
	• Of 230 respondents, 169 (about 74%) respondents reported that their hospitals did not impose any restrictions on the availability or use of droperidol, 22 (about 10%) reported that droperidol stock locations were changed by their hospitals, and 50 (about 22%) respondents reported that their hospitals imposed restrictions on the use of droperidol.
	• Before or after the black box warning, there was no association between type of practice (academic or private) and physicians' decisions regarding the use of droperidol for prophylaxis or treatment. Also, there was no association between the type of practice (academic vs private) and physicians' change of practice regarding droperidol use after the warning. The authors reported that the same was found with physicians' years of experience, except that prior to the BW, physicians who had more than 10 years of experience were more likely to prescribe droperidol for prophylaxis than physicians with fewer than 10 years of experience (P=0.008).
	
	60% of 284 participants reported that they would use droperidol as their first line medicine for postoperative nausea and vomiting prophylaxis if the alert was lifted.

Bhatia et al. (2008).	• This study included professionals from different backgrounds (physicians, nurses, and physician assistants) who were either family medicine clinicians, paediatric clinicians, or psychiatric clinicians. • The awareness level among the participants about the existence of the alert was 96.8%. • The authors reported that the awareness level was consistent across specialities (mean 95.0%, standard deviation 8.2%). • 49.2% of the clinicians were "moderately comfortable" to "comfortable" about prescribing antidepressants to children and adolescents, a finding that was consistent between urban (48.7%) and rural (51.9%) clinicians. • Only 8.3% of respondents were "very comfortable" prescribing antidepressants. • The most likely group of clinicians to report feeling "very comfortable" were psychiatric clinicians (27.2%), followed by paediatric clinicians (8.3%) and family medicine clinicians (5.1%), although it was not reported whether these differences were significant or not. • About 21.9% of the respondents reported that caregivers or patients refused antidepressant medication treatment because of the alert. Clinicians who report refusals report that, on average, 20.1% (SD 19.2%) of caregivers and 9.1% (SD 15.1%) of patients refuse treatment with antidepressants.

Cheung et al. (2008).	Awareness about the existence of the antidepressants alert among participants was 72%.
	• The authors compared the participants' stopping of treatment with SSRIs at two points:
	  o Among those who observed or did not observe activation (aggressive behaviour or agitation):
	  ▪ 18% (n=18) of those who observed stopped SSRIs compared to 4% (n=17) stopping the SSRIs among those who did not observe activation stopped treatment (P< 0.001).
	  o Among those who had observed any of the side effects included in the alert (worsening depression or suicidality, or new-onset suicidality).

	▪ 25% (n = 10) of physicians observing any of the side effects stopped treatment with SSRIs compared to 6% (n =2 5) stopping SSRIs among those who did not observe any of the side effects (P<0.001). About 7.9% of 484 participants reported that at least one of their patients stopped medicines by themselves because the patient was concerned about the alert.
Cordero et al. (2008).	• Awareness about the existence of the antidepressants alerts was 96%. 74% of the participants had read the BW label. • 91% of participants inaccurately thought that patients had died from suicide in the aggregated clinical trials. • Those who were more likely to disagree with the presence of the warning were more likely to believe inaccurately that patients had died in aggregated trials (p=0.037). • There was no relationship between the length of a license and experience and the likelihood of making an error regarding the nature of the risk in the alert. • Steps taken by HCPs to understand the warning included: Pursuing additional supervision, consultation, continuing education and reading. • 41 participants were somewhat concerned about adverse events, while 14 were very concerned. Areas of concern were the risk to patients (reported by 89 individuals), malpractice (reported by 35 individuals), and lawsuits (reported by 31 individuals). The percentages did not sum to 100% due to skipped questions by the participants, and some questions allowed doe multiple responses. • Having a false belief that suicide deaths occurred in the aggregated clinical trials did not predict that the patients would refuse to take antidepressants. •
Fogler et al. (2009).	• Awareness about the existence of the nelfinavir mesylate alert was 57%. • Knowledge about the nelfinavir mesylate alert differed across specialities as the following: o Infectious disease physician (21/26; 80.8%). o Obstetrician/gynaecologist (12/36; 33.3%). o Primary care physician (family/internal medicine): (15/29; 51.7%). o Other physicians (3/5; 60%). o Nurse practitioner/certified nurse-midwife: (13/18; 72.2%). o Pharmacist: (5/7; 71.4%). • At the time of the study, one participant had a pregnant patient taking nelfinavir without being aware that the medicine should be discontinued. • The lowest level of awareness was among obstetricians, who were about half as knowledgeable again as all other providers combined (57, 67.1%, P < .001). • Being aware significantly increased as the number of HIV-infected patients increased in the participants' practice (P=0.013). • Participants with more than 50 HIV-infected patients were 2.54 times as likely to be aware of the alert as participants with 1–3 HIV-infected patients (P < .01). • Among the 69 participants who knew about the alert, the most common source of information was Pfizer Inc's "Dear Healthcare Professional Letter". • The sources for being aware of nelfinavir alert (20 participants stated multiple sources, and 10 were unsure): o Pfizer Inc Dear Healthcare Professional letter (24 participants). o Colleague (12 participants). o Internet (e.g. FDA website. Medscape; 9 participants). o Email (8 participants). o FDA listserv (8 participants). o Other listserv (6 participants). o Pharmaceutical representatives, usually from a company manufacturing a competing protease inhibitor (6 participants). o Other (not specified in the article; 8 participants).
Harder et al. (2009).	• Participants described the official position of their hospital towards the alert as follows: o 14.7% of 143 participants described it as an absolute contraindication. o 61.5% of 143 participants described it as a relative contraindication, in which benefits might outweigh risks in some cases. o 22.4% of the 143 participants stated that their hospital had no clear position on the alert. • A source of knowledge about a specific safety issue was hospitals issuing a warning memo to healthcare professionals. The authors did not examine how healthcare professionals came to know about the alert, but this was reported as a hospital response to the alert, in which 57.9% of 145 participants reported that their hospitals sent a warning memo to healthcare professionals.

	• While 15.8% of the participants stated that ceftriaxone was the only third-generation cephalosporin on their respective hospitals' formularies, the majority (65.1%) reported that both ceftriaxone and cefotaxime were listed. • 25.7% of respondents believed that the recommended 48-hour separation of ceftriaxone and calcium-containing solutions should be adhered to strictly. • About 50.7% of the participants felt it was not necessary to adhere strictly to a 48-hour calcium avoidance window. • 23.7% of participants were undecided about the need to adhere strictly to the 48-hour calcium avoidance window. • 61.2% of the participants said they have or would have a direct role in influencing their hospital's responses to the alert. Among these respondents, 60.2% disagreed with the recommendation, followed by 17 participants (18.3%) who agreed, and the least portion were undecided. • 84.9% of participants reported concerns about Health Canada and the manufacturing warning; however, the specific area of concern was not reported. • 145 participants answered the question regarding their hospital's response to the alert, as follows: o 3.4% took no action. o 57.9% issued a warning memo to healthcare professionals. o 54.5% added a computer alert to notify pharmacists about concomitant orders for ceftriaxone and calcium-containing products. o 67.6% made policy changes related to the administration of ceftriaxone (an example given was policy change in the local IV monograph). o 0.7% was not applicable as ceftriaxone was not in their institutional formulary. • The open-ended responses indicated that several institutions adjusted restriction policies and introduced new auto-substitution policies to reduce the use of ceftriaxone in favour of cefotaxime. • The authors asked about the formulary implications of the alert. Of 142 participants, 106 (74.6%) reported that removal of ceftriaxone from the formulary was not considered, while only four participants (2.8% of 142 participants) stated that ceftriaxone was removed from the formulary or is being considered for removal due to the alert.
Karpel et al. (2009).	• Awareness about the existence of the long-acting ß-agonists (LABAs) alert was 97%. • Awareness of the alert among the different physicians' specialities was as the following: o Allergy: 100% of 395 allergists o Family practice: 93.2% of 132 family physicians o Internal medicine: 87.8% of 141 internists o Pulmonology: 98.1% of 429 pulmonologists o The awareness of ten paediatricians was not assessed independently due to their small number. • About 10% difference in self-reported levels of awareness were found among specialities (pulmonologists and allergists) compared to primary care providers (99 vs 90.8%, respectively) P<0.001. • 57% reported being very familiar, 28% somewhat familiar, and 14% not familiar with the Salmeterol Multicenter Asthma Research Trial (SMART). According to Karpel et al., it is a published study that led to the BW. • 7.8% of pulmonologists, 39% of internists, 48.1% of family practice physicians, and 1.3 of allergists were not familiar with SMART. • Participants' opinions regarding the alerts' placement were as follows: 50.6% disagreed, 29.5% agreed, and 19.9% were uncertain. • Primary care providers had a significantly higher agreement with the alert compared to other specialists (45.6% vs 24.2%, p<0.001). Specifically, 23.1% of allergists, 25.2% of pulmonologists, 52.9% of family physicians, 40.3% of internists agreed with the alert. • A spill-over effect was reported more with primary care providers than with specialists (p<0.001) in LABA prescribing in COPD.

Shneker et al. (2009).	• In the open-ended answers, participants reported the following:
	  o Suicide in patients with epilepsy was neither related to antiepileptics, nor epilepsy, but it is related to comorbid psychiatric conditions (n = 11).
	  o The suicide rate is low or not an issue in epileptic patients (n = 9), some reports based on personal experience.
	  o 13 participants reported concerns about the FDA's analysis and presentation of the data.
	• The FDA alert was not rated highly for clarity. The participants' mean rating (ranging from one to ten) of the clarity of the FDA alert was 5.3 (SD: 2.5), with one being very confusing and ten being very clear.
	• In the answers to the open-ended questions, the following was reported by the participants:
	  o Concerns were voiced relating to the alert's effect on decreasing patients' compliance and leading to a possible negative impact (n = 9).
	  o Concerns that the alert could lead to litigations (n = 5)
	  o Two comments mentioned an antiepileptic that might lead to suicidality in patients with epilepsy.
	• 96% of the participants indicated that there is no need to send letters to all patients regarding the alert.
	• The FDA alert did not score well on the appropriateness (ranging from one to ten), according to the authors. The mean of the participants' ratings of the appropriateness of the alert was 4.1 (SD: 2.1), from one (not appropriate) to ten (very appropriate). Nevertheless, it was not clarified on which aspect it was considered appropriate or not.

Garbutt et al. (2010).	• Awareness about the withdrawal of cough and cold medicines in children less than two years of age was 100%.
	• Sources by which physicians became aware of the alert were as follows (they could choose more than one source):
	  o non-medical media (87%)
	  o medical newspapers (59%)
	  o physician colleagues (38%)
	  o peer-reviewed medical journals (28%)
	  o patients/parents (13%)
	• 75% of the participants agreed with the alert on OTC cough and cold products, 13% disagreed and 12% were uncertain.
	• 46% of physicians reported no barriers to implementing the alert.
	• Barriers to implementing the alert reported by physicians included the following:
	  o treatment demands from parents (48%)
	  o reaching consensus among practice partners (15%)
	  o a lack of parents' educational material (14%)
	  o office staff education (10%)
	  o disagreeing with the alert (9%)
	• feeling the need to make a recommendation (4%)

Saad et al. (2010).	• Awareness about the existence of the Antipsychotic alert was 98%. • Most of those who were very familiar with the alert were practising in a nursing facility and a teaching hospital. • A need for guidelines to be developed to address the alert was reported by 85% of the participants. • Reasons for not considering the alert included a lack of alternative treatment, a lack of guidance, a lack of evidence and poor data availability. Participants cited barriers for considering the alert (participants could report more than one barrier) including: • No alternative treatment available (48%) • Lack of guidance (42%) • Lack of evidence (11%) • Poor data availability (8%)

	About 85% of participants reported that guidelines are needed to address the alert. •
Yaghmai et al. (2010).	• Awareness about the withdrawal of cough and cold medicines in children under the age of two was 100%. • About 82% knew the FDA is considering removing cough and cold active ingredients from medicines for children under the age of six. • Physicians who were aware of the FDA considering removing active ingredients from cough and cold products in children under the age of six y had significantly more years in practice than physicians who were not aware of this proposed recall (P = .050). • 78.2% of the participants agreed with the withdrawal of cough and cold medicines for children under the age of two, while 67% of participants would agree with the proposed removal of these medicines from children under the age of six. • 78.8% of respondents said that they were unlikely to change their practice in light of the withdrawal and FDA proposal since they did not routinely prescribe these medicines.
Esterly et al. (2011).	• Awareness about the existence of the Ceftriaxone-calcium interaction alert was 100%. • The number of employee hours invested by respondents' hospitals in interpreting the alert was as follows: o 70 hospitals devoted between 1 and 49 employee hours. o 7 hospitals spent between 50 and 99 employee hours. o 1 hospital invested more than 100 employee hours to address the alert. o 11 hospitals were unable to quantify the time invested. • Some hospitals had different interpretations of the same alert regarding ceftriaxone and calcium interaction. • A source of information about the alert: Information provided by institutions to their healthcare providers (sources were not specifically investigated). • The participants were asked how their hospitals interpreted and applied the alert at two points in time, immediately after it was released and a year after it had been released (in one survey). The following were reported: o Ceftriaxone should never be used in neonates (40 hospitals initial response, and 38 hospitals about one year later). o Ceftriaxone should never be used in neonates within 48 hours of administering calcium-containing products (45 initially, and 42 one year later). o Ceftriaxone should never be used in adults within 48 hours of administering IV calcium-containing products (26 initially, and 25 one year later). o Ceftriaxone should never be used in adults within 48 hours of administering any form of calcium-containing product (5 initially, and 1 one year later). o Ceftriaxone should never be used in any patients (0 initially, and 0 one year later). • After the FDA alert, about 52% (n=49) of participants reported that at least one drug use policy change had been implemented at their institution. • Respondents who specified changes reported the following: o In 22 institutions, computerised alerts to the medication order entry system and/or the ceftriaxone intravenous bag label before dispensing were added. o A pharmacist review was the method used by three institutions to identify potential interactions. o Ceftriaxone was prohibited in 14 institutions if the patient had been receiving any calcium-containing product within the previous 48 hours. Seven of the 14 institutions used cefotaxime as an alternative treatment. o Fourteen of the institutions informed their providers about the alert, but they left the decision regarding concomitant ceftriaxone and calcium use to the prescribing physician. o Ceftriaxone was prohibited in 11 institutions. o One institution reported banning ceftriaxone use in infants up to 3 months old. o In four institutions, ceftriaxone was not permitted for infants under one year of age. • Only one institution reported that ceftriaxone was removed from their formulary after the FDA alert. • After the FDA alert, 11 institutions added at least one item to their formulary, with cefotaxime being the most commonly added item (reported by nine institutions). • 49 respondents listed the most commonly involved decision-makers in drug use policy changes, which included committees (Pharmacy and Therapeutics or Antimicrobial subcommittees; n=49, 100%) and infectious disease pharmacists (n=37, about 76%).
Théophile et al. (2011).	• Awareness about the existence of the vitamin D alert was at 67% among pharmacists, 49% among paediatricians, and 48% among general practitioners.

	• Among the twenty GPs who reported they did not change their explanation because of the alert, two mentioned that they had already been explaining the administration of vitamins similar to the alert before its release. There was no explanation as to why the remaining GPs, pharmacists, and paediatricians did not change their counselling.
Piening et al. (2012).	• HCPs' alert-related knowledge levels ranged from 56% (for etoricoxib) to 88% (for clopidogrel). • Among HCPs, 16% were unfamiliar with DHPCs (ranging from 5% hospital pharmacists to 28% of the general practitioners, $p<0.001$). • Pharmacists in this study were more aware than physicians in all safety issues ($p<0.001$) except etoricoxib, in which primary care HCPs, including GPs and community pharmacists, (67% and 71%, respectively) were more aware than secondary care providers (interns and hospital pharmacists: 40% and 51%, respectively; $p<0.001$). Details about each profession's awareness levels of each letter are presented in a figure, in which the percentages can be estimated but the exact numbers cannot be determined. • The sources by which most HCPs became aware of the four alerts were professional journals (59%) and DHPC (49%). • The MEB website was less frequently cited (5%) as a source from which HCPs learnt about the four alerts. • 58% of the HCPs read only the DHPCs that are relevant to them, with 30% of community pharmacists reading all pharmaceutical industry letters ($p\leq0.001$). • 64% of the respondents never visited the MEB website to learn more about safety issues. • 7% of HCPs were unaware that MEB existed. • The MEB was more known by hospital and community pharmacists and more frequently visited by them than internists and general practitioners ($p\leq0.001$), but 38% of pharmacists visited the MEB website monthly or every six months. • The MEB website was visited by only 6% of respondents weekly and only 1% daily. • HCPs' satisfaction with the current way (at the time of the study) for communicating medicine risk information (DHPCs) was rated as 6.9 (mean) + SD 1.9 (scale from 1: Very poor to 10: very good). This ranged from an average of 6.0 + 2.1 by GPs to 7.6 + 1.4 by community pharmacists ($p \leq 0.001$). • Most health professionals were neutral or did not have an opinion on whether updating their knowledge about medicine safety takes too much time (mean + SD [2.56 + 0.9]) as assessed by a 5-point Likert scale (1: strongly disagree to 5: strongly agree). • GPs (2.80 +1.0) more commonly indicated that being updated with medicine safety information is time-consuming, and community pharmacists were the least frequently updated (2.39 + 0.9; $p \leq 0.001$). • HCPs considered the MEB knowledgeable about medicines (4.06+0.7) as assessed by a 5-point Likert scale (1: strongly disagree to 5: strongly agree). • HCPs considered the pharmaceutical industry knowledgeable about medicines (3.91+ 0.7). • HCPs trusted risk information from the MEB (4.13 + 0.6) more frequently than the information from the pharmaceutical industry (2.70 + 0.8; $p \leq 0.001$) as assessed by a 5-point Likert scale (1: strongly disagree to 5: strongly agree). • Specifically, GPs trusted the information provided by the MEB significantly more than information provided by the pharmaceutical industry ($p \leq 0.001$). • Safety information was considered important (mean + SD [4.67 + 0.6]) by most HCPs as assessed by a 5-point Likert scale (1: strongly disagree to 5: strongly agree), which ranged from an average of 4.55 + 0.5 (GPs) to 4.77 + 0.5 (hospital pharmacists; $p<0.0001$). •
Bell et al. (2013).	• 73.9% knew about the presence of at least 4 of the 5 alerts (one was a control question with no risk, and another was an evolving risk at the time of the study). • 29.3% of neurologists knew the exact risk of at least 4 of the 5 alerts related to antiepileptics, only 6.7% of the participants knew about all the five alerts. • Using a speciality organisation as a general source of drug safety information was associated with an increased level of general knowledge (knowing the presence of an alert ($p = 0.001$)) and specific knowledge ($p = 0.012$). • A modest increase in knowledge was associated with the number of epileptic patients treated annually (general knowledge, $p < 0.001$; specific knowledge, $p = 0.002$). • Participants' type of practice, region of practice, years in practice and age were not associated with their knowledge about the alerts. • Neurologists reported their sources of medicine safety information as speciality organizations (67.1%), published literature (67.1%), colleagues and/or peers (53.1%), and CME or other educational programs (52.9%), product insert (48.5%), MedWatch (43.6%), free speciality journals (43.6%), pharmaceutical representatives (40.8%), and the FDA website (16%). • The authors reported that many neurologists had more than one source for medicine safety information.

	• Many of the sources of drug safety information used by responding neurologists in academic and private practices were similar. • Academic neurologists were more likely to obtain their knowledge from colleagues and peers (59.2% private, 75.1% academic), while private practice neurologists were more likely to acquire their knowledge from pharmaceutical representatives (54.8% private, 23.4% academic). • Neurologists' awareness about the existence of the alert was as follows: ○ Awareness about FDA recommendation to perform haplotype screening before initiating carbamazepine therapy in patients with Asian heritage: 81.2% ○ of respondents reported that they were aware of this 2007 FDA recommendation. ○ Suicidal ideation with newer AEDs ○ Of the respondents, 80.6% were aware of the FDA warning regarding ○ suicidal thoughts. ○ Increased risks for birth defects with Valproate exposure (79.0%) ○ of respondents were aware of the increased risk of birth defects in the offspring of mothers treated with divalproex. ○ IQ changes with Valproate (83.2%) • The authors of this study used lacosamide as a control, in which 368 (72.9%) correctly responded that there were no BW for locsamide. • Neurologists' knowledge about a specific detail in the alert was as follows: ○ Knowledge about the exact level of risk Hypersensitivity reactions in Asian patients (73.9%). ○ Identifying the risk of suicidal ideation with newer AEDs as 4.3 per 1000 (60.2%). ○ Congenital malformations with Valproate (33.5%). ○ IQ changes with Valproate (48.9%). 16.9% were unaware of the risk of Valproate exposure during pregnancy on the IQ risk of the child, while 30.7% reported that these risks are not established. Although at the time of the study the authors reported that the Valproate product insert does not mention this specific risk, it mentions that there have been reports of developmental delay, autism, and/or autism spectrum disorders in children born to mothers who were exposed to Valproate during pregnancy. • The authors reported that many neurologists commented that: ○ The findings and recommendations of the FDA are controversial. ○ Suicidality is a vague concept. ○ Good clinical practice does not require knowledge of the exact risk of suicidality. • The authors also reported that many neurologists stated awareness of an increased risk for birth defects might be sufficient, but not of this particular risk. • Most respondents (93.3%) counselled female patients who are planning pregnancy about the risk of valproate birth defects.
Flood et al. (2014).	• Awareness about the existence of the midazolam alert was 63% (32% were not aware, and 5% did not answer the question). • The risks of midazolam overdose were known among 93% of the participants, before the release of the alert (2% were not aware, and 5% did not answer the question). • Participants in the study were asked if they were aware of the potential risks to patients of routinely using flumazenil as a reversal agent for midazolam before the release of the alert. Of the participants, 89% were aware, 6% were not aware and 5% did not answer this question. • Concerns about insufficient sedation in patients following the midazolam alert were reported by four respondents, especially with more junior staff afraid to use higher doses when they were clinically appropriate. • One participant expressed a concern that patients might have inadequate sedation that could result in an unpleasant and distressing experience for the patient. The same physician expressed the view that they should learn about the safe use of sedation rather than reducing it. • 49 individuals (49%) reported knowing the lead person responsible for implementing the NPSA report (46% do not know the lead person, and 5% did not answer the question). • Four of the free-text responses (out of 15 qualitative responses) mentioned that prescribing low-strength midazolam was a recent change that has become widespread. • 20 % of the participants reported that before the release of the alert, low-strength midazolam was not routinely available in the wards. • When asked whether low-strength midazolam is routinely available in the wards of the participants' healthcare institutions, 80% responded yes, 11% no, 6% did not know, and 3% did not answer this question. However, it was not specified whether this question reflected the periods before or after the release of the alert.

	• Another participant reported that patients who previously undertaken the procedures reported having a most unpleasant experience. After reviewing the sedation doses, the participant found the doses much lower than before. The participant also commented that incomplete procedures caused by patient discomfort are important. The same participant indicated that inexperienced endoscopists need greater doses of sedation. This could be to compensate for sedation wearing off.
Sabblah et al. (2016).	• 38.34% of participants knew of at least one letter. • Participants in this study were most familiar with diclofenac (60%) and least familiar with codeine (37.18%). • 82.57% of the participants who knew about the letters remembered their content. (It was not mentioned if a specific part or information included in the letters was used to evaluate the HCPs' recall of the letters. However, the authors reported the proportion of participants remembering the content and the safety issues presented in the letters). • A higher percentage of nurses (68.42%) knew of at least one of the six letters than pharmacists, physicians' assistants, or doctors, $p<0.0005$. Details about each profession's awareness levels of each letter are presented in a figure, in which the percentages can be estimated but the exact numbers cannot be determined. • A greater percentage of nurses (92.31%) remembered the content of the letters compared to physician assistants (86.05%), pharmacists (81.25%) and doctors (75.61%). • Of 911 respondents to this question, 497 (54.56%) had never received a letter from the FDA (Ghana) and the rest had. • Among participants who read the letters, 192 (54.82%) and 151 (43.14%) participants rated the level of understanding of the language as good and satisfactory, respectively, while only two participants (0.57%) rated the language as poor. • No significant difference was found between the health workers' ratings of the language used in the letters. • 235 (65.73%) respondents rated the relevance of the DHP letters as good and 122 (34.27%) respondents rated them as satisfactory. • 183 (53.67%) of those who were aware of the letters received them directly from the Food and Drug Administration, followed by 136 (39.88%) from their hospital facility. Other sources included colleagues, professional associations, the internet, Medscape and regulatory bodies like the Ghana Medical Council, the Pharmacy Council and the Nursing and Midwifery Council. • Most of those who received the letter 318 (90.86 %) received it as a hard copy and the rest as a soft copy. The medium of delivery was deemed effective by 255 respondents (72.86%). • Among those who received the letters, 161 (46%) received them within two months, while 134 (38.19%) received them two months after their issuance. • 55 (15.71%) responded that they could not recall at what time these letters were received. Nearly all regions received the letters around the same time. Regions did not differ in how long it took to receive the letters.

Smollin et al. (2016).	• 36.3% of participants correctly identified medicines with BWs.
	• Only 13.3% remembered the alerts' content. Participants' ability to correctly identify the content of the BW ranged from 2.5% for haloperidol to 28.4% with metformin.
	• The ability of attendings and residents to correctly identify the content of a BW did not differ statistically significantly. In addition, no statistically significant difference was found in residents' ability to identify the content of the BW based on their year of training.
	• Among the five medicines with BWs, the most identifiable medicine was haloperidol (by about 65% of participants) and the least was midazolam (by about 12% of participants).
	• 90% of the respondents described BW's definition correctly.
	• Attending physicians and fellows were more able to identify medicine with/without BW than residents ($P<0.05$).
	• A significant increase in the ability to identify medicines with or without BWs with increasing years of training was found among the residents ($P<0.05$).
	• 83.8% of the participants had accurately identified medicines without BWs (over 75% accuracy for each of the medicines without BW, while more than 50% of the participant incorrectly identified ondansetron as having a BW).
	• Of respondents, 29% indicated that they were not up to date with BW information or had no way of being updated.
	• Sources by which participants are updated with new medicines safety information include:
	  o Websites or mobile applications (Lexicomp or Epocrates as examples) were reported by 31% of the participants.
	  o Clinical pharmacists, reported by 22%.
	  o Word of mouth (specific source was not mentioned), indicated by 9% of the respondents.

	○ Other sources were reported without specifying the percentage of participants citing them, including the FDA website, CME courses, newsletters, podcasts, email notifications, and journals. • Among emergency physicians, 37% stated that they consider BW in their prescribing practice. • Among paediatricians, 52% indicated that they consider BW in their prescribing practice. • Among attending physicians, 74% reported that they consider BW in their prescribing practice.
de Vreis et al. (2017).	• Generally, GPs were more familiar with DHPCs than national competent authorities (NCA) communications and educational materials. • GPs in Spain, Norway, and Sweden were more aware of NCA communications than DHPCs. • GPs' overall awareness of DHCP was 94% (mean of country percentages: 91%; range from 81% in Sweden to 96% in Denmark, Spain, Ireland, United Kingdom). • GPs' overall awareness of NCA national communications was 89% (mean of country percentages: 79%; range from 21% in the Netherlands to 97% in Spain). • GPs' overall awareness of educational materials was 64% (mean of country percentages: 65%; ranged from 56% in Denmark to 76% in Ireland [Norway and Sweden's surveys did not include questions about educational materials]).
de Vries et al. (2018).	• Awareness about the existence of diclofenac alert was 96% among GPs, 91% among pharmacists, and 79% among cardiologists. • Awareness about the existence of contraceptives alert was 88% among GPs, 90% among pharmacists, and 61% among cardiologists. • Awareness about the existence of valproate alert was 76% among GPs, 80% among pharmacists, and 34% among cardiologists. • Awareness about the existence of ivabradine alert was 70% among GPs, 66% among pharmacists, and 91% among cardiologists. • The authors investigated whether there was a significant difference between the three professional groups in the different countries, and found the following: ○ In six countries (Denmark, Italy, the Netherlands, Norway, Spain, and the UK) cardiologists were significantly less aware of the contraceptive alert than GPs and/or pharmacists. ○ In three countries (Spain, Italy, and Norway), cardiologists were significantly less aware of the diclofenac alert than GPs and/or pharmacists. ○ In five countries (Italy, the Netherlands, Norway, Spain, and the UK) cardiologists were significantly less aware than GPs and/or pharmacists of the valproate alert. ○ In Sweden, cardiologists were significantly more aware of the valproate issue (69%) than GPs (38%), $p = 0.033$. ○ In four countries (Croatia, the Netherlands, Sweden, and the UK), cardiologists were significantly more aware of the ivabradine alert than GPs. ○ In two countries (Croatia and Italy), pharmacists were significantly more aware of the contraceptive alert than GPs. ○ In the Netherlands, pharmacists were significantly more aware of the ivabradine alert than GPs. ○ In the UK, pharmacists were significantly more aware of the diclofenac alert than GPs. However, in Ireland, GPs were significantly more aware of the diclofenac alert than pharmacists. ○ In three countries (Ireland, the UK, and the Netherlands) pharmacists were significantly more aware of the valproate alert than GPs. However, in Norway, GPs were significantly more aware of the valproate alert than pharmacists. ○ The authors reported that pharmacists in Spain were not targeted, but a few answered the survey. ○ Pharmacists in Sweden were also not targeted, and no pharmacists completed the survey. They also reported not assessing the ivabradine alert in Norway because ivabradine was not on the market there. • Participants' (GPs, pharmacists, cardiologists) overall familiarity with DHPCs was 92%. Among the three professional groups, the authors observed only small differences in their familiarity with DHCPs. • In Italy, a significant difference was detected between professionals in terms of their familiarity with DHPCs ($p = 0.016$), as more pharmacists were familiar with DHPCs than GPs (99% vs 90%, $p = 0.004$). • The highest familiarity was observed in the four countries (Ireland, Italy, Spain and the UK), where more than 90% of each of the professional groups reported familiarity with DHPCs. • The lowest familiarity with DHCPs was observed in certain professional groups including GPs in Sweden, cardiologists in Croatia, and pharmacists in Norway. • The most commonly reported sources by which healthcare professionals became aware of the alert included: ○ GPs: ▪ DHPC (ranging from 45% for contraceptives alert to 60% for the valproate alert)

	▪ Message on a website or in a newsletter (ranging from 37% for the valproate alert to 39% for the other alerts).). o Cardiologists: ▪ DHPC (ranging from 33% for contraceptives alert to 61% for the valproate alert). ▪ Medical journals (34% for the diclofenac alert, 42% for ivabradine alert, and 46% for the contraceptive alert). ▪ Message on a website or in a newsletter (ranging from 20% for the contraceptive alert to 30% for the valproate alert). o Pharmacists: ▪ DHPCs (ranging from 41% for the contraceptive alerts to 51% for the ivabradine alert). ▪ Message on a website or in a newsletter (ranging from 42% for the contraceptives and valproate alerts to 46% for the diclofenac and the ivabradine alerts). • The sources through which HCPs became aware of the safety alerts varied between countries. For example, professional bodies as a source were more commonly reported in the Netherlands than in other countries. • DHPCs were more commonly the source for HCPs in Italy than in other countries. • The "other" sources were more commonly reported by HCPs in Norway than in other countries. The authors explained that the "other" sources included the information centre of the National Competent Authority which was only assessed in the survey targeting Norwegian HCPs.

Appendix 11: Statements reported in the included studies as future recommendations regarding the sources of medicine risk communications

Author (Year)	Source	Format/development	Content	Mode of delivery
Morrato et al. (2008).	Involve professional organisations to notify HCPs about upcoming alerts, and ask them to publish them in their bulletin or for their opinion on whether their audiences were appropriate for the warning.	None	Facts should be stated clearly and succinctly, alerts should be put into the relevant context, statistics should be easy to understand, and the alerts should have very specific recommendations.	1. Should be rapid and automatic. 2. Direct communication with physicians and emails targeted at physicians. As patients do not know how to put the information into context, information should be directed to physicians.
Kesselheim et al. (2017).	None	None	None	1. Send information on the risk of medicines via readily available sources, such as Listserv and emails, directly to target audiences. 2. Send risk information via a central repository or database provided by the FDA. It should be accessed easily online and linked to medical practices to disseminate it internally or presented automatically via systems of electronic medical records. 3. Some participants prefer to receive safety updates via traditional channels of communication, such as pharmaceutical companies' representatives visiting HCPs' practice, brief letters, or medical journals.

