# Development of a Roadmap and Evaluation of Quality Decision-Making Practices during Medicines Development, Regulatory Review and Health Technology Assessment

---

Magdalena Gabriela Bujar

Submitted to the University of Hertfordshire
in partial fulfilment of the requirements
for the degree of Doctor of Philosophy (PhD)

May 2018

**"*The roads we take are more important than the goals we announce. Decisions determine destiny.*"**

Frederick Speakman

## ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisors. Thank you to Prof. Stuart Walker and Prof. Sam Salek for believing in me from day one, as well as for sharing their knowledge and enthusiasm, which have been an inspiration. It has been an absolute privilege to learn from them and I am grateful for this experience, which has enriched me personally and professionally. I am excited for what the future will bring and hope to continue our work and friendship.

I am also indebted to my colleagues from the Centre for Innovation in Regulatory Science (CIRS), most importantly Dr Neil McAuslane, whose insights, wisdom and impressive memory have challenged as well as guided me throughout this project and helped to broaden my thinking. I am also grateful to Dr Lawrence Liberti and Prisha Patel for encouraging me to take on this task and for being so supportive.

I would like to thank Pat Connelly for her editorial help in publishing my research and whose remarkable attention to detail helped me to finally learn to correctly hyphenate (or not) 'decision making'. I am also thankful to Sarah Conaway for her help in tabulating a portion of the results in Chapter 6 and 7 as well as other colleagues from CIRS: Tina Wang, Gill Hepton and Dr Jesmine Cai for cheering me on throughout this endeavour. I am also very grateful to Dr Julian Walker for taking the time to carry out the secondary review in Chapter 5 and for the kind words of advice.

This research would not have been possible without the contributions from executives within the pharmaceutical industry, regulatory authorities and health technology assessment agencies, with respect to data provision and discussions. Thank you for facilitating the timely completion of this project.

Most importantly, thank you to my family and friends for being my source of strength, particularly my dad, for always believing in me and for teaching me the importance of education and determination; I owe it all to you! To my life coach, my best friend and my love, Nick, as well as his family, particularly Lynda and Omar; thank you for being my rock and for encouraging me with words and chocolate. I could not have done this without you! Lastly to Selkie for tirelessly sitting at my side and being my companion from dusk to dawn. I love you all dearly.

## PUBLICATIONS AND PRESENTATIONS

### Journal Articles

Bujar, M., Donelan, R., McAuslane, N., Walker, S. and Salek, S. (2016). Assessing the Quality of Decision Making in the Development and Regulatory Review of Medicines: Identifying Biases and Best Practices. *Therapeutic Innovation & Regulatory Science*, 51(2), pp.250-256.

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2016). Quality of Regulatory Decision-Making Practices: Issues Facing Companies and Agencies. *Therapeutic Innovation & Regulatory Science*, 50(4), pp.487-495.

Bujar, M., McAuslane, N., Walker, S. and Salek, S. (2017). Evaluating Quality of Decision-Making Processes in Medicines' Development, Regulatory Review, and Health Technology Assessment: A Systematic Review of the Literature. *Frontiers in Pharmacology*, 8(189).

### Poster presentations

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2016). Innovation in regulatory science: Development and validation of an instrument for assessing the quality of decision making. Poster presentation at: University of Hertfordshire School of Life and Medical Sciences Research Conference, April 5 2016, Hatfield, UK.

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2016). Factors influencing quality decision making in medicines development and regulatory review: Biases and best practices. Poster presentation at: Drug Information Association (DIA) Annual Meeting, June 26-30 2016, Philadelphia, PA, US. *First Prize Winner at Student Poster Competition.*

Bujar, M., McAuslane, N., Walker, S. and Salek, S. (2017). Quality of decision-making process in the development, review and reimbursement of medicines; its importance and implication. Poster presentation at: The Organisation for Professionals in Regulatory Affairs (TOPRA) Annual Meeting, October 3 2017, London, UK. *First Prize Winner at Student Poster Competition.*

McAuslane, N., Bujar, M., and Walker, S. (2018). How well do HTA agencies build quality into their decision making? Poster presentation at: HTAi 2018 Meeting, June 1-5 2018, Vancouver, Canada.

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2018). Assessment of the Quality Decision-Making Practices; Case Studies with a Pharmaceutical Company, Regulatory and HTA Agency. Poster presentation at: Drug Information Association (DIA) Annual Meeting, June 24-28 2018, Boston, MA, US.

**Oral presentations**

Bujar, M., McAuslane, N., Walker, S. and Salek, S. (2017). Evaluating quality of decision-making processes in medicines' development, regulatory review and health technology assessment. Oral presentation at: 6th FIP Pharmaceutical Sciences World Congress(PSWC), May 21-24 2017, Stockholm, Sweden.

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2017). What are the key issues for companies and agencies (Regulatory and HTA) in their internal decision-making processes. Oral presentation at: Centre for Innovation in Regulatory Science (CIRS) Workshop, June 15-16 2017, Tysons Corner, VA, US.

**Reports**

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2017). *R&D Briefing 61: Building Quality into Decision-Making Processes in Medicines' Development, Regulatory Review and Health Technology Assessment.* Centre for Innovation in Regulatory Science (CIRS). London, UK. Available at http://www.cirsci.org/wp-content/uploads/2017/01/CIRS-RD-Briefing-61-Decision-making.pdf [Accessed 4 April. 2018]

Walker, S., McAuslane, N., Bujar, M., Connelly, P. and Liberti, L. (2018). *Quality decision-making practices: Their application and impact in the development, review and reimbursement of medicines*. 1st ed. Based on the proceedings of a Workshop convened by the Centre for Innovation in Regulatory Science CIRS), June15-16 2017, Tysons Corner, Virginia.

## ABSTRACT

The science of decision making has been established, but research is limited regarding the quality and transparency of the decision-making processes through which medicines become available. Indeed, it is not always clear what explicit processes pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies are using to arrive at their decisions. Previous research resulted in the development of the ten Quality Decision-Making Practices (QDMPs), which are considered as the best practices in decision making in the lifecycle of medicines, as well the Quality of Decision-Making Orientation Scheme (QoDoS), which is a technique that can be used to measure the incorporation of these QDMPs in companies and agencies.

The aim of this research, therefore, was to develop a roadmap for improving the quality of decision-making processes for key strategic decisions made by pharmaceutical companies, regulatory authorities and HTA agencies, by firstly evaluating current processes in place; secondly by assessing the ten QDMPs and thirdly by developing approaches for incorporating the ten QDMPs into organisational processes. In formalising the study design, various methodologies were appraised and it was rationalised that in order to fulfil the aim of the study, it would be appropriate to adopt a mixed method approach i.e. combination of self-administered questionnaires, focus groups as well as case studies. In addition, a systematic review of literature was conducted to identify the most robust and psychometrically sound technique for assessing the QDMPs.

Results from four questionnaires developed for the purpose of this research demonstrated that companies and agencies do not always utilise frameworks for key decision-making processes, namely regulatory submission processes, regulatory approvals, HTA submissions and HTA appraisals. Moreover, the majority of organisations with established frameworks did not incorporate all ten QDMPs into their processes, although all these practices were considered relevant. The study also identified challenges in decision making as well as biases, where all the participants believed there was room for improvement and suggested a number of solutions, which included training and the use of structured processes.

The results also uncovered that organisations do not generally have formal assessments in place to measure the quality of decision making. However, a systematic literature review of techniques for evaluating the QDMPs during the lifecycle of medicines revealed a paucity of available techniques, which could explain why such assessments are not taking place. The QoDoS was considered as the most promising technique out of the 13 identified in the review.

A subsequent case study with QoDoS demonstrated its reliability and relevance in target audiences. Three additional QoDoS case studies, with a company, a regulatory authority and an HTA agency, demonstrated its practicality in assessing the consistency of favourable and unfavourable practices in organisations.

Finally, three focus groups with individuals from companies, agencies and academia resulted in the development of practical approaches for embedding quality into strategic decision-making processes. These recommendations, as well as the outcomes from the other studies, were used to develop a checklist for incorporating the ten QDMPs into a project matrix structure including the steps and variables to be documented at the time of decision making.

The methods and approaches developed and validated during this programme of research, namely the questionnaires, the QoDoS and the checklist, led to the development of a roadmap for improving the quality of decision-making processes within companies and agencies for key strategic decisions. The goals are to raise the awareness of the importance of quality decision making during the development, regulatory review and HTA of medicines, secondly to improve the probability of good outcomes and finally to increase public trust as a result of more transparent and consistent decisions.

## TABLE OF CONTENTS

## LIST OF FIGURES

## LIST OF TABLES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AIFA | Italian Medicines Agency |
| BFI | Big Five Jackson Inventory |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CEO | Chief Executive Officer |
| CI | confidence interval |
| CIRS | Centre for Innovation in Regulatory Science |
| DOSPERT | Domain Specific Risk Taking scale |
| EMA | European Medicines Agency |
| EUnetHTA | European Network for Health Technology Assessment |
| FDA | Food and Drug Administration |
| GRevP | Good Review Practices |
| HEOR | Health Economics and Outcomes Research |
| HTA | health technology assessment |
| ICC | Intra-Class Correlation Coefficient |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| ISO | International Standards Organization |
| MCDA | Multi-Criteria Decision Analysis |
| MeSH | Medical Subject Headings |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NDA | new drug application |
| PrOACT-URL | Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, Linked decisions |
| Q&A | Question and answer |
| QDMP | Quality Decision-Making Practice |
| QoDoS | Quality of Decision-Making Orientation Scheme |
| R&D | research and development |
| SDG | Strategic Decision Group |
| SME | small and medium enterprise |
| SPSS | Statistical Package for the Social Sciences |
| SRA | Stringent Regulatory Authority |
| SWOT | Strengths, Weaknesses, Opportunities and Threats |
| UMBRA | Unified Methodologies for Benefit-Risk Assessment |
| US FDA | US Food and Drug Administration |
| WHO | World Health Organisation |
| WYSIATI | What You See Is All There Is |

# General Introduction

## BACKGROUND

Although the well-established principles of good decision making are common sense, they are nevertheless not always common practice and this applies to both how individuals make decisions on a daily basis, as well as how organisations make key strategic decisions across a range of industries, including the pharmaceutical industry (Spetzler et al., 2016). Indeed, the various decisions made around the availability of medicines are under constant scrutiny by patients seeking increased access to the most promising therapies. In addition, the process through which medicines become available is long and characterised by high risk and uncertainty (Pritchard et al., 2003). Despite this, there is a lack of research and insight into the decision-making approaches for individuals and organisations involved in medicines research and development. Consequently, there is a need to explore and improve the decision making of the three key stakeholders involved in this process, namely the pharmaceutical companies that develop the medicines, regulatory authorities which are responsible for pre-market assessment of medicines, as well as health technology assessment (HTA) agencies which recommend the reimbursement of medicines via national health services (Liberti et al., 2013).

### Brief history of decision making and the importance of evaluating the process

The word “decision”, which originates from Latin, has the same root as the word “scissors”. Indeed to decide means to "to cut off” alternatives and pursue a selected course of action (Trewatha and Newport, 1982). The research on decision making stretches back over many centuries and encompasses a wide range of academic disciplines – from philosophy and mathematics to sociology, psychology and economics (Buchanan and O'Connell, 2006). Initial application of decision-making principles goes as far as prehistory, where human decisions were guided by instincts and the interpretations of nature (Buchanan and O'Connell, 2006). More recently, in the 17$^{th}$ century, Rene Descartes, a famous philosopher and mathematician, established one of the first decision-making tools, namely the “Descartes Square”, which structures decision making around four questions “What will happen if this happens?”, “What will happen if this doesn’t happen?”, “What won’t happen if this doesn’t happen?” and “What won’t happen if this happens?” (Lowy and Hood, 2004). The second part of the 17$^{th}$ century and the start of the 18$^{th}$ century mark the introduction of the field of decision theory, which is the study of the reasoning underlying an individual’s choice (Steele et al., 2015). Here, a number of mathematicians, most notably Blaise Pascal and Daniel Bernoulli, developed methods for calculating probabilities for chance events, which laid the foundation for risk assessment and utility theory, which is a measure of preferences over some set of goods and services (Peters, 1987).

In the 19th and 20th century, the research on decision making evolved further into the field of psychology, through the work of Sigmund Freud (1915) on the unconscious influences on people's actions, as well as into the field of economics through the work of Irving Fisher (1907) who introduced net present value as a decision-making tool, which indicates how much value an investment or projects adds. The 20th and 21st century are characterised by a number of notable events and research in the field of decision making as listed in Table 1.1.