Barker et al. (2019).	1. Pharmacy managers prefer to have one source of safety information (instead of searching for and combining information from different sources). 2. Pharmacy managers prefer simplified access to the multiple information sources that they have. This is because it requires time to access the various sources available.	1. Pharmacy managers prefer that pharmacists be actively involved in the design of patient safety information sources. 2. Several managers prefer to have influence over the packaging of the information that they receive to make implementation easier for them.	1. Pharmacy managers recommend providing community pharmacies with relevant information and tailoring it to their needs, rather than providing them with information related to hospitals, to avoid source overload and content overload and manage the time required to navigate through all of the information. 2. Pharmacy managers prefer safety content to be with better usability and targeted messaging. 3. A pharmacy manager expressed that they prefer to hear back about errors that happen and how they are solved, because he or she would use this information as opposed to the error reports that are related to hospitals. 4. Pharmacy managers expressed a desire to be aware of systemic issues happening in more than one pharmacy. He or she stated that they do not receive a large amount of information on the pharmacy's	1. Due to the time constraints faced by pharmacists, pharmacy managers prefer emails regarding safety information to be user-friendly, straightforward, brief, informational, and detailed. 2. A pharmacy manager mentioned that he or she prefers to receive information via fax and pick it up personally, as opposed to getting lost in the large volume of emails that he or she receives. The participant reported that by doing so, he or she can read, sign, and leave the information for others to read and sign, and then place it in their binder. 3. Not enough time to seek information from the staff; thus, participants prefer that information be easily available, as increasing the number of staff might add to chaos and not decrease errors related to human factors.

			problems, or, at least, he or she does not know how to access this information. 5. On the other hand, another manager expressed that they do not know the value of knowing about an error that was made by 10 other pharmacies (this was related to error reporting).	
Théophile et al. (2011).	None	1. Special envelop, e.g. an envelope that is yellow in colour, for DDLs. 2. Use specific pictograms on envelops and letters showing medicine safety issues. 3. Place warning stickers on the boxes of medicines. 4. Involve stakeholders in healthcare systems, like professional associations, pharmacovigilance centres, or wholesale distributors (the last reported for pharmacists).	None	1. Present warning information in prescriptions or dispensing software updates. 2. Send alerts through a postal letter (42% of participants) or through emails/Internet (25% of participants).
Piening et al. (2012).	1. Ratings (mean [SD]) of different sources as alternative sources were as follows: MEB (8.13 (1.5)); Lareb (8.06 (1.7)); professional associations (7.98 (1.7)); pharmacists (rated by physicians) (7.35 (2.3)); drug compendiums	None	None	1. Different sources delivering information simultaneously (rated out of 10 as 6.3±2.4) and repetition (rated out of 10 as 5.8±2.4) seen as moderately useful by participants. 2. In the open-ended question about the specific combinations, 184 responded with paper-based DHPC and an email (which was higher than reporting both sources alone).

	(6.71 (2.5)); pharmacotherapy meetings (5.76 (2.5)); physicians (rated by pharmacists) (4.46 (2.5)); media (3.79 (2.2)). 2. Except for media, the authors reported significant differences among the four healthcare professional groups' ratings of sources. 3. The authors reported significant differences amongst respondents between the initial mailings and the two subsequent reminders in two points: a. Late-responding physicians rated safety information from pharmacists higher than did early respondents (P=0.007). b. Late-responding healthcare professionals rated pharmacotherapy meetings higher than did respondents to the initial mailings (P ≤ 0.001).			3. The highest ratings for alternative channels on a 10-point Likert scale were for email (7.59 (SD 2.3)), medical journals (7.49 (SD 2)), computerised prescription systems (7.14 (SD 2.7)), and electronic newsletters (6.14 (SD 2.7)). Ratings of other channels included for text messages (2.47 (SD 2.1)), Twitter (1.81 (SD 1.4)), and RSS (Really Simple Syndication) feeds (3.98 (SD 2.8)). The authors reported significant differences among the four healthcare professional groups' ratings of channels. 4. Twitter was rated the lowest (1.81 (SD 1.4)) in terms of the participants, with text messages rated as 2.47 (SD 2.1). Others included RSS feeds (3.98 (2.8)).
Bell et al. (2013).	None	None	Pharmaceutical companies should inform physicians of all updates on major safety information, not merely boxed warnings.	1. Participants' preferences for receiving updates on medicine safety information were as follows: a. Formal warning process via specialist organisations (n=190). b. Sending updated product insert warnings via emails to specialists (n=176).

				c. It was reported by a few participants (n=24) that they would prefer continuing with the same system (unchanged) of medicine risk communications. d. A few participants (n=14) chose to depend on information from the FDA website.
Sabblah et al. (2016).	None	None	None	1. Participants chose text messages (47.97%), professional journals (23.77%), professional meetings (33.41%), and the FDA website (22.70%). 2. Of 106 HCPs answering the open-ended questions, 85.85%, 9.43%, and 3.77% preferred emails, social media, and electronic media, respectively. 3. A significant difference in choosing "professional journals" was detected between pharmacists, doctors, physician assistants, and nurses (ranging from 17.25% by pharmacists to 41.05% by nurses), as well as the FDA website (ranging from 18.96% by pharmacists to 36.84% by nurses). 4. In the open-ended question regarding other preferences for risk communications, which was answered by 106 participants, responses included: emails (91 participants), social media (10 participants), and electronic media (four participants).
de Vries et al. (2017).	1. The highest-valued senders for GPs were the NCA and professional bodies, and the least-valued senders were lay press and pharmaceutical companies.	1. Overall, 63% (ranging from 36% in Sweden to 72% in Spain) preferred an electronic format to a hardcopy format (overall: 22% (ranging from 13%	None	1. Repetition was seen to be useful by 89% of respondents. 2. The most preferred channels for communication were medicine reference books and national clinical guidelines.

	2. Differences were reported between countries in terms of the preferences regarding sources.	in Spain to 47% in Sweden). 2. Differences were reported between countries in terms of the preferences regarding the format.		3. The most preferred alternative communication channels that are not currently commonly used by the NCA were point-of-care alerts and emails. 4. Other much less preferred alternative channels included mobile health apps, mobile phone text messages, and social media. 5. GPs in Denmark valued personalised letters and medicine reference books. 6. The authors reported that Spanish GPs in particular appreciated emails. 7. The authors also reported that mobile (health) apps, mobile phone text messages, and social media were much less preferred, particularly by GPs from Ireland, the Netherlands, Norway, Sweden, and the UK. 8. They also reported that GPs from Denmark valued almost all channels quite negatively, except for personalised letters and medicine reference books.

DDL: Dear Doctor Letter, DHPC: Dear Healthcare Professional Communication, FDA: Food and Drug Administration, GP: General Practitioner, HCP: Healthcare Professional, MEB: Dutch Medicines Evaluation Board, NCA: National Competent Authority, SD: Standard Deviation.

Appendix 12: Reported impact of medicine risk communications

Study reference	ATC type of medication (drugs involved)	ADR of concern	Self-reported impact (synthesised the results section)/type of impact
Richards et al. (2003).	Nervous system (droperidol)	**Cardiac disorders** (QT-interval prolongation, torsade de pointes, sudden cardiac death)	**Reported changes in their practice:** Those who still use droperidol reported that they obtain an ECG prior to administration, which is required if the use of the medicine outweighs its risk, but the study did not report on other intended effects such as monitoring after treatment. **Decreased prescribing of the medicine of concern:** This impact aligns with the warning, as it stated that the medicine of concern should be reserved for cases in which other treatments fail[67]. **Did not prescribe (stopped prescribing) the medicine of concern after the warning:** This impact aligns with the warning, as it stated that the medicine of concern should be reserved for cases in which other treatments fail[67]. It was also reported that the warning had directly affected their ability to treat patients in the emergency department (no further details were provided regarding this statement). **Impacted the choice of medicine:** Participants cited equal or more effective alternatives to droperidol in certain conditions. Although the effect of the warning upon the use of alternative medicines was not reported in this study, it was reported that some of the physicians who used droperidol for certain conditions reported that there were no other medicines with greater efficacy[67]. **Impact on patient:** Zero point four per cent (n=2) of physicians reported arrhythmias (the ADR) occurring in their patients, and no deaths were reported (it was not reported whether or not this had affected HCPs' behaviours towards the warning).

			Opinion on the utility of the medicine of concern: A significant decline was reported in opinions on the utility of the medicine of concern in the emergency department following the warning, where more physicians rated the FDA warning [droperidol??] as extremely useful before the warning in comparison to after the warning. **Impact on the availability of medicine of concern:** Some respondents reported that the medicine of concern was no longer available in the emergency department following the FDA warning.
Habib et al. (2008).	Nervous system (droperidol)	**Cardiac disorders** (QT-interval prolongation, torsade de pointes, sudden cardiac death)	**Reported change in their practice:** It was reported that some respondents do not use droperidol unless other treatments fail (it was not indicated what is an intended impact in the study). **Did not prescribe (stopped prescribing) the medicine of concern after the warning** **Did not make changes in their practice** **Impacted the choice of medicine:** There were significant changes from before to after the warning in the choice of medicines. Changes and choices in terms of using the medicine of concern were not related to the type of practice (academic versus private) or the years of experience, except that before the BW, physicians with more than 10 years of experience were significantly more likely to report using droperidol before the warning than were those with less than 10 years of experience. **Impact on the availability of medicine of concern** **Impact of institutional policies/protocols:** The location of droperidol stocks was changed, as well as restrictions placed on its use or no changes (restrictions) at all.
Cordero et al. (2008).	Nervous system (antidepressants)	**Psychiatric disorders** (suicidality/suicidal thoughts)	**Referral:** The authors reported that they did not find that the participants were more likely to refer or refuse care for patients requiring SSRIs. Increased referrals were reported by 18% of participants. **Reported change in their practice:** Eighty-four per cent provided additional verbal information explaining the label.

			Participants reported taking additional steps to ensure an accurate understanding of the warning. Increased consultations with colleagues and mental health specialists. Increased time with patients. Shorter follow-up periods. Counselling patients and families more frequently. Spending more time with patients and families explaining the rationale behind the medicine. **Impact on patient:** Thirteen per cent of participants reported a decrease in patients' willingness to take the medicine of concern. **Reported no change in clinical practice** No change in clinical practice was reported by 35% of participants.
Bhatia et al. (2008).	Nervous system (antidepressants)	**Psychiatric disorders** (suicidality/suicidal thoughts)	**Referral:** There were increased referrals to specialists after the warning, including referrals to psychiatrics, psychologists, social workers, or counsellors. There was a reported increase in psychiatric referral times, which could be caused by the increased referrals[46]. **Reported change in their practice:** There was modification in monitoring, including more frequent patient contact when initiating treatment, but only 7.5% reported contacting patients (as recommended by the FDA) by seeing patients weekly for the first month. **Reported the intended impact:** Seven point five per cent reported contacting patients (as recommended by the FDA) by seeing patients weekly for the first month. **Decreased prescribing of the medicine of concern:** Clinicians reported a decrease in prescribing antidepressants to children and adolescents following the warning. **Did not prescribe (stopped prescribing) the medicine of concern after the warning:** The rate of stopping prescribing the medicine of concern was 11.5% among paediatric clinicians, 3.9% among family medicine, and 0.8% among psychiatric clinicians. **Did not make changes in their practice**

			Impact on family members/carers: Reported caregivers refusing treatment due to the warning. **Impact on patient:** Reported patients refusing treatment due to the warning.
Shneker et al. (2009).	Nervous system (antiepileptics)	**Psychiatric disorders** (suicidality/suicidal thoughts)	**Reported change in their practice:** Provided one-to-one counselling to patients. Others written material with counselling[72] differed in counselling whether only when starting certain antiepileptics, any antiepileptics, only patients with epilepsy or only counsel patient with comorbid psychiatric conditions[72]. Note that the authors reported in their introduction that the risk was associated more in patients with epilepsy[72]. Ninety-six per cent of participants reported that there is no need to send letters to all patients regarding the alert. **Did not make changes in their practice**
Richardson et al. (2007).	Nervous system (antiepileptics)	**Psychiatric disorders** (suicidality/suicidal thoughts)	**Referral:** Did not count whether referrals had increased, but reported more emphasis on referrals by certain providers[57]. **Reported change in their practice:** Sceptically reported that change only included improved patient education and documentation[57]. **Decreased prescribing of the medicine of concern:** Did not count the decrease in prescribing (did not report this directly), but reported hesitance and reluctance to prescribe. Delayed prescription. Emphasised counselling. Prescribed when there were no other options[57]. **Did not prescribe (stopped prescribing) the medicine of concern after the warning:** A few refused to prescribe antidepressants unless there was an initial prescription from a psychiatric or the patient had anxiety as a comorbidity[57]. **Did not make changes in their practice** **Impacted the choice of medicine:** About half of prescribers reported that now they use only fluoxetine to avoid off-label use[57].

			Possible impact: Some primary care providers might change their practice (provide a follow-up) in coordination with a psychologist; however, this is questionable due to the lack of communication[57]. **Impact of institutional policies/protocols:** No policies were developed in response to the alert[57].
Cheung et al. (2008).	Nervous system (antiepileptics)	**Psychiatric disorders** (suicidality/suicidal thoughts)	**Referral:** Referred patients to psychiatrics. **Reported change in their practice:** Followed patients more frequently (31.8%) and modified dosage (11%). **Did not prescribe (stopped prescribing) the medicine of concern after the warning (in at least one patient):** Physicians who observed activation (p<0.001) or any side effect reported in the FDA warning (P<0.001) stopped treatment significantly more than did those who did not observe activation or any side effect. **Did not make changes in their practice** **Impacted the choice of medicine:** Reported changed SSRI. **Impact on patient:** Patients stopped medicine due to their concerns surrounding the box warning.
Bell et al. (2013).	Nervous system (antiepileptics [divalproex (valproate semisodium); carbamazepine])	**Psychiatric disorders** (suicidality/suicidal thoughts) Congenital, familial and genetic disorders ("birth defects" preferred item based on terminology used in the study). Congenital, familial and genetic disorders ("teratogenicity" preferred item based on terminology used in the study).	**Reported change in their practice:** Counselled patients on the risk of suicidal ideation. Reported counselling patients who were planning pregnancy (exact recommendation not reported in this study). **Impact on patient:** ADR occurred in patients (reported by HCPs; it was not reported whether the ADR occurrence had affected HCPs' behaviour towards the warning). **Reported the intended impact:** Conducted haplotype screening before initiating carbamazepine in patients of Asian descent.

		Immune system disorders (hypersensitivity reactions).	
de Vries et al. (2018).	Nervous system (valproate). Musculoskeletal system (diclofenac). Cardiovascular system (ivabradine). Genitourinary system and sex (combined hormonal contraceptives).	**Vascular disorders** (venous thromboembolism). **Cardiac disorders** (risk of cardiovascular events). Congenital, familial and genetic disorders (teratogenicity preferred item based on terminology used in the study).	None
Saad et al. (2010).	Nervous system (antipsychotic medicines)	**Nervous system disorders** (cerebrovascular accident/stroke)	**Reported change in their practice** **Did not make changes in their practice** **Supportive/non-pharmacological measures:** The most common non-pharmacological interventions reported to be used were music therapy, massage therapy, pet therapy, and redirection. However, there were no comparisons before and after the warning, or a specification on the time of non-pharmacological measures being used in relation to the warning.
Flood et al. (2015).	Nervous system (midazolam)	**Injury, poisoning and procedural complications** (overdose)	**Impact on patient:** HCPs reported being involved in midazolam overdose incidents, but even before the rapid response report[53] (ADR was not a result of the warning, and it was not reported whether this had affected HCPs' behaviours). One physician reported that patients who received lower doses of sedation complained about an unpleasant experience. **Impact on the availability of medicine of concern:** Not the medicine of concern, but rather related to the availability of the alternative (low-dose midazolam).

Smollin et al. (2016).	Nervous system (midazolam). Nervous system (halpoperidol). Anti-infective for systematic use (ciprofloxacin). Alimentary (gastrointestinal) tract and metabolism (metformin). Musculoskeletal system (naproxen). Musculoskeletal system (naproxen).	**Nervous system disorders** (cerebrovascular accident/stroke). **General disorders and administration site conditions** (death). **Musculoskeletal and connective tissue disorders** (tendonitis/tendon rupture). **Respiratory, thoracic and mediastinal disorders** (respiratory arrest/respiratory depression). **Cardiac disorders** (cardiovascular thrombotic events). **Cardiac disorders** (myocardial infarction). **Gastrointestinal disorders** (serious gastrointestinal adverse events). **Metabolic and nutritional disorders** (lactic acidosis).	None
Sabblah et al. (2016).	Nervous system (paracetamol). Anti-infective for systematic use (azithromycin). Anti-infective for systematic use (ketoconazole). Musculoskeletal system (diclofenac).	**General disorders and administration site conditions** (drug–drug interactions). **Respiratory, thoracic and mediastinal disorders** (respiratory arrest/respiratory depression). **Cardiac disorders** (QT-interval prolongation, torsade	**Reported change in their practice:** Changed their prescribing practice, and patient counselling. **Did not make changes in their practice:** Those who stated that the letters had not changed their practice gave reasons like the information already being known and the medicines involved not being used by them.

	Respiratory (codeine).	de pointes, sudden cardiac death). **Cardiac disorders** (risk of cardiovascular events). **Immune system disorders** (skin reactions). **Social circumstances** (driving skills impaired). **Hepatobiliary disorders** (severe liver injury). **Endocrine disorders** (adrenal gland problems (disorders)).	
Kesselheim et al. (2017).	Nervous system (zolpidem). Nervous system (eszopiclone).	**Nervous system disorders** (decreased level of consciousness/alertness). **Nervous system disorders** (memory impairment).	**Reported that physicians had discussions with patients about medicines' risks, although the authors did not specify whether or not these were before the alert:** Cautioned and had discussions with patients most frequently about drowsiness or dependence, also cautioning patients about limiting their use of the medicine of concern. One physician expressed that it would be 'a real battle' to help patients to understand safety issues, especially when they are not sleeping (they are fatigued, their work production is affected), and that many of her patients are willing to risk addiction to use a sleep aid to help them with their ability to sleep. **Possible impact:** Physicians welcomed the warning because it strengthened physicians' argument against using these medicines.
Fogler et al. (2009).	Anti-infective for systematic use (nelfinavir mesylate)	**Product issues** (impurity)	There were none, but one participant had a pregnant patient receiving nelfinavir without being aware of the need to discontinue this medicine at the time of the study.

Esterly et al. (2011).	Anti-infective for systematic use (ceftriaxone). Alimentary (gastrointestinal) tract and metabolism (calcium).	**General disorders and administration site conditions** (drug–drug interactions)	**Decreased prescribing of the medicine of concern:** Eighteen per cent reported a minor decrease, and 4% reported a major decrease; however, most institutions (63%) reported no change. Moreover, 4% reported a minor increase. **Did not make change in their practice:** Reported no change in the use of medicine. **Spillover effects:** Spillover effects were noted in institutions' interpretations of the warning, including that ceftriaxone should never be used in neonates; furthermore, ceftriaxone should never be used in adults within 48 hours of receiving any form of calcium-containing products. The form of calcium-containing products in one statement was not specified: 'Ceftriaxone should never be used in neonates within 48 hours of receiving calcium-containing products.' Institutions' prohibition in certain situations could lead to spillover effects, e.g. some institutions prohibited ceftriaxone use if the patient had received any calcium-containing product within the previous 48 hours. **Increased prescribing of the medicine of concern:** It was also reported that there was no change in medicine use or decreased medicine use. ^{⁴⁷} **Impact on the availability of medicine of concern:** One institution reported removing ceftriaxone from the formulary following the warning. **Impact of institutional policies/protocols:** Included examples of policy changes like adding computerised alerts to the medicine order entry system and/or ceftriaxone intravenous bag label before dispensing, pharmacist reviews, prohibiting the use of the medicine of concern in certain situations, removing the medicine of concern from the formulary, and/or adding the alternative to the formulary[47]; meanwhile, other institutions provided the information and let the decision be made by the prescribing physician.
Harder et al. (2009).	Anti-infective for systematic use (ceftriaxone).	**General disorders and administration site conditions** (drug–drug interactions)	**Impact on the availability of medicine of concern:** Removed or considered removing the medicine of concern from the formulary (2.8% out of 142 participants) due to the warning. **Impact of institutional policies/protocols:**

	Alimentary (gastrointestinal) tract and metabolism (calcium).		Changes were made in policies, released memoranda, and the computerised alert system for pharmacists. Several institutions adjusted restriction policies and implemented new auto-substitution policies to reduce the use of ceftriaxone in favour of cefotaxime.
Piening et al. (2012).	Anti-infective for systematic use (moxifloxacin). Alimentary (gastrointestinal) tract and metabolism (rimonabant). Alimentary (gastrointestinal) tract and metabolism (proton pump inhibitors). Musculoskeletal system (etoricoxib). Blood and blood-forming organs (clopidogrel).	**Psychiatric disorders** (depression risk ["rimonabant"]). **Vascular disorders** (hypertension ["etoricoxib"]). **General disorders and administration site conditions** (drug–drug interactions ["proton pump inhibitors"]). **General disorders and administration site conditions** (drug–drug interactions ["clopidogrel"]). **Immune system disorders** (skin reactions ["Moxifloxacin"]). **Hepatobiliary disorders** (hepatotoxicity ["moxifloxacin"]).	**Reported change in their practice:** Adjusted therapy, informed colleagues, and discussed with patients; this was in response to 29% of the DHPC, ranging from 23% (internists) to 37% (community pharmacists) (P<0.001).
Théophile et al. (2011).	Alimentary (gastrointestinal) tract and metabolism (vitamin D)	**Injury, poisoning and procedural complications** (too rapid administration of a product)	**Reported the intended impact:** Changed their prescribing behaviours and/or advice to families (50% of 16 paediatricians, 68% of 68 GPs, and 68% of 62 pharmacists). **Did not make changes in their practice:** Two GPs out of those who reported having not changed their practice gave the reason that they used to give similar advice before the warning.

Karpel et al. (2009).	Respiratory (long-acting ß-agonist [LABA])	**General disorders and administration site conditions** (death)	**Did not make changes in their practice:** Most primary care providers (53.8%) and specialists (62.6%) did not change their practice of treating asthma after the warning. **Reported change in their practice:** Note: When asked about their preferred first-line treatment for mild persistent asthma, 11.4% of primary care providers chose LABA monotherapy in comparison to 2.1% among specialists (P<0.001)[51]. Most participants chose ICSs as the preferred first-line treatment for mild persistent asthma, regardless of their speciality. Most primary care providers and specialists did not change their practice of treating asthma after the warning, but primary care providers were 6% more likely to have changed their practice than were specialists (P=.005). For asthmatic African Americans, primary care providers were almost half as likely to change their practice as specialists (P<0.001). Specialists were significantly (p<0.001) more likely to discuss boxed warnings with their patients than were primary care providers[51]. Allergists and pulmonologists were significantly more likely to initiate discussions of the BW with their patients. Compared to primary care providers (32.5%), specialists (70.3%) were more likely to report that their patients had initiated the discussion about the BW (p<0.001). **Spillover effects:** Primary care providers were nearly twice as likely as specialists to report altering their practice in COPD (P<0.001).
Garbutt et al. (2010).	Respiratory (over-the-counter cough and cold medications)	**Nervous system disorders** (convulsions). **General disorders and administration site conditions** (death).	**Reported the intended impact:** Some physicians were reported to be less likely to prescribe these medicines in children <2 years old after the advisory. **Supportive/non-pharmacological measures** **Reported change in their practice:** Providing advice on safe use. Recommending supportive measures (honey or chicken soup). **Did not prescribe (stopped prescribing) the medicine of concern after the warning:**

			Stopping the medicine of concern in the reported age group was an intended impact. Moreover, stopping the medicine in ages 2–11 was reported (the FDA advised to understand that these products will not treat the cause of symptoms or decrease the duration — they are only for symptom relief). **Did not make changes in their practice**
Yaghami et al. (2010).	Respiratory (over-the-counter cough and cold medications)	**Nervous system disorders** (convulsions). **General disorders and administration site conditions** (death).	**Reported the intended impact** **Decreased prescribing of the medicine of concern** **Did not prescribe (stopped prescribing) the medicine of concern after the warning:** Comment: Stopping the medicine of concern aligns with the warning. **Did not make changes in their practice:** Reported the reason that they do not routinely prescribe these medicines (as recommended by the warning); however, others reported that they would continue prescribing the medicine of concern. **Supportive/non-pharmacological measures:** Did not compare before and after the warning or specify it as being after the warning.
Reed et al. (1999).	Cardiovascular system (nitrate). Genitourinary system and sex (sildenafil).	**General disorders and administration site conditions** (drug–drug interactions)	**Impact of institutional policies/protocols:** Seventeen per cent of the respondents said that their chest pain protocol had changed in response to the release of sildenafil. **Reported the intended impact:** Fifty per cent of respondents reported that they ask chest pain patients about sildenafil use, but about 28% of respondents stated that sildenafil use would not affect the medicine that they administer to chest pain patients.
Mazor et al. (2005).	No specific medicine was reported (did not specify the medicine/no specific medicine).	None	**Possible impact:** Would likely change their practice in response to most of the letters that they rate. [PROXY FOR INTENTION]?
Morrato et al. (2008).	No specific medicine was reported (did not	None	None

	specify the medicine/no specific medicine).		
de Vries et al. (2017).	No specific medicine was reported (did not specify the medicine/no specific medicine).	None	None
Kloet et al. (2017).	Checked for BW[3] nonadherence.	Types of ADRs reported in BWs were not reported. However, the authors reported that (overall) 11.6% of medicines with BW resulted in initial nonadherence, which included 25 drug–disease interactions, two drug–laboratory interactions, and seven drug–drug interactions.	**Reported the intended impact:** Not self-reported, but rather assessed by a pharmacist (indirectly reported the intended impact by reporting the percentage of initial BW nonadherence (before pharmacists' intervention)). Intensive critical care unit: BW nonadherence occurred with 11 medicines, six of which were home medicines; fellows and PGY1 residents mostly ordered medicines with BW nonadherence (27.3% anti-infectives and 27.3% immunosuppressants; 11 medicines, six of which were home medicines). In general medicine: BW nonadherence occurred in 23 medicines, 13 of which were home medicines; PGY1 residents (followed by PGY2 residents) constituted most prescribers of BW nonadherence (74% of BW nonadherence was related to NSAID). **Impact on patients – impact of nonadherence to BW:** Based on a causality assessment, one case of nonadherence to BW in the ICU led to a probable ADR. Additionally, one case of nonadherence to BW on general medicine floors led to a possible ADR.
Barker et al. (2019).	No specific medicine was reported (did not specify the medicine/no specific medicine).	None	None

ADR: Adverse Drug Reaction, BW: Boxed Warning, COPD: Chronic Obstructive Pulmonary Disease, DHPC: Dear Healthcare Professional Communication, ECG: Electrocardiogram, FDA: Food and Drug Administration, GP: General Practitioner, HCP: Healthcare Professional, LABA: Long-Acting Beta Agonist, NCA: National Competent Authority, NSAID: Non-Steroidal Anti-Inflammatory Drugs, SSRI: Selective Serotonin Reuptake Inhibitor.

Appendix 13: Ethics Approval from Kuwait Ministry of Health (2018)

State of Kuwait
Ministry of Health
Asst. Undersecretary
for Planning & Quality

دولة الكويت
وزارة الصحة
وكيل الوزارة المساعد لشئون
التخطيط والجودة

المرجع: 7811

التاريخ: 1-11-2018

To Whom it May Concern

***From**: Ministry of Health – Kuwait*

The Standing Committee for Coordination of Medical Research

To : Dr.Amal Alharbi - PhD Student

*University College: **University of Hertfordshire***

Study title: An Evaluation of Medication Safety Related Communications the Patient Healthcare Pathway

(916 / 2018)

The above mentioned Proposal was given an ethical approval by the Committee on its meeting (#9/2018) held on Tuesday October 30, 2018

The research will be conducted in in MOH Hospitals and Primary Health Care Centers.

Asst. Undersecretary for Planning & Quality

Head, Standing Committee for Coordination of Medical Research

Ministry of Health – State Of Kuwait

31/10/2018

Dr. Mohammad Jaseem Al Khashti
Asst. Undersecretary for
Planning & Quality

P.O. Box : (5) 13001 Safat, State Of Kuwait
Tel.: 24622230/24622228 - Fax : 24866514

ص. ب. (٥) الرمز البريدي ١٣٠٠١ الصفاة، الكويت
تلفون: ٢٤٦٢٢٢٣٠ / ٢٤٦٢٢٢٢٨ - فاكس: ٢٤٨٦٦٥١٤

Appendix 14: Ethics Approval from Kuwait Ministry of Health (2020)

a. English translated version

[Emblem: [State of Kuwait]] State of Kuwait
Ministry of Health
Asst. Undersecretary
For Planning & Quality

[Logo: NEWKUWAIT]

Ref.: 1595 Date: 8-10-2020

To: His Excellency, Dr. Ministry Undersecretary

Greetings,

Subject: Facilitating the Task of the Ph.D. Student and Researcher, Amal Alharbi, and Others In The UK, the University Of Hertfordshire Research No. 916/2018) Entitled: An Evaluation of Medication Safety Related Communications the Patient Healthcare Pathway

This is to kindly inform you that the Standing Committee for Coordination of Medical Research, formed in accordance with the Ministerial Decision No. 207 of 2012, held its fiftieth meeting (9/2018), on Tuesday 30/10/2018. The committee recommended approval on conducting research No. (916/2018) submitted by **the Ph.D. researcher student \ Amal Alharbi, at the University of Hertfordshire in the UK** on 23/10/2018. The title of the research is:

An Evaluation of Medication Safety Related Communications The Patient Healthcare Pathway

This came after the said committee had consulted with the competent parties concerned with the subject matter of the research; as provided in the Ministerial Decision No. 207 of 2012 and in accordance with the circulation No. 156 of 2012, issued from the Assistant Undersecretary of the Ministry. Accordingly, the Assistant Undersecretary for Legal Affairs was consulted in accordance with letter No. 7730 dated 25/10/2018. Furthermore, the Director of the Pharmaceutical Services Department issued his approval as per the department's letter No. 1092, dated 29/10/2018.

1

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Tel.: 24622230/2462228 - Fax: 24866514

[Emblem: [State of Kuwait]]

State of Kuwait
Ministry of Health
Asst. Undersecretary
For Planning & Quality

[Logo: NEWKUWAIT]

Ref.: 1595 Date: 8-10-2020

The research will be conducted through making interviews and using a questionnaire to collect the data from the respondents targeted in the research, as the protocol of the study provides (**the period of the research project will be 3 years**).

The research will not involve any experiments or prescribing any medications or collecting bio samples.

His Excellency the Undersecretary of the Ministry issued a letter, under No. 7799 dated 1/11/2018, that the said mission shall be facilitated. In effect of which the concerned parties were informed accordingly.

On 15/6/2020, the committee received a letter from the said researcher in which she requested **approval to use the questionnaire to collect the data through the internet (internet survey). The survey is targeted at health practitioners (doctors, pharmacists, pharmacy technicians, and nurses)** [and it will be processed] In accordance with the recommendation issued by the committee on its sixty-eighth meeting (6/2020) held on 29/9/2020 (**VIRTUAL MEETING**).

This is for your kind perusal and your guidance as you may see fit, with a view to granting your approval on the recommendation of the committee, and your approval to communicate with the relevant authorities concerned about the subject matter of the research of the foregoing facts.

(His excellency, Dr. Assistant Undersecretary of the Medical and Food Control Affairs, His Excellency Dr. Assistant Undersecretary for Medical Drugs Instruments, Her Excellency Dr. Assistant Undersecretary for Public Medical Services, the respected regional health directors, and the director of the Pharmaceutical Services Department) in this respect, and in order to facilitate the mission of the researcher to conduct the research (**to use the internet survey**).