**Table 1.1 A selection of notable people, events and research in the field of decision making during the 20th and 21st century**

| |
|---|
| **1900:** Sigmund Freud's work on the unconscious suggests that people's actions and decisions are often influenced by causes hidden in the mind. |
| **1907:** Economist Irving Fisher introduces net present value as a decision-making tool, proposing that expected cash flow be discounted at a rate that reflects an investment's risk. |
| **1921:** Frank Knight distinguishes between risk, in which an outcome's probability can be known (and insured against) and uncertainty, in which an outcome's probability is unknowable. |
| **1938:** Chester Barnard separates personal from organisational decision making to explain why some employees act in the firm's interest rather than in their own. |
| **1950s:** Research conducted at the Carnegie Institute of Technology and Massachusetts Institute of Technology will lead to the development of early computer-based decision tools. |
| **1960s:** Edmund Learned, C. Roland Christensen, Kenneth Andrews and others develop the SWOT (strengths, weaknesses, opportunities, threats) model of analysis, useful for making decisions when time is short and circumstances complex. |
| **1968:** Ron Howard's and Howard Raiffa's Decision Analysis approach explains many fundamental decision-making techniques, including decision trees and the expected value of sample (as opposed to perfect) information. |
| **1972:** Irving Janis coins the term "groupthink" for flawed decision making that values consensus over the best result. |
| **1979:** Amos Tversky and Daniel Kahneman (Nobel prize winner for Economics in 2002) publish their Prospect Theory, which demonstrates that the rational model of economics fails to detect the difference between decision utility and experience utility. |
| **1984:** Daniel Isenberg explains that executives often combine rigorous planning with intuition when faced with a high degree of uncertainty. |
| **1995:** Anthony Greenwald develops the Implicit Association Test, meant to reveal unconscious attitudes or beliefs that can influence judgment. |
| **2005:** In *Blink*, Malcolm Gladwell explores the notion that our instantaneous decisions are sometimes better than those based on lengthy, rational analysis. |
| **2017:** Richard Thaler, one of the founding fathers of "nudge theory" receives a Nobel Prize in Economics for his work on behavioural economics. |

Adapted from Buchanan and O'Connell, 2006

More recently, the science of decision making has been established regarding behavioural economics to enable better decision making through the pioneering works of Hammond and

colleagues (1999), Thaler and Sustein (2009), Kahneman (2011) as well as Howard and Abbas (2015) who uncovered interesting patterns and potential biases (heuristics) in the way in which people make decisions. According to the research of Hammond and colleagues (1999), one of the most fundamental distinctions in decision making is that between the process and the outcome. Indeed, in an uncertain world, it is possible to apply a good decision-making process that results in unfavourable consequences and, equally, to have a bad decision-making approach that will have a favourable outcome. Although a decision-making process does not always guarantee a favourable outcome, on balance, however, the long-running use of good systems for making decisions will give more consistent and generally better outcomes (Kahneman, 2011). Consequently, the decision-making processes of pharmaceutical companies, regulatory authorities and HTA agencies should be evaluated separately in addition to the large volume of projects focusing on decision-making outcomes (Patel et al., 2016; Liberti et al., 2017).

**Decision making throughout the medicines research and development**

The process through which a new medicine is developed, from molecule to market place, is long and complex, lasting a minimum of 11 years on average from initial discovery to marketplace (Tufts, 2014). This process involves three key stakeholders, namely the pharmaceutical companies, regulatory authorities and finally HTA agencies, where each organisation, at certain stages relevant to their role in the process, makes countless decisions regarding a medicine. The overall average cost of developing a successful medicine is estimated as £2 billion, which also covers the cost of failures, such as the hundreds of thousands of compounds initially screened and assessed in the early research and development (R&D) process ahead of entering clinical testing. The overall probability of success, here defined as the likelihood that a medicine entering clinical testing will eventually reach the market, is estimated to be less than 12% (PhRMA, 2015). Nevertheless, this does not take into account the fact that certain medicines may be withdrawn from the market following initial approval, most frequently due to new evidence emerging regarding the safety of a medicine. As a result of the high risk, cost and uncertainty during the development of medicines, there is a need to characterise and evaluate the decision-making processes of the three key stakeholders and uncover how to improve the efficiency and ultimately increase the probability of favourable outcomes.

The role of pharmaceutical companies during this process is to develop medicines starting from early research and discovery phases, through to clinical evaluation, manufacturing and finally leading to a decision to file the medicine for regulatory review and HTA. The decision making relies on input from a complex network of teams and committees, which are made up

of individuals from a range of disciplines, such as research and development, clinical development, marketing, legal, finance, regulatory affairs, health economics and outcomes research, public policy and senior management. The key decision points are defined often as the "go/no-go stage gates", where teams and committees make decisions regarding whether or not a compound should be advanced through the stages of research and clinical trials. An example is moving from a Phase 2 trial, where the aim is to evaluate efficacy of a new medicine, into the significantly larger and more expensive Phase 3 trial in order to confirm its efficacy and safety and compare it with current standard of care. Nevertheless, the ultimate decision points are in the end regarding whether or not sufficient and appropriate evidence has been generated in order to submit the dossiers to regulatory authorities and HTA agencies (Pritchard et al., 2003). Interestingly, improvements in decision making by decreasing the influence of cognitive biases, which are subjective shortcuts used by the brain to process information that can lead to flawed thinking if not accounted for, have recently been linked to significant enhancements of R&D productivity within pharmaceutical companies, but there is a need for this to be further explored (Smietana et al., 2015).

The marketing approval of a medicine depends on the decision making of regulatory authorities, which are most commonly national government agencies whose mission is to protect public health by recommending only appropriately safe and effective medicines. Regulatory authorities make their decisions based on the data submitted by companies, particularly data collected from clinical trial phases. The initial assessment is most commonly carried out by the authority's reviewers and a decision is made either by an individual or a committee based on the benefit-risk profile of a medicine in order to ensure that the medicine has appropriate quality, safety and efficacy. However, regulatory authorities are being increasingly challenged to find a balance between the need for rapid patient access to new medicinal products and at the same time to ensure availability of comprehensive data on their assessment of benefits and risks. Indeed, there is a need to ensure that the processes have appropriate transparency, particularly if a different decision about the same product is made by regulatory authorities in order to strengthen public accountability and trust (Breckenridge et al., 2011; Tafuri, 2013). Consequently, authorities have been looking to improve their decision-making practices during the regulatory review. Most notably the US Food and Drug Administration (FDA), a leading regulatory authority, recommended "to develop a rigorous definition of the science of therapeutic regulatory decision-making and its application to the cycles of therapeutic development, marketing approval, post-marketing monitoring and modification of indications and safety" (Edlavitch and Salmon, 2015). It has also recently committed to enhance its clarity, transparency and consistency of benefit-risk assessment decision-making (FDA, 2018). In addition, a recent expert committee report called for the

need to improve the regulatory decision-making process of the UK Medicines and Healthcare products Regulatory Agency (MHRA) particularly regarding transparency around available process flexibilities (such as adaptive licensing) as well as the provision of scientific advice and stakeholder interaction (MHRA, 2013).

Lastly, health technology assessment, which is carried out by HTA agencies, hospital formulary committees and other healthcare bodies, aims to evaluate the social, economic, organisational and ethical issues of a medicine or a health intervention to inform its reimbursement by national health systems. The HTA is generally a two-step decision-making process, which first of all involves the clinical and economic assessment of a medicine to determine its cost-effectiveness, comparative-effectiveness and budget impact, and secondly appraisal of the information by a committee, which involves both technical agency and external members as well as lay representatives, patient groups, payers and industry, in order to make the final decision. Nevertheless, it should be noted that the decision made, namely whether or not a medicine should be reimbursed under a national health system, in many cases is not binding and is consequently referred to as a recommendation (Pichler et al., 2010). In recent years, HTA has experienced an increase in importance due to pressures from governments to ensure efficient spending of national budgets on health care interventions (Goodman, 2014). Nevertheless, challenges remain as the current global HTA environment is very diverse, particularly the European system which is fragmented compared to the harmonised regulatory system under the European Medicines Agency (EMA). Projects are already underway to initiate a more efficient and aligned HTA practice and one that is more aligned with regulators in terms of process and occulting more closely together in time (Breckenridge et al., 2010). These various initiatives also aim to develop tools to support decision making in healthcare in order to improve transparency and consistency of HTA decisions (Allen et al., 2013; Oortwijn et al., 2017).

## THE IMPORTANCE OF A QUALITY DECISION-MAKING PROCESS

### Defining quality of decision making during medicines development, review and HTA

Despite the considerable interest from pharmaceutical companies, regulatory authorities and HTA agencies in ensuring favourable outcomes, there has been limited research into the quality of decision-making processes of the three organisations (Tafuri, 2013; Donelan et al., 2015). Although quality is difficult to define due to its subjective nature, it is nevertheless possible to identify the elements of a quality decision-making process. Indeed, the general principles and steps for making a quality decision have been characterised by a number of academic and consultancy groups (Matheson and Matheson, 1998; Hammond et al., 1999; Blenko et al., 2010; SDG, 2011). This include identifying the problem and objectives; having

creative implementable options; obtaining meaningful, reliable information upon which to base a decision; identifying clear consequences and trade-offs for each supportive element; considering uncertainty and eliminating biases; using logically correct reasoning; and making a commitment to action. More recently, these principles have been recognised and advocated across a number of disciplines such as aviation, economics, environmental protection, clinical practice, nuclear safety and government affairs, to facilitate quality decision making (Rafliff et al., 1999; Hunink et al., 2001; Dowding and Thompson, 2003; Morton et al., 2009; Thaler and Sustein, 2009; Gawande, 2011; Wagner, 2013; Avorn, 2018). However, despite the increasing number of publications about the importance of psychology of decision making (Kahneman, 2011), research on this topic in the area of medicines development, regulatory review and HTA is less well articulated and it is not certain how it is being applied by organisations and individuals (Donelan et al., 2015).

In the absence of an alternative evaluation criteria system that captures issues relevant to the areas of medicines development, regulatory review and HTA, the best practices for making quality decisions during the lifecycle of medicines were characterised (Figure 1.1). These Quality Decision-Making Practices (QDMPs) were developed based on the outcomes of semi-structured interviews by Donelan and colleagues (2015) with 29 key opinion leaders from regulatory authorities and pharmaceutical companies to investigate and identify the important issues that influence quality decision making during the medicines development and regulatory review. Moreover, this set of holistic practices is underpinned by the key frameworks used during medicines development, particularly in the area of regulatory benefit-risk assessment of medicines (Leong et al., 2015), as well as the science of decision making (Matheson and Matheson, 1998; Hammond et al., 1999; Blenko et al., 2010; SDG, 2011; Heath C and Heath D, 2013). A framework can be defined as a set of principles, guidelines and tools to guide decision making in organising, understanding, summarising, quantifying and communicating the basis of the decision (Ferguson, 2008). The ten QDMPs were thematically organised into four quadrants, ‘Structure and Approach’, ‘Evaluation’, ‘Impact’ and ‘Transparency and Communication’.

In a subsequent review, these QDMPs were presented to a focus group of companies and agencies, and were considered as appropriate and relevant for ensuring quality decision making (Patel et al., 2016). However, it is not clear how these practices are theoretically incorporated into the formal frameworks of organisations or what markers could a company, a regulatory authority or an HTA agency instigate to ensure that these QDMPs are practically embedded into the key decision-making processes. One way to measure decision making could be based on a pre-specified agreement regarding an anticipated positive outcome.

Nevertheless, as previously discussed, an assessment of the outcome only may not be a good measure of the decision-making process. Indeed, this has been recognised by Donabedian and colleagues (1988) where information about the quality of healthcare can be drawn from three distinct categories: "structure," "process," and "outcomes". These interconnected categories provide a framework for examining the quality of health services, where indeed increasing the quality of process has been linked to better outcomes.

However, despite the challenges to the direct measurement of the quality of the decision making, by understanding the components of quality decision-making practices, it may be possible to build a checklist, which would aim to measure performance against each practice and ultimately ensure that each QDMP is embedded within organisational and individual processes. The checklist could therefore be used to document the outcome of a decision-making process at the time of decision making. A checklist approach, although having a number of potential challenges such as adherence, has successfully transformed the efficiency of decision making in medicine, aviation and investing in order to raise awareness of best practices, ensure they are consistently and transparently followed and ultimately increase the probability best quality outcomes (Gawande, 2011). Such an approach will therefore be explored in the pharmaceutical industry through this research.

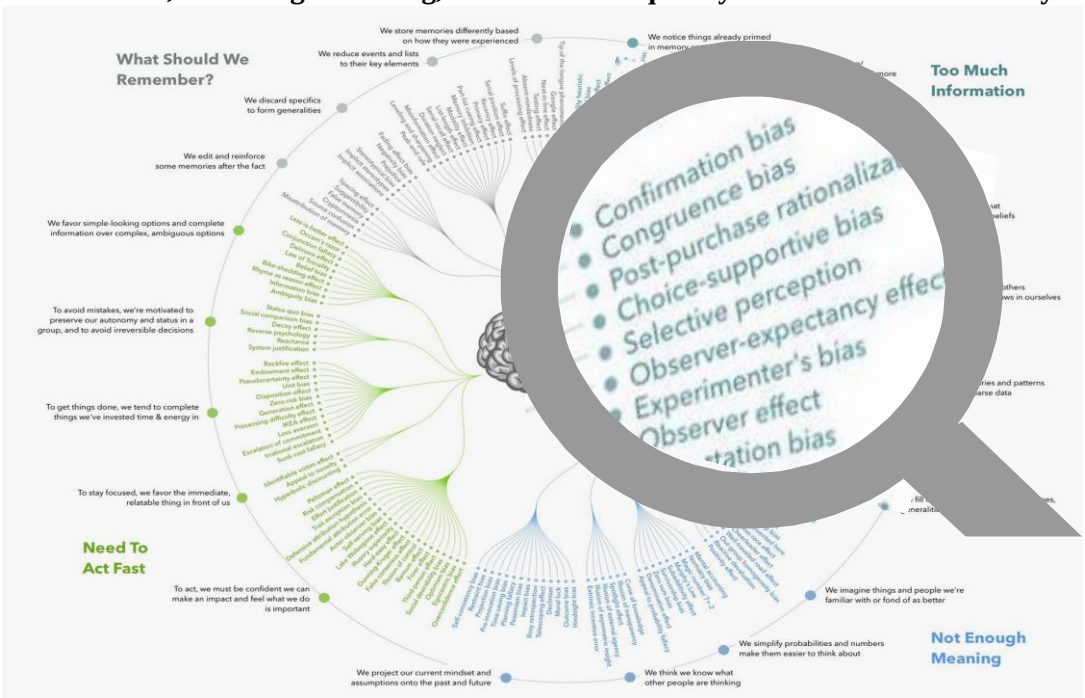
**Figure 1.1 The ten Quality Decision-Making Practices (QDMPs)**


*, **: These two QDMPs were originally a single QDMP and were separated in subsequent phases of this research project
Adapted from Donelan et al., 2015

**Challenges to quality decision making**

Many factors can influence an individual's approach to decision making including subjective and subconscious influences. This applies to the area of medicines development, review and HTA as well as beyond. Indeed the human mind and intuition work in ways that are sometimes in conflict with achieving a quality decision-making process (Hammond et al., 1999; Kahneman, 2011). As defined by Kahneman (2011), 'System 1' thinking is fast and emotional and takes numerous shortcuts according to the "What You See Is All There Is" principle (WYSIASTI). System 2 thinking is deliberative and analytical and can be used to solve complex problems. Nevertheless, in order to avoid biases in the way which minds solve complex decision problems, individuals and organisations need to be educated on the topic of biases and secondly trained in the types of procedures, interventions and preventions that should be applied to prevent them. Figure 1.2 depicts 190 biases that can influence an individual's decision making, whilst a number of additional factors exist such as personality and habitual effects, as well as social influences. These 190 biases have been identified and catalogued by behavioural scientists in academic studies over the last five decades and new classifications are being discovered to date (Benson, 2016).

**Figure 1.2 A categorisation of 190 biases into 4 groups: biases that arise from too much information, not enough meaning, the need to act quickly and the limits of memory**




Magnifying glass enlarges a portion to illustrate a subset of the content
Adopted from Benson, 2016

The impact of biases on decision making is high (Kahneman, 2011; Heath C and Heath D, 2013) and as these biases are frequently subconscious, where many individuals and

organisations are not aware of their existence. Spetzler and colleagues (2016) have defined six categories used to organise the many individual-level biases, namely:

- **Protection of Mindset:** Mindset is the basis of our beliefs and preferences. Individuals use their mindset to make judgments and their instinct dictates them to reject evidence that conflicts with initial mindset and to accept evidence that agrees with current beliefs, referred to as 'confirmation bias'. Other types of biases are also relevant here, such as 'hindsight bias', when individuals look back and rationalise a present situation based on past evidence; 'self-serving bias', referring to overestimating positive qualities while writing off failures to situational factors or bad luck; and 'status quo bias', whereby individuals cling to the current position too strongly. In order to overcome biases in this category, individuals should gain awareness of these phenomena, thereby learning how to maintain an open and flexible mindset.
- **Personality and Habits:** Every individual has specific habits and personality traits and although this is part of human nature and is not problematic *per se*, this creates a source of bias as we see any decision or situation from a personal point of view (WYSIATI) rather than objective 'as it is' viewpoint. Individuals can nevertheless uncover and raise awareness of their preference-based habits using various personality tests, the most popular being the Myers-Briggs Type Indicator (Briggs and Myers, 1987).
- **Faulty Reasoning:** Even if individuals are in a careful thinking mode to counter mindset and personality related biases, other challenges may arise, for example when dealing with large volumes of data or with complex multi-dimensional problems with interrelated factors or high uncertainty. Examples include 'selective attention' to specific variables or data and 'substitution bias' to replace a difficult question with an oversimplified one to the degree that this becomes a different problem. Finally, with high uncertainty around decision making, it is important to realise that overreliance on intuition is not appropriate.
- **Relative Thinking:** Individuals tend to make judgments based on connections, comparisons and associations and this too can lead to biases. Examples are 'availability bias', where an event appears more likely because it is easily imagined and 'narrative fallacy bias', where compelling stories that are not necessarily true can nevertheless convince individuals. Solutions include encouraging more scientific reasoning and approach to assessing evidence and decision making.
- **Automatic Associations:** These refer to distortions in our judgement based on the fact that people form associations when making decisions. Examples of biases include 'halo effect bias', where the overall impression of a person or idea influences how individuals feel and think about the entity's character or properties; 'anchoring effect bias' where people rely or 'anchor' on one trait or piece of information when making decisions, often

in the presence of uncertainty; and 'framing effect bias' where individuals react to a particular choice in different ways depending on how it is presented, for example as a loss or a gain. This should be countered by looking at the information objectively and holistically.

- **Social Influences:** These arise in the presence of the desire for conformity and acceptance, such as 'authority bias' leading individuals to prefer the opinion of an authority figure; 'groupthink bias' where individuals discourage diverse views in order to minimise conflict and strive for consensus at all cost; and 'suggestibility' where a person will accept the suggestions of another person and act accordingly. Such biases reduce the quality of decision making as they limit the number of alternatives considered and therefore should be countered by encouraging debate and dissent.

In addition to individual-level biases described by Spetzler and colleagues (2016), Lovallo and Sibony (2010) have developed a universal typology of biases, as outlined in Table 1.2, that occur most frequently and have the largest impact on the quality of organisational and business decisions, such as those made by companies, regulatory authorities and HTA agencies.

**Table 1.2 Characteristics and definitions of biases**

| Bias type | Definition | Characteristics |
|---|---|---|
| Action-oriented | A bias that drives us to take action less thoughtfully than we should | • Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling |
| Interest | A bias that arises in the presence of conflicting incentives, including emotional ones | • Misaligned individual incentives<br>• Inappropriate attachments<br>• Misaligned perception of corporate goals/hierarchy |
| Pattern-recognition | A bias that leads us to recognise patterns even where there are none | • Confirmation bias to seek out information that supports a favoured decision<br>• Generalising based on examples that are recent or memorable<br>• Evaluating a plan or proposal based on the track record of the person presenting it, more than on the facts supporting it |
| Stability | A bias that creates a tendency toward inertia in the presence of uncertainty | • Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. |

Adapted from Lovallo and Sibony, 2010

Although certain organisations involved in the development and review of medicines have started to investigate the occurrence of specific biases within regulatory authorities (Marangi et al., 2014) this has not been carried out in a systematic or comprehensive manner across pharmaceutical companies, regulatory authorities and HTA agencies. There is, therefore, scope to initially raise the awareness of biases in decision making across the three stakeholders and secondly evaluate whether these types of biases occur in the processes of the three organisations as well as whether differences and similarities exist across the groups.

**Evaluating quality of decision-making processes**

Routine assessment of the quality of the decision-making process (as opposed to just measuring outcomes) has been recognised as key for identifying process challenges and areas for improvement in order to ultimately increase the efficiency and productivity of decision making within any organisation (Kahneman, 2011). In the apparent absence of an appropriate technique, Donelan and colleagues (2015, 2016) initiated a study using a standardised approach comprised of qualitative and quantitative techniques to develop and validate an instrument, the Quality of Decision-Making Orientation Scheme (QoDoS), for assessing the quality of decision making in medicines development and regulatory review. In the initial qualitative phase of this research, in-depth structured interviews were conducted with 29 key opinion leaders from regulatory authorities and pharmaceutical companies regarding their subjective understanding of the approaches, influences and other factors in individual and organisational decision making in pharmaceutical development and regulation. Analysis of the output from these interviews resulted in the identification of overarching themes. It was hypothesised that these emergent themes could provide insight into a framework for quality decision making. Consequently, these themes were distilled into the ten QDMPs as described earlier. The overarching themes were used to develop 96 initial QoDoS items.

In the quantitative approach used in phase 2 of the research, content validation and psychometric evaluation testing of the 96 items from phase 1 resulted in a reduced list of 76 items. This was followed by content validity testing, using a panel of experts for language clarity, completeness, relevance and scaling, resulting in a favourable agreement by panel members with an intra-class correlation coefficient value of 0.89 (95% confidence interval = 0.56, 0.99). Factor analysis was performed on the resulting 76-item instrument and produced a 47-item measure with response options on a Likert frequency scale (Figure 1.3). In order to capture the views of the individuals regarding their decision-making competency and that of their organisation, this instrument was divided into four sections containing questions regarding the individual's assessment of their organisation's decision-making approach and culture as well as their own decision-making competence and style (Donelan et al., 2016).

**Figure 1.3 The Quality of Decision-Making Orientation Scheme (QoDoS)**

## The Quality of Decision-Making Orientation Scheme (QoDoS) ©

The statements in the questionnaire relate to your views on your personal and your organisation's *decision-making processes for major strategic choices within your organisation.*

Please mark clearly one box for each statement. Assume that Not at all = 0% of time; Sometimes = 25% of time; Frequently = 50% of time; Often = 75% of time; Always = 100% of time. If not sure, please tick the box that you feel is the most appropriate.

No data that will identify an individual or an organisation will be reported, or details made to a third party.