Taking into consideration that the researcher will observe the right of the respondents involved in the research with respect to privacy, and confidentiality of the information; none of which will be disclosed outside the framework of the research. And that she will coordinate with the heads of the sections in which the study will be conducted in accordance with the pertinent regulations.

With due respect, yours sincerely,

Dr. Muhammad Jassim Al-Khashti
Assistant Undersecretary for Affairs
Planning and quality
8/10/2020

[Rectangular blue colour stamp:
Dr. Mohammed Jassem Al Khashti
Assistant Undersecretary for Affairs
Planning and Quality]
[Signed]

Approved
In accordance with the regulations
Undersecretary of the Ministry of Health

[Rectangular blue colour stamp:
Dr. Mohammed Jassem Al Khashti
Assistant Undersecretary for Affairs
Planning and Quality]
[Signed]

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b. Arabic (original version)

State of Kuwait
Ministry of Health
Asst. Undersecretary
for Planning & Quality

كويت جديدة
NEWKUWAIT

دولة الكويت
وزارة الصحة
وكيل الوزارة المساعد لشئون
التخطيط والجودة

التاريخ : ٨-١٠-٢٠١٨ المرجع : ١٥٩٥

السيد الفاضل / د. وكيل الوزارة المحترم

تحية طيبة وبعد،،،

الموضوع / تسهيل مهمة الباحثة / أمل الحربي وآخرون طالبة دكتوراه Ph.D. University of Hertfordshire في المملكة المتحدة
(رقم البحث 2018/916) تحت عنوان:
An Evaluation of Medication Safety Related Communications the Patient Healthcare Pathway

يرجى التفضل بالإحاطة بأن اللجنة الدائمة لتنسيق البحوث الطبية والصحية المشكلة بموجب القرار الوزاري رقم 207 لسنة 2012 قد أوصت باجتماعها الخمسون (9 / 2018) المنعقد يوم الثلاثاء الموافق 30 / 10 / 2018 بالموافقة على إجراء البحث رقم (916 / 2018) المقدم من الباحثة/ أمل الحربي وآخرون طالبة دكتوراه Ph.D. University of Hertfordshire في المملكة المتحدة بتاريخ 2018/10/23 تحت عنوان:

An Evaluation of Medication Safety Related Communications the Patient Healthcare Pathway

وذلك بعد أن قامت اللجنة استنادا للقرار الوزاري رقم 207 لسنة 2012 والتعميم الصادر من السيد / وكيل الوزارة برقم 156 لسنة 2012 باستطلاع آراء الجهات ذات العلاقة بموضوع البحث حيث تم استطلاع راي السيد / الوكيل المساعد للشئون القانونية بالكتاب رقم 7730 بتاريخ 25 / 10 / 2018 ووافق السيد / مدير ادارة الخدمات الصيدلانية بالكتاب رقم 1092 بتاريخ 2018/10/29.

1

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ص. ب. (٥) الرمز البريدي ١٣٠٠١ الصفاة، الكويت
تلفون: ٢٤٦٢٢٢٣٠/٢٤٦٢٢٢٢٨ - فاكس: ٢٤٨٦٦٥١٤

التاريخ : ٨ - ١٠ - ٢٠٢٠ المرجع : ١٥٩٥

ويتم البحث من خلال إجراء المقابلات وإستخدام إستبيان لجمع المعلومات من المستهدفين بالدراسة حسب بروتوكول البحث **(مدة مشروع البحث 3 سنوات).**

ولا يتضمن البحث إجراء أي تجارب طبية أو إعطاء أدوية أو أخذ عينات حيوية.

وقد صدر كتاب تسهيل المهمة من السيد الفاضل / وكيل الوزارة برقم 7799 بتاريخ 1/11/2018 وتمت مخاطبة الجهات ذات الصلة بذلك.

وبتاريخ 2020/6/15 تلقت اللجنة الكتاب رقم 291 من الباحثة متضمناً طلب **الموافقة على إستخدام الاستبيان لجمع المعلومات عن طريق الانترنت (استبيان عبر الانترنت) يستهدف الممارسين الصحيين (الأطباء - الصيادلة – فنيي الصيدلة – الممرضين)** ووفقاً لتوصية اللجنة المتخذه بإجتماعها الثامن والستين (6/2020) المنعقد بتاريخ 29/9/2020 **(VIRTUAL MEETING)**

برجاء التفضل بالاطلاع والتوجيه بما ترونه مناسباً نحو اعتماد توصية اللجنة والموافقة على مخاطبة الجهات ذات الصلة بموضوع البحث بما سبق **(السيد / د. الوكيل المساعد لشئون الرقابة الدوائية والغذائية / السيد / د. الوكيل المساعد لشئون الادوية والتجهيزات الطبية / السيدة / د. الوكيل المساعد لشئون الخدمات الطبية الاهلية / السادة / مدراء المناطق الصحية / السيد / مدير إدارة الخدمات الصيدلانية)** بهذا الشأن للعمل على تسهيل مهمة الباحثة لإجراء البحث **(باستخدام استبيان عبر الانترنت).**

مع مراعاة التزام الباحثة بالمحافظة على حقوق المشاركين بالبحث بالخصوصية وسرية المعلومات وعدم تداولها خارج إطار البحث والتنسيق مع رؤساء الأقسام التي ستجري بها الدراسة وفقا للضوابط المنظمة لذلك.

وتفضلوا بقبول فائق الاحترام،،،،

الدكتور / محمد جاسم الخشتي
الوكيل المساعد لشئون التخطيط والجودة
رئيس اللجنة الدائمة لتنسيق البحوث الطبية والصحية

يعتمد
حسب النظم
وكيل وزارة الصحة

د/ محمد جاسم الخشتي
وكيل الوزارة المساعد لشئون التخطيط والجودة

٢٠٢٠/١٠/١٩

د/ محمد جاسم الخشتي
وكيل الوزارة المساعد لشئون التخطيط والجودة

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ص. ب. (٥) الرمز البريدي ١٣٠٠١ الصفاة، الكويت
تلفون: ٢٤٦٢٢٢٣٠/٢٤٦٢٢٢٢٨ - فاكس: ٢٤٨٦٦٥١٤

Appendix 15: Ethics Approval from the University of Hertfordshire (2019)

University of Hertfordshire UH

HEALTH, SCIENCE, ENGINEERING AND TECHNOLOGY ECDA ETHICS APPROVAL NOTIFICATION

TO Amal Alharbi
CC Dr Nkiruka Umaru
FROM Dr Simon Trainis, Health, Science, Engineering & Technology ECDA Chair. **DATE** 05/08/2019

Protocol number: **LMS/PGT/UH/03808**
Title of study: An Evaluation of Medication Safety Related Communications in the

Patient Healthcare Pathway.

Your application for ethics approval has been accepted and approved with the following conditions by the ECDA for your School and includes work undertaken for this study by the named additional workers below:

Dr Nada Shebl
Dr Sherael Webley

General conditions of approval:

Ethics approval has been granted subject to the standard conditions below:

Permissions: Any necessary permissions for the use of premises/location and accessing participants for your study must be obtained in writing prior to any data collection commencing. Failure to obtain adequate permissions may be considered a breach of this protocol.

External communications: Ensure you quote the UH protocol number and the name of the approving Committee on all paperwork, including recruitment advertisements/online requests, for this study.

Invasive procedures: If your research involves invasive procedures you are required to complete and submit an EC7 Protocol Monitoring Form, and copies of your completed consent paperwork to this ECDA once your study is complete.

Submission: Students must include this Approval Notification with their submission.

Validity:

This approval is valid: From: 05/08/2019
T o: 31/08/2020

Please note:

Failure to comply with the conditions of approval will be considered a breach of protocol and may result in disciplinary action which could include academic penalties.
Additional documentation requested as a condition of this approval protocol may be submitted via your supervisor to the Ethics Clerks as it becomes available. All documentation relating to this study, including the information/documents noted in the conditions above, must be available for your supervisor at the time of submitting your work so that they are able to confirm that you have complied with this protocol.

Should you amend any aspect of your research or wish to apply for an extension to your study you will need your supervisor's approval (if you are a student) and must complete and submit form EC2.
Approval applies specifically to the research study/methodology and timings as detailed in your Form EC1A. In cases where the amendments to the original study are deemed to be substantial, a new Form EC1A may need to be completed prior to the study being undertaken.

Failure to report adverse circumstance/s may be considered misconduct.

Should adverse circumstances arise during this study such as physical reaction/harm, mental/emotional harm, intrusion of privacy or breach of confidentiality this must be reported to the approving Committee immediately.

Appendix 16: Ethics Approval from the University of Hertfordshire (2020)

University of Hertfordshire UH

HEALTH, SCIENCE, ENGINEERING AND TECHNOLOGY ECDA ETHICS APPROVAL NOTIFICATION

TO Amal Alharbi
CC Dr Nkiruka Umaru
FROM Dr Simon Trainis, Health, Science, Engineering & Technology ECDA Chair **DATE** 28/05/2020

Protocol number: **aLMS/PGT/UH/03808(1)**
Title of study: An Evaluation of Medication Safety Related Communications in the Patient

Healthcare Pathway

Your application to modify and extend the existing protocol as detailed below has been accepted and approved by the ECDA for your School and includes work undertaken for this study by the named additional workers below:

Nada Shebl Sherael Webley

Modification: Detailed in EC2

General conditions of approval:

Ethics approval has been granted subject to the standard conditions below:

Original protocol: Any conditions relating to the original protocol approval remain and must be complied with.

Permissions: Any necessary permissions for the use of premises/location and accessing participants for your study must be obtained in writing prior to any data collection commencing. Failure to obtain adequate permissions may be considered a breach of this protocol.

External communications: Ensure you quote the UH protocol number and the name of the approving Committee on all paperwork, including recruitment advertisements/online requests, for this study.

Invasive procedures: If your research involves invasive procedures you are required to complete and submit an EC7 Protocol Monitoring Form, and copies of your completed consent paperwork to this ECDA once your study is complete.

Submission: Students must include this Approval Notification with their submission.

Validity:

This approval is valid: From: 31/08/2020

To: 31/08/2021

Please note:

Failure to comply with the conditions of approval will be considered a breach of protocol and may result in disciplinary action which could include academic penalties.
Additional documentation requested as a condition of this approval protocol may be submitted via your supervisor to the Ethics Clerks as it becomes available. All documentation relating to this study, including the information/documents noted in the conditions above, must be available for your supervisor at the time of submitting your work so that they are able to confirm that you have complied with this protocol.

Should you amend any aspect of your research or wish to apply for an extension to your study you will need your supervisor's approval (if you are a student) and must complete and submit a further EC2 request.
Approval applies specifically to the research study/methodology and timings as detailed in your Form EC1A or as detailed in the EC2 request. In cases where the amendments to the original study are deemed to be substantial, a new Form EC1A may need to be completed prior to the study being undertaken.

Failure to report adverse circumstance/s may be considered misconduct.

Should adverse circumstances arise during this study such as physical reaction/harm, mental/emotional harm, intrusion of privacy or breach of confidentiality this must be reported to the approving Committee immediately.

Appendix 17: Training sessions attended by the researcher

The researcher was developing herself in aspects related to this research by attending training sessions, reading, and training with supervisors. Training sessions attended by the researcher are as the following:

Research degree programmes (RDP) (EndNote/ creating research impact, sample size, obtaining ethical approvals; overcoming obstacles in research; the British PhD; engaging with multiple methods, research development spring school). Royal Pharmaceutical Society: preparing a research proposal.

Training attended during the second year: Social Research Association: Interpreting and Writing up your Qualitative Findings (6th of November, 2018 London); Conducting Focus Groups (20th November, 2018, Cardiff); Qualitative Data Analysis course (21 of November, 2018 Cardiff). University of Surrey: Introduction to Qualitative Interviewing course (14th of November, 2018). Doctoral Training Alliance autumn school (November 2018); Doctoral Training Alliance summer school (July 2019).

Training through RDP: Quantitative analysis of survey data (26th of November, 2018); Poster Presentation (18th of October, 2018); Qualitative Methods (24th of October, 2018); Qualitative Data Analysis: Methods And Techniques (24th of October, 2018) Getting published and promoting your research (25th of October, 2018), Becoming a member of your discipline (25th of October, 2018) (RDP summer school (mixed methods & conceptual frameworks 13th September, 2019).

Stress reductive techniques during your PhD 30/3/2020 (RDP session online). Academic writing reduce anxiety 11/05/2020 (through the Doctoral Training Alliance; online). How to write a scientific paper 03/06/2020 (RDP session online). Survey design and population size calculation 07/06/2020 (online session)Survey design and population size calculation 17/06/2020 (online session)Critical reading and writing 02/07/2020 (RDP session online). Statistical support online session 21/07/2020Statistical support online session 02/12/2020. Statistical support online session 05/01/2021.Getting Started: Launching a Survey 02/02/2021 (through Qualtrics, online). Thesis, What Thesis? 04/02/2021 (RDP session online).

VIVA survivor 04/05/2021 (through the Doctoral Training Alliance; online).

Appendix 18: Data extraction instrument for the document analysis (Identifying and classify medication KDFC's safety-related communications; adapted from Bjerre et al. (2018)

Format:
Reason for communication (not for DHCP):
Language used: English ( ) Arabic ( ) Both ( )
Name used for the medication involved Generic ( ) Brand ( ) Both ( )
Date of posting/ issuing ….
KDFC mentioned as the regulatory agency (yes, no)
Included information on the source of the initial information (yes, no) Source of the original information: …….
Scientific justification (specific reference to the literature or to reported cases) (absence)
Attachments (Specific for DHPC)
Pharmaceutical company/ companies (Presence, absence)
Author of/ or person responsible for the letter (Presence, absence)
Letter include links to additional articles (Presence, absence)
Quantitative information on efficacy (Presence, absence)
Channel of delivery
Intended receivers
Medication & safety information:
Indication (Presence, absence)
Letters describes adverse effects associated with medications (yes, no)
Letters gives quantitative data for adverse associated with medications (yes, no)
Letters describe specific guidance/ recommendation (yes, no)
Patient population of concern
Age
Gender: M ( ) ; F ( )
Medication
ATC 1st level classification (2016 edition)
Safety information
SOC MedDRA classification:

Appendix 19: Code book used in the document analysis (Identify the process of creating and disseminating medications safety) communications

Code book item & sub-items
Item 1: Source of the safety information (This includes the source of original information or the source delivering the information to KDFC) International Regulatory Agency (MHRA, FDA, EMA(and PRAC); WHO (1); Regional Ministry of Health (GCC/ MAH informed regional regulatory agency)/ The Executive Office of the GCC council of Health Ministries or Gulf Health Council (2) Pharmaceutical Company informed KDFC/ Innovator company provided KDFC with RMM (which was approved by KDFC) (3); Rumour circulated in social networks in Kuwait about the safety of a product (4); Specific source not named but mentioned (International/worldwide reports; fatal cases worldwide, recent published reports, international published reports, international reference agencies, clinical trials, post market reports) (5) Media/social media (6) KDFC meeting with a special commission, but did not specify this commission(7).
Item 2: Action taken by KDFC in response to the information. no action was required (1); KDFC sent RMMs (risk minimisation measures) to HCPs (checklist/ prescribing guide/ added conditions for prescribing and monitoring) (2); KDFC required pharmaceutical company to change label/ insert/leaflet/ patient guide (3); asked for education workshops to be conducted with pharmaceutical companies (4); KDFC informed/ cautioned pharmaceutical company about the issue or any consequences or asked the pharmaceutical company whether they have applied or will apply the changes (5) KDFC withdrew the product (withdrawal from the market) (6) Suspension of the medication (suspension of the registration of the product, does not mention withdrawal from the market) (7); KDFC asked patients to stop using the medication of concern and to contact their treating physicians for alternatives (8); KDFC asked pharmaceutical companies to send DHPL or letters to HCPs (9); KDFC is following-up with the drug safety/ KDFC assured they are following product safety or update from international agencies related to it (10); KDFC informed HCPs about the information (11); KDFC issued advise or clarified information to the public (12).
Item 3: Channel used for delivering information sent by KDFC Press-release (KUNA, local newsletter, not specified in the document where it was released) (1); Fax (2); Social media (3); KDFC (website) (4) DHCP by the KDFC (5); included in KuFDA newsletter (6); KDFC required MAH to deliver DHCP/ KDFC approved DHCP distribution by the MAH (7) KDFC coordinates with MAHs to do lectures and workshops (8). KDFC asked drug company to update drug leaflet/ drug package insert (9).

KDFC asked drug company to update patient guide (10).
Item 4: Receivers of safety communications sent by KDFC Director of health area (1); Director of governmental hospital (2); (head of hospital) Director pharmaceutical services at MOH (3); Director Health promotion/health awareness departments at MOH (4); Public (5). Chairman of the Council of Medical Departments (6). Chairman of paediatric departments council (7). Head of pharmaceutical service office in a health area (in specific health area) (8); Chairman of diabetes specialised centre (9); HCPs as intended receivers (10); Kuwait Oil Company- related hospital (11)
Item 5: Involvement of stakeholders in the development/ approval of KDFC actions/ communications Physicians (1) Not reported (2)

Appendix 20: Examples of the initial extraction of documents using the Anatomical Therapeutic Chemical classification system (ATC) and Medical Dictionary for Regulatory Activities (MedDRA)

The coding process was conducted based on (MedDRA, 2019; The National Center for Biomedical Ontology, 2018; World Health Organization Collaboration Centre for Drug Statistics Methodology, 2019).

Dear Healthcare Professional Communications (DHCP letters)			
Name of the medication	**ATC 1st level class**	**Reported safety issue**	**MedDRA system Organ class classification**
Fluoroquinolone (levofloxacin, ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin and gemifloxacin)	Anti-infective for systematic use	Systemic: Hypoglycaemia, also reported hyperglycaemia depending on the fluoroquinolone class. Systemic: Psychiatric adverse reaction Systemic: Grouped as mental health/CNS side effects: Agitation, nervousness, memory impairment, disturbances in attention , disorientation Systemic or inhalation: Aortic aneurysm and dissection Systemic or inhalation: Long lasting side effects involving bones, muscles, tendons and the nervous system.	Hypoglycaemia → Metabolism and nutrition disorders Glucose metabolism disorders (hypoglycaemic conditions: hypoglycaemia or hyperglycaemic conditions: hyperglycaemia). Psychiatric adverse reaction →Psychiatric disorders Agitation→ nervous system disorders. Nervousness → psychiatric disorders. Memory impairment → nervous system disorder. Disturbances in attention → psychiatric disorders. Disorientation → psychiatric disorders. Aortic aneurysm→ vascular disorders. Aortic dissection → vascular disorders. Long lasting side effects involving bones, muscles, tendons and the nervous system→Not specific to classify bone and nervous symptoms. Symptoms related to muscles and tendons → Musculoskeletal and connective tissue disorders.

Canagliflozin Dapagliflozin Xigduo (metformin/dapagliflozin)	Alimentary tract and metabolism	Ketoacidosis Urosepsis and pyelonephritis Kidney injury Additional for canagliflozin: bone fracture and decreased bone mineral density Additional for canagliflozin: leg and foot amputations	Ketoacidosis →Metabolism and nutrition disorders. Urosepsis→Infections and infestations. Pyelonephritis→ Renal and urinary disorders. Renal and urinary disorders. Bone fracture→ injury, poisoning and procedural complications (preferred name: fracture). Decreased bone mineral density → Investigations (preferred name: bone mineral content decreased) Leg and foot amputations → Surgical and medical procedures (bone and joint therapeutic procedures, limb therapeutic procedures).
Communications to the public (press release)			
Red Juice	No registered. Classified as "systematic hormonal preparations, excluding sex hormones and insulins" based on the description provided in the communication.	Sexual dysfunction (in men). Infertility (in women). Baldness. Enlarged prostate. Liver damage/elevated liver enzymes. Kidney failure Cancer Enlarged cardiac muscle. Sudden hormone interruption causes cardiovascular disorders. Insomnia. Nausea. Non-sterile manufacturing of the product.	All together will be classified as performance enhancing product use→ intentional product use issues → off label uses and intentional product misuses/use issues → class: Injury, poisoning and procedural complications.
KuFDA June, 2016			
Bendamustine hydrochloride	Antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues.	Infection reactivation. Pancytopenia Atrial fibrillation, congestive heart failure, myocardial infraction, palpitation, Injection site reactions, infusion site reactions. Anaphylaxis Pneumocystis jiroveci pneumonia. Pneumonitis Stevens-Johnson syndrome (with concomitant medications known to cause the syndrome like allopurinol) Toxic epidermal necrolysis (with concomitant medications known to cause the syndrome like allopurinol).	Infection reactivation → Infections and infestations. Pancytopenia→ blood and lymphatic system disorders. Atrial fibrillation → cardiac disorders. Congestive heart failure → cardiac disorders. Myocardial infraction→ cardiac disorders. Palpitation → cardiac disorder. Injection site reactions→ Injury, poisoning and procedural complications. Infusion site reactions → Injury, poisoning and procedural complications. Anaphylaxis → vascular disorders. Pneumocystis jiroveci pneumonia→ infections and infestations. Pneumonitis → respiratory thoracic and mediastinal disorders. Stevens-Johnson syndrome→ immune system disorders.

			Toxic epidermal necrolysis→ Injury, poisoning and procedural complications
Phenytoin injection	Nervous system, antiepileptics.	Cerebral atrophy.	Nervous system disorders (did not consider it as toxicity because it was reported to appear more likely in settings of elevated phenytoin levels and/**or** long term phenytoin use).
Darunavir tablets	Antiinfectives for systematic use.	Hepatotoxicity Severe skin reactions Diabetes mullites/ hyperglycaemia Fat redistribution Immune reconstitution syndrome Haemophilia Drug interactions: (HIV-protease inhibitors, other HIV-protease inhibitors, except atazanavir). Do not administer in paediatric patients (in the not recommended below three years of age; here the sentence was not complete).	Hepatotoxicity→ hepatobiliary disorders. Severe skin reactions→ immune system disorders. [although this is too general to classify, skin reactions are not necessarily immune medicated]. Diabetes mullite/ Hyperglycaemia → metabolism and nutrition disorders [note: blood sugar increased is in investigations]. Fat redistribution→ metabolism and nutrition disorders. immune reconstitution syndrome→ immune system disorders. Drug interactions→ General disorders and administration site conditions. Do not administer in paediatric patients (searched as contraindication to medical treatment) → social circumstance [deaths occurred in animal data (rats postnatal day 5)
Aubagio tablets (Teriflunomide)	Antineoplastic and immunomodulating agents	Anaphylaxis, angioedema and serous skin reactions. Decrease in white blood cell count: thrombocytopenia. Hypersensitivity and skin reactions: anaphylaxis and severe allergic reactions. Cases of serious skin reactions including Stevens Johnson syndrome and a case of toxic epidermal necrolysis. Very rare cases of DRESS reported with the parent compound leflunomide. Interstitial lung disease, including acute interstitial pneumonitis. Pancreatitis.	Anaphylaxis (as anaphylactic reactions)→ vascular disorders. Angioedema → immune system disorders. Skin reactions→ immune system disorder Thrombocytopenia → blood and lymphatic system disorders. Stevens Johnson syndrome→ immune system disorder. Toxic epidermal necrolysis→ Injury, poisoning and procedural complications. With the parent compound: DRESS → skin and subcutaneous disorders. Interstitial lung disease → immune disorders (contains acute interstitial pneumonitis in its class, but also acute interstitial pneumonitis found in Respiratory, thoracic and mediastinal disorders. Pancreatitis→ gastrointestinal disorders.
KuFDA newsletter no 4, 2018			
Eltrombopag	Blood and blood forming organs	Interference with bilirubin and creatinine test results.	Investigations.

Azithromycin containing products	Antiinfectives for systematic use	Increased risk of cancer relapse with long term use of the product after donor stem cell transplant	Preferred term (condition worsened, condition aggravated)→ general disorders and administration site conditions. Death → general disorders and administration site conditions.
SGLT2 inhibitors containing products: **Canagliflozin [Invokana, Vokanamet).** **Dapagliflozin (Xidgudo XR, Forxiga).** **Empagliflozin (Synjardy, Jardiance)**	Alimentary tract and metabolism	Rare occurrence of serious infection (necrotizing fasciitis of the perineum) of the genital area	Necrotizing fasciitis→ infections and infestations. Also in musculoskeletal and connective tissue disorders.
KuFDA newsletter no 5, 2018			
Rivaroxaban	Blood and blood forming organs	Increase in all cause of mortality, thromboembolic and bleeding events	Death (did not find mortality)→ General disorders and administration site conditions. Thromboembolic events → vascular disorders. Bleeding events→ vascular disorders.

ATC: Anatomical Therapeutic Chemical classification system; **MedDRA:** Medical Dictionary for Regulatory Activities; **CNS:** Central Nervous System**; DRESS:** Drug Reaction with Eosinophilia and Systemic Symptom; **SGLT2:** Sodium-Glucose cotransporter 2

Appendix 21: Data extraction of documents using a code-book developed by the researcher (to identify the process of creating and disseminating medications safety communications)

Code book item / Document number	Item 1 source of the safety information[1]	Item 2 action taken by KDFC[2] in response to the information	Item 3 Channel used by KDFC[2] to deliver the information	Item 4 receivers of the information sent by KDFC[2]	Item 5 Stakeholders' involvement[3] (other than KDFC staff)
F1 Public announcement (Red Juice).	Not reported.	(12) KDFC warned the public about an unregistered drug (red juice) and advised the public against its used.	(1) press-release via local newsletter. (3) social media (KDFC[2] published their press-release in KDFC twitter account). (4) KDFC[2] website (KDFC published their press-release in KDFC[2] website).	(5) The public.	(2) not reported.
F2 Public announcement (One Alpha).	(4) Rumours circulated in social networks in Kuwait. (3) KDFC contacted the manufacturer (KDFC confirmed from them that they did not issue any warning).	(12) KDFC clarified an information to the public (that there was no warning) and asked the public not to help in spreading rumours, and to keep using the product as prescribed.	(1) press-release via Kuwait News Agency (KUNA). (3) social media (KDFC[2] published their press-release in KDFC twitter account). (4) KDFC[2] website (KDFC[2] published their press-release in KDFC[2] website).	(5) The public.	(2) not reported.

F3 Public announcement (Diane 35 and Daphne).	(5) Specific sources were not reported (international reports of cases of blood clots and deaths)	(7) KDFC suspended the registration of the product. (8) KDFC advised patients to stop the medication of concern and to contact their physicians to discuss alternative treatments.	(1) press-release, however the channel was not specified in the document. (3) social media (KDFC[2] published their press-release in KDFC twitter account). (4) KDFC[2] website (KDFC[2] published their press-release in KDFC[2] website).	(5) The public.	(2) not reported.
F4 Public announcement (Reductil)	(1) US[7] FDA[8].	(6) KDFC withdrew the product from the market and banned it in the private pharmacies.	(1) press-release via Kuwait News Agency (KUNA). (3) social media (KDFC[2] published their press-release in KDFC[2] twitter account). (4) KDFC[2] website (KDFC published their press-release in KDFC[2] website).	(5) The public.	(2) not reported.
F5 Public announcement (Avandia)	(1) US[7] FDA[8]. (1) EMA[9].	(6) KDFC withdrew the product from the market and banned it in the private pharmacies and governmental pharmacies (8) KDFC advised patients to stop the medication of concern and to see their physicians to prescribe other alternatives.	(1) press-release, however the channel was not specified in the document. (3) social media (KDFC[2] published their press-release in KDFC[2] twitter account). (4) KDFC[2] website (KDFC published their press-release in KDFC[2] website).	(5) The public.	(2) not reported.

F6 KUFDA newsletter No. 5 (2018).	(1) US[7] FDA[8]. (1) MHRA[10]. (1) WHO[11] newsletter. In one of the drugs: (5) Specific source not named, but mentioned other international reference agencies, fatal cases reported worldwide due to improper use of the medicine.	(11) KDFC included information about a reminder (of a medicines contraindications, warnings and precautions), warnings and advise for HCPs in KuFDA newsletter.	(6) KuFDA newsletter.	(10) For most drugs mentioned in the KuFDA newaletter (all except the reminder) a section headed "advice for healthcare professionals" was included.	(2) Not reported.
F7 Report to an assistance undersecretary regarding Gilenya (attached to it the US FDA warning).	(1) US[7] FDA[8]. (2) Executive Office of the Gulf Cooperation Council of Health Ministries for the Cooperation Council Countries, Current name Gulf Health Council (they sent to KDFC the US warning).	(10) KDFC is following-up information related to the drug of concern from international health organisations, manufacturer and the MAH. (9) KDFC[2] asked the MAH[4] to deliver an urgent DHCP[5] letter. (3) KDFC[2] asked the MAH[4] to update the drug leaflet/product package insert and to update the patient guide.	(7) KDFC[2] asked the MAH[4] to deliver an urgent DHCP[5] letter to HCPs in Kuwait. (9) KDFC[2] asked the MAH[4] to update the drug leaflet/product package insert. (10) KDFC[2] asked the MAH[4] to update the patient guide. NB: the report mentioned that the MAH confirmed that they will update the drug leaflet/product package insert and the patient guide.	Not applicable "Report to an assistance undersecretary".	(2) Not reported.
F8	(2) United Arab Emirates Ministry of Health and Prevention (which was informed by the MAH[4]). (2) Executive Office of the Gulf Cooperation Council of Health Ministries for the Cooperation Council Countries (Current name Gulf Health Council). (3) MAH[4] in Kuwait.	(9) KDFC approved the content of the DHCP letter provided by the MAH. (10) KDFC assured following up with international drug agencies, while collaborating with	(7) KDFC[2] approved DHCP letter distribution by the MAH[4].	Not applicable "Report to an assistance undersecretary".	(2) Not reported.

		the manufacturer and MAH.			
F9	(2) United Arab Emirates Ministry of Health and Prevention (which was informed by the MAH[4]). (2) Executive Office of the Gulf Cooperation Council of Health Ministries for the Cooperation Council Countries (Current name Gulf Health Council). (3) MAH[4] in Kuwait.	(10) KDFC assured following up with international drug agencies, while collaborating with the manufacturer and MAH. (1) no action was required. although the two medications are available in Kuwait. The risk comes from using them together. And this indication is not approved in Kuwait nor the clinical trial was conducted in Kuwait.	Not applicable. KDFC[2] decided that it is not required to send DHCP letters to HCPs[6]	Not applicable "Report to an assistance undersecretary".	Not applicable no action was required.
F10	(1) US[7] FDA[8].	(11) DHCP sent by KDFC including information and points to remember, to report ADRs, and asked them to encourage patients to read the medication guide.	(5) DHCP[5] letter sent by KDFC[2] (letter title: Drug safety communication).	(10) HCPs as intended receivers. (2) Director of governmental hospital. (11) KOC (without specifying the recipient). (3) Director of pharmaceutical services MOH. (9) Chairman of diabetes specialised centre.	(2) Not reported.
F11	(1) MHRA[10].	(11) DHCP sent by KDFC including information, advise, and to report ADRs.	(5) DHCP[5] letter sent by KDFC[2] (letter title: Drug safety communication).	(10) HCPs as intended receivers.	(2) Not reported.
F13	(5) international reference agency and fatal cases	(11) DHCP sent by KDFC including	(5) DHCP[5] letter sent by KDFC[2] (letter	(10) HCPs as intended receivers.	(2) Not reported.

	worldwide (specific sources were not reported).	information, points to remember to report ADRs.,	title: Drug safety communication).		
F14	(2) Gulf Health Council. (2) United Arab Emirates Ministry of Health and Prevention (which was informed by the MAH[4]).	Not applicable (email from Gulf Health Council).	Not applicable. The document was an email from Gulf health counsel.	Not applicable. The document was an email from Gulf health counsel, decision from the KDFC was not included.	Not applicable.
F16	Not applicable (cover letter).	Cover letter of medication safety circular, without the main document.	Not applicable (cover letter).	(6) Chairmen of the council of medical departments.	(2) Not reported.
F17	(3) MAH[4] in Kuwait.	voluntary withdraw of the medication by the pharmaceutical company. (5) KDFC requested the pharmaceutical company to ensure that no item from the voluntary withdrawn batch to be distributed or sold.	Not applicable (the document was a letter from KDFC[2] to MAH[4] regarding voluntary recall of a batch of a drug).	Not applicable.	Not applicable.
F18	Not applicable (cover letter).	Two Cover letter sof medication safety circular, without the main document.	Not applicable (cover letter).	(6) Chairmen of the council of medical departments. (3) director of pharmaceutical services (MOH).	Not applicable.
F19 KuFDA newsletter May 2016, one report directed to an assistant undersecretary in the MOH, which included as an attachment a print of the safety issue from the FDA (leaflet update),	(4) Social media. (8) Media. (KDFC referred mentioned media and social media at the beginning of the report (with regard to safety issue of the drug spread in media and social media), then referenced the international regulatory agencies.	(3) KDFC asked the MAHs to change the drug leaflet. (5) KDFC sent the US FDA document to the MAHs in Kuwait and asked them to inform KDFC whether they had	(6) KuFDA newsletter. (9) KDFC[2] asked the MAH[4] to update the drug leaflet/product package insert urgently.	(19) not reported.	(2) not reported.

letters to different MAHs that that had the same product. All had a common drug (azithromycin), KUFDA newsletter had an additional drug rosuvastatin	(1) US[7] FDA[8]. (1) EMA[9]. (1) MHRA[10] (KDFC check that US FDA, EMA, and MHRA did not withdrew the product). (1) MHRA[10]. Note: MAH[4] in Kuwait (one of them) provided a document to KDFC to update the drug leaflet (however this was not mentioned as a source for the information). (5) For the second drug in KuFDA it included: Clinical trial experiences (5) specific source not mentioned in KuFDA newsletters (it mentioned Cases reported (fatalities and cases of the ADR); however, the sources above were regarding the same drugs in the report to assistance undersecretary.	applied or planning to apply the changes. (11) KDFC included the information about drug leaflet update in KuFDA newsletter, also the newsletter included leaflet changes, adverse reactions from clinical studies or post market experience, warning and precautions. (10) KDFC is following up with the drug safety (international authorities and MAHs).			
F20 (Committee meeting, decisions).	(1) US[7] FDA[8]. (1) EMA[9]. (5) clinical trials and post marketing studies (specific sources were not reported).	(2) Did not change the registration of drugs of concern but added conditions for prescribing and monitoring. (2) prescribing checklist will be prepared by the committee.	(5) DHCP by KDFC. (8) KDFC coordinates with MAHs to do lectures and workshops.	(10) HCPs intended receivers from the DHCP & the lecture/workshops. (6) sent how to report ADR to the chairmen of council of the medical departments.	(1) Physicians, council of the medical departments to approve KDFC's DHCP. (1) Physicians, council of the medical asked for conducting lectures.