### Background questions

Gender: ☐ Male ☐ Female ☐ Other

Job title: _____

How many years of professional experience have you to date? _____

Organisation: ☐ Regulatory Agency ☐ Pharmaceutical Industry ☐ HTA ☐ Academia ☐ Other

### Part I: Organisational-level influences

| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-Making Approach** | | | | | | |
| 1. My organisation evaluates the impact of the decisions it makes | | | | | | |
| 2. My organisation's decision making is transparent | | | | | | |
| 3. My organisation's decision making is consistent | | | | | | |
| 4. My organisation uses a structured approach in its decision making | | | | | | |
| 5. My organisation's decision making is influenced by external stakeholder's demands | | | | | | |
| 6. My organisation assigns qualitative values to its decision-making criteria | | | | | | |
| 7. My organisation assigns quantitative values to its decision-making criteria | | | | | | |
| 8. My organisation is open to using better alternatives in its decision making | | | | | | |
| 9. My organisation encourages innovative decision making | | | | | | |
| 10. My organisation considers uncertainties in relation to its decision making | | | | | | |
| 11. My organisation provides training in the science of decision making | | | | | | |
| 12. My organisation re-examines its decision making as new information becomes available | | | | | | |
| **B. Decision-making culture** | | | | | | |
| 13. My organisation has suffered a negative outcome due to slow decision making | | | | | | |
| 14. My organisation's culture has resulted in its inability to make a decision | | | | | | |
| 15. My organisation's decision making is influenced by organisational politics | | | | | | |
| 16. My organisation's decision making results in making the same mistake as in the past | | | | | | |
| 17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | | | | | | |
| 18. My organisation underestimates problems which adversely impact its own decisions | | | | | | |
| 19. My organisation continues with projects/products which should be terminated at an earlier stage | | | | | | |
| 20. My organisation's decision making is influenced by similar organisations or competitors | | | | | | |
| 21. My organisation's decision making is influenced by incentives or penalty payments | | | | | | |
| 22. My organisation effectively communicates the decisions it makes | | | | | | |
| 23. My organisation provides clear and unambiguous instructions for decision making | | | | | | |

1 

**(continued) Figure 1.3 The Quality of Decision-Making Orientation Scheme (QoDoS)**

**Part II: Individual-level influences**

| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-making competence** | | | | | | |
| 24. My decision making is knowledge based | | | | | | |
| 25. My decision making is consistent | | | | | | |
| 26. I consider uncertainty and unknowns in my decision-making approach | | | | | | |
| 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | | | | | | |
| 28. I present contingencies or achievable options as part of my decision making | | | | | | |
| 29. My decision making is transparent | | | | | | |
| 30. I understand the context of the decision I am being asked to make | | | | | | |
| 31. I understand the importance of the decisions I make | | | | | | |
| 32. I use a structured approach in my decision making | | | | | | |
| 33. I assign qualitative values to its decision-making criteria | | | | | | |
| 34. I assign quantitative values to its decision-making criteria | | | | | | |
| 35. I receive training in the science of decision making | | | | | | |
| 36. I use intuition or "gut-feeling" in my decision making | | | | | | |
| 37. My professional experience is important when having to make challenging decisions | | | | | | |
| **B. Decision-making style** | | | | | | |
| 38. Emotion is part of my decision making | | | | | | |
| 39. I have experienced "paralysis by analysis" caused by my slow decision making | | | | | | |
| 40. I have experienced a negative outcome by a decision not being made | | | | | | |
| 41. In my decision making, I make the same mistakes as in the past | | | | | | |
| 42. Recent or dramatic events greatly impact my decision making | | | | | | |
| 43. My procrastination has resulted in a negative outcome | | | | | | |
| 44. My decision making could be improved by assigning relative importance to decision criteria | | | | | | |
| 45. I underestimate problems which adversely impact my decision making | | | | | | |
| 46. I continue with projects/products which should be terminated at an early stage | | | | | | |
| 47. I feel that I could make better quality decisions | | | | | | |

2

The 47 items of the final instrument can be mapped to the ten QDMPs (Table 1.3). The applicability of QoDoS in regulatory authority and pharmaceutical company setting was confirmed through a study with 76 participants (50% from regulatory authorities and 50% from pharmaceutical companies) to identify differences in decision making between individuals and their perception of their organisation as well as between companies and agencies across the QDMPs (Bujar et al., 2016).

**Table 1.3 Quality of Decision-Making Orientation Scheme (QoDoS) 24 individual and 23 organisational items mapped to the ten Quality Decision-Making Practices (QDMPs)**

| Ten QDMPs | 24 QoDoS individual items | 23 QoDoS organisational items |
|---|---|---|
| 1. Have a systematic, structured approach to aid decision making | 24, 25, 27, 30, 32, 35, 36, 39, 40, 43 | 3, 4, 11, 13, 14 |
| 2. Assign clear roles and responsibilities | 37 | 15, 23 |
| **3.** Assign values and relative importance to decision criteria | 33, 34, 44 | 6, 7 |
| **4.** Evaluate both internal and external influences/biases | 38, 42 | 5, 17, 20, 21 |
| **5.** Examine alternative solutions | 28 | 8, 9 |
| **6**. Consider uncertainty | 26, 45 | 10, 18 |
| **7.** Re-evaluate as new information becomes available | 46 | 12, 19 |
| 8. Perform impact analysis of the decision | 31, 47 | 1 |
| 9. Ensure transparency and provide a record trail | 29, 41 | 2, 16 |
| 10. Effectively communicate the basis of the decision | | 22 |

Although the work by Donelan and colleagues (2016) led to the development of a robust technique for assessing the quality of decision-making processes during medicines development and review, there is a further scope for work. This could aim to first of all find out directly from companies, regulatory authorities and HTA agencies whether they utilise other in-house techniques for measuring quality of decision making and furthermore whether other tools have been published in journals or grey literature for the same purpose. A systematic assessment of the public domain as well as stakeholder views could demonstrate whether QoDoS is indeed the best available technique for measuring the quality of the decision-making process throughout the lifecycle of medicines, or perhaps whether other instruments exist that could be used in parallel. Furthermore, although, the initial applicability

of the instrument in a regulatory authority and pharmaceutical company setting was confirmed using a mixed group of participants (Bujar et al., 2016) there is a need to test the instrument in terms of its reliability (stability and consistency of scores), as well as to utilise the instrument to assess the level of implementation of the QDMPs in organisations and consequently determine the practicality of QoDoS for identifying areas of strength and the need for improvement.

**Frameworks for improving decision making in companies, regulatory authorities and HTA agencies**

As described earlier, pharmaceutical companies, regulatory authorities and HTA agencies make many decisions every day with regards to new medicines. Faced with an increasingly complex environment, these groups have been incorporating various frameworks and tools in order to make their decisions scientifically sound and transparent. Firstly, the area of regulatory benefit-risk assessment has adapted certain concepts in decision making through the use of qualitative and quantitative tools by pharmaceutical companies and regulatory authorities (Guo et al., 2010; EMA, 2011; Tafuri, 2013; Leong et al., 2015; Pignatti et al., 2015; FDA, 2018). Examples of frameworks include the PrOACT-URL framework utilised by EMA, where each letter represents a step in the framework (Problem; Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risks and Linked decisions); the Unified Methodologies for Benefit-Risk Assessment (UMBRA) framework; the US Food and Drug Administration (FDA) benefit-risk framework, along with other alternative quantitative approaches for assessing the benefit-risk balance of a medicine (EMA, 2011; Walker et al., 2014; Pignatti et al., 2015). The above frameworks are also underpinned by the use of decision trees, which are diagrammatic displays of options, as well as Multi-Criteria Decision Analysis (MCDA), which is a qualitative and stepwise process that allows quantification of two or more decision alternatives (Dodgson, 2009). In HTA, a number of projects have also focused on the various ways to improve the assessment and appraisal methodologies and practices (Daniels, 2000; Wahlster et al., 2016;), particularly regarding inclusion of multiple decision criteria (Cole et al., 2016) and a structured assessment of comparative added benefit of a technology against the cost of treatment (Cherny et al., 2015; Schnipper et al., 2015).

The second key area that has benefitted from more structured decision making is portfolio management, where companies have been using frameworks (Sharpe and Keelin, 1998; Cook et al., 2014) as well as quantitative methods and algorithms (Hassanzadeh et al., 2011; Jekunen, 2014) in order to analyse and optimise the portfolio of medicines and ultimately avoid late terminations in Phase 3 development. Frameworks have also been developed in order to provide better structure around evidence generation during medicines development in

order to capture the HTA and payer requirements as well as to try and put systems in place to better align with regulatory requirements (Dunlop et al., 2016; McAuslane et al., 2016).

The third area has been around the use of good submission and review practices (GRevP) by pharmaceutical companies and regulatory authorities respectively (WHO, 2015) as well as in HTA agencies to standardise evidence generation (EUnetHTA, 2016) and to analyse the various decision-making systems for the assessment of health technologies (Rogowski et al., 2008). Finally, pharmaceutical companies, regulatory authorities and HTA agencies have developed specific frameworks and guidelines to formalise the decision-making process of various committees (EMA, 2007; FDA, 2008; Hassanzadeh et al., 2011; CADTH, 2012; NICE, 2015).

While the above frameworks serve their purpose and describe the specific process steps and principles regarding decision making during the development, regulatory review and HTA, they do not account for the subjective elements, such as behaviours and influences that affect the process with which individuals and organisations arrive at the final decision. Indeed, although the regulatory authorities and HTA agencies, as well as companies, already take into account the various medical, social, economic and ethical information needed to carry out the appraisal of medicines, it is not always obvious how the decisions, which require human judgment and interpretation, are made around the data (Cole et al., 2016).

Furthermore, as the use of frameworks by regulatory authorities and HTA agencies as well as companies increases, it is not certain whether these frameworks enable quality and transparency. Consequently, there is a need to explicitly define, evaluate and furthermore improve the quality of deliberative decision making defined by the ten QDMPs, as advocated by the key stakeholders in this area, namely the major pharmaceutical companies, regulatory authorities and HTA agencies (McAuslane et al., 2014; Patel et al., 2016). Such an approach would seek to utilise QoDoS as an instrument for evaluating quality of key strategic decision-making processes. A checklist could be then used to establish where improvements could be made as it would list the appropriate markers and process features organisations should have in place to ensure that the QDMPs are integrated. Ultimately, the various methods and approaches, including QoDoS and a checklist, could be brought together into an overarching roadmap that organisations could utilise as a strategy for improving the quality of decision-making processes for key strategic decisions during medicines development, review and HTA.

## AIM AND OBJECTIVES OF THE STUDY

### AIM

The aim of this study is to develop a roadmap for improving the quality of decision-making processes for key strategic decisions during the development, regulatory review and health technology assessment (HTA) of medicines.

### OBJECTIVES

The objectives across the three stakeholders, namely the pharmaceutical companies, regulatory authorities and HTA agencies are to:

- Identify and evaluate existing decision-making practices and frameworks for making key decisions
- Identify the techniques and measures used to evaluate quality decision-making practices (QDMPs)
- Appraise the published techniques for measuring QDMPs in order to determine whether the Quality of Decision Making Orientation Scheme (QoDoS), developed through previous research, is the most appropriate technique for evaluating quality decision making
- Further validate QoDoS by assessing its reliability and relevance in target audience
- Assess the practicality of QoDoS for evaluating the level of incorporation of the ten QDMPs within organisations
- Identify practical approaches for integrating the ten QDMPs into decision-making processes, including the development of a checklist that will support a timely, transparent, consistent and predictable process.

# Study Rationale and Methodological Framework

**STUDY RATIONALE**

Chapter one highlighted the relative paucity of research in quality decision making during medicines development, regulatory review and health technology assessment (HTA), despite demand from patients seeking increased access to safe and effective therapies. In addition to presenting the study rationale and purpose for carrying out the outlined studies, this chapter also reviews the appropriate methodological framework for the research project.

Whilst over the past decade resources have been invested to analyse data requirements and outcomes, medicines development, review and HTA are characterised by high uncertainty and should be judged not just by the quality of scientific data or the consequences of the decision, but also by the quality of the decision-making process, which is the focus of this thesis. Based on the information reviewed so far, it is proposed that studies will be carried to:

- Determine the existing use of frameworks, systematic decision-making processes and quality decision-making practices
- Provide an insight into the decision-making approaches pharmaceutical companies, regulatory and HTA agencies
- Assess the key challenges to quality decision making as well as potential solutions
- Identify the practical approaches for integrating quality into the decision-making processes within pharmaceutical companies, regulatory authorities and HTA agencies, including the development of a checklist
- Develop a roadmap for ensuring process consistency, transparency and quality.

Furthermore, as noted in the introduction, the focus of research by Donelan and colleagues (2015, 2016) was to develop a technique for assessing Quality Decision-Making Practices (QDMPs), which resulted in the development of the Quality of Decision-Making Orientation Scheme (QoDoS), which requires further validation and application in a target audience. There is also limited research into identifying what other techniques are available, as well as their practical application. Consequently, it is suggested that follow-on studies are carried to:

- Evaluate the use of techniques, such as tools, surveys, questionnaires and other studies, for measuring QDMPs
- Demonstrate the reliability and relevance of QoDoS to further strengthen its measurement properties and appraise the potential for being accepted as a gold standard in evaluating quality of decision making during the lifecycle of medicines.
- Assess the incorporation of the ten QDMPs into decision-making processes
- Determine the practicality of QoDoS for increasing awareness of the issues in quality decision making

### Study purpose

Research projects are undertaken for different purposes and can be categorised as exploratory, descriptive and explanatory. Exploratory research seeks to determine the nature of the problem by exploring new insights into a phenomenon, asking questions and assessing the problem in a new light. The purpose of descriptive research is to produce an accurate description of variables such as people, events or situations. Finally, explanatory research focuses on studying people, events or situations in order to explain relationships between variables. Furthermore, descriptive and explanatory research can be combined, known as descripto-explanatory studies, in order to draw conclusions from data being described (Robson, 2002; Saunders et al., 2009).

Due to the paucity of research on this topic, the purpose here will be therefore predominantly exploratory. An advantage of such an approach is flexibility as the purpose can be indeed adapted as a result of new data or insights. Nevertheless, as Robson (2002) has described, research may have more than one purpose and this may indeed change over time. Consequently, although the initial studies, such as the assessment of current decision-making approaches of companies and agencies, will be exploratory in nature, subsequent decision-making studies across organisations will be as descripto-explanatory where the descriptions gathered will be used as a precursor to explanation.

## METHODOLOGICAL FRAMEWORK

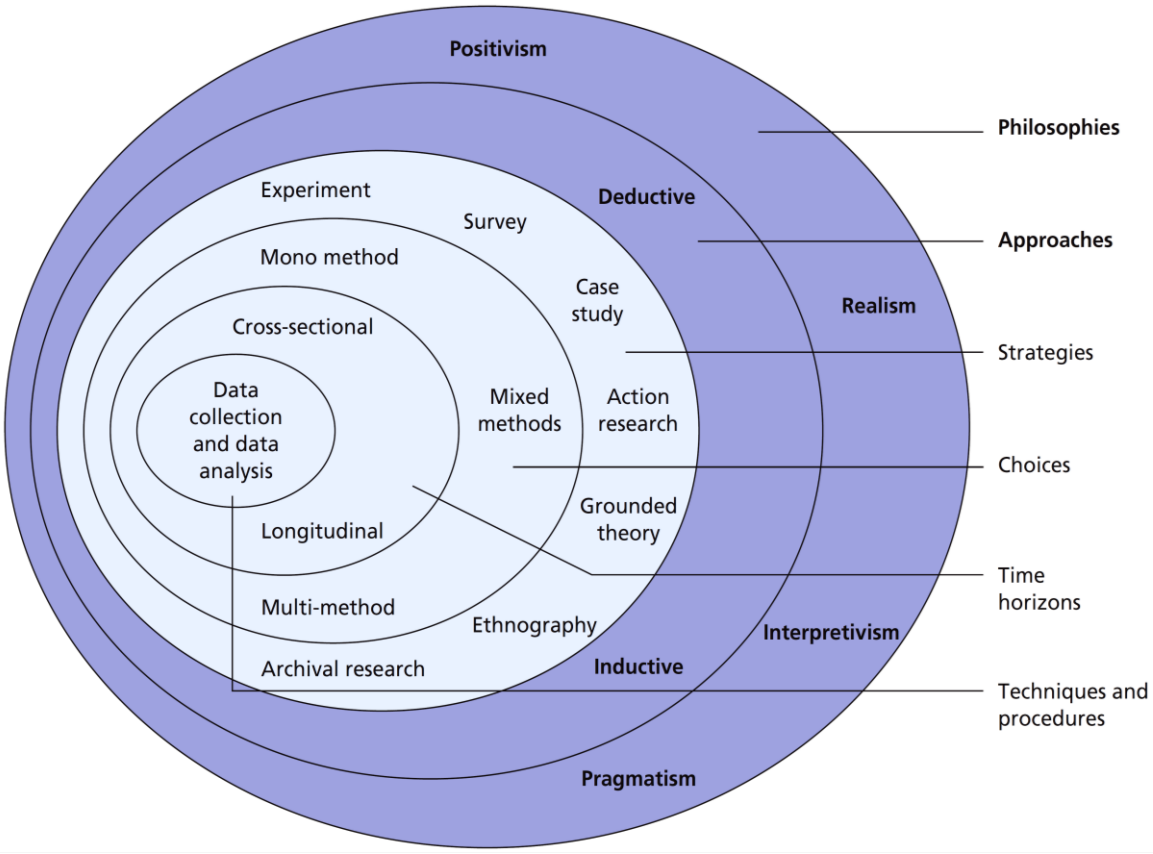
The choice of a methodological framework, including how each study will be carried out, is one of the most crucial decisions made during research (Yin, 2003). Nevertheless, before specific methods for gathering and analysing data are decided, it is important to note that the choice of such techniques will be influenced by the research philosophy and approach that aligns most closely with the objectives of the research. This will in turn influence the research strategies, choices and time horizons. This process is represented in the form of a ‘research onion’ (Saunders et al., 2009), where each layer represents a step that should be undertaken during planning of the research methodology (Figure 2.1). Each layer will be subsequently discussed in more detail, as well as decisions made at each step for the purpose of this project.

### Philosophy

Since the aim of a thesis is to develop and examine knowledge in a particular field, it is important to define and understand the values and assumptions as defined by the various research philosophies. These assumptions form the foundation of research and will underpin the research approach and data collection strategies undertaken during the investigation in order to create valid findings. Each research philosophy can be characterised by the

relationship between knowledge and how it is developed in terms of ontology, epistemology and axiology. Ontology is a branch of philosophy which is concerned with what constitutes reality and being. Epistemology, which is the theory of knowledge, is concerned with what constitutes valid knowledge. Finally, axiology studies judgments about value. The four main research philosophies, namely positivism, realism, interpretivism and pragmatism are compared in Table 2.1.

**Figure 2.1 The 'research onion'**




Adopted from Saunders et al., 2009

*Selected philosophy*

From these four philosophies, a pragmatic stance seemed the most appropriate in this case. Pragmatists argue that the key determinant of epistemology, ontology and axiology adopted are the research objectives themselves and no single philosophy by itself can answer them. Indeed this philosophical underpinning supports the study of both the objective and subjective aspects in quality decision making, thereby fitting more closely with the research purpose and rationale outlined above. Moreover, a pragmatic approach could yield better research results with the opportunity to use a mixture of different methods throughout the project to meet the study objectives which cannot be addressed using a singular method (Bryman, 2006; Gray, 2014).

**Table 2.1 A comparison of the four main research philosophies**

| | Positivism | Realism | Interpretivism | Pragmatism |
|---|---|---|---|---|
| **Ontology** (*the researcher's view of the nature of reality or being)* | External, objective and independent social actors | Is objective. Exists independently of human thoughts and beliefs or knowledge of their existence (realist) but is interpreted through social conditioning (critical realist) | Socially constructed, subjective, may change, multiple | External, multiple, view chosen to best enable answering of research question |
| **Epistemology** *(the researcher's view regarding what constitutes acceptable knowledge)* | Only observable phenomena can provide credible data, facts. Focus on causality and law like generalisations, reducing phenomena to simplest elements | Observable phenomena provide credible data, facts. Insufficient data means inaccuracies in sensations (direct realism). Alternatively, phenomena create sensations which are open to misinterpretation (critical realism). Focus on explaining within a context or contexts | Subjective meanings and social phenomena. Focus upon the details of situation, a reality behind these details, subjective meanings motivating actions | Either or both observable phenomena and subjective meanings can provide acceptable knowledge dependent upon the research question. Focus on practical applied research, integrating different perspectives to help interpret the data |
| **Axiology** *(the researcher's view of the role of values in research)* | Research is undertaken in a value-free way, the researcher is independent of the data and maintains an objective stance | Research is value laden; the researcher is biased by world views, cultural experiences and upbringing. These will impact on the research | Research is value bound, the researcher is part of what is being researched, cannot be separated and so will be subjective | Values play a large role in interpreting results, the researcher adopting both objective and subjective points of view |
| **Data collection techniques most often used** | Highly structured, large samples, measurement, quantitative, but can use qualitative | Methods chosen must fit the subject matter, quantitative or qualitative | Small samples, in-depth investigations, qualitative | Mixed or multiple method designs, quantitative and qualitative |

Adopted from Saunders et al., 2009

**Approach**

The second layer is the research approach, which can be classified broadly into inductive and deductive. A deductive approach involves the development of a hypothesis based on an existing theory and subsequent testing through a structured research strategy in order to either reject or accept it on the basis of the evidence. Conversely, an inductive approach involves the development of a theory based on observations of empirical data. The aim here is to explore a particular field and to generate hypotheses that may be subsequently tested (Collis, 2009; Gray, 2014).

*Selected approach*

Since the purpose of this research project is exploratory, namely to look for ideas and patterns in order to collect data and develop a roadmap for improving the quality of decision-making processes, the research approach will be predominantly inductive. Nevertheless, the two approaches are not mutually exclusive and an approach that combines induction and deduction is becoming more widely used (Saunders et al., 2009). Indeed, a combined approach can provide a better understanding of a specific research topic. In this case, in addition to an inductive approach that will be used for data collection and generation of theories/hypotheses and concepts, a deductive approach will be used during data analysis to evaluate results emerging from the various stages of this research, as well as to connect them to the previous research concepts, such as those developed by Donelan and colleagues (2015, 2016).

**Strategies**

According to Saunders and colleagues (2009), the choice of a research strategy is guided by the research objectives, the extent of previous work and the knowledge existing in this area; the amount of time and resources available to carry out the project, as well as the philosophical underpinnings and approaches discussed above. The main types of research strategies are outlined.

- *Experiment* is a deductive technique, used to study links between variables. This is achieved through defining a hypothesis; selecting and randomly allocating samples; introducing a planned intervention; choosing control variables and measuring other dependant variables. Although an experiment produces accurate, primarily quantitative measurement of the outcomes, the design requirements of experiments are complex and demanding, requiring ethical considerations as well as a representative captive audience (Saunders et al., 2009).
- *Survey* is also a primarily deductive technique used to collect information in a structured format from a group of individuals to explore relationships between variables and subsequently produce theories. Surveys are often carried out in the form

of a questionnaire, though it should be noted that this can be combined with interviews. Surveys are popular due to the possibility to collect information efficiently and economically, though issues may arise due to dependence on others for information, such as timeliness, quality of data obtained as well as achieving a high response rate (Robson, 2002).

- *Case study* involves the development of in-depth knowledge about a single 'case' or a small number of related 'cases'. It provides a rich understanding of individuals and variables in a real life context and can be a good source of new research questions, despite being seen as less scientific compared to the survey or experiment strategy. A case study can be categorised into four groups through two dimensions (Yin, 2003):
    - *Single case vs. multiple case*, where a single case is used in an extreme or unique situation, for example by analysing a single organisation; whereas multiple cases are used across several organisations/individuals. This would help determine whether the findings from one case can be generalised to others. Consequently, a multiple case is seen as preferential.
    - *Holistic case vs. embedded case* refers to the unit of analysis, where a holistic case is one where research is concerned with, for example, an organisation as a whole, whereas an embedded case would examine a number of logical sub-units, such as departments within an organisation.
- *Action research* refers to a primarily inductive strategy, where a problem is diagnosed in order to generate a list of actions and solutions to a specific problem. As part of this, the researcher may become involved and co-operate with practitioners and the results of the research should result in a call to action, such as promoting change within an organisation (Robson, 2002).
- *Grounded theory* is another case of a primarily inductive approach to predict and explain behaviour in order to build a theory. This strategy is highly creative and interpretative in nature and starts with data being generated from observation as well as existing literature and theory on this topic, which is then subsequently tested (Wertz, 2011).
- *Ethnography* is a strategy derived from anthropology, where the researcher becomes part of a community or situation in order to interpret the world through an inductive approach over an extended period of time (Saunders et al., 2009).
- *Archival research* uses documents and records as sources of data in order to formulate research questions and carry out exploratory, explanatory or descriptive analysis of data over a period of time. Nevertheless, it is constrained by the quality and availability of data (Gray, 2014).

*Selected strategy*

This project, defined by a pragmatic philosophy as well as a combined inductive and conductive approach, will integrate a number of various strategies in order to address the previously outlined research objectives. A survey approach will be used to assess use of frameworks and techniques within pharmaceutical companies as well as regulatory and HTA agencies. Grounded theory will be used as part of this research in order to conceptually analyse personal experiences captured through the survey. Conversely, case studies, specifically multiple and embedded cases, will be used during quality decision-making studies with QoDoS within departments and across multiple companies and agencies. As these studies will also be used to further validate QoDoS, an experiment strategy will be adapted in order to control variables and ensure the validity of the results. Finally, as this research will aim to promote improvements in quality decision making across individuals and organisations, action research strategy will also be adopted in order to achieve this.