		(11) inform HCPs about the information. (11) sent information about how to report ADR to the chairmen of council of the medical departments. 4) KDFC coordinates with MAHs to do lectures and workshops to raise the awareness of HCPs about the latest safety information related to the medication of concern (this was requested by the physicians' members of the medical counsel)			(1) Physicians, council of the medical and KDFC discussed the safety of a product in a meeting (SGLT2 inhibitor).
F21 Cover letter KDFC sent an urgent and an important circulation related to products containing valproic acid asking the recipients to circulate it to HCPs in their institutions.	Not applicable (cover letter).	(11) KDFC informed HCPs about the information (based on information in the cover letter).	Not reported - Not applicable (cover letter).	(10) HCPs (KDFC asked the recipients to circulate the circulation among HCPs in their institutions). (2) Heads of governmental hospital. (11) KOC (without specifying the recipient). (3) Director of pharmaceutical services MOH. (9) Chairman of diabetes specialised centre. (1) director of health area.	Not reported - Not applicable (cover letter).
F22 Cover letter of drug safety newsletter of registered drugs in Kuwait (the cover	(1) International regulatory agency (US FDA). (1) International regulatory agency, (EMA).	(11) KDFC informed HCPs about the information (DHCP).	(5) DHCP by KDFC.	(6) chairman of the council of medical departments.	Mentioned after a meeting with special commission, but

letter did not specify if it related to the attached DHCP or was KuFDA newsletter) + Drug safety communication (Dear Healthcare professionals"canagliflozin & dapagliflozin containing products), attached to it with the same date.	(9) KDFC meeting with a special commission, but did not specify this commission.	(2) KDFC sent a prescribing checklist regarding the medications of concern with the DHCP.		(10) HCPs as intended receivers (from "dear healthcare professional mentioned in the letter).	did not specify this commission.
F23 Cover letter of drug safety newsletter of registered drugs in Kuwait with urgent DHCP	(1) MHRA	(11) KDFC informed HCPs about the information (DHCP).	(5) DHCP	(1) Director of health areas. (3) Director of pharmaceutical services MOH. (10) HCPs as intended receivers (from "dear healthcare professional mentioned in the letter).	2) not reported.
F25 Cover letter of drug safety newsletter of registered drugs in Kuwait	Not applicable (cover letter).	Not applicable (cover letter).	Not applicable (cover letter).	(1) Director of health areas.	Not applicable (cover letter).
F26 Drug safety communication (DHCP "fluoroquinolone").	(1) US[7] FDA[8]. (1) EMA[9]. (1) MHRA[10]	(11) KDFC informed HCPs about the information (DHCP).	(5) DHCP[5] letter sent by KDFC[2] (letter title: Drug Safety Communication).	(10) HCPs as intended receivers (from "dear healthcare professional mentioned in the letter).	(2) not reported.
F27 Urgent drug safety communication (DHCP "	(1) MHRA[10] (3) MAH[4] in Kuwait.	(11) KDFC informed HCPs about the information (DHCP). (2) KDFC sent RMMs to HCPs (attached to the DHCP, including guide for HCPs, patient information booklet, risk information form, patient guide).	(5) DHCP[5] letter sent by KDFC[2] (letter title: Urgent Drug Safety Communication).	(10) HCPs as intended receivers.	(2) not reported.

F28 (9/11 Cover letter)	Not applicable (cover letter).	Not applicable (cover letter).	Not applicable (cover letter).	(6) Chairman of the Council of Medical Departments (3) Director pharmaceutical services at MOH. (4) Director Health promotion/health awareness departments at MOH	Not applicable.
F29 (metformin)	(1) EMA[9].	(11) KDFC informed HCPs by DHCP.	(5) DHCP[5] letter sent by KDFC[2] (letter title: Safety Notification).	(10) HCPs as intended receivers.	(2) not reported.
F29a (SGLT2)	(1) US[7] FDA[8]. (1) EMA[9].	(11) KDFC informed HCPs by DHCP.	(5) DHCP[5] letter sent by KDFC[2] (letter title: Drug Safety Communication).	(10) HCPs as intended receivers.	(2) not reported.
F29b (13/11 Cover letter).	Not applicable (cover letter).	Not applicable (cover letter).	Not applicable (cover letter).	(4) director of health promotion department (MOH).	Not applicable.
F30	Not applicable (cover letter).	Not applicable (cover letter).	Not applicable (cover letter).	(1) Director of health area. (2) director of governmental hospital. (3) Director of pharmaceutical services MOH. (7) chairmen of paediatric departments council. (11) Director of a Kuwait Oil Company- related hospital	Not applicable.
F31 (SGLT-2 inhibitors).	(1) US[7] FDA[8]. (1) EMA[9]. (5) worldwide reports of serious life-threatening cases of the safety issue (specific sources were not reported).	(11) DHCP sent by KDFC including information to HCPs, to report ADRs, and asked them to encourage patients to read the medication guide.	(5) DHCP by KDFC. (2) Fax (from transmission verification report).	(8) Head of the pharmaceutical services office in a health area. (2) Director of a governmental hospital. (3) Director of pharmaceutical services administration MOH.	(2) not reported.

		(10) KDFC will continue to investigate the issue.		(10) Intended receivers: HCPs.	
KuFDA2018(4)	(1) US[7] FDA[8]. (1) EMA[9]. (1) MHRA[10] (1) WHO[11] newsletter.	(11) KDFC informed HCPs about the label changes, advise for HCPs, recall information, safety information from other regulatory agencies, a reminder of risk, & warnings in KUFDA newsletter.	(6) KuFDA newsletter.	(10) For each drug mentioned in the KuFDA newsletter a section headed "advice for healthcare professionals" was included.	(2) Not reported.
17.PDF (KUFDA June 2016)	(5) Specific source not mentioned (although mentioned in some medications: FDA approved patient labelling, boxed warning, animal studies, clinical trials or post-market experience).	(11) KDFC shared information about the changes/ updates and additions of different sections of drugs' leaflets (KuFDA).	(6) KuFDA newsletter.	(19) Not reported.	(2) Not reported.
DHCP benzocaine	(1) US FDA	(11) KDFC informed HCPs about the information. (10) KDFC will follow-up with the drug safety issue.	(5) DHCP by the KDFC.	(10) HCPs as intended receivers.	(2) Not reported.

[1] Source of the safety information includes the source of the original information and/or the source delivering it to KDFC. [2]KDFC: Kuwait Drug and Food Control. [3] Stakeholders involvement in the development and/or approval of KDFC actions or KDFC communications. [4] MAH: Marketing authorisation holder. [5]DHCP: Dear HealthCare Professional. [6]HCP: Healthcare professionals. [7]US: United States. [8] FDA: Food and Drug Administration. EMA[9]: European Medicine Agency. [10]MHRA: Medicines and Healthcare products Regulatory Agency (the United Kingdom). [11]WHO: World Health Orgnization.

Appendix 22: KDFC interview transcript (transcript 1)

Amal: aa hello and thank you for participating

Interviewee: thank you so much

Amal: in my interview

INTERVIEWEE: ahha first I will ask general questions

INTERVIEWEE: okay

Interviewer: aaa how many years of experience do you have?

INTERVIEWEE: aaaah since xxxx so a I started working in this depar department since xxxx It's almost xx years يعني

Amal: okay and amm for the medication safety also xx years ? or

INTERVIEWEE: yeah yeah for the a a at the same department from xx years

Amal: okay

INTERVIEWEE: a a I started working here the the name of this department was quality assurance and then after that imm recently we we are starting to change the the title of the unit for pharmacovigilance department or unit okay aaa mmm because umm a internationally there is aa a huge umm interest in the pharmacovigilance aa and safety efficacy of the medications aa post-marketing and also aa mm aa aa يعني em aa there is an an importance so mm our work now more specified for the safety and the efficacy of the aa registered products in Kuwait

Amal: okay great aam What is your highest academic degree?

INTERVIEWEE: aa bachelorette of pha pharmacy

Amal: aaa to your knowledge

INTERVIEWEE: em

Amal: are there any legal requirements aa that influence medication safety in Kuwait?

INTERVIEWEE: aa aam legal?

Amal: yes

INTERVIEWEE: yes of course there is guidelines okay we are working with aaam these are guidelines is amm adopted from the Arab guidelines which is based on the European a guidelines Okay aaam all these aaam are adopted from the European ar guidelines okay aa regarding the safety efficacy which includes amm the SURs aa ICSRs amm safety communisations which contains also DHCPs aaa amm liter يعني amm news aa journals like

this okay so of course there is guidelines we are working with okay aa which is adopted from the Arab guidelines

INTERVIEWEE: you will find that it's almost the same in the Arab region

Amal: aam what are the categories of medication safety communications aa that you deal with?

INTERVIEWEE: aa I deal with pharmaceutical products medicinal a amm sorry medicinal mm aa the health product which which is aam food supplements herbal products cosmetic products and aaa أجهزة طبية

Amal: em okay aam can you describe your role in the process of medication safety communications?

INTERVIEWEE: aaa can you illustrate the?

Amal: aa like in the process of medication ri safety communications like aa what is what is your role?

INTERVIEWEE: my role?

Amal: like the creation of aa certain things or

INTERVIEWEE: okay aa my work is observation okay [Amal: em] aa for all every day I come here to work to to see what's new in the international websites if there is any news if there is any aa ss new side effects published in the international websites okay Also we deal with the companies if there is any signal assessment any new adverse events or any aa new actions should be taking aa taken to the medicine aa regarding the safety for example if there is a recall for some batch regarding after specification if there is amm change in the leaflet aa if there is new precautions which have to be aa illustrated to the healthcare providers a before aa giving the medicine to the patient okay like this so these are the things that I'm aa working with okay so the the the main aaa the main aim أو أو the main object that I do every day is to updated with the new information regarding the safety and efficacy of the medicine

Amal: okay aa so

INTERVIEWEE: لا sorry I'm I'm saying medicine but I don't mean only pharmaceutical products okay as I told you before aa I'm I'm checking all the cosmetic products aa all the emm food supplements emm special foods which include for example baby aa aa baby milk okay aa special formulations like redboul like this we also aamm check these products if there is any problem in the safety o mm my work is to inform other departments here okay to aamm for example there is alert there is new information regarding this product or something and they will do their work Okay

Amal: okay aa

INTERVIEWEE: it means that I am the first step okay if if there aa to inform others about the problem the new signals okay and if there is action also you will take it but the decision from them

Amal: a okay from the other departments ?

INTERVIEWEE: yeah from other depart if they are going to recall I I am aware only of the pharmaceutical products [Amal: em] okay

INTERVIEWEE: But for example if there is amm medicnal mm aa for food supplements okay [Amal: em] I will send amm the information or a letter to the department the food department that this product there is a recall for example for some batch or something okay and please inform me aa if it's registered in Kuwait or if this batch arrived to Kuwait and what the action that you will take [Amal: em] they gona tell me if this product should be recalled or we didn't receive this batch it didn't enter Kuwait okay

Amal: em yes

INTERVIEWEE: so I I will inform them at the beginning they will tell me what to to do and then the action will be from me I will aa contact the company to tell a tell them that they have for example to recall to make a leaflet update or something and then I will tell other regulatory departments [Amal: em] for example inspection department aaa mm aa central score a s a s aa central medical stores like this

Amal: okay and aa from where do you get the initial information ? you told me you you observe the information

INTERVIEWEE: I have many sources I have aa from the other aa international aaa health authorities okay like EMA US FDA MHRA okay aa Saudi FDA Emirates okay aaa from aa mm mm the meetings okay some here in the mm الخليق (الخليج) العربي [Amal: em]
okay they are doing meetings regular meetings together to discuss the situation of some products the safety and usually they are taking aa general decisions okay which will will be applied in all the countries okay this is the main co aa main source aa sometimes from the company itself because now a regarding the new regulations of the pv aa its obligatory for for the company if there is any safety issue if there is any aa safety signal or something they have to inform the authority and tell tell us what the action regarding that we will study the case and check if this action is suitable for us or not

Me & INTERVIEWEE: okay

Amal: aa how would you decide on whether to communicate or not communicate the aa safety information

INTERVIEWEE: aaa umm after evaluation okay after the evaluation aa we study all the aa circumstances the seriousness of the amm the case okay and the previous action that we took okay after that aa also we communicate with the company because sometimes there there is aam some safety communication or something and but the company will decide to take action regarding this risk management plan from voluntary from the company okay in this case we will observe what the company will do

Amal: em

INTERVIEWEE: okay

Amal: okay

INTERVIEWEE: so aa that's related to the case the serious of the serious of the case and also to the action of the company

Amal: okay And how would how would you decide whether the case was serious or not aa

INTERVIEWEE: aaa amm after evaluation of the study imm يعني for example aa يعني mm I don't know بصراحةhow how to على ايه aa for me at the beginning all everything is serous okay until I check that aa no maybe it's common side effect or its already aa written in the leaflet okay but rate is is will should be increased for example it's it's rare then I found after so many ICSRs or so many safety issues I find that no it should be not not rare it should be common aa we will upgrade the seriousness of the case [Amal: em] okay

Amal: yeah

INTERVIEWEE: okay okay but For me for myself at the beginning everything is serious

Amal: am now on what bases would you choose the tool for medication safety communication?

INTERVIEWEE: aa you mean amm to to send for example DHCP from us or from the company

Amal: yes yeah

INTERVIEWEE: or aha there is regulation for all of this okay but aa e as I told you before that depends on the company for example if there is a safety communication have to be aa published okay first of all I I if I I saw it should be published I will refer to the company and ask them to send a DHCP by the way any anything should be published from the company should take approval from us first [Amal: em] they will send me the copy okay I will study it and check that everything is need I need is included in the paper and then they will take approval also if there is a promotional material or something for the patient patient guide patient card everything should be approval approved from our department first okay So make sure that if the company is publishing anything it should be approved from us first

INTERVIEWEE: okay and then aa if we make sure that the aa company aa published this okay خلاص if if it's not serous if it's just a routine or something we will نكتفي [Amal: ehm] بذلكbut if it's not emm not enough for us we will issue a DHCP from our side and we will aa send it to all healthcare providers okay aaa also a umm I just want to inform you that aa we here publish is publishing every two month a newsletter from our department okay which contains all the safety communication that was amm that happened in the two two month okay so at the year we we publish six newsletters okay to every two two month we publish one okay and if you search that you will find that everything aa mm mentioned in this newsletter newsletter For example let me show you something because I'm working on it now

Amal: yeah

[the INTERVIEWEE showed me the screen in her computer]

INTERVIEWEE: as you see newsletter okay you will find for example there there was a an alert published in the aa MHRA regarding a denosumab aa which is pp prolia and z aa xgeva aa this products okay aa they found a various cases of hypoglycaemia after discontinuation of this product Hyperglycaemia sorry [Amal: em] okay what happen there will be a leaflet update ihh [as tired from talking] to inform the doctors aa when we a stop the medication suddenly there is a risk of hyperglycaemia will happened to the patient okay and aa the MHRA EMA published aamm aaa instructions for the healthcare aa to inform the patient the aa signs of hyperglycaemia aa how to discountin how to stop the medicine aa not immediately okay gradually okay and what's the cases that this product should be given to the aa patient and shouldn't aa and the cases that the patient shouldn't take this medicine okay you ~~can~~ will check this newsletter okay I can give you one old one from from us okay it contains all safety communication that is published internationally and which was aa aa mm aa published from us okay aa This aa newsletter we give it to the healthcare providers aa every two month we send it by email to amm رؤساء الأقسام in all Kuwait's hospitals government

Amal: the government sector?

Amal: aa What about the private sector ?

INTERVIEWEE: no

Amal: and for the aa d Dear healthcare professional communication [INTERVIEWEE also government] is it only for government?

INTERVIEWEE: also for government

Amal: okay

INTERVIEWEE: also for government
Amal: and how would the private section know or find ?
INTERVIEWEE: aa this mission will be to the should be taken aa from the company
Amal: em
INTERVIEWEE: because as I told you the mm we we send w a from our side we send a DHCP and also the companies should aa am aa disseminate a DHCP to the healthcare providers
Amal: okay aa and will they inform you that they have disseminated the?
INTERVIEWEE: yes And they give me they gave me after taking approval from us we gave them aa15 day during this 15 day they have to disseminate this aa DHCP then they re aa amm reply to us by aa checklist for the [sound of message ring] doctors that they disseminated this aa letter to them
Amal: okay amm do you usually d you said you prepare aa the newsletter and the direct healthcare professional communication aa Do you usually aa So you usually prepare draft for these first or?
INTERVIEWEE: yes of course
Amal: aamm you told me about the newsletter that it contains [I started reading what it contained from her computer screen] the medication name and aa you showed it to me [INTERVIEWEE: ehm] the manufacture the classes and what's the warning or the update
INTERVIEWEE: yes yes
Amal: amm
INTERVIEWEE: and the reference a you see here [she was showing me the newsletter at the computer screen] aa at the end of the column you will see the the action that we take okay food and drug administration had requested DHCP letter to be circulated to the aa healthcare providers from the company In this case we will not issue a DHCP [AMAL: okay] because
INTERVIEWEE: we already asked the company to send and they sen they I didn't write it yet but they send us a draft [Amal: em] to be approved from our side and they get approval already
Amal: okay and in that case they will send to all the government [INTERVIEWEE: Yes] and the private
INTERVIEWEE: and then after that they will reply us with a list checklist for the doctors tha that have has aa received a received DHCP
Amal: okay [INTERVIEWEE: okay] and for the direct healthcare professional communication what do they usually contain the information or

INTERVIEWEE: aamm احم aa you mean amm di how directly I deal with the healthcare providers

Amal: no no I mean the the direct the dear healthcare professional communications

INTERVIEWEE: em

Amal: or the letters

INTERVIEWEE: em

Amal: aa what do do what kind of information do they contain?

INTERVIEWEE: amm information which doesn't contain aa an action what I mean doesn't contain a recall doesn't contain aa cancellation

Amal: okay

INTERVIEWEE: it contains precautions aa for the use aa mm sometimes it contains amm contraindications if the this product is contraindicated in some cases

Amal: okay

INTERVIEWEE: for specific patients or something okay after DHCP in some cases regarding the case also and regarding the ee the decision that we are taking okay aa we make a leaflet update we ask the company to make a leaflet update to be containing all this instructions but sometimes it's not because it's for example it's like routine

Amal: okay

INTERVIEWEE: okay aa so a sometime I say that DHCP letter is the first step if there is a safety communication there should be a DHCP letter okay for for the healthcare providers after that because you know sometimes the changing in the leaflet aaa if aa pack the package if there is a change in the package or something okay it takes time so but first we have to tell the healthcare providers that there is a problem in this issue okay after that the action will take time

Amal: okay aamm so d these letters or risk communication do they aa contain information about the benefits of the medication also?

INTERVIEWEE: benefits amm you mean if a as I understand [Me:em] if if aa for example there is an assessment or for the product and aa there is the positive aa and negative ratio aa benefit risk assessment is positive you mean that we have to inform the aa the hea ال healthcare [Amal: aa] providers Or what do you mean?

Amal: aa what I mean is that when you when you do the letters usually say for example it con it has the risk of this side effect

INTERVIEWEE: aha

Amal: or this risk issue [INTERVIEWEE: okay] but within when telling about the risk issue is there is also information about the benefits or aa only aa it only it concentrates about the
INTERVIEWEE: aa mm
Amal: risk issues
INTERVIEWEE: usually I concentrate about the the issue the the safety [Amal: okay] the safety commu aa communication the the risk okay [Amal: okay] the new risk the new signal okay
Amal: em
INTERVIEWEE: I don't talk about the usually this is the form [Amal: em]okay because there is a a specific also information you have to give to the healthcare provider [Amal: okay (at the same time)] okay I I think that the healthcare provider knows the the advantages or the benefits[Amal: okay] of the product so there is no need to illustrate aa but maybe it it can be mentioned like this there is a risk of aa for example hyperglycaemia but it still can be used in some cases like this this this this but it's contraindicated for example for amm diabetic patients [Amal: em] okay?
Amal: em okay
INTERVIEWEE: you know what I mean
Amal: yeah
INTERVIEWEE: okay
Amal: yeah
INTERVIEWEE: it's still this product is useful but its contraindicated in this cases
Amal: okay
INTERVIEWEE: this is the information I I'm interested giving to the [Amal: okay] d healthcare provider
AMAL: okay so your saying when you give about the benefits you give on what is used or in that context…you want..
INTERVIEWEE: yes yes
AMAL: one [not clear] is correct to me
INTERVIEWEE: yes yes
Amal: amm is there any quality control procedures aa for checking the draft before aa you communicate it or before its final approval?
INTERVIEWEE: aa yeah of course what what I'm searching for reg a reg for myself يعني is the the information the safety information [Me:em] which have to be first clear okay for the heal aa not mis it shouldn't be misleading [Amal: em] okay Direct okay aaa which aa which

means the dose should be like this okay [Amal: em] aamm and also amm a I guess this is the main thing it have to be direct [me:okay] it have to be clear aaa not misleading amm it should be also simple [Amal: em] okay

INTERVIEWEE: to to be easy for every healthcare provider to understand it

Amal: okay [INTERVIEWEE: okay] and would it be usually pre-tested?

INTERVIEWEE: aaa

Amal: like aa for example if you are sending it to doctors would doctors read it before you sen would a representive [a repsentive??] doctor read it or a pharmacist .or .

INTERVIEWEE: no pharmacist from here from the department[??] [sound of a phone message ring] okay [Amal: em] of course after I prepare the draft دكتورة[H1] and دكتورة[S1] read them the the draft and they tell tell me it approved or not approved and they if there is any change they want to do okay if there is anything they want to change they after studying with each other we prefer the final form but not from outside the d drug [Amal: okay] food and drug control

Amal: okay so also there's no other stakeholders involved like patients healthcare providers ?

INTERVIEWEE: لأ

Amal: aa marketing authorization holders?

INTERVIEWEE: mmm no

Amal: okay aa

INTERVIEWEE: because it's an internal work

Amal: okay

INTERVIEWEE: okay [sound of a phone message ring] but it يعني mm the infor [sound I was removing the recorder from near her phone] the information is based on the mm oo our knowledge here and also the information which is published as I told you internationally [Amal: em] Okay

Amal: okay

INTERVIEWEE: it's not a single decision

Amal: em

INTERVIEWEE: okay

AMAL: so

INTERVIEWEE: there is so many sources but the final form will be from us

Amal: okay

INTERVIEWEE: you understand

Amal: yeah I got your point And then like H1 دكتورة or you told me they should…
INTERVIEWEE: they should they should amm revise and they aa [Amal: approve it or not] approve it or not
Amal: okay aa who are your targeted audiences from the medication safety communications?
INTERVIEWEE: aa mainly healthcare providers okay pharmacists
Amal: em
INTERVIEWEE: okay [me okay] and we were planning to make aaa for example a محاضرات [translation: lectuers] studies workshops for the healthcare providers and pharmacists to assist on the especially on the ADR reporting okay
AMAL: em
INTERVIEWEE: because it's a very very very important part from our work because as as you see I am here I I'm depending on the aa information witch is which is published aa or on from the I internet form newspapers from literature literatures like this okay [Amal: em] [a small laugh from the sound while talking, not an actual laugh] but they are the people who is dealing with the patients
Amal: em
INTERVIEWEE: okay so we are insisting on getting information from them many times in many aa presentations we took emails from healthcare providers to communicate [Amal: em] with each other of course that's not from me only from دكتورة[S1] and دكتورة[H1] because they are the heads okay aa they are dealing with other departments for inspection for example aa cen a the em central medical stores to exchange information aa if there is any safety issue aa if there is any new adverse event arised
INTERVIEWEE: okay they're dealing with there is a communication with all between all the authorities
Amal: em okay and would you communicate with to other ministry of health departments like the central medical stores or the inspection [INTERVIEWEE: of course] okay?
INTERVIEWEE: yes of course
Amal: and the pharmaceutical services
INTERVIEWEE: yes Of course
Amal: and amm what about like aa
INTERVIEWEE: but but not me the heads
AMAL: okay
INTERVIEWEE: okay
AMAL: the heads

Amal: and what about aa for example a healthcare providers that are in clinical trials?
INTERVIEWEE: em [as listening]
Amal: do you communicate with them also [sound of a message ring] or no
INTERVIEWEE: no but aam from the companies aa we receive reports from healthcare providers[sound of a message ring] in clinical trials and aaa a in the if if there is any problem if there is aa any complain from amm medicine [Amal: em] or something we are getting aa all this from the companies by the way its obligatory aa if there is any adverse event serious adverse event
Amal: em
INTERVIEWEE: they have to submit it to us within 15 days it is obligation
Amal: okey
INTERVIEWEE: okay it is international obligation
AMAL: okay
INTERVIEWEE: okay especially [sound of a message ring] inside Kuwait [Amal: em] but if it is outside they have to inform us but there will be no regulations there will be no [sound of a message ring] [???? I could not hear it as well] or something
Amal: em you mean if it's aa if if the medication is inside Kuwait or if the adverse drug reaction was INTERVIEWEE: Domastic no [?? Talking at the same time]
INTERVIEWEE: domestic case the medication should to be registered [Amal: okay]
in Kuwait
INTERVIEWEE: okay but I mean [sound of a message ring] .domestic case [sound of a message ring] just one second please [the interviewee asked for a second and checked her phone] sorry
silence
INTERVIEWEE: دكتورة[S1] see one of our works for example [noise only noise nothing was said] if there is an active ingredient or if there is a safety issue regarding an active ingredient in a a product okay
Amal: em
INTERVIEWEE: they are sending it to us to get information get studies published studies regarding the safety the uses the upper limit of this product
Amal: em
INTERVIEWEE: okay this is a part from our work
Amal: okay so that's just in time [small laugh while talking] to show it
INTERVIEWEE: [laugh] yeah just in time

Amal: em

Amal: okay so how would you deliver a safety communication aa to to your targeted audiences?

INTERVIEWEE: amm via I guess up they are sending aa mm aa from up fax I guess

Amal: faxes

INTERVIEWEE: yeah I guess they are sending faxes and emails because when I prepare the aaa [Amal: em [as listening]] for example

INTERVIEWEE: the newsletter or something I send it to doctor [D1] and by himself he send it also by emails to the healthcare providers that he the heads in all other departments that he know So it's maybe by emails aa not by hands by fax usually fax or email

AMAL: okay so to the hea to the hospitals [INTERVIEWEE: em] to the head

INTERVIEWEE: fax or emails

Amal: or emails okay to the head of the departments? [INTERVIEWEE: yes] the pharmacy departments or a ?

INTERVIEWEE: مكاتب الصيدلانيات [Amal: okay] what's the meaning?

Amal: the pharmaceutical services

INTERVIEWEE: yes

AMAL: yeah Aa is there a deadline for the delivery process?

INTERVIEWEE: of course there is a lines ~~deadlines~~ okay

Amal: em [as listening]

INTERVIEWEE: aaam as per the Arab guidelines okay it have to be delivered within 15 days

Amal: em

INTERVIEWEE: after getting approval from us يعنيfor example if the company [Amal: em] we ask them to send a DHCP as I told you they are you preparing [Amal: em] the template aa the form okay and they sending sending it to us After studying it by the way this DHCP is should be studied aam as fast as we can

Amal: em [as listening]

INTERVIEWEE: for example if we receive it at morning at the end of the day it has be approved

Amal: okay

INTERVIEWEE: or not approved okay aaa then the company is getting approval after getting approval within 15 days they have to be disseminated Okay

Amal: okay

INTERVIEWEE: for us also it'sthe same because am if there is anything aa DHCP at the same day I get approval from up [me em] after signature and sending within 15 days it will be send it to to the healthcare providers .[me okay]
Amal: so that's all it's all all the types is 15 days???
INTERVIEWEE: aa not all the types it differs from one case to other
AMAL: em [as listening]
INTERVIEWEE: okay but this is the the
Amal: the average
INTERVIEWEE: اه the average
Amal: what how if there is a serious case or [INTERVIEWEE: a] does it differ?
INTERVIEWEE: at the same time If it serous [Amal: em] at the same time
Amal: okay and a
INTERVIEWEE: because sometimes for example there is action has been taken regarding a product for example Lemtrada there was a problem between these days these two months or something about this product okay Lemtrada aa because they did a study and they found that there is the aaa the ri the risk assessment is negative the the uses of this product is is not useful okay
Amal: em [as listening]
INTERVIEWEE: so what we are making here the decision we are cancelling the aa amm we are cancelling this product [Amal: em] regarding this issue this is an urgent issue [Amal: em [as listening]] okay
INTERVIEWEE: so we prepare all the papers at the same time we get approval and then we disseminate it all over the people that we know
AMAL: okay
INTERVIEWEE: so its regarding the seriousness of the case
AMAL: em [listening/understanding] and the recall issues or cancellation of medication
INTERVIEWEE: aa if there is a recall or something we we don't send a DHCP
AMAL: em [listening]
INTERVIEWEE: what what will happen if there is a recall first I check recall for the whole range or at the batch
Amal: okay
INTERVIEWEE: that depends okay first of all I have to check if we received for a sample ~~sami??~~ a this batch is registered a we received it in Kuwait or not if its available in the Kuwaiti market we will inform the company that the recall should be have taken okay

INTERVIEWEE: at at the same time we send aa letter to the inspection department
AMAL: okay
INTERVIEWEE: okay to recall this product
Amal: okay aa now for when you send to healthcare providers or your audiences aa the medication safety communications, do you have any channel or any way for getting their feedback?
INTERVIEWEE: by email usually by email
Amal: okay s
INTERVIEWEE: usually by email There is amm form [me em] [looking in computer sound computer mouse [INTERVIEWEE: not ??] / stand up for searching file manually] unfortunately I don't have a copy now [Amal: em] but usually we are preparing brochures okay and aa d em if there is any any mm meeting any presentation outside or something we are giving it to healthcare providers which contains the the work of our department
Amal: em [as listening]
INTERVIEWEE: okay aa how to communicate with us we will the you will find the email
Amal: eh
INTERVIEWEE: the telephone number of the
AMAL: okay
INTERVIEWEE: a food and drug control And also you will find the fax if there is any questions of any information [Amal: em] they need to get also there is an website they can enter even the patient they can enter this website and there is.. if there is any complain aa any ADR report
they want to give[AMAL: em [listening]] us
INTERVIEWEE: they will aa put it in the website [walked to check the cabinet] let me check if I have I have a copy of brochure if I don't have I will just print it to you no
Amal: no problems okay
INTERVIEWEE: Unfortunately I will give it I will print it to you as a paper [sound of walking "walking back"]
AMAL: okay aa would the targeted audiences be provided with aa training or guidance
INTERVIEWEE: hm [as listening]
AMAL: for how to implement the safety communication
INTERVIEWEE: hm [as listening] aaamm that's the next step which should be taken
Me & T [at the same] time okay

INTERVIEWEE: we are working on this to to make am workshops for the first healthcare providers [~~me صح??~~] pharmacists okay to how to report to us if there is any problem if there is any aa safety issue or something

AMAL: em [as listening]

INTERVIEWEE: or something الجو حر صح[me أ أ) … [asked if I was feeling hot and I said its okay with me so she said no problem]

AMAL: انا عادي

INTERVIEWEE: انت عادي؟

Amal: انت عادي انت اذا

Interviewee: لالا…

INTERVIEWEE: okay and then after that our next step inshallah will be the patients

AMAL: okay

INTERVIEWEE: okay aa ….[she is doing something in her computer][Translation: I want to photocopy for you]

INTERVIEWEE: okay a continue

AMAL: okay aamm after you send the safety communication would you repeat sending the same information

INTERVIEWEE: a after sending the safety communication you mean for whom for the company for for [AMAL: aa]

ME & INTERVIEWEE [about the same time] for the healthcare providers

INTERVIEWEE: if there is a reminder يعني sometimes

Amal: em [as listening]

INTERVIEWEE: there is an issue okay we send already DHCP for example from two to three month

AMAL: okay

INTERVIEWEE: sometimes its republished in the for example the WHO newsletter [Amal: em] I put the reminder aa I will add it to the aa newsletter

AMAL: okay

INTERVIEWEE: our newsletter okay

AMAL: okay

INTERVIEWEE: but we write it's a reminder it's just a remin it's not a new issue it's just a reminder

AMAL: okay

INTERVIEWEE: which means that the same issue is still ingoing okay so take the same precautions take the same aam aa steps the ca same aa contraindications there is no change [Amal: em] the same issue

INTERVIEWEE: okay but as I told it's not important but from our side because it's already published this month but we already take took action before we will just give them a reminder

AMAL: okay

INTERVIEWEE: but we will not send a single DHCP

AMAL: okay

INTERVIEWEE: em

Amal: a what about if there is an update in the information?

INTERVIEWEE: a of course we will put it we will add it if there is any update if there is any new change have to be applied we we resend it again

Amal: the dear healthcare professional [INTERVIEWEE: yes]

communication

Amal: okay aa what

INTERVIEWEE: update you mean new information new aa

Amal: update in the a in the infor update in the infromations [me??]

INTERVIEWEE: yeah there is new information so in this case we should we should aa send that update

Amal: okay what would be you expected outcomes from these communications?

INTERVIEWEE: emm a outcomes first of all aa the the healthcare providers will be updated of the latest information regarding the safety of the medicines the m aaaa the all the medicinal products okay

INTERVIEWEE: the main aa target for for us the safety of the patient okay so they will take all the aam a appropriate aa steps with the patient or the aa a الطريقة المثلى [Translation: ideal/appropriate steps/method]

Amal: emm

INTERVIEWEE: for giving the medication to the the patient be aware of the aa risks that is arising

INTERVIEWEE: every now [Amal: em] and then from a medication or something and this is the main thing also we are يعنيwe are trying to encourage healthcare pr professional by getting this information to to inform us if there is they can see any anything that not published yet

INTERVIEWEE: we didn't inform them

Amal: okay

INTERVIEWEE: If there is a hidden adverse events

Amal: okay

INTERVIEWEE: okay w we don't know about it because they should be our a way of a knew the updates knowing the updates because they are the the ones who is dealing with patients [Amal: em] okay so sometimes a we don't know that for example this product aa causes headache

AMAL: em [as listening]

INTERVIEWEE: okay how will we know? from the healthcare providers

INTERVIEWEE: okay

INTERVIEWEE: so they are the way of knowing the the the next aa adverse event from the medicine

Amal: okay

INTERVIEWEE: okay [Amal: yeah] so we are trying by to build a communication between between us and the healthcare providers we to encourage them to inform us with the the the new new information that we don't know yet

AMAL: em [as understand] okay

INTERVIEWEE: okay

AMAL: aa do you monitor the outcomes of the safety communications?

INTERVIEWEE: of course of course

AMAL: how?

INTERVIEWEE: amm mm a if يعني for example if the m the new recommendations is suitable for the case and everything is controlled خلاص no problem but for example a even after doing all the aaa re precautions that we already informed the healthcare providers the still the problem is aa is the amm is appearing is a a is appearing with the medication so there is a a other steps have to be taken maybe we will a restudy the case maybe we will revaluate the [Amal: em] medication maybe no this medication should be for example a the dose should be changed the the a indication should be contraindicated in some patients [Amal: okay] more patients

INTERVIEWEE: there must be more studies sometimes the the information that we get is not sufficient for us so we will send the to the company [Amal: em] aa to ask them for more studies if there is more studies can be done regarding this issue and in some cases we suspend the the the medication for some time until these studies is prepared

AMAL: when you say when say you mean that if the medication still having problem if the adverse drug reactions still occurring
INTERVIEWEE: em [as assuring]
Amal: so that's why you are doing the other steps
INTERVIEWEE: yes yes
AMAL: a what about the actions of the healthcare providers if they are adhering to the recommendation or not adhering do you monitor this?
INTERVIEWEE: mainly they are aam no
AMAL: a okay
INTERVIEWEE: from my side no
Amal: okay
Interviewee: From my side no
AMAL: aam what k medication safety communication have you recently been involved with aa following the process you described?
INTERVIEWEE: mm [at the same time with mm [Amal: a]] I can give you copies
INTERVIEWEE: of the latest DHCP
AMAL: em
INTERVIEWEE: aa that we issued from our department [Amal: ehm
] okay
INTERVIEWEE: I wil I willl give you a copy of of but you need a signed copy ؟ صح
Amal: a no no d do you remember their names or their
INTERVIEWEE: Lemtrada this is the latest one [Amal: okay] I will I will show it to you [moved to get the example] and also I can give you aa copy from the WHO aa aa sorry ال amm our newsletter if you want
AMAL: okay
INTERVIEWEE: to know what's important for you
INTERVIEWEE: [sound of looking for papers and putting a file on the desk, sound of papers being searched] a a I will make a copy for you [sound of flipping papaers] amm لازم أسأل I have but it's not singe a em not signed copy from the W from the newsletter
AMAL: okay
INTERVIEWEE: I will give it to you
AMAL: you mean it is not yet disseminated
INTERVIEWEE: no its disseminated

INTERVIEWEE: but [without??[sound of noise]] I don't have the the signed one [me okay] the signed is up

Amal: aaokay I got your point[sound of the mouse of the computer]

INTERVIEWEE: look we don't have a problem in the dissemination because we already do our work and get approval send send it [Amal: em] sign and disseminate

AMAL: okay

INTERVIEWEE: [at the same time as me okay] but the problem as the previous point we are talking of talked about the is the doctor is obeying this aa healthcare provider aa information

ME & INTERVIEWEE [at the same time]: or not [Amal: aha]

INTERVIEWEE: okay but from our side we are doing the the the~~[Amal: dis]~~ job the steps as it should be okay but we don't know after that what happen that's why in in many cases we are asking the company also to to send a D DHCP not only sending they have the the medical الrepresentatives which is working in the company also verbally have to inform the pa the doctor regarding this new information okay this new restrictions aa new amm precautions okay [Amal: em] so the doctor will will know the information from many sources [Amal: okay] it written from the company aa written from us and also verbally from the a medical representative of the company okay

AMAL: okay aa to your knowledge are safety communications aa developed by the Kuwait drug and food control

INTERVIEWEE: em[as listening]

AMAL: are they publicly available?

INTERVIEWEE: aaa yes there is should be there was a problem previously in the website [Amal: em] but it should be published in the m website you can ask this question for دكتورة [H1]

Amal: aa okay [INTERVIEWEE :okay] but aa okay so all the things are published in the website

INTERVIEWEE: em em

AMAL: or only specific things?

INTERVIEWEE: no I I guess all things [Amal: okay]but to be honest this is not my job [Amal: okay] I'm not the one who is publishing so I I I'm not sure of that [Amal: okay] but aa you can ask دكتورة[H1] but as as as I know [Amal: em] everything should be published

AMAL: okay amm from your perspective are there any areas for improvement in the process of medication safety communications?

INTERVIEWEE: of course aa as I see amm at the beginning you know that I'm working here from xx years okay in the last two years two or three years I I find a very huge increase in the participation between our department and the healthcare provider also our departments in Kuwait health authorities okay no there is amm an increase in the a awareness of the PV aa guideline

INTERVIEWEE: the safety of the medications aa Also ss a p a very big e a important part from our work work is the a receving the RCSRs adverse event reporting [Amal: ehm] okay

INTERVIEWEE: aa before يعني I get yearly 50 for example 50 reports or something Now no aa last year we received more than 1000, 1000 or something

AMAL: okay

INTERVIEWEE: okay and this year no we exceed this number

AMAL: a

INTERVIEWEE: I I am receiving it from the companies Aa some individual cases aa some doctors are contacting دكتورة[H1] دكتورة[S1] and sending faxes okay [Amal: em] aa regarding amm special adverse event they can see or something

AMAL: em [as listening]

INTERVIEWEE: so a a I feel that there is a a big increase in the awareness of the importance of PV aa work

Amal: work or

AMAL: aam after they send what happens next d does it res any actions results from their aa incidence reporting or adverse drug reaction reporting?

INTERVIEWEE: s a am we study the case [Amal: em] okay if if there is a case for f aa a certain medicine or something we study the case aamm and we check the seriousness we check if the this adverse event is listed or not listed because sometimes main the main aaa mm conclusion of the adverse events that we are receiving that the the this adverse event is listed okay [Amal: okay] after that every for example three or four month we are doing a signal detection Aa we are counting the rates of the cases Because sometimes as I told you it's listed but it's listed that it's rare

AMAL: em em[as understood]

INTERVIEWEE: okay but regarding the pep population and the number of cases no it's not it's n [Me; em] it shouldn't be rare aa rare it have to be increased the seriousness of the seriousness of the case should to be increased sometimes we communicate with the company if the cases is not a complete for example or it needs a follow up we need a follow up report

or something yeah we are taking action in some cases and most of the cases are kept in our aa documents okay to to check the rate of the cases

AMAL: okay amm do you have any suggestions to improve the aa current work or current process of medication safety communications?

INTERVIEWEE: aa aamm o I had su suggestions before but I guess now they are trying to improve this side [H1] [doctora S1] [and doctora M1] [Amal: em] if if you hear about her they are trying to improve the PV aa work here in Kuwait I guess there is steps should [Amal: em] be taken before يعني aaa aa ne a insha Allah ne a next within next year or somethings there there are huge steps will be taken I guess

Amal: em but for you do you have any areas or things you think needs to be improved or ?

INTERVIEWEE: the main thing that I I amm I hope okay aa from the healthcare care providers not to hesitate to inform us if there is any aa safety signal they can see for a medication or something because I as I told you before they are the s the main source the more the main important source [Amal: em] for the information the accurate information

Amal: okay

INTERVIEWEE: okay that is the thing that I have hope that it it will be done initiated I don't know how to do it but

Amal: okay

INTERVIEWEE: healthcare providers [Amal: aa] They are the the main the main thing

Amal: do you want to add any other information relevant to this topic that we have not covered ?

INTERVIEWEE: hhh [a tiered sound] mm we we talked about safety communication a we talked about the ICSRs aa about the regulations that the company have to be a stepped in which is based on from the Arab guidelines regarding the safety which is aa to a to submit to us aa a routine aa files like the periodic safety updates which also contains aa safety information safety changes aa safety aa cases which is related to the medicine even if it's not serious if even if it's not complete aa mm there is timelines

INTERVIEWEE: for submitting this this [Amal: em] aa files there is aa risk management plans which is very very important in the safety of the aa aa medication because aa this plans emm contains all the safety communication we are talking about all the aa educational tools that have to be aa prepared for the patient for the doctors aa also the changes leaflet updates aa cancellation aa emm suspension of a product recall of batch specific batch or something it's very important what else amm I guess we covered all the parts as a as a as I [Amal: em]

AMAL: okay so to summarise you told me that Kuwait is a is following the Arab pharmacovigilance guideline mainly and which is aa adopted from the European medicines aychen agency's guideline
INTERVIEWEE: correct
AMAL: aa you told me that are the categories are different we have the direct healthcare professional communications we have the newsletters aa you told me mainly your role is to observe aa like what's happening in other sources and not only for medication but also for foods for food supplements for cosmetics [INTERVIEWEE: ehm] and you inform them and AMAL: a they will tell you what action [INTERVIEWEE: em] need to be done
INTERVIEWEE: em [assuring]
AMAL: amm you also told me that there is a specific deadline for the companies for the delivery which is 15 days which is unified which also the same case here aa in this department also aa unless if there is a serious issue like aa some medication should be cancelled it's within the same day
INTERVIEWEE ehm [assuring]
AMAL: you told me that healthcare the companies needs your approval before aaa disseminating the dear healthcare professional [INTERVIEWEE: yes of course] communication
INTERVIEWEE: any communication not only DHCP
Amal: okay
INTERVIEWEE: any communication if there is a educational material the they will use if there is a patient guide if there is aa patient aa brochures or something consents
AMAL: okay
INTERVIEWEE: you know some products need a a consent a d to to be signed from the patient before taking[Amal: em] the medication
INTERVIEWEE: anything anything regarding the safety of the medicine has to be approved from our d aa our aa department first
AMAL: even the verbal communications or the lectures and that they do
INTERVIEWEE: LL no not not the lectures
INTERVIEWEE: the written the written tools
AMAL: ehm [me & INTERVIEWEE at the same time :okay]
INTERVIEWEE: [Amal: also aa] aam not only the written to be honest aa there is sometimes there is an application [Amal: em]
INTERVIEWEE: for it to be used by the patient

INTERVIEWEE: for example the the patient who is taking insulin or something
Amal: em
INTERVIEWEE: there is some applications to enter the dose the the
INTERVIEWEE: everything have to be approved but may be from not the PV the other departments pharmaceutical or something
INTERVIEWEE: but I mean from the food food and drug control
Amal: okay aa you said you prepare a draft for the direct healthcare professional communication and the newsletter also It should be approved by the heads of the department and also دكتورة[S1]
INTERVIEWEE: revised after [me revised] revised
Amal: yeah
Interviewee: after revision
AMAL: revision and head
MR: and you told me the qualities the quality of the information you make sure about the quality of the information that you are including aa it's not pre-tested and a patients and healthcare provider they are not involved in the a preparation process aamm you told me mainly the aa dissemination is through fax or emails to the head of the departments and aa you said that there is an email and there is information about contact information
INTERVIEWEE: I I will give it to you [Amal: okay] if if you need them
AMAL: aa for the I mean for the healthcare providers to give you feedback
INTERVIEWEE: ehm
Amal: and aaa you told your targeted targeted audience including the healthcare provider the
INTERVIEWEE: pharmacists
AMAL: pharmacists and a the within the ministry of health the central medical stores and the inspection aam you told you resend the information if its resended in the for example in the WHO [INTERVIEWEE: ehm] aa or if if there is an update you're gonna [INTERVIEWEE: as a reminder] resend
INTERVIEWEE: [Amal: yes] as a reminder
Amal: but if there is an update you're gonna send it
INTERVIEWEE: yeah yeah
Amal: an amm you're expected outcomes from communications was mainly about the patient
INTERVIEWEE: em

Amal: and aa there is a the actions of the healthcare providers are not monitored
[INTERVIEWEE: em] aamm you told me about what medication you have recently communicated which was aa
INTERVIEWEE: you need a copy from it? This is the last okay
Amal: yeah
INTERVIEWEE: this is the last in July okay its regarding aa the product Lemtrada
AMAL: Lemtrada [INTERVIEWEE: okay] okay
INTERVIEWEE: okay we found that there is ra rare but aa You want a copy you want to take a photo?
AMAL: maybe I'll take a photo yeah
INTERVIEWEE: okay
AMAL: yeah
INTERVIEWEE: rare but serious risk of stroke and blood vessels aa wall tears with m a o it's MS product [Amal: em] okay
INTERVIEWEE: with this and you will find here the mm the conclusion of the case what happened
AMAL: okay
INTERVIEWEE: okay
AMAL: and a you told me that has been an improvement in the awareness of healthcare providers or a that about the pharmacovigilance
INTERVIEWEE: ehm [assuring]
Amal: which is now there is more a incidents reports are being sended
INTERVIEWEE: ehm
Amal: but you said there is an area for improvement aa fro for the healthcare providers to increase their engagement maybe [INTERVIEWEE; ehm] in [yes] the incident reporting
INTERVIEWEE: yes
Amal: aamm and that's that's is to summarise
INTERVIEWEE: yes
AMAL: thank you thank you very much for your time
INTERVIEWEE: welcome and if there is anything more you want to ask I'm available any time
AMAL: okay
Intervwee: okay
Amal: okay thank you so much

INTERVIEWEE: I aa if you want [sound of door opened] you can take a copy to to know the form of template of the DHCP [Amal: okay] usually am amm giving a short [phone ring] short note about the the problem okay

INTERVIEWEE: aamm the points [Amal: em] which the DHCP providers the the p healthcare providers should take care of okay and in this case it's a conclusion because Lemtrada has a problems from the the beginning of 9 2019 okay

Amal: em

INTERVIEWEE: so this summary for what happened during the last year okay

AMAL: okay

INTERVIEWEE: you will find so many problems regarding this issue

AMAL: em

INTERVIEWEE: okay so I pr I prefer if you are taking a photo from it

AMAL: okay

INTERVIEWEE: okay we will illustrate the product we will write advise t given to the to the patient

INTERVIEWEE: advise to healthcare professional [Amal: em] because aa the healthcare professional is the one who will give aa advise to the to the

AMAL: patient & INTERVIEWEE [at the same time]: patients

INTERVIEWEE: okay okay of course its it should be signed but aa here its signed from دكتورة[S1] it's two copies

AMAL: em

INTERVIEWEE: this for us from دكتورة[S1] and the one who is aa which is aa dem em disseminated okay the one who is signed from the director[Amal: okay] okay you will find the references I'm always attaching everything which is published internationally

AMAL: em

INTERVIEWEE: our sources is US FDA [sound of paper] okay and EMA [Amal: em] [sound of paper] okay you will find everything is here this is the latest okay also th this is aam a reply from the company the DHCP which is which was aa done by the company [Amal: em] and they disseminate it ab after aa approval from our side

AMAL: okay so this in this case there was two

INTERVIEWEE: yeah

AMAL: there was from you [INTERVIEWEE: yes from] and from

INTERVIEWEE: why because this issue was very very serious all over the world

Amal: em

INTERVIEWEE: and it’s updated many times

AMAL: em

INTERVIEWEE: aa at the beginning of a year [someone came and INTERVIEWEE said good morning talking with the person who came]

INTERVIEWEE: … دكتورة [Amal: em]شوفي ….risk minimsing tool [Amal: okay]

INTERVIEWEE: …

Interviwee: doctors guides

AMAL: okay

INTERVIEWEE: aa pharmacists guide aa information to the aa ل

Amal: em

Interviewee: ل للرجال و للنساء

INTERVIEWEE: instructionsيعني اللي هو بروشور أمم بيحتوي على كل ال

Amal: em

INTERVIEWEE: اللي لل

INTERVIEWEE: patients okay... ا

AMAL: okay

INTERVIEWEE: ….

AMAL: okay

INTERVIEWEE: فin this case …

AMAL: em

INTERVIEWEE: …

[Amal: em]

Intervviwee: …

INTERVIEWEE: approval مني

Amal: okay

Interviewee: okay

INTERVIEWEE: …

INTERVIEWEE: safety

AMAL: em

INTERVIEWEE: have to be approved from our side [sound of paper flipping talking to the person who came]

INTERVIEWEE: [she showed me the paper for the peron] …

icsr لل ال

INTERVIEWEE: الشركات اللي…

INTERVIEWEE: لو serious within 15 days …

INTERVIEWEE: و لو nonserious within 90 calendar days [paper flipping [with the person who came]]

AMAL: you said 90 days or 19 days

INTERVIEWEE: nine nighty nine zero [sound of the air-conditioner]

INTERVIEWEE: nonserious cases…

AMAL: okay and this is called the IS

INTERVIEWEE: I I I ICSR individuals case

INTERVIEWEE: …

AMAL: em

INTERVIEWEE: أأ ازا ال

INTERVIEWEE: case listed already

INTERVIEWEE: او احنا يعني شايفين ان هو مع ال

INTERVIEWEE: active ingreadiant

Interviewee:…

INTERVIEWEE:..؟؟some

AMAL: em

INTERVIEWEE: هو وrelated

… listed

خلاص احنا

INTERVIEWEE: we keep it in our database okay

AMAL: okay

INTERVIEWEE: علشانlater on

INTERVIEWEE: بنعملsignal assessment

INTERVIEWEE: عشان الrate

INTERVIEWEE: …

leaflet

INTERVIEWEE: اللي مكتوب فيه ولا لا

AMAL: okay

INTERVIEWEE: …

action …

AMAL: and you said you have database Does your database contain all the communication you did or only

INTERVIEWEE: not communication it’s it’s only for the aa a adverse event reporting

AMAL: and what about communications is there any

INTERVIEWEE: it's kept in our computers a I have a template for every single safety communication

INTERVIEWEE: we sanded before [Amal: em] since xxxx it's it's here in my computer يعني

INTERVIEWEE: also there is aa aa signed copy aa from up in the secretary

AMAL: okay so everything you sent or

INTERVIEWEE: I have it here but not signed

AMAL: okay

INTERVIEWEE: before sending

AMAL: okay its everything you did or [INTERVIEWEE: اه] or everyone else

INTERVIEWEE: amm no

AMAL: only

INTERVIEWEE: What I did

Amal: what you did

INTERVIEWEE: everyone is responsible for the thing that he did

AMAL: okay great just the last point because aa before the [INTERVIEWEE: em] the individual came

AMAL: you said that this was two letters were sent from your side [INTERVIEWEE: aha] and from the company

INTERVIEWEE: from our side why why did we prefer to do from our side because this aa this issue aa ha aa have been published many times there was so many aa questions about this issue what will happen with Lemtrada so we con concluded summarised all the information aa regarding this issue and put it in only one DHCP it will be much easier for the a a healthcare providers to get all the information the latest information regarding this product

AMAL: okay great thank you for your time thank you so much

INTERVIEWEE: okay you need copies from anything

Amal: أي

AMAL: l'll I'll take photo copies

INTERVIEWEE okay

AMAL: from the newsletter

INTERVIEWEE okay but it's not signed is it okay with you

AMAL: yay a its okay

INTERVIEWEE: you can get the signed one from up

AMAL: yeah no problem the non the non-signed is okay

INTERVIEWEE: okay

[I closed the recording and then re-opened it with permission because the participant was telling me something relevant]
AMAL: you were saying there was many cases published
INTERVIEWEE: aa regarding Fluroquinolone
AMAL: em [listening]
INTERVIEWEE: okay so we we did the same we concluded every information from this [Amal: em] and every action we did [Amal: em] regrading this issue [Amal: em] in one DHCP letter [Amal: em] and we aa prepared here disseminated to all healthcare healthcare providers
Amal: em [listening]
INTERVIEWEE: also we published it in the aa newsletter
AMAL: okay
INTERVIEWEE: I will give you a copy from it also
[sound of recorder switched of]

Then the Interviewee: said something and I took permission to take note of it and add it This was:

حاطين ايميل الإدارة بكل DHCPبكل adverse event بال DHCP

Appendix 23: Framework used and examples of the analysis process of the framework analysis

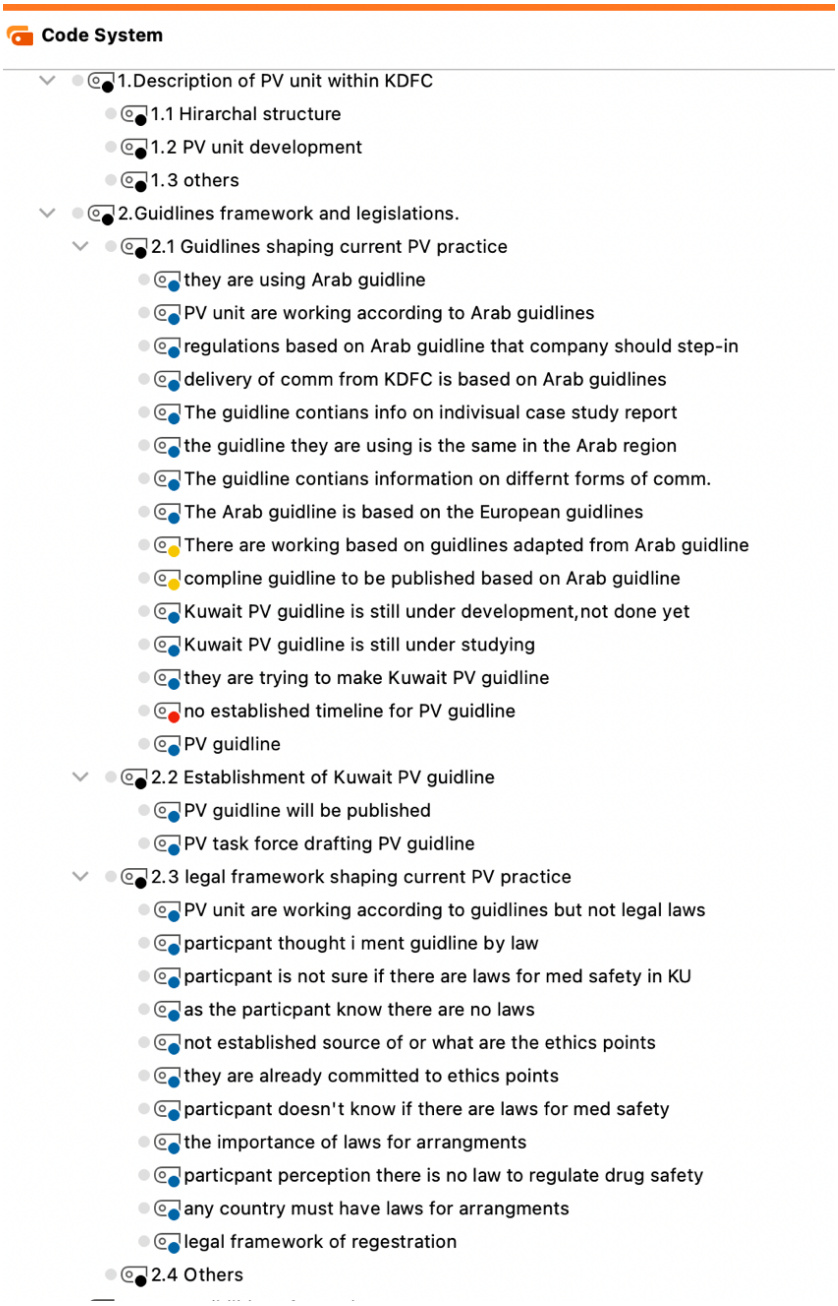
a. Framework used (based on communication model that was adjusted after analysing the interviews).

The items in red were not supported by any quotation.