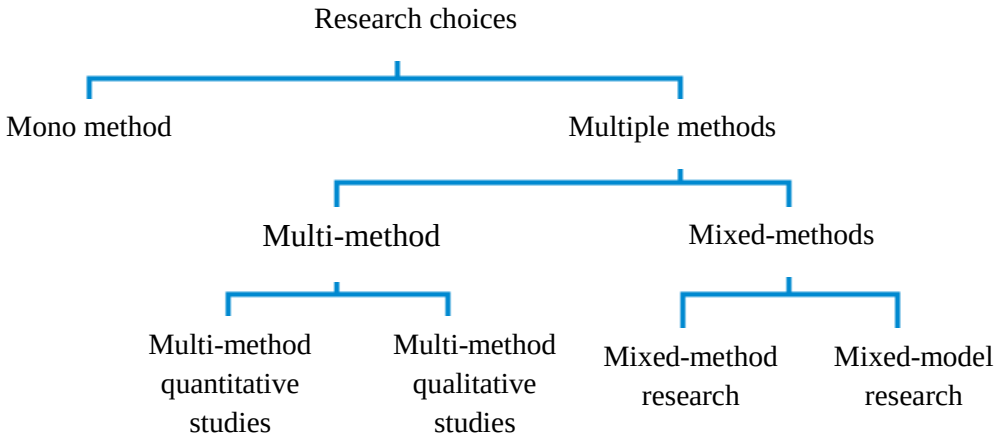
**Choices**

The third layer is the research choice in order to decide how quantitative or qualitative methods will be used or combined in research to collect and analyse data. Quantitative research involves numerical data collection and statistical analyses and graphs, whereas qualitative research is concerned with non-numerical data collection and the interpretation of results in order to generate accounts, opinions and description (Saunders et al., 2009). The research choices are illustrated in Figure 2.2, where a mono-method is the use of a single method (quantitative or qualitative) as opposed to the use of multiple methods, where either a number of methods of the same type (quantitative or qualitative) are used (multi-method) or different types of methods are mixed. For the mixed-method research, quantitative data are analysed quantitatively and qualitative data are analysed qualitatively, whereas for the mixed-model research qualitative data may be analysed quantitatively and vice versa.

*Selected choice*

In this project, a mixed-method choice will be used in order to combine both qualitative and quantitative techniques. For example, both qualitative and quantitative questions will be asked in a survey and quantitative data will be analysed quantitatively, whereas qualitative data (such as free text responses) will also be analysed quantitatively to determine the frequency of emerging themes. In addition, quantitative methods will be used during the studies with QoDoS in order to assess the quality of decision-making processes and the implementation of the ten QDMPs, as well as during the validation of the technique through the use of various statistical tests. Finally, qualitative methods will be used in the development of a checklist. Consequently, both the mixed-method and mixed-model research choices will be used.

**Figure 2.2 Research choices**




Adopted from Saunders et al., 2009

There are a number of advantages, as described by Bryman (2006) for the use of a mixed approach. Firstly, the use of two or more research strategies helps to capture various aspects of an investigation which can complement each other and provide deeper meaning. This technique, termed as research triangulation, describes the use of two or more data collection methods or research strategies. It ensures comprehensiveness and robustness of the knowledge and theories generated, whilst strengthening the validity of the study findings. For example, the same research objectives will be used in this project to query the public domain as well as the target audience. The use of multiple independent sources of data also provides contextual understanding and provides greater interpretability in order to help explain relationships between variables. Finally, it also facilitates generalisability (i.e. external validity) of the results so that they can be applied to settings other than that in which they were originally tested.

**Time horizon**

The final aspect to consider prior to deciding the data gathering and analytical tools is the timescale. Two main categories exist, firstly cross-sectional research where the data is collected using a snapshot approach at one point in time, making it relatively cost- and resource effective, and secondly a longitudinal study, which is used to measure a phenomenon over an extended period of time with multiple collection points thereby resulting in large amount of data being collected to provide a more comprehensive and representative picture of the variables under investigation (Gray, 2014).

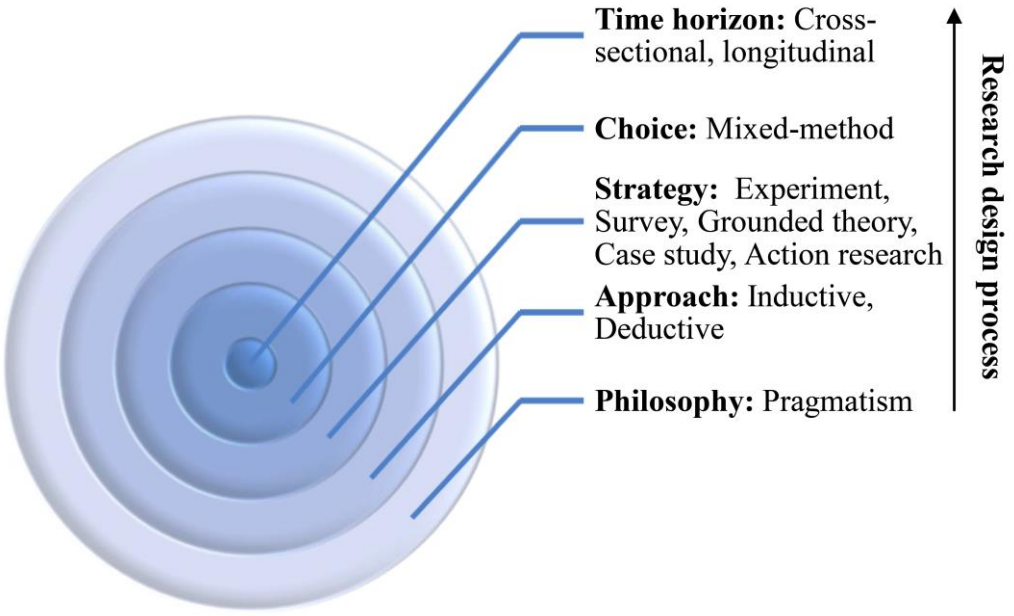
*Selected time horizon*

For the purpose of this project, cross-sectional timeframe will be utilised for the survey strategy for assessing current decision-making approaches of companies and agencies as well as case studies for assessing quality decision making with QoDoS. Nevertheless, a longitudinal timeframe will also be employed during the case study/action research strategies in order to assess quality decision making at different points in time. For example, this approach will be used for assessing the reliability of QoDoS, which refers to the extent to which the tool measures something in a consistent and reproducible manner (Streiner et al., 2015), where QoDoS will be applied on two occasions.

**Implications for this research**

The formulated research design, based on the approach developed by Saunders and colleagues (2009), is illustrated in Figure 2.3, which summarises the philosophy, approach strategy, choice and time horizon relevant to this research.

**Figure 2.3 The research design process based on the 'research onion' approach**




Adapted from Saunders et al., 2009

## DATA SOURCES

### Public domain sources

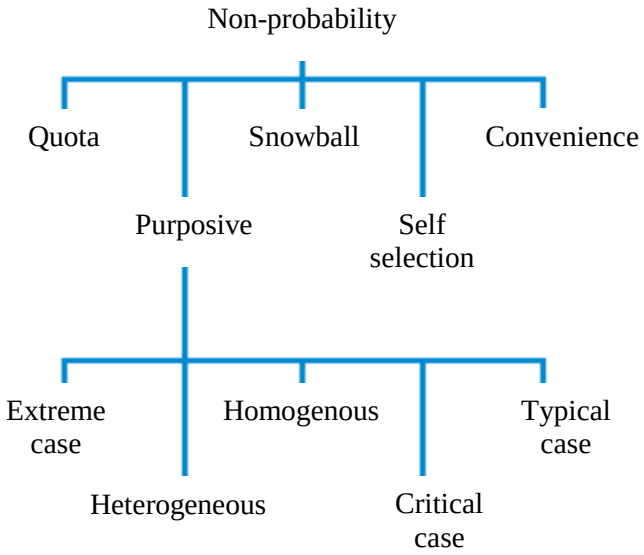
Bibliographic databases, namely MEDLINE (using PubMed), Web of Knowledge, Google Scholar and Open Access theses and dissertations, will be searched for scientific publications, books, academic conference proceedings. Gray literature will also be explored using Google as well as using country-specific regulatory and HTA agency and pharmaceutical company websites.

### Sampling techniques

In statistics, a population includes all members of a defined group being studied from which the sample is selected. In this case, the population will comprise individuals from major international pharmaceutical companies as defined by their research and development (R&D) expenditure; international mature regulatory authorities defined as stringent regulatory authorities (SRA) by the World Health Organisation (WHO) (2017) and major HTA agencies which are part of the International Network of Agencies for Health Technology Assessment (INAHTA, 2018) or European Network for Health Technology Assessment (EUnetHTA, 2018) to ensure that these various organisations have well established decision-making systems. As this research will aim to identify facts and opinions on strategic decision-making processes within organisations, senior individuals with at least 5 years experience in a managerial position will be selected for the survey techniques, although more junior individuals will be included for the various studies with QoDoS. Regarding companies, individuals will be recruited from regulatory and health economics and outcomes research departments (HEOR), whereas reviewers and decision-making committee members will be selected from agencies (Saunders et al., 2009).

Sampling is concerned with the selection of cases from the population for the purpose of the study. The techniques can be broadly divided into two groups, namely probabilistic and non-probabilistic. Probabilistic sampling is random where each case from the population has an equal chance of being selected and the results are therefore less likely to be biased and more likely to be generalisable as they reflect the entire population. Conversely, in a non-probabilistic technique, the probability of selecting an individual is not known and although the results are likely to be generalisable, this is usually not possible on statistical grounds (Gray, 2014). For the purpose of this research, probability sampling is not suitable as it would be impossible to obtain the sample frame, which is the list of all the individuals from the specified population. Consequently, a non-probability sampling technique will be used and the most relevant types which will be considered are illustrated in Figure 2.4 and discussed below (Saunders et al., 2009).

**Figure 2.4 Non-probability sampling techniques**




Adopted from Saunders et al., 2009

- *Quota sampling* is based on the idea that the sample will represent the population as the variability in the sample for various quota variables is the same as that in the population. Quota sampling is therefore a type of stratified sample in which selection of cases within strata is non-random.
- *Purposive sampling* is a technique where the judgement of the researcher is used to select the cases that make up the sample on the basis of the type of case needed to meet the research objective. A case can be either critical, extreme, typical or one that seeks homogeneity or heterogeneity.
    - *Extreme case sampling* focuses on unusual or special cases
    - *Heterogeneous sampling* focuses on obtaining the maximum variation in the cases selected
    - *Homogeneous sampling* focuses on selecting cases from one particular subgroup in which all the members are similar
    - *Critical case sampling* focuses on selecting cases which are important to make a particular point or meet an objective
    - *Typical case sampling* focuses on selecting cases that are illustrative.

  Purposive sampling aims to ensure that the full variety of responses is obtained from a range of respondents from the population in order to enable generalisability. Nevertheless, the sample is usually considerably smaller compared to quota sampling.
- *Snowball sampling* is used when there is a challenge in identifying the sample. The technique relies on making initial contact with one or two cases in the population and

asking those cases to help identify new cases and then carry on with this process until the sample is satisfactory. Although this technique is useful for populations that are difficult to identify, making the initial contact is difficult and there is also a high potential for bias.

- *Self-selection sampling* requires people who are interested in the topic, where the researcher publicises the research and data is collected from those cases that respond. This technique may introduce considerable bias depending on the advertising technique selected and it can be relatively costly.
- *Convenience sampling* involves selecting cases that are easier to obtain and is used when the timescales available for the project are short. Despite the wide use of this technique, convenience sampling has a number of limitations, most importunately that it is very prone to bias.

*Selected sampling method*

The sampling technique, which is deemed the most appropriate based on the research objectives, the characteristics of the population as well as resources and access to the organisations, is purposive sampling, This will ensure that the data is information-rich and allows to explore the research themes in order to gain theoretical insights into quality decision making and meet the study objectives. More specifically, heterogeneous sampling will be used in order to capture the variance in quality decision-making practices across organisations, which will ensure that the roadmap developed will be applicable to a broad spectrum of companies and agencies. In order to ensure timeliness and success of the projects, the sample will comprise organisations that are members and/or have a working relationship with the Centre for Innovation in Regulatory Science (CIRS, 2018).

## DATA COLLECTION TECHNIQUES

The data collection methods were carefully selected in order to meet the research objectives. The various qualitative and quantitative data collection techniques are reviewed below based on their strengths, weaknesses and applicability. Finally, the most appropriate methods selected for the studies are outlined.

### Literature Review: systematic and narrative

In the first place, a literature review will be carried out to identify recent developments in the field of quality decision making, both from a broader perspective as well as specific to medicines development and regulatory review. Secondly it will also seek to identify from the public domain the use of techniques, such as tools, surveys, questionnaires and other studies, for measuring the quality of decision-making processes during the lifecycle of medicines. For

the purpose of this research, two types of reviews were considered, namely a systematic literature review and a narrative literature review, which vary in terms of goals, components and value in research as well as in hierarchy of evidence they produce (Cook et al., 1997):

- *A narrative literature* review provides a qualitative summary on a topic using informal methods to interpret and collect data. The key advantage is that it provides a broad and comprehensive overview of a topic, but the conclusions are less likely to be based on the summary of the evidence considered.
- *A systematic review* provides answers to a specific focused question, with components such as pre-specified criteria, a systematic search strategy, independent secondary review, assessment of the validity of the findings and interpretation of the results. The key advantage is the scientific rigour, which ensures robustness and validity of the results and elimination of bias. Nevertheless, such an approach is time and resource intensive.