Item

- 1. Description of PV unit within KDFC
  - 1.1 Hierarchal structure
  - 1.2 PV unit development
  - 1.3 others
- 2. Guidlines framework and legislations
  - 1.1 Guidlines shaping current PV practice
  - 2.2 Establishment of Kuwait PV guideline
  - 2.3 legal framework shaping current PV practice
  - 2.4 Others
- 3. Responsibilities of PV unit
  - 3.1 Type of products
  - 3.2 Type of safety information
  - 1.3 PV documents
  - 3.4 Knowing about a new safety information
  - 3.5 Dealing with companies
  - 3.6 Dealing with other KDFC departments
  - 3.7 Others
- 4. Safety information assessments and decision processes
  - 4.1 People involved in the assessment process
  - 4.2 Assessment criteria
  - 4.3 Assessment confirmation and decision making
  - 4.4 Timeline
  - 4.5 Others
- 5. Actions in response to the safety information
  - 5.1 Who will take the action
  - 5.2 Timeline for taking the action
  - 5.3 Information storage
  - 5.4 Others
- 6. Message preparation
  - 6.1 Content
  - 6.2 Tools
  - 6.3 Timeline and deadlines
  - 6.4 Others
- 7. Message quality control procedures
  - 7.1 Process
  - 7.2 Stakeholders involved
  - 7.3 Timeline
  - 7.4 Others
- 8. Message dissemination
  - 8.1 Channel of delivery
  - 8.2 Dissemination deadline
  - 8.3 Repetition
  - 8.4 Others
- 9. Receivers of medicine safety communications
  - 9.1 Targeted audiences
  - 9.2 Feedback from the targeted audiences
  - 9.3 Training provided by the targeted audiences
  - 9.4 Others
- 10. Outcomes of medicines safety communications
  - 10.1 Expected outcomes
  - 10.2 Monitoring the expected outcomes
  - 10. 3 Actions taken in response to the outcomes
  - 10.4 Others
- 11. Storage of medicines safety communications
  - 11.1 Storage
  - 11.2 Availability to the public
  - 11.3 Others
- 12. Examples of previous medication safety communications
- 13. Suggestions for improving medication safety communications
- 14. Others

b. Indexing open codes into the items of the matrix

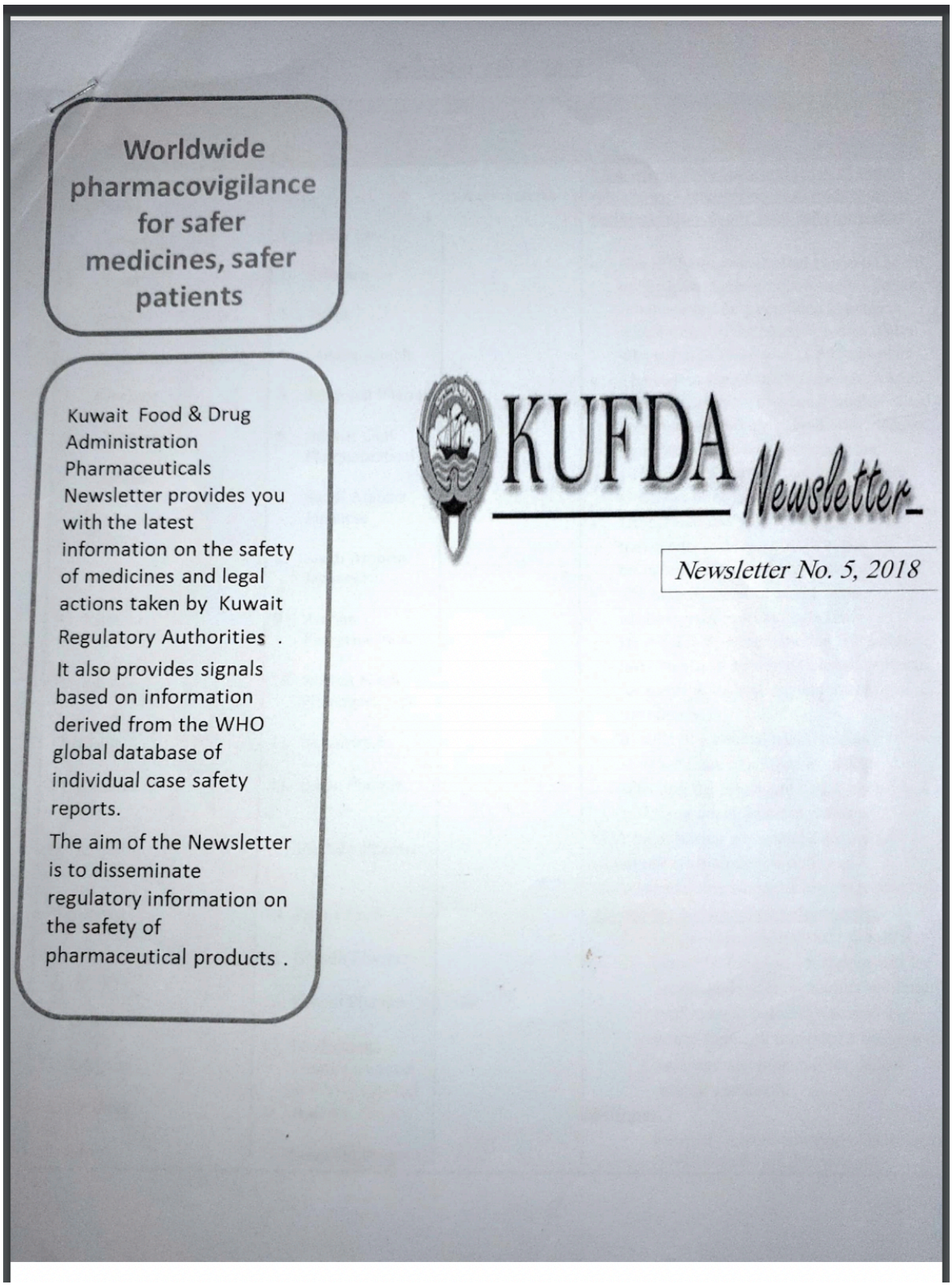


c. Extract from the matrix table (with the participants quotations) before reaching final theme

6. Message preparation	Participant 1 KDFC	Participant 2 KDFC	Participant 3 KDFC
6.1 Content	1. Amal: okay amm do you usually d you said you prepare aa the newsletter and the direct healthcare professional communication aa do you usually aa so you usually prepare draft for these first or? Interviewee: yes of course Amal: aamm you told me about the newsletter that it contains [I started reading what it contained from the interviewee computer screen] the medication name and aa you showed it to me [Interviewee: ehm] the manufacture the classes and what's the warning or the update Interviewee: yes yes and the reference a you see here [the interviewee was showing me the newsletter at the computer screen] aa at the end of the column you will see the the action that we take okay food and drug administration had requested DHCP letter to be circulated to the aa healthcare providers from the company 2. Amal: no no I mean the the direct the dear healthcare professional communications Interviewee: em Amal: or the letters Interviewee: em Amal: aa what do do what kind of information do they contain? Interviewee: amm information which doesn't contain aa an action what I mean doesn't contain a recall doesn't contain aa cancellation it contains precautions aa for the use aa mm sometimes it contains amm contraindications if the this product is contraindicated in some cases 3. Interviewee: benefits amm you mean if a as I understand if if aa for example there is an assessment or for the product and aa there is the positive aa and negative ratio aa benefit risk assessment is positive you mean that we have to inform the aa the heaال healthcare providers or what do you mean? 4. Interviewee: usually I concentrate about the the issue the the safety the safety commu aa communication the the risk okay the new risk the new signal okay I don't talk about the usually this is the form okay because there is a a specific also information you have to give to the healthcare provider okay I I think that the healthcare provider knows the the advantages or the benefits of the product so there is no need to illustrate aa but maybe it it can be mentioned like this there is a risk of aa for example hyperglycaemia but it still can be used in some cases like this this this this but it's contraindicated for example for amm diabetic patients okay? 5. Interviewee: it's still this product is useful but its contraindicated in this cases this is the information I I'm interested giving to the d healthcare provider 6. Amal: okay so your saying when you give about the benefits you give on what is used or in that context…you want.. Interviewee: yes yes Amal: one [not clear] is correct to me Interviewee: yes yes 7. Interviewee: I aa if you want you can take a copy to to know the form of template of the DHCP usually am amm giving a short short note about the the problem okay aamm the points which the DHCP providers the the p healthcare providers should take care of okay and in this case it's a conclusion because Lemtrada has a problems from the the beginning of 9 2019 okay so this summary for what happened during the last year okay 8. Interviewee: okay we will illustrate the product we will write advise t given to the to the patient advise to healthcare professional because aa the healthcare professional is the one who will give aa advise to the to the Amal: patient & Interviewee: patients okay okay of course its it should be signed but aa here its signed from …دكتورة [Translated by Amal: Doctor…] it's two copies this for us from …دكتورة[Translated by Amal: Doctor…] and the	1. لا [translated by Amal: no] no template no template its we we make a draft and w we can discuss with aa doctor… or doctor… And after that aa signed for it but no[not a complete word] not there is no tamp exactly tamplet according also to the issue em 2. Kind of information is amm aam a of course the product a the active ingredient aaa the problem aamm and the recommendation aa ال aa by for the for the doctors for the patient aa and aa if if we are want to change PIL or او [Translated by Amal: or] a a planning to to ask for the company to change PIL but mainly it's advice for healthcare professional and for the patient 3. Amal: do you include information about benefits in this draft about the benefits of medications Interviewee: benefits of no no no benefits we also mention the problem and aa how to aa to deal with	Amal: do usually prepare drafts for medication safety communications? Interviewee: "yes" Amal: aw what is it usually content contains Interviewee: ahh the usual content also depends on the case if it's a dear health care professional the content will be what are what's the case what's the advice for the health care professional sometimes advice for the patient and am how to report if there any problem happen a a you should report it to drug control at the end aa usually this is the template or this is how the form looks like for a dear health care professional letter Amal: okay it is a usually include information about the benefits of medications? Interviewee: aa if aa if it's important to be mentioned then we can add because most probably you will have a phrase that says that some population will still benefit from the drug and that the still the risk am am the benefit risk balance is positive so sometimes you have this phrase that says that the product is important for am a special population and that that's why we need it aa we're gonna keep it it will not be suspended it not be recall we're gonna keep it but with extra precautions aa like 1 2 3

	one who is aa which is aa dem em disseminated okay the one who is signed from the director okay you will find the references I'm always attaching everything which is published internationally our sources is US FDA okay and EMA okay you will find everything is here this is the latest okay		
6.2 Tools	1. also a umm I just want to inform you that aa we here publish is publishing every two month a newsletter from our department okay which contains all the safety communication that was amm that happened in the two two month okay so at the year we we publish six newsletters okay to every two two month we publish one okay and if you search that you will find that everything aa mm mentioned in this newsletter newsletter for example let me show you something because I'm working on it now 2. I can give you one old one from from us okay it contains all safety communication that is published internationally and which was aa aa mm aa published from us okay aa this aa newsletter we give it to the healthcare providers aa every two month we send it by email to amm رؤساء الأقسام [Translated by Amal: head of departments] in all Kuwait's hospitals government 3. for specific patients or something okay after DHCP in some cases regarding the case also and regarding the ee the decision that we are taking okay aa we make a leaflet update we ask the company to make a leaflet update to be containing all this instructions but sometimes it's not because it's for example it's like routine 4. okay aa so a sometime I say that DHCP letter is the first step if there is a safety communication there should be a DHCP letter okay for for the healthcare providers after that because you know sometimes the changing in the leaflet aaa if aa pack the package if there is a change in the package or something okay it takes time so but first we have to tell the healthcare providers that there is a problem in this issue okay after that the action will take time 5. Amal: you were saying there was many cases published Interviewee: aa regarding Fluroquinolone okay so we we did the same we concluded every information from this and every action we did regrading this issue in one DHCP letter and we aa prepared here disseminated to all healthcare healthcare providers also we published it in the aa newsletter	1. amm yeah we we sometimes a it's from the recommendation we make dear doctor letters so we a regarding [I heard z or th] what issue aa sometimes we we make this aa dear healthcare professional a from aa our department or sometimes we just make approval for the company a dear doctor letter 2. Amal: aa on what basis aa you choose the tool for medication safety communication I mean (Interviewee m? em) a you said sometimes it's aa through the PIL Or sometimes (Interviewee أه [Translated by Amal: yes]) It's a dear healthcare professional letter (Interviewee أه [Translated by Amal: yes]) or sometimes Interviewee: thi mainly according to the recommendation the recommendation amm If FDAs so [so not a complete word] usually it's writing written that It must a send dear health care provi aa letter to the providers aaa it must make a safety update for the PIL a ف manily it's like this Amal: and the FDA you mean be the stat a US FDA FDA [I heard right] Interviewee: US US FDA and MRHA like this sources all the sources 3. Amal: okay a would you use more than one tool for the same information? Interviewee: sometimes yeah maybe sometimes we we aa we ask for أو may يعني as usually it's L when they need aa PIL update leaflet update aa it's you know it's to to make this update it's maybe take for one year or for six months according to you know it's a submit for the file undertaking the approval ف during this we we have to send a l a a dear doctor letter from us or from the company aa to circulate aamm to a to to be the communication for the providers to leave more quickly aa tell we finish for the approval for the new update for the PIL فاا usually it will be both of them	1. regarding what we issue aa we issue dear health care professional letters 2. and am am mainly these are the safety communications we issue the dear healthcare professional letters and this and also newsletters we have am a periodically newsletter issued by Kuwait a Drug and Food Control that include all the updates that took place within two month time 3. Amal: aam would you use more than one tool to deliver the same aa safety information Interviewee: a you mean by different aa tools a Amal: I mean like a a Interviewee: yes we do you Amal: the dear healthcare professional letter and the newsletter Interviewee: ya we do yes 4. Amal: okay and is it now practiced delivering it to the media or Interviewee: some cases not so much few few very few cases but as i told you it's it's am it's very nice tool but it should be done properly with proper restrictions to to to avoid any panic or any wrong information to come to the public we need to address it properly 4. Amal: and would the deliver to the patient differ or is also through the a newsletter or interviewee: yeah it would be through newsletter through through letters like this
6.3 Timeline and deadlines	-	1. لأ [translated by Amal: no] as soon as possible aa because it aa aam always an urgent a يعني we we also we we mm usually aa consider that a dear doctor letter once we aa [th or that] the company submit we have to approve or once we see the issue if we want to make this drug safety communication aa by u by our department we have to do as soon as possible 2. Amal: em and what you mean by as soon as possible like how many days? Interviewee: maybe the same day t aa the يعني a the second day يعني within two days three two [I heard three] days يعني as soon as possible Amal: as soon Interviewee: we work on it once we deliver or once we aa aam aa no for يعني a aa see this aa issue in any online aa sources aa or fro from the company if يعني once the company submit this we have to deal with	3. Amal: aw what is your deadline for the preparation process? Interviewee: aamm basically we don't have a deadline so far Amal: you don't have Interviewee: so far we don't have a deadline yeah but we treat it on urgent basis because we know amm aam usually it's it's it's an urgent safety communication so usually we treat it aaa on urgent basis but we don't have a written guideline am specifying timeline

Appendix 24: Examples of KDFC medication safety communications (KuFDA newsletter number 5)



Worldwide pharmacovigilance for safer medicines, safer patients

Kuwait Food & Drug Administration Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by Kuwait Regulatory Authorities .

It also provides signals based on information derived from the WHO global database of individual case safety reports.

The aim of the Newsletter is to disseminate regulatory information on the safety of pharmaceutical products .

KUFDA Newsletter

Newsletter No. 5, 2018

Active ingredient\Product name	Manufacturer	Sub Class and Therapeutic Use	Warning or Updates
Azithromycin containing products: 1. Zithromax 2. Zimax 3. Zetron 4. Azithromycin Sandoz 5. Azi-Once 6. Azomycin 7. Azomax 8. Zithrox 9. Xithrone 10. Zithrox 11. Mazit 12. Zithrova 13. Azipar 14. Azitrox 15. Azimac 16. Glozimax 17. Z-Mycin 18. Zithrotel 19. Azitro	1. Pfizer Inc. 2. Spimaco 3. Tabuk 4. Sandoz Gmbh 5. Jamjoom Pharma 6. Julphar Gulf Pharmaceutical 7. Saudi Arabian Japanese 8. Saudi Arabian Japanese 9. Amoun Pharmaceutical 10. Kuwait Saudi Pharmaceutical 11. Neopharma 12. Oman Pharma 13. Plethico Pharma 14. Zentiva K.S 15. Riyadh Pharma 16. Global Pharma 17. Medpharma Pharmaceuticals & Chemicals Ind 18. Anfarm Hellas 19. Deva Holding	**Antibacterial**	**FDA warns about increased risk of cancer relapse with long-term use of azithromycin antibiotic after donor stem cell transplant** • The antibiotic contain azithromycin should not be given long-term to prevent a certain inflammatory lung condition in patients with cancers of the blood or lymph nodes who undergo a donor stem cell transplant. • The serious lung condition for which long-term azithromycin was being studied called bronchiolitis obliterans syndrome is caused by inflammation and scarring in the airways of the lungs, resulting in severe shortness of breath and dry cough. • Cancer patients who undergo stem cell transplants from donors are at risk for bronchiolitis obliterans syndrome. • The manufacturer of brand name azithromycin is providing a Dear Healthcare Provider letter on this safety issue to health care professionals who care for patients undergoing donor stem cell transplants. • Results of a clinical trial found an increased rate of relapse in cancers affecting the blood and lymph nodes, including death, in these patients. FDA is reviewing additional data and will communicate their conclusions and recommendations when the review is complete. **Advice for healthcare professionals:** 1. Health care professionals should not prescribe long-term azithromycin for prophylaxis of bronchiolitis obliterans syndrome to patients who undergo donor stem cell transplants because of the increased potential for cancer relapse and death. **Reference:** • Safety Alerts for Human Medical Products, US FDA, 3 August 2018 (www.fda.gov)

...tonavir-containing products: **1-Kaletra** **2-Norvir** **3-Viekirax**	**1-Abbott Laboratories** **2-Abbvie Ltd.** **3- Abbvie Ltd.**	• Ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older). • Ritonavir is also indicated for the treatment of chronic hepatitis C as part of a fixed-dose combination of ritonavir/ombitasvir/paritaprevir.	**Ritonavir-containing products: reports of interaction with levothyroxine leading to reduced thyroxine levels:** • The MHRA published in 11 October 2018 a warning to Monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month after starting and ending ritonavir treatment. • The potential for an interaction with levothyroxine is already known for antivirals used in chronic hepatitis C treatment because paritaprevir and ombitasvir are inhibitors of uridine diphosphoglucuronate-glucuronosyltransferase 1A1. • An EU review has assessed evidence for an interaction between ritonavir and levothyroxine following a signal of reduced thyroxine concentrations and increased TSH plasma concentrations in patients concomitantly taking these medicines. Some of the cases reported were symptomatic, including cases of hypothyroidism. • This interaction has been added to the Summaries of Product Characteristics and Patient Information Leaflets for ritonavir-containing medicines and levothyroxine. • Levothyroxine has a narrow therapeutic index and if ritonavir is stopped, any previous modifications to levothyroxine dose may have significant consequences for thyroxine levels. Induction of metabolism (glucuronidation) of levothyroxine by ritonavir is a possible mechanism for this interaction. **Advice for healthcare professionals:** • Reduced thyroxine levels have been reported in patients concomitantly taking ritonavir-containing products and levothyroxine. • Monitor thyroid-stimulating hormone (TSH) in patients treated with levothyroxine for at least the first month

			after the start and end of ritonavir treatment. • Report suspected adverse drug reactions resulting from interactions. **Reference:** • https://www.gov.uk/drug-safety-update/ritonavir-containing-products-reports-of-interaction-with-levothyroxine-leading-to-reduced-thyroxine-levels
Rivaroxaban: **1-Xarelto**	**1-Bayer Ag**	Direct inhibitor of coagulation factor Xa (Antithrombotic)	**Rivaroxaban after transcatheter aortic valve replacement: increase in all-cause mortality, thromboembolic and bleeding events in a clinical trial:** • The MHRA published in 11 October 2018 a warning Rivaroxaban treatment in patients who undergo transcatheter aortic valve replacement (TAVR) should be stopped and switched to standard of care. **Xarelto▼ (rivaroxaban) is a direct inhibitor of coagulation factor Xa with the following indications:** • Co-administered with acetylsalicylic acid alone or with acetylsalicylic acid plus clopidogrel or ticlopidine, for prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (2.5 mg) • Co-administered with acetylsalicylic acid, for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events (2.5 mg) • Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (10 mg) • Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (15 mg and 20 mg) • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in

			adults (10 mg, 15 mg, and 20 mg). Rivaroxaban is not approved for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients. **Advice for healthcare professionals:** • Preliminary analysis of a phase 3 clinical trial show risks of all-cause death and bleeding post-TAVR were approximately doubled in patients assigned to a rivaroxaban-based anticoagulation strategy compared with those assigned to receive an antiplatelet-based strategy (clopidogrel and aspirin) • Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in such patients • Rivaroxaban treatment in patients who undergo TAVR should be stopped and switched to standard of care • The direct-acting oral anticoagulants apixaban and edoxaban have not been studied in patients with prosthetic heart valves and their use is also not recommended in these patients; the use of dabigatran is contraindicated in patients with prosthetic heart valves requiring anticoagulant treatment. **References:** • https://www.gov.uk/drug-safety-update/rivaroxaban-xarelto-after-transcatheter-aortic-valve-replacement-increase-in-all-cause-mortality-thromboembolic-and-bleeding-events-in-a-clinical-trial
All Ceftriaxone containing injections	**Many companies**	Antibacterial	**Pharmaceutical And Herbal Medicines Registration And Control Administration upon reviewing the safety information published by other international reference agencies and also due to fetal cases reported worldwide because of improper use of ceftriaxone containing injections which**

causes hypersensitivity reactions (anaphylactic shock), has decided to remind you with the following points:

Ceftriaxone injection should not be prescribed if:

1. The patient is allergic to ceftriaxone
2. The patient had a sudden or severe allergic reaction to penicillin or similar antibiotics (such as cephalosporins, carbapenems or monobactams).
3. The patient is allergic to lidocaine and the Ceftriaxone injection will be given as IM.
4. Hypersensitivity test must be done to the patient before Ceftriaxone injection is administered.

Ceftriaxone for injection must not be given to babies if:

- Ceftriaxone is contraindicated in premature neonates up to a postmenstrual age of 41 weeks (gestational age + chronological age).
- The baby is newborn (up to 28 days of age) and has certain blood problems or jaundice (yellowing of the skin or the whites of the eyes) or is to be given a product that contains calcium into their vein.

Warnings and precautions for use:

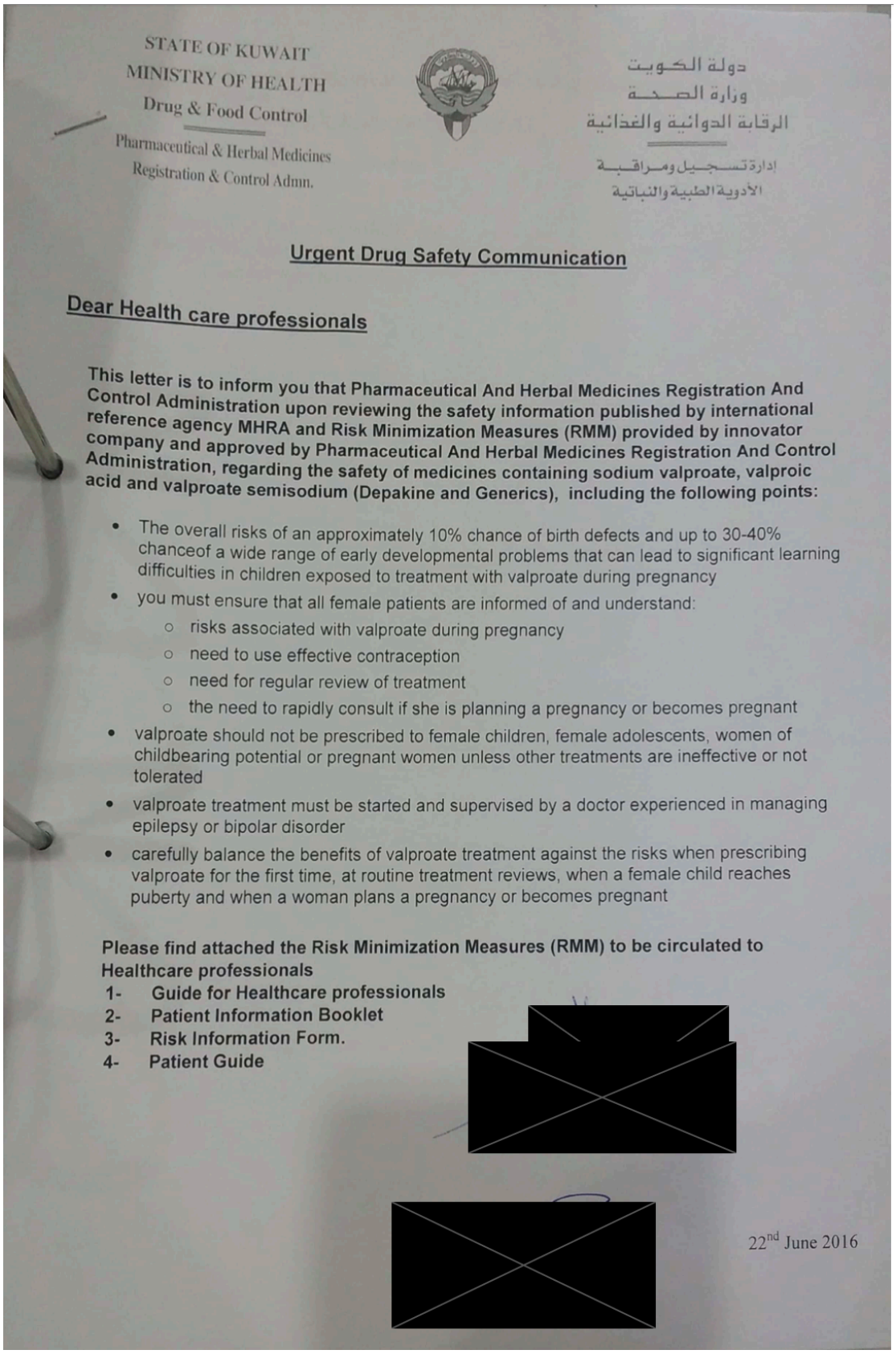
1. For IV injection 1 g ceftriaxone is dissolved in 10 ml of water for injections pheur. The injection should be administered over 5 minutes, directly into the vein or via the tubing of an intravenous infusion.
2. Ceftriaxone can be administered by intravenous infusion over at least 30 minutes (preferred route) or by slow intravenous injection over 5 minutes. Intravenous intermittent injection should be given over 5 minutes preferably in larger veins
3. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient.

			4. For doses greater than 2 g intravenous administration should be used. 5. In neonates, intravenous doses should be given over 60 minutes to reduce the potential risk of bilirubin encephalopathy 6. Ceftriaxone is contraindicated in neonates (≤ 28 days) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium 7. Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. 8. Diluents containing calcium, (e.g. Ringer's solution or Hartmann's solution), should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Therefore, ceftriaxone and calcium-containing solutions must not be mixed or administered simultaneously 9. For pre-operative prophylaxis of surgical site infections, ceftriaxone should be administered 30-90 minutes prior to surgery. 10. Ceftriaxone solutions containing lidocaine should never be administered intravenously.

References:

1. MHRA: Letters sent to healthcare professionals in September 2018
2. MHRA: Letters sent to healthcare professionals in October 2018
3. MHRA Drug Safety Update - September 2018
4. MHRA Drug Safety Update - October 2018
5. FDA medwatch
6. WHO Newsletter 5/2018

Appendix 25: Example of KDFC communications: DHCP letter (Valproate)



STATE OF KUWAIT
MINISTRY OF HEALTH
Drug & Food Control
Pharmaceutical & Herbal Medicines
Registration & Control Admn.

دولة الكويت
وزارة الصحة
الرقابة الدوائية والغذائية
إدارة تسجيل ومراقبة
الأدوية الطبية والنباتية

Urgent Drug Safety Communication

Dear Health care professionals

This letter is to inform you that Pharmaceutical And Herbal Medicines Registration And Control Administration upon reviewing the safety information published by international reference agency MHRA and Risk Minimization Measures (RMM) provided by innovator company and approved by Pharmaceutical And Herbal Medicines Registration And Control Administration, regarding the safety of medicines containing sodium valproate, valproic acid and valproate semisodium (Depakine and Generics), including the following points:

- The overall risks of an approximately 10% chance of birth defects and up to 30-40% chanceof a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy
- you must ensure that all female patients are informed of and understand:
  - risks associated with valproate during pregnancy
  - need to use effective contraception
  - need for regular review of treatment
  - the need to rapidly consult if she is planning a pregnancy or becomes pregnant
- valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated
- valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder
- carefully balance the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant

Please find attached the Risk Minimization Measures (RMM) to be circulated to Healthcare professionals

1- **Guide for Healthcare professionals**
2- **Patient Information Booklet**
3- **Risk Information Form.**
4- **Patient Guide**

[redacted]

[redacted]

22nd June 2016

You are encouraged to Report adverse events involving Depakine or other drugs on MOH KW website
http://www.moh.gov.kw/Departments/5/5-6/5-6-6/

Your cooperation is highly appreciated

Director of Pharmaceuticals and
Herbal Medicines Registration and
Control Administration

or those MA which include epilepsy and bipolar disorder indications. The MAHs are encouraged to collaborate in order to agree one document with the National competent authority in each Member State.]

Guide for Healthcare professionals

This Guide is provided as part of the risk minimisation measures developed for valproate to inform valproate prescribers of the risks associated with the use of valproate by women of childbearing potential and during pregnancy.

The Guide will provide up-to-date information about the risk of neurodevelopmental disorders in children of women who have taken valproate during pregnancy in addition to the known risk of congenital malformations in exposed babies.

This guide should be used with the Patient information booklet and Acknowledgment of Risk Information form. The Acknowledgement of Risk Information form must be signed by you and your patient

To learn more about valproate, please read the complete Summary of Product Characteristics before prescribing valproate.

WHAT YOU SHOULD KNOW ABOUT THE RISKS OF VALPROIC ACID USE IN FEMALE PATIENTS

VALPROATE contains valproic acid, an active ingredient with known teratogenic effects which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of developmental disorders. These risks are briefly described below.

1. CONGENITAL MALFORMATIONS

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29), which represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data.

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

2. DEVELOPMENTAL DISORDERS

Exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies[2-5] in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics[9]. Although the role of confounding cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population[7].

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[8].

Treatment of female Patients with valproate

A. FEMALE CHILD FIRST PRESCRIPTION

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).

- Discuss the following topics with your patient and relevant family members/care-givers:
  - Risks to pregnancy that are associated with the underlying condition; ○ Risks related to treatment, including risks related to valproate in case of pregnancy; ○ Need for an effective contraception method to avoid unplanned pregnancy.
  - Need for regular review of treatment

- Assess the most appropriate timing to provide advice on effective contraception methods and refer your patient to a specialist if needed.

- Ensure that your patient/family members/caregivers of the patient have understood the potential consequences in case of pregnancy and has/have an adequate level of understanding of the risks.

- Two documents have been developed to help you:
  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlights key points for treatment management:

- Read it, as it may help you to deliver appropriate information to your patient ▪ Give one copy to your patient

- **A Patient Acknowledgment of Risk Information form (see Annex 2):**
  - It should be signed by the patient and/or her legal representative
  - One copy should be given to the patient and/or her legal representative

- Keep in the patient's medical records:
  - One copy of the signed Patient Acknowledgment of Risk Information form

- Advise your patient to contact you immediately ○ If she becomes pregnant or thinks she might be pregnant.

- Plan to review the need for treatment when she becomes capable of pregnancy.

B. WOMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING PREGNANCY

After medical evaluation, you are considering prescribing valproate to your patient:

- Confirm that treatment with valproate is appropriate for your patient (i.e. all other treatments have been tried and failed).

- Discuss the following topics with your patient:
  - Risks to pregnancy that are associated with the underlying condition; ○ Risks related to treatment, including risks related to valproate in case of pregnancy; ○ Need for an effective contraception method to avoid unplanned pregnancy.
  - Need for regular review of treatment

- Assess the relevance of preconception counseling.

- Ensure that your patient has understood the potential risks to the child of using valproate during pregnancy and has an adequate level of understanding of the risks, and that she agrees to comply with the conditions for pregnancy.
  For this, the following documents have been developed to support you:
  - A Patient information booklet (Annex 1) which summarizes the teratogenic safety information and highlight key points of treatment management
    - Give one copy to your patient

○ A Patient Acknowledgment of Risk Information form (see Annex 2):
  - It should be signed by the patient
  - One copy should be given to the patient

- Keep in the patient's medical records ○ One copy of the signed Patient Acknowledgment of Risk Information form

- Advise your patient to contact you ○ If she becomes pregnant or thinks she might be pregnant; ○ in case of any adverse events associated with her treatment.

C. WOMAN OF CHILDBEARING AGE WHO IS PLANNING PREGNANCY

- Remind your patients of teratogenic risks and risks of developmental disorders that can be seriously debilitating when taking valproate but also the risks of untreated seizures or bipolar disorder.

- Reassess the benefit/risk of valproate therapy, whatever the indication:
  - Consider if stopping treatment or switching to an alternative is possible.
  - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms. ○ Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
  - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.

- Consider referring your patient to specialists for preconception advice.

- Ensure that your patient has understood the potential risks to the pregnancy, and has an adequate level of understanding of the risks ○ A Patient information booklet (Annex 1) should be given to the patient which summarizes the risks:
  - Give one copy to your patient

○ A Patient Acknowledgment of Risk Information form (Annex 2)
  - It should be signed by you and the patient ▪ One copy should be given to the patient

- Keep in the patient's medical records ○ A copy of the signed Patient Acknowledgment of Risk Information form.

- Advise your patient to contact their family doctor as soon as she becomes pregnant or thinks she might be pregnant in order to initiate appropriate pregnancy monitoring, including prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations.

- <It is recommended that pregnancies where the women are taking valproate are enrolled in registries of antiepileptic drugs and pregnancy and/or such data collection at a national level. {to be adapted at national level}>

D. WOMAN WITH UNPLANNED PREGNANCY

- Schedule an urgent consultation with your patient to review treatment as soon as possible to reconsider the benefits and risks of valproate.
- Tell her to keep taking her treatment until you have seen her, unless you are able to give other advice based on your assessment of the situation.
    - If further to a careful evaluation of the risks and benefits, valproate treatment is to be continued, it is recommended to divide the daily dose into several small doses to be taken throughout the day at the lowest effective dosage possible. The use of a prolonged-release formulation may be preferable to other treatment forms.
    - Both valproate monotherapy and valproate polytherapy are associated with congenital malformations. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of abnormal pregnancy outcome than valproate monotherapy.
    - Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk of birth defects associated with in utero valproate exposure.
    - Ensure that your patient:
        - has truly understood the risks related to valproate in case of pregnancy
        - has received the Patient information booklet (Annex 1)
    - Ensure that your patient:
        - has received and signed the Patient Acknowledgment of Risk Information form (Annex 2)
        - one signed copy of the Patient Acknowledgment of Risk Information form is kept in the patient's medical records.
- Initiate specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.
- <It is recommended that pregnancies where the women are taking valproate are enrolled in registries of antiepileptic drugs and pregnancy and/or such data collection at a national level. {to be adapted at national level}>

Summary

A. FEMALE CHILD FIRST PRESCRIPTION

1. Explain potential risks of the disease itself for the unborn child and the risks associated with use of sodium valproate in pregnancy
2. Assess your patient's need for treatment with sodium valproate
3. Inform your patient about the need to use effective contraception as soon as it is relevant
4. Ensure that your patient has received the Patient information booklet and signed the Patient Acknowledgment of Risk Information *[for national consideration]*
5. [Ensure that one signed copy of the Patient Acknowledgment of Risk Information form is kept in the patient's medical records[*[for national consideration]*
6. Where applicable, advise your patient to contact you immediately if e becomes sh pregnant or thinks she might be pregnant.

B. /OMEN OF CHILDBEARING AGE WHO ARE NOT PLANNING REGNANCY [and signed]

1. Explain potential risks of treatment and of untreated disease for the u
2. child
3. Assess your patient's need for treatment with valproate
4. Inform your patient about the need to use effective contraception En your patient has received the Patient information booklet th
5. Acknowledgment of Risk Information form] *[for national cor*
6. [Ensure that one signed copy of the Patient Acknowledgment of Infor form is kept in the patient's medical records
   Advise your patient to contact you immediately if she becomes pregna thinks she might be pregnant.

C. /OMAN OF CHILDBEARING AGE WHO IS PLANNING REGNANCY

1. Explain potential risks of the disease itself on the unborn child, indepe
2. from valproate's own risks.
3. Re-assess benefit/risk of patient's therapy
4. Adapt current treatment
   Advise your patient to contact you when she becomes pregnant or thi might be pregnant

5. Ensure that your patient has received the Patient information booklet [and signed
6. the Patient Acknowledgment of Risk Information form] *[for national consideration]*
   Ensure that one signed copy of the Patient Acknowledgment of Risk Information form is kept in the patient's medical records *[for national consideration]*

D. VOMAN WITH UNPLANNED REGNANCY

1.
2. Inform her to keep taking her treatme he
3. Schedule an urgent consultation
4. Re-assess the benefit/risk of her therapy
   Ensure that your patient has understoc proate in case of pregnancy
5. Ensure that your patient has received the Patient information booklet [and signed the Patient Acknowledgment of Risk Information form] *[for national consideration]*
6. Ensure that one signed copy of the Patient Acknowledgment of Risk Information form is kept in the patient's medical records *[for national consideration]*.

References

1. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81(1):1-13.
2. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October;51(10):2058-65.
3. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009;360 (16): 1597- 1605
5. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236
6. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J,Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):24452
7. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013;309(16):1696-1703
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years. Epilepsy Behav. 2011; 22(2):240-246
9. Meador K et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 (NEAD study): a prospective observational study. Lancet Neurol. 2013 March;12(3): 244-252

Annexes

1. Patient Information booklet
2. Acknowledgment of Risk Information form [*[for national consideration]*]

[For all MAs with Epilepsy/Bipolar disorder indications. The MAHs are encouraged to collaborate in order to agree one document with the National competent authority in each Member State.]

PATIENT INFORMATION BOOKLET –VALPROATE

The information in this booklet is for women who are being prescribed valproate and are able to get pregnant (of child-bearing age). Read this leaflet along with the patient information leaflet which comes in the medicine box and if you have any questions talk to your doctor or pharmacist.

There is a lot of information and it is recommended that you show this booklet to friends and family to help you discuss and understand your treatment. This booklet was last updated on dd/mm/yyyy.

Keep this booklet. You may need to read it again.

Make sure you have signed the acknowledgement of risk information form which should be given to you and discussed with you by your doctor or pharmacist.

RISKS TO THE UNBORN CHILD

Valproate can be harmful to unborn children when taken by a woman during pregnancy.

Whether taken on its own or with another epilepsy medicine, valproate seems to carry a higher risk if taken during pregnancy than other epilepsy medicines. The higher the dose, the higher the risks but all doses carry a risk.

t can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include *spina bifida* (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects.

you take valproate during pregnancy you have a higher risk than other women of having a child with rth defects that require medical treatment. Because valproate has been used for many years we ow that in women who take valproate around 10 babies in every 100 will have birth defects. This mpares to 2-3 babies in ever 100 born to women who don't have epilepsy.

It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow to walk and talk , intellectually less able than other children, and have difficulty with language and memory.

Autistic spectrum disorders and childhood autism are more often diagnosed in children exposed to valproate and there is some evidence children may be more likely to be at risk of developing symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.

Before prescribing this medicine to you, she or he will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.

FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective method of contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:

- **Make sure you are using an effective contraception**
- **Tell your doctor at once if you are pregnant or think you might be pregnant.**

CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should discuss with your doctor well before you become pregnant so that you can put several actions in place so your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your doctor may need to change the dose of valproate or switch you to another medicine before you start trying for a baby. If you become pregnant, you will be monitored very closely both for the management of your epilepsy/ bipolar disorder as well to check how your unborn child is developing.

Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/ bipolar disorder is controlled and the risks to your baby are reduced**
- **Tell your doctor at once when you know or think you might be pregnant.**

AN UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

Babies born to mothers who have been treated with valproate are at risk of birth defects and problems with early development which can be debilitating. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your epilepsy/ bipolar disorder medicine until your doctor tells you to.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of *spina bifida* and early miscarriage that exists with all pregnancies. However, it it unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:

- **Tell your doctor at once if you know you are pregnant or think you might be pregnant.**
- **Do not stop taking valproate unless your doctor tells you to.**

Acknowledgement of Risk Information Form - Treatment with valproate for female patients

A. Checklist for Prescribers

Name of Patient /carer

I confirm that the above named patient does not respond adequately or tolerate other ☐ treatments or medical treatments and requires valproate

I have discussed with the above named Patient/carer:

The overall risks of an approximately 10% chance of birth defects and up to 30-40% chanceof a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy.	☐
Individual risk can be minimised by use of the lowest possible effective dose	☐
The need for contraception (if child bearing age)	☐
The need for regular review of the need for treatment	☐
The need for urgent review if the patient is planning a pregnancy	☐
I have given the patient/carer a copy of the patient information booklet	☐

Name of Prescriber Signature Date

B. Patient /Carer Checklist

I, the undersigned, understand

Why treatment with valproate rather than another medicine is considered necessary for me	☐
The risks of an approximately 10% chance of birth defects and up to 30-40% chance of a wide range of early developmental problems that can lead to significant learning difficulties in children exposed to treatment with valproate during pregnancy.	☐
That I am advised to use contraception if not planning a pregnancy	☐
That my treatment should be reviewed regularly	☐
That I should request an urgent review if planning a pregnancy PRIOR to attempting to conceive	☐

Name of Patient/ Carer Signature Date

ey Facts – Valproate ▼ Depakine® and Pregnancy

ame: Date:

- Valproate is an effective medicine used to treat epilepsy in Gulf.*
- Valproate can seriously harm an unborn child when taken during pregnancy and should be not taken by women and girls unless nothing else works.
- When taking valproate always use reliable contraception so you do not have an unplanned pregnancy.

▼ This medicine is subjected to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects to the email address : Gulf.pharmacovigilance@sanofi.com or Contact : 00971 56 1747001

Gulf countries include UAE - Oman - Kuwait - Qatar - Bahrain and Yemen

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What you must do

- Speak to your doctor if you are thinking about having a baby, and do not stop using contraception until you have done so.
- Tell your doctor at once if you think you may be pregnant or know you are pregnant.
- Never stop taking valproate unless your doctor tells you to, as your condition may become worse.

Keep this card safe so you always know what to do.

April 2016

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Appendix 26: Focus group schedule

Introduction

Welcome and Thank you all for taking the time to participate in our discussion.
I am Amal Alharbi, and this is my supervisor **Dr Fatemah Alsaleh**.
Our discussion is about medicines-related safety communications.
The purpose of today's discussion is to get your point of view to help produce recommendations to the MOH to optimise medications safety communications.
There are no right or wrong answers to the questions I am about to ask. We expect that you will have differing points of view.
Please feel free to share your points of view even if it differs from what others have said.
You have the **Freedom to withdraw** from this discussion at any point
We are also **tape-recording** the session because we don't want to miss any of your comments.
Your **names will be removed** from any reports.

المقدمة

أهلا ومرحبًا بكم، بداية نتوجه إليكم **بالشكر** على الوقت الذي خصصتموه للمشاركة في نقاشنا
أنا **أمل الحربي**, و معانا مشرفتي **د فاطمة الصالح**
نقاشنا اليوم عن الاتصالات المتعلقة بالسلامة الدوائية
الهدف من نقاش اليوم ان نحصل على وجهات نظركم عن هذا الموضوع
ليست هناك إجابات صحيحة أو خاطئة على الأسئلة التي سأطرحها عليكم، وما نتوقعه أن تكون هناك وجهات نظر مختلفة بين جميع المشاركين
يُرجى عدم التردد في مشاركة وجهة نظرك حتى وإن كانت مختلفة عن وجهات نظر الآخرين
لكم **حرية الانسحاب** في أي مرحلة من هذه المناقشة
سيتم تسجيل النقاش اليوم، ولكن **لن يتم وضع أي اسم** في التقارير.

Opening question: Everyone introduces themselves

1. Have you **heard** about the terms "**medication safety communications**"?
   a) What do you know about it?
   b) Medication safety communication is the process of disseminating medication safety related information to healthcare professionals, patients or the public.

١. هل سمع أحدكم بعبارة "اتصالات السلامة الدوائية"؟
أ. ماذا تعرفون عنها؟

ب. اتصالات السلامة الدوائية هي عملية توزيع المعلومات المتعلقة بالسلامة الدوائية على الممارسين الصحيين والمرضى والعامة.

2. What **sources** you use in your practice to update the knowledge on medication safety information?
   - **a)** Internet-based/ software (e.g., Lexicomp/up-to-date);
   - **b)** Direct Healthcare Professional Communications.
   - **c)** Books
   - **d)** Food and Drug Administration or equivalent websites
   - **e)** medical journal
   - **f)** news; media.
   - **g)** Sources in Kuwait specifically, e.g., pharmaceutical companies.
   - **h)** Other sources.

٢. ما هي المصادر التي تستخدمها عادة لتحديث معرفتك بشأن معلومات السلامة الدوائية؟
أ. البرامج المتاحة على الإنترنت.
ب. الاتصالات المباشرة لممارسي الرعاية الصحية
ج. الكتب
د. إدارة الأغذية والعقاقير أو المواقع الإلكترونية المشابهة؛
ه. الدوريات\ المجلات الطبية؛
و. متابعة الأخبار؛ وسائل الإعلام
ز. مصادر الكويت تحديدًا، مثل شركات الأدوية
ح. مصادر أخرى

3. From these sources, what do you mostly prefer?
   - **a)** Why? (**strengths** and **limitations)**

٣. من بين هذه المصادر، ما هو مصدرك المفضل؟
أ. لماذا؟ (نقاط القوة وجوانب الضعف)

4. What medication safety information you receive **locally in** Kuwait?
   - **a) From where?**
   - **b)** In what **forms** (e.g., letters, newsletters)
   - **c)** How frequently?
   - **d)** What you like, you don't like?
   - **e)** In the **last three years** what was the **most popular** safety information?
   - **f) If needed show them**) **newsletter, DHPC).**

٤. هل تلقيتم معلومات بشأن السلامة الدوائية محلياً من الكويت؟
أ. من أي جهة؟
ب. بأي صيغة)رسائل على سبيل المثال) ؟
ج. كم مرة تتكرر؟

د. ما عجبكم بها وما الذي لم يعجبكم بها؟
ه. خلال السنوات الثلاث التي مضت ماهي أشهر معلومة (اتصال) متعلق بالسلامة الدوائية؟
و. إذا لزم الأمر أريهم نماذج.

5. Do you think you should **follow** the **recommendations** regarding medication safety information?
   a) **Why**?
   b) Where there any **situation** that you **didn't apply** the recommendations? **Why?**

٥. هل باعتقادكم أنه يجب اتباع توصيات الاتصالات المتعلقة بالسلامة الدوائية؟
أ. لماذا باعتقادكم أنه يجب اتباع التوصيات؟
ب. هل كانت هناك مواقف لم تتبعوا فيها التوصيات؟ ولماذا؟

6. Have you received safety information specifically related to the use of **valproic acid in female patients**?
   a) What was the information?
   b) What **source/form**?
   c) How many people in the room **came across female patients using valproic acid?**

NOTE: show them dear doctor letter on valproic acid

٦. هل تلقيت اتصال سلامة يتعلق تحديدًا باستخدام حمض فالبرويك من قبل مرضى من الإناث؟
أ. ماهي المعلومة التي احتواها الاتصال؟
ب. من أين تلقيته؟ بأي صيغة؟
ج. من بين الموجودين في القاعة، كم عدد الأشخاص الذين قدموا رعاية صحية لمرضى من الإناث اللاتي يستخدمن حمض فالبرويك ؟

7. For those **who heard about it,** have this communication (of safety information) **affected your practice**?
   a) If its prescribers – has it changed your **prescribing pattern**?
   b) If its pharmacists/pharmacy technicians – has it changed your **counselling** or service provision practice?
   c) If its nurses – has it changed your medication **administration or care practice**?

٧. هل أثر هذا الاتصال على ممارستك المهنية منذ وقت تلقيه؟
أ. بالنسبة لمقدمي الوصفات الطبية - هل غير ذلك النمط الذي تتبعه لتقديم الوصفات؟
ب. بالنسبة للصيادلة / فنيي الصيدلة - هل غير ذلك في ممارستك المهنية المتعلقة بتقديم المشورة أو الخدمات؟
ج. بالنسبة للممرضين هل غير ذلك ممارستك المهنية في تقديم الدواء أو الرعاية؟

8. For those who **did not receive** it (safety information), what do you think were the **barriers** for **not receiving** this safety information?
   a) Knowing about this safety information, **how would it affect your practice?**

٨. بالنسبة للأشخاص الذين لم يصلهم هذا الاتصال, ماهي المعوقات التي حالت دون ذلك؟
أ. بعد معرفة المعلومات المتعلقة بهذا الاتصال, كيف ممكن أن يؤثر ممارستك المهنية؟

9. In general, what are the **barriers and facilitators** in implementing the recommendations regarding medications safety communications?
   a) Knowing about the **valproic acid safety** information, what are the **barriers and facilitators** in implementing them?

٩. ما هي العوامل المعوِّقة والمُيَسِّرة لتنفيذ التوصيات المقدمة في اتصالات السلامة الدوائية؟
أ. بعد معرفة المعلومات المتعلقة بهذا الاتصال, ما هي العوامل المعوِّقة والمُيَسِّرة التي تجعل مقدمي الرعاية الصحية (الصيادلة أو فنيي الصيدلة أو الممرضات أو الأطباء) ينفذون التوصيات الواردة في اتصال حمض فالبرويك ؟

10. Do you have any **suggestions / recommendations** to **improve** medication safety communications in Kuwait?

١٠. هل لدى أي شخص مساهمات لم يتم مناقشتها خلال الجلسة لتحسين الاتصالات المتعلقة بالسلامة الدوائية؟

11. Does anyone have any **contributions** which have **not been discussed** in during the session?

١١. هل لدى أي شخص مساهمات لم يتم مناقشتها خلال الجلسة

12. closure

١٢. الختام

Appendix 27: Example of a focus group transcript (extraction from pharmacists focus group)

Amal: aa welcome all and thank you for taking the time to participate in our reasrch today I'm Amal Alharbi I'm a PhD candidate at the university of Hertfordshire in the UK and this is my [sound not a word or a letter" a"] supervisor Dr Fatemah Alsaleh From Kuwait University our discussion today is about medicines related [sound of something like table] safety commincations the purpose of todays' discussion is to get your points of views as pharmacists about this topic in order to produce recommendations to the ministry of health there are no right or wrong answers in today's discussions we expect that all of you have different points of views [sound of people talking far outside?]so please feel free to share your point of view [sound of something like table] even if it differs what others have said but please because we're recording a try not to talk [sound of chair movment] at the same time so it will be clear for us in the records [sound of chair movment] you have the freedom [sound of something like table] to withdraw from the session at any point [sound of someone talking very low voise, someone said تفضلي]

Different people talking about the AC, side talking, sound of hem نحنحة, sound of cough

Amal: So a I want to emphasise [sound of paper] that we are [sound of paper] tape recording today but we're going to remove your names from any reports and any studies [someone made a sound very low but not a word] aa if you can kindly put your phones on silence [sound of pressing on a pen [like to open or close it]] so it doesn't disturb you while the discussion [side talking very low voice] aaa [paper flipping]
So we'll start with the first question aa have you heard about the in terms medication safety communications?
PH 1M: again please
Amal: Did you hear about the term medication safety communications
PH 1M: no this first time
Amal: o what do you think what is it about?
PH 1M: I think this is communications [sound of something like table] aa between the all members of healthcare to to [sound of something like table] use more safety procedures to our patients
Ph-women: [not clear "for" or "or"] the counselling
PH 1M: counselling like that yeah
Pwomen2: counselling the patient
Amal: okay
Pwomen2: good counselling to the patient [sound of something like a table during this discussion]
Amal: okay
Amal: aa
Ph 2 W: communication between healthcare professionals that affect the patient safety
Amal: okay great does anyone have any other idea about medication safety communications [sound of something like a table during this discussion]
PH 3 M: I guess it's all communication regarding patients and other healthcare [women maybe Ph 2 W: health care] staff not only for particular one
PH 4 W: and communicated from different like point like from the ?? from the condition from the seminar (not clear I heard: from many aspects)
Amal: okay
W: [not clear] (I heard plosion?)
PH 4 W: solutions
Amal: yeah

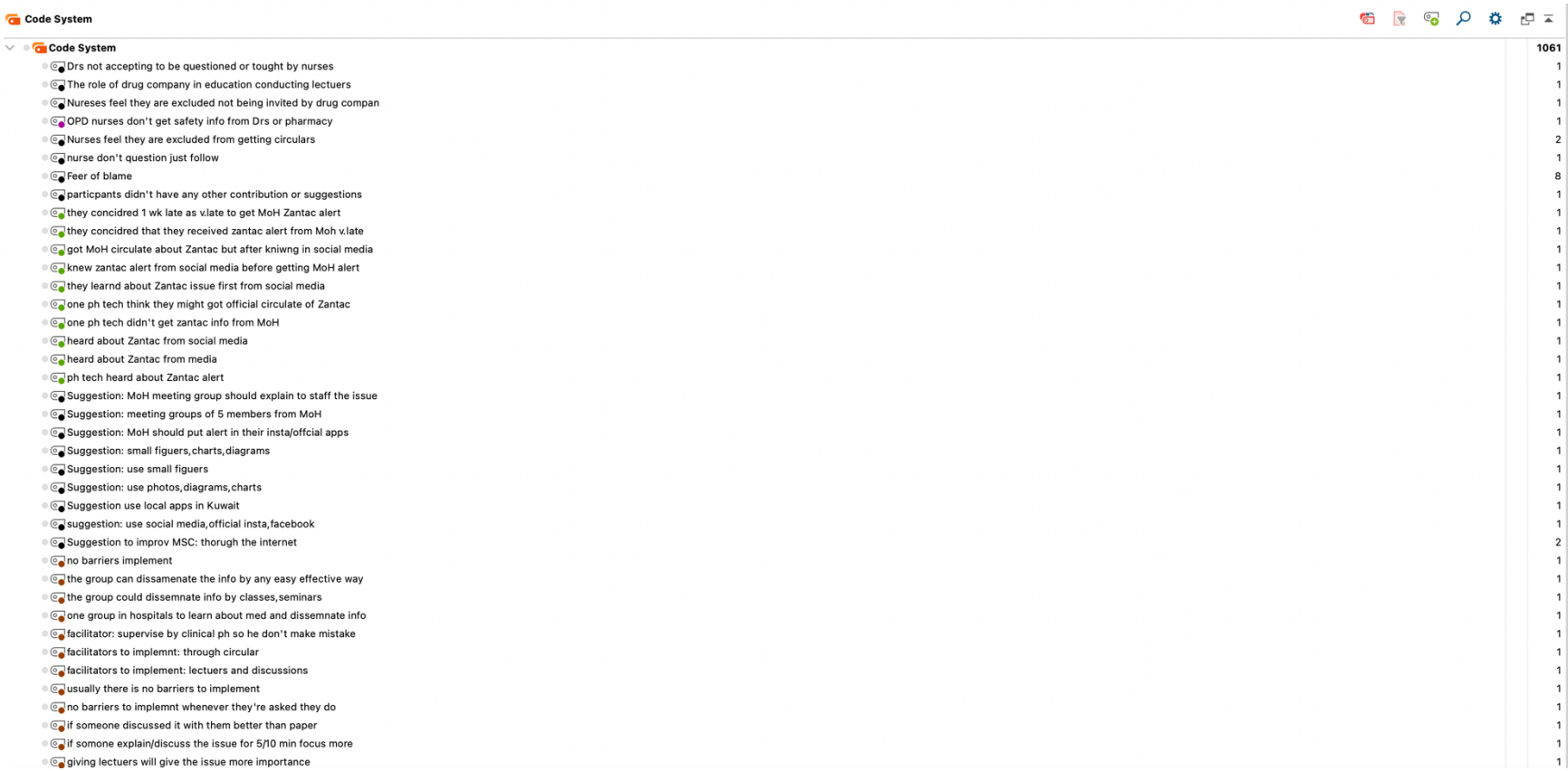
PH 4 W: different kinds of (sound of putting cup down)
Amal: so medication safety communications that we are concerned about today is the process of disseminating [noise outside from here to the end of the sentence] safety information healthcare professionals like pharmacists nurses and physicians and to the patients and the public

Amal: so let me ask you what sources aa do you use in your practice in order to update your knowledge in medication safety information?
PH 3 M: UpToDate
Two women voices: UpToDate)
Women: Medscape
PH 1M: It is something there like conference like Medscape [very low voice someone said em] like internet a like (not clear I heard: books text book)
Amal: okay
Two participants (man & women: BNF)
Two other participants: BNF
PH 1M: BNF like that
PH 4 W: books also
Amal: yeah
Man (new voice): a mainly UpToDate Lexicomp Epocrates (Amal: em) because I heard that they use it in Canada and BNF
Amal: okay amm (someone said hem نحنحة) do you use the news or the media?
Very low voice: no
Another low voice: [not clear]
Women: media [at the same time the first two words below]
PH 1M: what about the media what you may use [in or يعني]
Amal: like do you do you search the news to see about medicines safety information or
PH 1M: if there [Women: yeah] is some conference
Man: otherwise this we cannot do
Women: even if started
PH 3 M: aa yes sometimes if there is any complain for example what happened for the ranitidine it was first distributed in the media [chair noise sound] then there was a reaction from the ministry of health [table noise] this is what we heard about
B: sometime we get some information from articles maybe reading papers [not clear]
PH 3 M:إي
Sound of chair/table movement
Amal: do you use websites like FDA or any other websites
More than one: yes yeah yes
Man: MHRA
Amal: em
Women?: FDA
Amal: okay do you use sources that are specific for from Kuwait like for example pharmaceutical companies
PH 3 M: sometimes
PH 4 W: yeah sometimes
PH 4 W: if there is some problem
PH 3 M: if there is a new medication
PH 4 W: yeah
PH 3 M: it will be available in Kuwait sometimes we need a to get the information from the company in Kuwait
PH 4 W: yeah we are doing sometimes especially for the injections for the [not clear] there was problem when the expiry [not clear] so we are confirming from them [Amal: okay] from the pharmaceutical company

Amal: okay aam do you have any other sources
PH 1M:no whatever you have new drugs new [not clear] information we have all here are all central [someone: em?] information centres send us information per colleagues here hear operated so can ask them to make a lectures or brief sheets about this drugs [someone said em] he can search anywhere and some pares [papers] containing data about this new
Amal: okay
PH 1M: or similar resources in side our centre pharmacy [Ph4 W/someone said something not clear] information

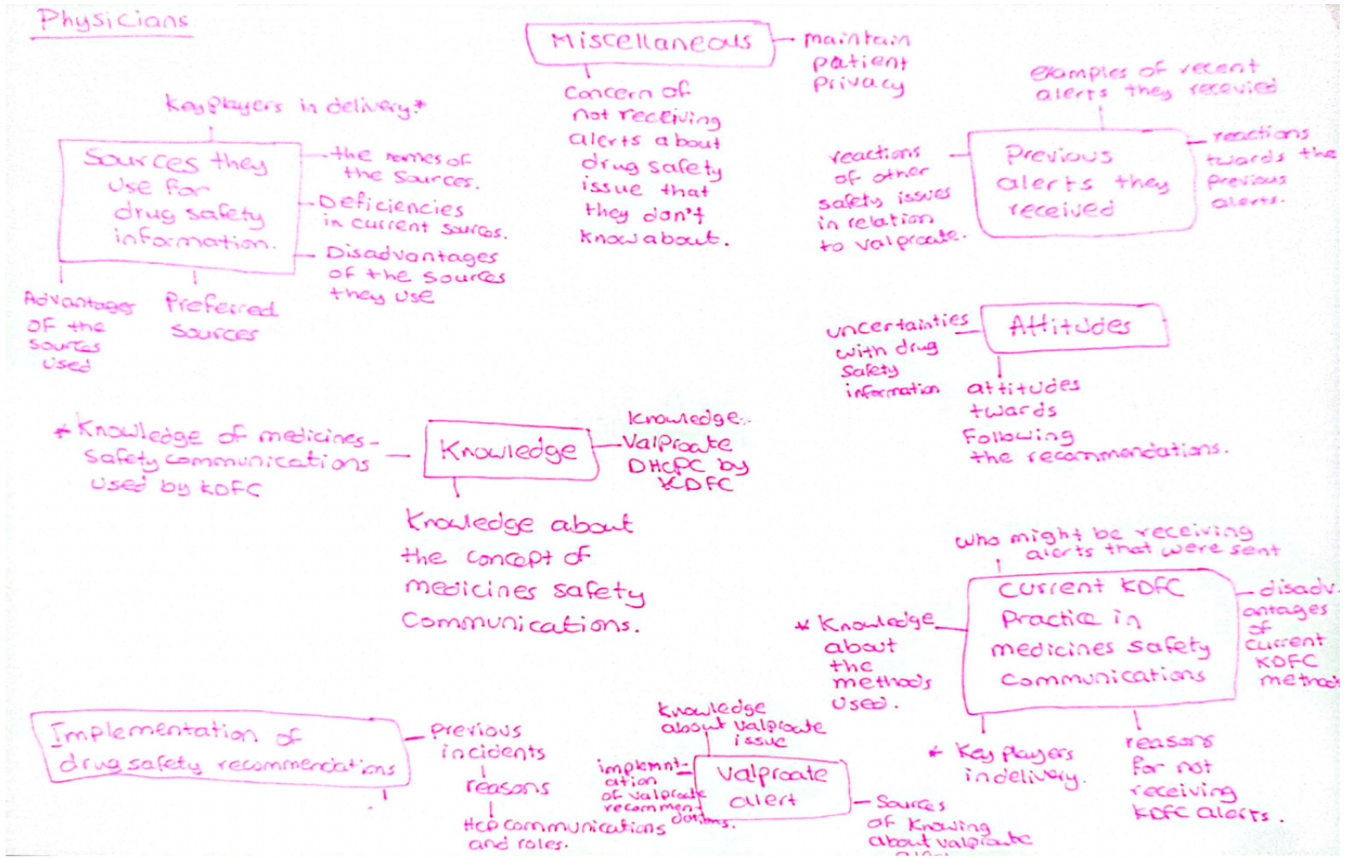
Appendix 28: Examples of the analysis process of the focus group discussions (phase 2- healthcare professionals focus groups)

a. Example of open-coding



Code System	
Code System	1061
Drs not accepting to be questioned or tought by nurses	1
The role of drug company in education conducting lectuers	1
Nureses feel they are excluded not being invited by drug compan	1
OPD nurses don't get safety info from Drs or pharmacy	1
Nurses feel they are excluded from getting circulars	2
nurse don't question just follow	1
Feer of blame	8
particpants didn't have any other contribution or suggestions	1
they concidred 1 wk late as v.late to get MoH Zantac alert	1
they concidred that they received zantac alert from Moh v.late	1
got MoH circulate about Zantac but after kniwng in social media	1
knew zantac alert from social media before getting MoH alert	1
they learnd about Zantac issue first from social media	1
one ph tech think they might got official circulate of Zantac	1
one ph tech didn't get zantac info from MoH	1
heard about Zantac from social media	1
heard about Zantac from media	1
ph tech heard about Zantac alert	1
Suggestion: MoH meeting group should explain to staff the issue	1
Suggestion: meeting groups of 5 members from MoH	1
Suggestion: MoH should put alert in their insta/offcial apps	1
Suggestion: small figuers,charts,diagrams	1
Suggestion: use small figuers	1
Suggestion: use photos,diagrams,charts	1
Suggestion use local apps in Kuwait	1
suggestion: use social media,official insta,facebook	1
Suggestion to improv MSC: thorugh the internet	2
no barriers implement	1
the group can dissamenate the info by any easy effective way	1
the group could dissemnate info by classes,seminars	1
one group in hospitals to learn about med and dissemnate info	1
facilitator: supervise by clinical ph so he don't make mistake	1
facilitators to implemnt: through circular	1
facilitators to implement: lectuers and discussions	1
usually there is no barriers to implement	1
no barriers to implemnt whenever they're asked they do	1
if someone discussed it with them better than paper	1
if somone explain/discuss the issue for 5/10 min focus more	1
giving lectuers will give the issue more importance	1

b. Example of a mind-map of one group (before reaching the overall themes).



Appendix 29: Correlation Matrix (Principal Component Analysis: sources to update knowledge, Iteration 4)

Correlation	MOH	KDFC	Professional organisations	International Drug regulatory agencies	Books	Medical programs, applications or websites	Scientific journals	Colleagues	Patients	Media	Social media	Conferences	Lectures presented by hospital staff
MOH	1.000	0.624	0.480	0.144	0.190	0.103	0.169	0.296	0.197	0.376	0.293	0.224	0.290
KDFC	0.624	1.000	0.441	0.349	0.153	0.169	0.101	0.253	0.296	0.302	0.286	0.239	0.240
Professional organisations	0.480	0.441	1.000	0.193	0.204	0.097	0.190	0.253	0.356	0.350	0.317	0.289	0.322
International Drug regulatory agencies	0.144	0.349	0.193	1.000	0.267	0.416	0.384	0.193	0.148	0.079	0.060	0.350	0.095
Books	0.190	0.153	0.204	0.267	1.000	0.522	0.413	0.322	0.227	0.174	0.196	0.283	0.247
Medical programs, applications or websites	0.103	0.169	0.097	0.416	0.522	1.000	0.513	0.342	0.149	0.162	0.171	0.302	0.166
Scientific journals	0.169	0.101	0.190	0.384	0.413	0.513	1.000	0.290	0.187	0.189	0.098	0.498	0.236
Colleagues	0.296	0.253	0.253	0.193	0.322	0.342	0.290	1.000	0.326	0.357	0.407	0.256	0.346
Patients	0.197	0.296	0.356	0.148	0.227	0.149	0.187	0.326	1.000	0.351	0.335	0.318	0.188
Media (e.g. newspapers)	0.376	0.302	0.350	0.079	0.174	0.162	0.189	0.357	0.351	1.000	0.684	0.250	0.331
Social media	0.293	0.286	0.317	0.060	0.196	0.171	0.098	0.407	0.335	0.684	1.000	0.137	0.307
Conferences.	0.224	0.239	0.289	0.350	0.283	0.302	0.498	0.256	0.318	0.250	0.137	1.000	0.363
Lectures presented by hospital staff	0.290	0.240	0.322	0.095	0.247	0.166	0.236	0.346	0.188	0.331	0.307	0.363	1.000

MOH: Ministry of Health in Kuwait; KDFC: Kuwait Drug and Food Control

Appendix 30: Total Variance Explained for the frequency of using the different medicine safety sources (Iteration 4)

Total Variance Explained									
	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.314	33.186	33.186	4.314	33.186	33.186	2.666	20.508	20.508
2	1.824	14.033	47.219	1.824	14.033	47.219	2.536	19.506	40.014
3	1.219	9.376	56.595	1.219	9.376	56.595	2.156	16.581	56.595
4	0.916	7.046	63.641						
5	0.852	6.551	70.192						
6	0.733	5.640	75.832						
7	0.654	5.027	80.860						
8	0.580	4.462	85.322						
9	0.526	4.050	89.372						
10	0.422	3.249	92.621						
11	0.389	2.991	95.612						
12	0.303	2.333	97.945						
13	0.267	2.055	100.000						
Extraction Method: Principal Component Analysis.									

Shaded values components with initial Eigenvalues > 1.