*Selected data collection using both a narrative and systematic literature reviews*

For the purpose of this research, both techniques of narrative and systematic review will be utilised; the scope and rationale are explained in the following paragraphs. Initially, a narrative literature review will be undertaken and summarised in the 'General Introduction' Chapter 1, where the aim will be to undertake an exploratory search of the recent developments in quality decision making during the lifecycle of medicines as well as more broadly regarding the art and science of decision making. The review will be undertaken by searching bibliographic databases and gray literature. Key search words to be included are: decision-making process, quality, decision analysis, medicine development, regulatory review, health technology assessment, tools, instruments, frameworks, influences, best practices, biases, subjective. In addition, the results of the narrative review will be used to refine the research context and objectives.

A systematic literature review will also be undertaken in order to answer a specific question, namely to determine the existence and use of techniques (tools, questionnaires, surveys and studies) for measuring quality of the decision-making practices across pharmaceutical companies, regulatory authorities and HTA agencies. Bibliographic databases will be searched for journal articles and Google will be used to search the gray literature. The review will be limited to English-language articles and cover a period from 1996 to 2017, which reflects the proliferation of publications in this area. Structured search terms will be constructed using PubMed guidelines and MESH terms and these will be used in database searches against selected criteria:

- For inclusion: (1) All articles which identify a technique (tool, instrument, or questionnaire) for evaluating quality of decision making applicable to the area of medicines development, regulatory, or HTA; (2) Techniques evaluating the decision, the decision-making process or key aspect(s) of the process and associated preferences, influences and behaviours; (3) Studies that assess the performance of the technique by evaluating hypothetical or real (historical) decisions, vignettes, or a reflection of individual style or approach.
- For exclusion (1) General discussions on decision making and quality within the area of medicines development, review and HTA; (2) Techniques for measuring quality of decision making used specifically in disciplines other than medicines development, regulatory review and HTA; (3) Frameworks for structuring and documenting decision-making processes and for enabling quality to be built into decision making.

To ensure robustness and minimise bias throughout the systematic review, an independent secondary review will be carried out in the development of the search strategy and selection criteria, as well as article selection and data extraction. In addition, the measurement properties of each technique will be assessed and compared to identify the research gaps and recommend the way forward. Of interest would be to find a technique that is applicable to all three stakeholders, namely companies, regulatory and HTA agencies, in order to have a common platform for discussing, sharing and comparing issues in quality decision making throughout the lifecycle of medicines.

**Survey techniques: questionnaires, interviews and focus groups**

Having selected a survey strategy, three major techniques are considered for collecting data directly from the pharmaceutical companies, regulatory and HTA agencies regarding the current approaches, measures and challenges to quality decision making. These are namely self-administered questionnaires, semi-structured interviews and focus groups.

- *A questionnaire* is a technique which uses a series of standardised, structured questions to allow a comparison of results within the sample. A self-administered questionnaire is a resource and time efficient technique as it can be distributed easily and the data can be collected from a large group of people simultaneously in person or alternatively via paper format, electronically or via the internet. Nevertheless, potential challenges exist such as obtaining a complete response rate, which relies on the recipients completing and returning the questionnaires. Moreover, in the case of a mail-delivered self-administered questionnaire, there is little opportunity to clarify questions as well as to accurately reflect the views of respondents in the case that the

choice of answers is restricted (Salant and Dillman, 1994; Needham and Vaske, 2008).

- *A semi-structured interview*, similarly to a questionnaire, is centred around a set of questions, generally a set of predetermined open-ended questions or a checklist, with other questions emerging from the dialogue between the interviewer and interviewees. The difference is that instead of being self-administered, it involves direct interactions, either face-to-face, over the phone or a teleconference (Dicicco-Bloom and Crabtree, 2006). The advantage of carrying out a semi-structured interview is the possibility of receiving responses instantaneously and at a high response rate. Moreover, respondents are more likely to provide better insights into the topics due to the proximity between the interviewer and interviewee as well as an enhanced understanding of the questions. Nevertheless, some limitations exist, such as having a less controlled environment compared to a questionnaire and potentially biased, if questions are leading. Moreover, they are resource intensive and costly to carry out as well as to analyse and compare. Semi-structured interview are therefore perhaps best suited for generation of ideas and themes (Valenzuela and Shrivastava, 2005; Needham and Vaske, 2008).
- *A focus group* technique can be used to carry out a qualitative exploration of opinions, values, knowledge and perceptions of individuals in regard to a particular topic, typically involving ten to 12 individuals who have knowledge or experience with the topic (Breen, 2006). The discussion is managed by a facilitator and a chair who lead the participants through a series of open-ended questions (Glitz, 1997). Focus groups are best suited for utilising group dynamics to generate a set of diverse qualitative data, to exchange viewpoints and discuss disagreements between individuals. Whilst focus groups may be less expensive than interviews, the key challenges is that they may become biased due to certain individuals being more engaged in the discussions and their views becoming more dominant (Gill et al., 2008). Nevertheless, in comparison with other forms of interview, interactions and responses are both encouraged and more closely controlled through a chair and facilitator to maintain the focus and to help minimise bias.

*Selected survey technique*

For the purpose of this research, the techniques of self-administered questionnaires and a focus group will be utilised to meet the objectives of this research. For the first part of this research, where factual data and responses will be sought regarding quality decision-making processes, a questionnaire is best suited in order to collect this data in a structured way and ultimately to allow comparisons between the various organisations. Questions will seek to

capture the use of frameworks, the prevalence of key influences and perceptions on barriers and challenges. The use of a self-administered questionnaire will also minimise the high costs and resources involved due to geographic variation in the location of the various companies, international agencies as well as the researcher.

In addition to self-administered questionnaires, a focus group technique will be used for the purpose of meeting another research objective, namely to explore and identify the practical approaches for ensuring the incorporation of the QDMPs, including a checklist, and ultimately to provide a roadmap for promoting consistency, transparency and quality during decision making. This will ensure that views and opinions are generated and validated across a broad range of individuals from companies and agencies (Saunders et al., 2009)

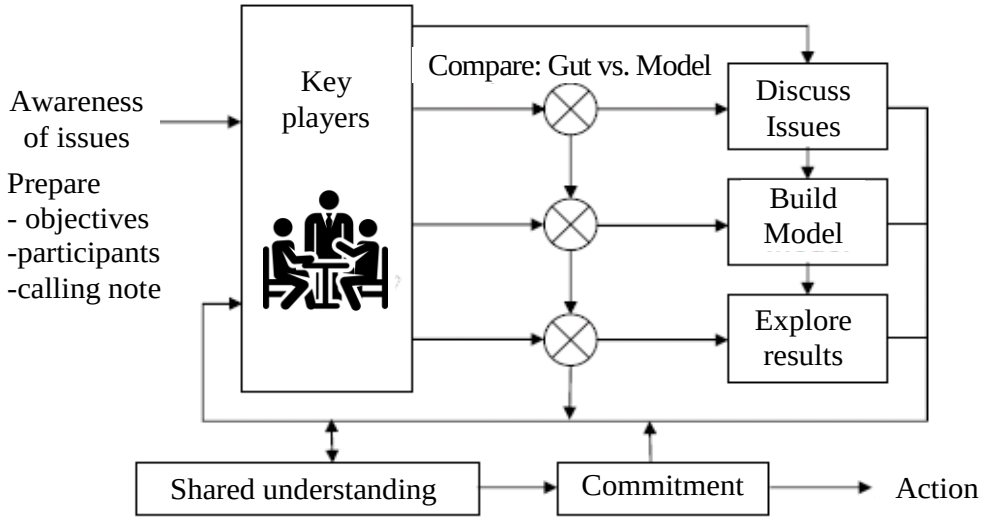
**Questionnaire development techniques**

Two techniques were explored for the development of the questionnaires, namely the Delpi technique and decision conferencing.

- *Delphi method* is a structured technique that involves an iterative process consisting of multiple rounds of structured discussions between a group of experts. The judgments and opinions are systematically captured through the discussions and are analysed in order to build a model which is fed back in a controlled way and the aim is then to seek reliable consensus of opinion from the expert group (Skulmoski et al., 2007). This technique has been used widely in science and healthcare and is a useful tool for the development of a questionnaire as it is largely anonymous and seeks to capture broad viewpoints and experiences whilst minimising bias and dominance. The technique can be a quick, inexpensive and a relatively efficient way of combining the knowledge and abilities of an expert group on a particular issue. A limitation is that consensus may be difficult to reach and it may result in a dilution of the key themes. For the purpose of a questionnaire, the first round involves application of an unstructured questionnaire to gain responses from the experts about a broad subject. From the summarised findings, subsequent questionnaires are derived and reviewed by the panel through multiple iterations in follow-on rounds until consensus is reached (Bunag and Savenye, 2013).
- *Decision conferencing* is also a technique used to systematically review a group's input. The process begins with an establishment of the objectives of the decision conference as well as the key players who will attend (Figure 2.5). A meeting is then called where the objectives are reiterated, which will be achieved by the group through the creation and review of a model that will capture the key elements that must be addressed to resolve an issue. Discussions would involve personal judgments

and intuitive opinions in order to improve the model until it reflects the perspectives of the group (Phillips, 2006). Decision conferencing during the design of a questionnaire is helpful to review the objectives of a questionnaire and generate a shared understanding of the questions, but without requiring consensus.

**Figure 2.5 A decision conference process**




Adopted from Phillips, 2006

*Selected questionnaire development technique*

As the purpose of the two questionnaires is exploratory and a body of knowledge has already been generated on the issues in quality decision making during the lifecycle of medicines based on interviews with key opinion leaders (Donelan et al., 2015), it was decided that the Delphi technique and Decision conferencing will not be appropriate due to the resource and time required. The questionnaires will therefore be developed based on the outcomes of the previous research (Donelan et al., 2015) as well as the literature reviews. A total of four questionnaires will be developed, where two questionnaires will capture issues on regulatory decision making, one from regulatory authorities and one from pharmaceutical company departments, and the other two questionnaires will survey concepts regarding medicines reimbursement, one across HTA agencies and one with HEOR company departments. Similar questions will be used in the four questionnaires where possible in order to facilitate comparisons.

**Questionnaire validation techniques**

The validity of the questionnaire forms the foundation of accurate measurement of the research outcomes. The key technique for ensuring validity is by ensuring content validity, which is the extent to which the questions in a questionnaire are well developed, can measure what they are intended to measure and possess the appropriate level of emphasis and focus. In order to achieve content validity, face validity must also be established. Face validity, defined as the appropriateness of the items in relating to the goals of the questionnaire, indicates whether, on the face of it, the instrument appears to be assessing the desired qualities based on a review of the measure by one or more experts to validate the content, layout, language and format (Nunnally and Bernstein, 1994; Streiner et al., 2015). In addition, it is important to ensure the internal validity of the study as the conclusions of the questionnaire are frequently generalised and extrapolated beyond the original research. The ultimate aim is to achieve construct validity, which is the extent to which the instrument accurately measures a theoretical construct it is designed to measure. This is typically demonstrated with correlations, in this case by comparing the outcomes of the questionnaire with the results from other relevant surveys (Streiner et al., 2015)

*Selected questionnaire validation technique*

Face validity will be performed by the internal research team during the development of the questionnaires. Content validity will be tested through feasibility pilot studies using structured feedback questions with at least 10% of the participating pharmaceutical companies, regulatory authorities and HTA agencies to determine the appropriateness of the questionnaire format; the language clarity; the ease of response and the relevance and accuracy of the questions for measuring theoretical construct. Comments from the pilot studies will then be incorporated and used to refine the questionnaires.

**Research instrument: Quality of decision-making orientation scheme**

In the absence of a validated instrument for measuring quality decision making during the lifecycle of medicines, QoDoS was developed (Donelan et al., 2016) and will be used for the purpose of this research to evaluate the quality of decision making in companies and agencies. It should be noted that QoDoS is a self-administered questionnaire (see Appendix 1).