Appendix 31: Correlation Matrix (Principal Component Analysis: perceived barriers, Iteration 2)

	Lack of guidance	Lack of space for consultation	The hospital management doesn't consider implementing medication safety recommendations a priority	Lack of a cooperative teamwork environment	Telling the patient about the safety recommendations may make the patient stop taking the medicine	When I do not agree with the medication safety recommendations.	When I think the medication safety recommendations are not evidence-based.	When I have other work to do that has higher priority.	I do not consider medication safety information in my clinical practice.	I do not have the necessary skills or knowledge to implement medication safety recommendations.	I do not think it is my role to implement medication safety recommendations.	Other professionals do not think it is my role to implement medication safety recommendations.
Lack of guidance is a barrier for implementing medication safety recommendations.	1.000	0.569	0.304	0.394	0.160	0.138	0.117	0.085	0.043	0.183	0.058	0.173
Lack of space for consultation is a barrier for implementing medication safety recommendations.	0.569	1.000	0.354	0.504	0.212	0.153	0.183	0.179	0.051	0.152	0.058	0.218
The hospital management doesn't consider implementing medication safety recommendations a priority	0.304	0.354	1.000	0.438	0.256	0.162	0.236	0.250	0.133	0.288	0.240	0.316
Lack of a cooperative teamwork environment is a barrier for implementing medication safety recommendations.	0.394	0.504	0.438	1.000	0.173	0.144	0.271	0.150	0.049	0.196	0.038	0.145
Telling the patient about the safety recommendations may make the patient stop taking the medicine	0.160	0.212	0.256	0.173	1.000	0.318	0.186	0.213	0.116	0.121	0.141	0.224
When I do not agree with the medication safety recommendations.	0.138	0.153	0.162	0.144	0.318	1.000	0.363	0.400	0.209	0.269	0.318	0.262

When I think the medication safety recommendations are not evidence-based.	0.117	0.183	0.236	0.271	0.186	0.363	1.000	0.311	0.159	0.182	0.216	0.216
When I have other work to do that has higher priority.	0.085	0.179	0.250	0.150	0.213	0.400	0.311	1.000	0.285	0.310	0.404	0.320
I do not consider medication safety information in my clinical practice.	0.043	0.051	0.133	0.049	0.116	0.209	0.159	0.285	1.000	0.471	0.474	0.309
I do not have the necessary skills or knowledge to implement medication safety recommendations.	0.183	0.152	0.288	0.196	0.121	0.269	0.182	0.310	0.471	1.000	0.580	0.505
I do not think it is my role to implement medication safety recommendations.	0.058	0.058	0.240	0.038	0.141	0.318	0.216	0.404	0.474	0.580	1.000	0.472
Other professionals do not think it is my role to implement medication safety recommendations.	0.173	0.218	0.316	0.145	0.224	0.262	0.216	0.320	0.309	0.505	0.472	1.000

Appendix 32: Total Variance Explained for both the the perceived barriers to implement medicines safety recommendations

Total Variance Explained									
	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.737	31.146	31.146	3.737	31.146	31.146	2.548	21.235	21.235
2	1.891	15.761	46.907	1.891	15.761	46.907	2.334	19.449	40.684
3	1.159	9.662	56.569	1.159	9.662	56.569	1.906	15.885	56.569
4	0.853	7.104	63.673						
5	0.771	6.425	70.098						
6	0.675	5.629	75.727						
7	0.646	5.382	81.110						
8	0.558	4.652	85.762						
9	0.506	4.217	89.979						
10	0.448	3.735	93.714						
11	0.401	3.341	97.054						
12	0.353	2.946	100.000						

Appendix 33: Correlation matrix of the perceived valproate-related barriers (2nd iteration after removing: Other professionals don't think it's my role to implement the recommendations)

Correlation Matrix

		I don't think the recommendations are useful	I think the recommendations will negativly affect the patient compliance	When I have other work to do that has higher priority	I am not familiar on how to implement the recommendations	I don't think it's my role to implement the recommendations	I think the recommendations are not evedince based	I am not confident in talking about pregnancy issues with female patients	I don't agree with the recommendations	I don't have the space to implement the recommendations	I don't concider medication safety information in my clinical practice	I don't work in a cooperative enviroment between different proffesionals	My hospital polcies doesn't encourge me to implement the recommendations
Correlation	I don't think the recommendations are useful	1.000	0.385	0.425	0.294	0.443	0.478	0.380	0.512	0.241	0.303	0.031	0.165
	I think the recommendations will negativly affect the patient compliance	0.385	1.000	0.398	0.433	0.438	0.488	0.465	0.453	0.440	0.345	0.325	0.393
	When I have other work to do that has higher priority	0.425	0.398	1.000	0.304	0.287	0.455	0.322	0.431	0.263	0.333	0.255	0.263
	I am not familiar on how to implement the recommendations	0.294	0.433	0.304	1.000	0.480	0.586	0.511	0.469	0.383	0.386	0.304	0.428
	I don't think it's my role to	0.443	0.438	0.287	0.480	1.000	0.585	0.541	0.523	0.381	0.429	0.218	0.349

implement the recommendations												
I think the recommendations are not evedince based	0.478	0.488	0.455	0.586	0.585	1.000	0.529	0.766	0.379	0.481	0.198	0.312
I am not confident in talking about pregnancy issues with female patients	0.380	0.465	0.322	0.511	0.541	0.529	1.000	0.599	0.473	0.460	0.257	0.371
I don't agree with the recommendations	0.512	0.453	0.431	0.469	0.523	0.766	0.599	1.000	0.455	0.511	0.187	0.333
I don't have the space to implement the recommendations	0.241	0.440	0.263	0.383	0.381	0.379	0.473	0.455	1.000	0.360	0.528	0.557
I don't concider medication safety information in my clinical practice	0.303	0.345	0.333	0.386	0.429	0.481	0.460	0.511	0.360	1.000	0.288	0.393
I don't work in a cooperative enviroment between different proffesionals	0.031	0.325	0.255	0.304	0.218	0.198	0.257	0.187	0.528	0.288	1.000	0.681
My hospital polcies doesn't encourge me to implement the recommendations	0.165	0.393	0.263	0.428	0.349	0.312	0.371	0.333	0.557	0.393	0.681	1.000

All items have at least one variable > 0.3

Appendix 34: Total Variance Explained table of the perceived valproate-related barriers (2nd iteration after removing: Other professionals don't think it's my role to implement the recommendations)

Total Variance Explained									
Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	5.483	45.690	45.690	5.483	45.690	45.690	4.363	36.355	36.355
2	1.542	12.854	58.544	1.542	12.854	58.544	2.663	22.189	58.544
3	0.849	7.073	65.617						
4	0.681	5.672	71.290						
5	0.625	5.212	76.502						
6	0.544	4.537	81.039						
7	0.528	4.404	85.442						
8	0.460	3.831	89.274						
9	0.439	3.658	92.932						
10	0.371	3.093	96.025						
11	0.292	2.430	98.455						
12	0.185	1.545	100.000						
Extraction Method: Principal Component Analysis.									

Appendix 35: Patients' interview guide (English version)

Welcoming the patient-introducing myself.

The questions that I am about to ask are part of a Ph.D. research about medications safety communications. (Medication safety communication is the process of disseminating medication safety related information to healthcare professionals, patients or the public) we are interested specifically about valproic acid (Depakine, Depakine Chrono). General questions: age, job, educational level, material status)

1. How long have you been on valproic acid?

2. What do you take valproic acid for?

3. Have there been any changes in the dose since you started taking it?

    [Ask how do you use it?]

4. Do you have all the information you need about your valproic acid?

5. Are you aware of the benefits and risks of taking valproic acid?

6. Did your doctor, pharmacist or nurse, explain the benefits and risks to you?

7. Are you aware of any safety information about valproic acid use in females during pregnancy?

8. How did you become aware of this information? [Note to self: don't make it as they were supposed to do that, in order not to affect the patient trust of their HCP. (I'm interested to know ..)]

    a. Have you ever been given by your healthcare provider (doctor, nurse, pharmacist) a booklet to explain the safety concerns of valproic acid in pregnancy?

    b. Have you previously signed an acknowledgment of knowing the risk of valproic acid to the foetus (unborn baby)?

9.Have you ever discussed with your healthcare provider about the possibility of being pregnant while on valproic acid?

    a. at what point do you discuss pregnancy?

10.Do you have previous experience of being pregnant while on valproic acid?

11.How was your condition managed during this period?

12.Do you have any suggestions to make sure that patients are aware of

and understand safety information related to their use of

medications?

13.Do you have any other suggestions or points you would like to add?

14.Summarise discussion

Appendix 36: Examples of a patient transcript (translated by a translator to English)

Researcher: Hello, AL-Salam Aliakoum
Patient: Alaikoum Al-Salam

Researcher: Mrs. ----, my name is Amal Al-Harbi. Is now a suitable time for you?
Patient: Yes, that is OK.

Researcher: Thank you for your time.
Patient:

Researcher: This research is about medication safety
Patient: Yes

Researcher: That is the distribution of medical safety information to patients and doctors, and and medical staff in general.
Patient: Yes

Researcher: I would like to ask you first if you are using Depakine or Depakine Chrono?
Patient: Chrono

Researcher: Now, I'm going to ask you general questions
Patient: I'm 48 years old

Researcher: Your job?
Patient: --------

Researcher: Last educational degree?
Patient: What? (Ha !?)

Researcher: What is your last educational degree?
Patient: Educational degree, means school?

Researcher: Yes, the certificate…
Patient: -------

Researcher: Your marital status?
Patient: Married with kids

Researcher: Nationality?
Patient: Excuse me? (Ha !?)

Researcher: Your nationality?
Patient: ------

Researcher: OK, now the questions. For how long have you been using the Depakine Chrono?

Patient: Since I was 14 years old.

Researcher: For What using it?
Patient: (Ha !?)

Researcher: For what use it?
Patient: Yes…

Researcher: Um... Why are you using Depakine Chrono?
Patient: Yes, for... for... a... Epilepsy

Researcher: Ok, so since you have started taking it, have any changes been made to your dose?
Patient: - I started whit three doses, then it became two.

Researcher: OK
Patient: Yes

Researcher: Do you have all the information you need in regard to the Depakine medicine?
Patient: - yes, I do know that it leads to gaining weight

Researcher: Um…
Patient: Yes…

Researcher: And what other information do you have?
Patient: that's it, a noticeable increase in weight, that's only I know.

Researcher: OK
Patient: Yes

Researcher: Ok, Are you aware of the benefits, and the possible side effects of Depakine?
Patient: No, no side effects. I mean, I am so comfortable with it, because I'm not facing "the condition" with it.

Researcher: Yes
Patient: I'm following the treatment

Researcher: Good. And the benefits?
Patient: Yes, it did not…

Researcher: not …?
Patient: It's helpful, that I'm not facing the "condition", that's it.

Researcher: Good
Patient: It didn't cure it; it only stopped it.

Researcher: OK. OK. Have a doctor, pharmacist, or nurse explained the benefits and side effects to you?
Patient: No actually, no one did.

Researcher: None of them? The doctor, the pharmacist, the nurse?

Patient: No, no, no.

Researcher: OK. The next question is, have you ever discussed with the health provider- whether the doctor, the pharmacist or the nurse - the possibility of pregnancy during taking Depakine?
Patient: Yes, yes, I got pregnant. I do remember I was pregnant, but I didn't take it, and "Subhanallah" for nine months, I didn't have the "condition".

Researcher: Mashallah
Patient: Yes, three times I got pregnant and didn't take it.

Researcher: I see, and you used to discuss pregnancy topics with them?
Patient: Yes, yes, no, no, I'm not… for two pregnancies... honestly, I didn't go for checkups.

Researcher: Um… means... Ok.
Patient: But I had the "condition" after the pregnancy; after giving birth (sound like sigh), I started taking medication again

Researcher: And during pregnancy, or before it, have you asked the doctor about using the medicine? Or has he told you himself?
Patient: No, I... she told me… he told me... I mean that I should come before pregnancy and so…

Researcher: Um…
Patient: But I… I know that this does affect the baby; it's not good.

Researcher: Um…
Patient: I mean… even the doctor said this does affect the brain and everything, before getting pregnant, I must take anti-malformation; and so.

Researcher: Yes...
Patient: Either give me a ---- dose, pills that wouldn't effect the baby; or stop it for a while to avoid any effection toward the baby (her way of talk changed, looks she is asking or remembering)

Researcher: OK
Patient: But I stopped it on my own

Researcher: You mean… um… you stopped it but didn't check it through with the doctor, correct?
Patient: Now I do go back to the doctor.

Researcher: Yes...
Patient: All my checkups are now online.

Researcher: Online?
Patient: Because they want ----- appointment.

Researcher: OK. And during your pregnancy, you stopped it, but without asking the doctor, right?
Patient: No, no, without going back to the doctor. It's common sense as it's not suitable for pregnancy.

Researcher: That is good. Now you told me information about what may harm the baby, information regards using it during pregnancy. Who gives you this information?
Patient: The doctor said that there is a possibility it caused deformation/ distortion

Researcher: The Neurologist?
Patient: Even there is a booklet that says it's not suitable for pregnant ladies.

Researcher: Um… From where did you get the booklet?
Patient: (Ha !?)

Researcher: Did they give you a flyer or a booklet to clear up the concerns about the -----? Did they give you a booklet or brochure clarifying the future effects of using Dopakine during pregnancy?
Patient: No, no, no. but

Researcher: What ….
Patient: But it is known this pill distorts the baby.
If you take this pill it distorts the baby.

Researcher: I see.
Patient: Even if you do not physically distort it, it will affect its brain, i.e., inside its body, causing congenital disabilities.

Researcher: Oh…
Patient: That is not good.

Researcher: And the booklet you told me about it, where did you see it?
Patient: From inside the medicine box [leaflet] (from this point till the anti-biotic example, the patient's tone changed)

Researcher: From inside the box?
Patient: But didn't say what it would cause to the pregnant lady, only that it is not suitable for her.

Researcher: OK.
Patient: That, I need to inform the doctor, and so.

Researcher: Yes…
Patient: It is the same case as the anti-biotic, I mean ----- won't be good to take it.

Researcher: Yes. So, Have they ever asked you to sign an acknowledgment (about or regards) the awareness of Depakine's risks, or Dpakine's safety during pregnancy?
Patient: No, no, not been told to sign such a thing.

Researcher: OK
Patient: I'm taking my medication during the period that I'm not pregnant.

Researcher: Yes
Patient: And Alhamdullah" I had my three kids.

Researcher: Mashallah
Patient: They are in good health

Researcher: God bless them
Patient: Thank you,,

Researcher: Now, almost the last two questions. Do you have any suggestions regarding ensuring that the patients are aware of, and understand safety information?
Patient: Yes, they must, because some people may take the drugs blindly during pregnancy.

Researcher: Yes…
Patient: maybe she won't read the booklet

Researcher: Um…
Patient: even if she didn't read it, any medication you take, you must know if it may harm the pregnant lady or not.

Researcher: OK
Patient: So I used to stop the drug when I'm pregnant

Researcher: Direct?
Patient: Once I feel my monthly period is late, I directly checkup.

Researcher: Yes
Patient: because I'm afraid

Researcher: And the…
Patient: so I cut the doubt

Researcher: yes
Patient: because I'm taking a medication

Researcher: Yes, and do you inform the Obstetrician, Neurologist, or internist?
Patient: The Obstetrician does know I have this illness ----

Researcher: That is good. About the suggestions, how can we ensure that a patient is increasing more information? What methods to suggest?
Patient: I tell you, do you know my current problem is that I'm now overweight

Researcher: Um…
Patient: I tried to change it to another drug

Researcher: Um…
Patient: I took another medication (---) the "condition" came back to me again

Researcher: Um…
Patient: means any patient using Depakine or else, shouldn't change it on her own.

Researcher: Yes

Patient: It was described for her because it the suitable for her case

Researcher: Um…
Patient: whether it causes gaining weight double, what is important is my health, I don't want to collapse while driving

Researcher: Um…
Patient: Yes.

Researcher: So, do you have any other suggestions or point to add?
Patient: No, nothing more.

Researcher: OK, so is it ok with you to give you the summary, and you tell me if it is correct or not
Patient: Yes, ok

Researcher: You have been using Dopakine since you were 14 years old, for Epilepsy?
Patient: Yes

Researcher: And it used to be three doses, then it became two doses?
Patient: Yes

Researcher: The information you ------ means you are comfortable with it; you are not having the "condition" Alhamdulillah.
Patient: yes, Alhamdulillah

Researcher: But it causes you to gain weight?
Patient: yes

Researcher: You do know the information that is related to the pregnancy, the doctor told you about it, and you had read the inside leaflet ~~booklet~~; hence, you start to stop it during pregnancy?
Patient: yes

Researcher: Alhamdulillah, you didn't have the "condition" during your pregnancy?
Patient: Alhamdulillah

Researcher: A… They never gave you a booklet before; and didn't ask you to sign an acknowledgment.
Patient: No, no.

Researcher: In regard to the suggestions, in order to increase patients' awareness about medication safety, you said, "the patient must know the information"
Patient: Yes, but also, I mean, even me… the Depakine ….

Researcher: Um…
Patient: I'm on a diet, and losing weight- Alhamdulillah- I mean, it doesn't have a significant impact, Alhamdulillah.

Researcher: Yes

Patient: It needs a nutrition system to have things that reduce fats

Researcher: yes
Patient: I feel that it has some influence on the body, and increases weight, so to avoid any more – which anyone should- must decrease what to eat.

Researcher: yes
Patient: Because food has nothing to do with the collapse, as some people have the wrong things, you may collapse because you are not eating, it's not the food, it's the wrong diet, and not taking the medication. Must be medication and a healthy diet.

Researcher: Yes, ok
Patient: Yes, and with a healthy diet and treatment, I will be all right.

Researcher: You said things that would reduce weight, like what?
Patient: They used to give me Omega3, but now it's not available in the Ministry

Researcher: Yes
Patient: I don't know, do you know why, I'll tell you why

Researcher: They?
Patient: Because they bring it to the patients

Researcher: Um…
Patient: What can people do? They manage to get it for them with a "helping push"

Researcher: Yes
Patient: Omega 3, when I go to the pharmacy, it's not available anymore

Researcher: yes
Patient: Hence, I'm buying it from other places, because the doctor described it to me long before. Omega 3 is excellent.

Researcher: Yes, so you start buying abroad.
Patient: Yes, and I'm still, what to do.

Researcher: Anything else?
Patient: They give me Vitamin D, because Vit.D is low in my blood.

Researcher: Um…
Patient: It's good the doctor sees my blood, and liver functions, if this medicine is helpful for my body, or not.

Researcher: so he is monitoring your body?
Patient: there is monitoring.

Researcher: There is an observation
Patient: There is an observation, yes, I do follow up with the doctor. I'm telling you, there was a time I neglected myself.

Researcher: Um…
Patient: Didn't go to a doctor, but later I found myself needing to do, otherwise, how to get medication

Researcher: It is ok to ask (…..Is it ok to ask?)
Patient: "pushups" are not working everywhere

Researcher: yes
Patient: so better to go to the doctor

Researcher: you mean a "pushup" to get you the medication
Patient: yes, yes

Researcher: Is it ok to ask about the period you had neglected yourself, why was that?
Patient: Yes, yes, it's just that I was so tired, I had an accident and collapsed down.

Researcher: yes. But what was the reason you didn't go for a checkup?
Patient: I wasn't in the mood to go around, and I get busy. I didn't take medicine because I was planning to lose weight

Researcher: Yes, I got what you mean
Patient: I did lose weight, but I ignored my medication, I shouldn't because I still can lose weight while I'm on medication, with no issues.

Researcher: Um…
Patient: It causes weight gaining

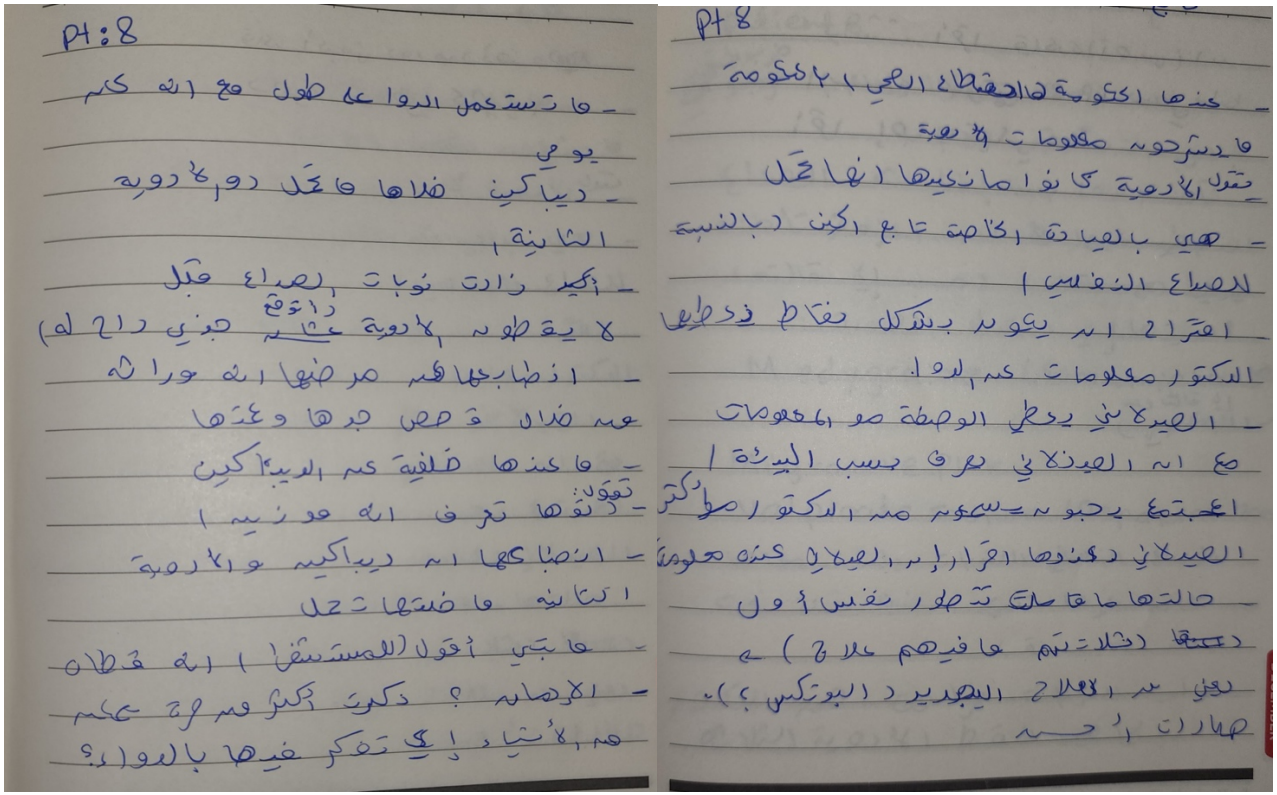
Researcher: Yes
Patient: but with at least a nutrition regime, I can limit this big increase.

Researcher: That is good. Thank you so much. Do you have anything further you would like to add?
Patient: No.

Researcher: Thank you for your time, take care.
Patient: You are welcome, take care.

Appendix 37: Examples of a patient analysis process

a. Example initial notes (Arabic)



b. Example of descriptive, linguistic and conceptual analysis (the researcher work below was translated to English by a translator for illustration

- normal text: descriptive analysis; ***Bold & italic***: linguistic analysis; <u>Underlined</u>: conceptional analysis:

The participant wants to start directly by talking about the medication (without the introduction I begins with)

<u>Maybe because she doesn't have time? Perhaps because she's interested in talking about the medication and her experience?</u>

"let's start directly," interrupting the conversation and rushing me out to skip the introduction.

She doesn't use the medicine (Depakine) all the time (continually, daily)

<u>Was the way of using Depakine not explained to her? Did she not use it as a precaution; because it improved her condition? Or does she not know about using it as a preventive procedure? Hasn't anyone (from the medical staff) asked her about her way of using the medicine? Is it due to the defect in delivering the information to her parents from the medical staff end? Or due to the influence or judgment of her parents about using it when she was a child? Did she suffer from it; therefore, she is not using it always? Did she read something that made her not willing to use it continually? Did her parents (or one of them) read something about the drug; that made them not want her to take it daily?</u>

<u>The patient's usage of the "honestly" word indicates her intention to be truthful to me and points out her knowledge that she should have used Depakine daily.</u>

"The participant used the word "honestly," indicating that she wanted to be honest with me, which also shows that she is not taking her medication as she was supposed to; hence, she tried to be frank with me.

The participant is not using her medication daily. She is supposed to use it daily, but she doesn't.

<u>Why doesn't she use it daily as long as she knows she must? Does she forget to take it every day? Is it considered a burden to take every day? Is it easier for her to take it only during the seizure? Is she unaware of the benefits of using it daily? Does she think the drug will harm her in case of daily usage? Does she know the difference between her precautionary medications and the to relief her during the headache seizure? Did she use it daily and get better (or get worse from Depakine), then decide not to take it every day? Whom was the one decided not to take it every day? Was she or one of her parents when she was a child? When was it decided not to take it daily? How far did her parents influence to use the medication at a young age and as she grew up? Has no one from the medical staff asked about her medication use? Did she suffer from it, and was that the reason not to take it all the time? Did she read something that made her not willing to use it continuously? Did her parents (or one of them) read something about the medication that caused her not to be willing to let her take it every day? Have they heard about others' experiences, so they decided (or she did) not to do daily?</u>

The patient's usage of the word "honestly" indicates her desire to be honest with me. It also shows her understanding that she was supposed to use Depakine daily basis.

What she meant by saying, "not using it daily?" Was she using it only for seizures?

The participant used the word "honestly" to indicate her desire to be honest with me. Also, it suggests that she is not taking her medication as she is supposed to, which is why she wanted to be frank; she used the word "must," which means that she did know that she has to take Depakine daily.

The participant takes the three medications only during the seizure. Only when the seizure attack is severe "tough."

The word "only" indicates that she's using it only during those times. "if it got tough": if the condition worsens, from a hardness/ headache perspective, or the headache pain.

Does she take the three types of medications (including Depakine) only if the condition becomes hard? Or during the headache attack in general? Has someone advised her to do so? Has someone advised her parents to take them (or the Depakine) this way? Has she tried this way once before, and it worked, so she decided to repeat it?

The participant was diagnosed with Migraine when she was nine years old.

"I think it was 2004. I don't know how old I was": the participant was not sure exactly what year she was diagnosed with the Migraine and her age at the time of the diagnosis.

When were the Migraine attacks started with the participant? Was it at the same time of the diagnosis? Have the different phases of her age, from childhood to adolescence to adulthood, her life, environment, and experiences influenced medication treatment? Have her experiences during all these life stages influenced her not to take the medication daily?

The participant is now 26 years old. The headache attacks increased (or became worse) and reached the neck. The participant couldn't get pregnant, so she went to a doctor. The doctor threw away her medications.

I couldn't get pregnant; I couldn't get pregnant; nothing was wrong with me: indicates the participant's desire to get pregnant.

***Later/now, I become 28 – 26, the seizures increased, reached the neck, and I couldn't get pregnant, I can't, nothing was wrong with me… I went to a doctor*:** When were the headache seizures increased/become worse? Was that at her current age? Why she went to the doctor, she spoke about? Was that due to the increased / development of the seizures? Or because she could not get pregnant? Or for both reasons?

The Doctor threw away her medicines (headache drugs) because they would not help her as the headache seizures increased/ developed/ worsened.

It reached the neck and shoulder: indicating the headache development, and the patient started to feel the seizures in the neck and shoulder.

OK, he threw them away because they won't be useful to me… the seizures increased to the neck and shoulder: Why does the participant think she won't get results from her three medications? Was that because of what the doctor she spoke about told her, that it wouldn't help her? Did she mean she won't get any use of the whole three medications? When she said- later- "the Doctor

said this is not good," did he/ she intend only the Depackine? Was no use of them because her headache seizures had developed?

The participant describes her headache development:

"Imagine: the participant wants to deliver how far or developed her pain is.

The Doctor gave the participant "Botox" instead of her three medications. The participant is pregnant. The participant got pregnant one month after cutting off the three medications.

"A month- swear to God- a month," the participant uses swearing- to emphasize her pregnancy one month after cutting off the drugs. In addition, she repeated "a month" to demonstrate the short period between stopping the medications and between her pregnancy. The two- together- may indicate the participant's assurance of the link between her medications and inability of pregnant and the connection between stopping the medications and her pregnancy.

Was her inability to be pregnant really related to the medications? But she took them only when it was necessary. Were her needs repeated? Has she got pregnant by coincidence after cutting off the medications? Did she get pregnant after taking Botox and controlling the seizures? Why didn't she mention if the seizure attacks went down or not, nevertheless that she mentioned the pregnancy first? Was that due to the pregnancy as a result more vital to her?

I cut off the drugs for a month, swear to God, a month, thereupon I got pregnant, I'm pregnant now: patient use of the word "thereupon" shows her belief that her pregnancy was a result of what was previously, which is cutting off the three medications.

The participant explains how her new doctor responded to her old medications. He threw the Depakine away and kept the rest, saying this drug was not good.

The Doctor is clever (he is good/professional), indicating her trust in his opinion.

This drug is not good: she emphasized the drug's side effects (maybe she meant for pregnancy) and didn't mean not getting benefits.

Excuse me for the word: it shows her embarrassment to say that the doctor threw Depakine away in the litterbin.

And the rest, the purple and this one, he took them, saying, "we keep them" I don't know why: the participant doesn't know why the doctor is keeping the two medications.

Did the patient describe the doctor as "clever" due to telling her those medications are harmful (not good) and throwing them into the litterbin? Was this description after being pregnant? Would she say the same if she wasn't pregnant? Did her condition get better, hence she called him "clever"? But she didn't use words indicating that till now? Did the participant ask the doctor why he is keeping those two medications? Was she able to ask the doctor why to keep those medications?

a. Patients' quotations and initial coding (example above) were coded to generate initial themes. For each patient, these were printed, cut and re-rearranged according to their similarity or differences. Then subthemes were generated and a comparison between each patient subtheme was made to reach to the final theme.

Theme/patient	Patient 1	Patient 2	Patient 3	Patient 6	Patient 7	Patient 8
1.	Timeline	Perceive knowledge about her medication (which also include perception about her information)	Patient's perceived information (which also include perception about her information)	Valproate related safety information	Timeline/medication history	Timeline of the patient experience
2.	Involvement of her mother in her healthcare	Perceived influence/effect of valproate on the patient	Patient's sources of information	Medication history	Turning point in terms of her perception toward weight-increase and adhering to the physicians visits	Attitudes towards medicines' use
3.	Patient's involvement in her healthcare	Timeline	Medication/ disease knowledge or identification	Timeline of her visits to the physicians	Medication/disease knowledge or identification	Attitudes towards her disease
4.	Patient's description of her disease	Patient's experiences with medicine safety communications (valproate)	Timeline – medication	Patient's knowledge about her medication/diagnosis (also include information about side effects)	Perception about her medication information (also includes perception about her medication)	Attitudes towards her medication
5.	Sources of drug information	Patient sources of information	Social influences on her health care services	Patient's perceived information/knowledge (which included perception about her information).	Her experience/medicine use (benefited from omega-3/took alternative to valproate)	Her perception towards the provided healthcare
6.	Perception about her medicine – related information	Patient description of her medicine/disease	Healthcare experiences (used plural tense to describe discussion)	The responsibility of the patient healthcare/mentioned key players (included parent; included healthcare professionals).	Responsibility of patient/healthcare professional	Her perception towards the healthcare professionals
7.	Patient's perception about her medicine	Interactions with the healthcare professionals	Valproate related safety information	Sources of information	Patient perception of her healthcare professionals	Patient perception about her medication knowledge/ information
8.	Patient's knowledge about her medicine	Miscommunication	-	-	Patient sources of information	Patient's sources of information
9.	Valproate safety information	-	-	-	Patient experience with medication (negative, also includes medicine use)	Patient's information about her medication
10.	-	-	-	-	Valproate-teratogenicity information	Healthcare professional communication and information sharing with the patient
11.	-	-	-	-	Patient experience with pregnancy	Healthcare professional role in shaping and

						influencing patients' attitudes and her medicine use
12.	-	-	-	-	Suggestions	The patient's experiences with medication safety communications
13.	-	-	-	-	-	The patient's preferences for future medication safety communications