The QoDoS was developed using a standardised, established approach for the design and psychometric evaluation of such measures (Donelan et al., 2015, 2016). The development of QoDoS included qualitative research into decision-making approaches and involved interviews with 29 key opinion leaders from the pharmaceutical industry (n=10), contract research organisations (n=10) and regulatory agencies (n=9), which resulted in the

identification of 32 decision-making themes. The key themes included: quality and validity of the data; political, financial, competitor and reward influences; analytical and logical approach; overconfidence in own judgement; plunging in or procrastinating with decision making; impact analysis of decisions; education and awareness of evolving decision-making techniques; and SWOT and alternate outcome planning. It was hypothesised that these emergent themes could provide insight into a framework for quality decision making. Consequently, these themes were distilled into best practices, namely the QDMPs. The QoDoS enables measurement against these practices (Donelan et al., 2015).

The QoDoS items generated from the 29 face-to-face semi-structured interviews with key opinion leaders yielded a 94-item initial version of the QoDoS with a five-point Likert frequency scale response option. Content validity was established using an expert panel to confirm that the emphasis and the focus of the QoDoS is fit-for-purpose. The experts rated the language clarity, completeness, relevance and scaling of each item on a four-point scale (Strongly agree, agree, disagree and strongly disagree) and the agreement among the panel members was high with an intra-class correlation coefficient value of 0.89 (95% confidence interval = 0.056, 0.99).

Factor analysis was performed on the resulting 76-item instrument and produced a 47-item measure (QoDoS) organised into four sections namely, organisational decision-making approaches, organisational decision-making culture, individual decision making competencies and individual decision-making style. The 47-item QoDoS showed high internal consistency (n = 120, Cronbach's alpha = 0.89), high reproducibility (n = 20, intra-class correlation = 0.77) and a mean completion time of ten minutes (Donelan et al., 2016).

*Psychometric properties of QoDoS*

The QoDoS instrument developed by Donelan and colleagues (2016) will be further tested to ensure it has adequate measurement properties relevant to decision making from the perspective of the individual and the organisation. The following validity aspects of QoDoS have already been determined by Donelan and colleagues (2016) as defined below (Trochim, 2006; Streiner et al., 2015):

- *Face validity* indicates whether the instrument, on the face of it, assesses the desired qualities based on subjective judgment from a review of the measure itself by one or more experts; empirical approaches are rarely used.
- *Content validity* is established when an instrument includes a representative and adequate set of items to uncover the concepts in the research objectives for the

intended population. The approach involves an expert panel as well as quantitative assessment techniques.

- *Construct validity* indicates whether the results obtained from the use of a measure fit the theoretical foundations from which it is designed and can be presented using a multi-trait-multi-method matrix, which examines convergence (evidence that different measurement methods of a construct give similar results) and discriminability (ability to differentiate the construct from other related constructs).
- *Internal consistency* examines whether the items and the subsets of items in the measuring instrument are correlated. The internal consistency, which addresses the relatedness/homogeneity of a single test form, may be assessed by correlating performance on 'two halves of a test', which is termed split-half reliability.

The measurement properties of the tool need to be further evaluated by assessing the reliability and sensitivity of the tool, as well as its relevance and practicality in companies, regulatory and HTA agencies for evaluating the ten QDMPs, as defined below (Trochim, 2006; Streiner et al., 2015):

- *Relevance* of an instrument would ensure the suitability of the tool which includes the respondent burden, resource requirements, the overall clarity and completeness of the tool and the scoring. This could be achieved through cognitive debriefing following QoDoS studies, a technique of actively testing the tool among representatives of the target population (Streiner et al., 2015; Brod et al., 2009).
- *Reliability* refers to the extent to which the tool measures something in a consistent and reproducible manner. The reliability coefficient expresses the proportion of the total variance (degree of error) in the measurement which is due to 'true' differences between subjects where 0 indicates no reliability and 1 indicates perfect reliability:

$$\text{Reliability} = \frac{Subject\ Variability}{Subject\ Variability + Measurement\ Error}$$

A test-retest method will be used by administering QoDoS to the same group on two different occasions, with an interval of 7 days, which should help minimise the bias due to memory of the respondents' answers to the items. Intra-class correlations (ICC) will be used to assess reliability, which is the ratio of variance of measurements of a given target to the variance of all targets. Results will be analysed using the Statistical Package for the Social Sciences (SPSS) software and a correlation of >0.7 will be sought (Paiva et al., 2014).

- *Sensitivity* is the ability of an instrument to detect change over time. In this case, a before and after measurement could be carried out with QoDoS to assess decision making of an organisation which has introduced appropriate measures to improve their decision making; one test will be applied prior to the intervention and the other post-intervention to determine whether the instrument has the sensitivity to identify the change. This will not be carried out as part of this research project due to time constraints.

In addition, as the development of QoDoS took place in 2013, a systematic review of literature will be performed, as outlined above, in order to verify whether other techniques have been developed since that time.

*Steps in a QoDoS study*

Firstly, the reliability of the instrument and its relevance will be evaluated in the target audience in order to further strengthen the psychometric properties of the technique. Secondly. QoDoS will be used to evaluate the incorporation of QDMPs in companies, regulatory authorities and HTA agencies. Multiple, embedded case studies will be conducted within specific groups in each organisation, such as committees and teams. Comparisons will be drawn within organisations as well as demographic breakdown using information regarding gender and professional experience. The general steps taken in each study have been defined as follows:

1. The participants will be introduced to concepts in decision making as well as QoDoS in person or via a teleconference. This approach will aim to ensure consistent baseline knowledge of concepts in decision making across the study participants. In the case of multiple applications of the QoDoS across the same participant group, such as during reliability testing, an introduction session will aim to minimise the 'learning effect' that might have occurred following the initial administration of QoDoS. Overall, the approach will aim to minimise 'confounding factors' (i.e. third variables that are not controlled or measured) that may negatively affect the internal validity of the study.
2. The participants will each be given a paper or electronic copy of the QoDoS, to be completed on the day.
3. The participants will be contacted with a gentle reminder by email to complete QoDoS
4. Overall results of the study will be circulated to the study leader within a specific organisation
5. A study feedback session will be organised to discuss the results, provide any clarifications, as well as to discuss the differences and possible areas of strength and weakness.

6. If applicable, a cognitive debriefing will be carried out by asking the participants to complete a feedback survey to determine the relevance and comprehension of the tool as well as the value of the feedback session.
7. A report will be prepared and sent to the participants containing the QoDoS study results and notes from the feedback session discussions.

*A summary of the selected data collection techniques*

The selected data collection techniques are outlined in Table 2.2, as well as the corresponding objectives and chapters.

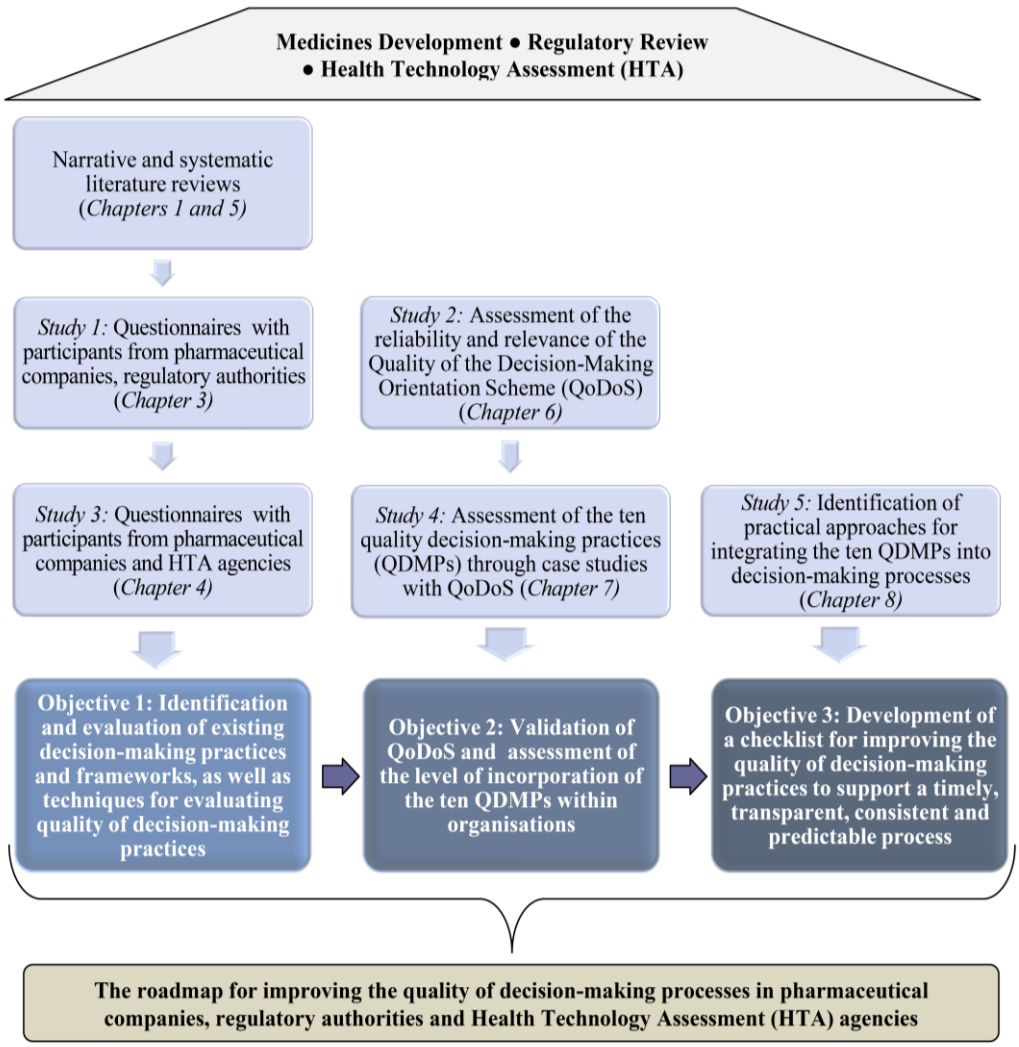
**Table 2.2 An overview of the planned data collection techniques**

| Data collection technique | Study objectives | Thesis Chapter |
|---|---|---|
| Narrative literature review | Exploration of concepts and issues in quality decision making particularly in the area of medicines development | Introduction |
| Systematic literature review | Identification of techniques for evaluating quality decision-making practices during medicines development, regulatory review and HTA | Chapter 5 |
| Self-administered questionnaires | Evaluation of current approaches, measures and challenges to quality decision-making process of:<br><br>1. Regulatory decision making of agencies and relevant company committees | Chapter 3 |
| | 2. Reimbursement decision making of HTA agencies and relevant company departments | Chapter 4 |
| QoDoS instrument (self-administered questionnaire) | Validation of the QoDoS instrument in terms of its reliability and relevance | Chapter 6 |
| | Evaluation of practicality of QoDoS in assessing quality decision-making practices in pharmaceutical companies, regulatory authorities and HTA agencies | Chapter 7 |
| Focus group | Identification of practical approaches for integrating quality into decision-making practices in medicines development, regulatory review and health technology assessment, including the development of a checklist | Chapter 8 |

**STUDY PLAN**

The study flow chart is illustrated in Figure 2.6; starting with a literature review and two questionnaires in order to meet the objective of identifying current decision-making frameworks, processes and techniques for measuring quality decision making, both from the point of view of public domain data as well as obtaining information directly from the target audience (Studies 1 and 3). The second objective of validation of the QoDoS instrument and evaluation of the level of implementation of the QDMPs will be met through QoDoS case studies with companies and agencies as well as a reliability study (Studies 2 and 4). Finally, the results from a focus group study (Study 5) aiming to develop practical approaches for integrating quality into decision-making processes will be brought together with other key study outcomes to develop a checklist. The ultimate aim will be to use all the study results and developed methods to build a roadmap for improving the quality of decision-making processes to ensure timeliness, transparency, consistency and predictability of decisions. This will be described in the General Discussion (Chapter 9).

**Figure 2.6 The study plan**



## DATA PROCESSING AND ANALYSIS

Data generated through the various studies will be analysed qualitatively and quantitatively. Quantitative data will be analysed with descriptive statistics such as medians and the lower and upper quartiles ($25^{th}$ and $75^{th}$ percentile values) using Microsoft Excel. In order to carry out the QoDoS reliability studies, statistical tests will be carried out using SPSS, such as the ICC and Cronbach alpha. Nevertheless, statistical tests will not be used for questionnaires or other exploratory QoDoS studies, which will be hypothesis generating as opposed to hypothesis testing.

Qualitative data, such as free text responses and comments from studies and questionnaires, will be coded through established methods, including grounded theory (Wertz, 2011) and constant comparison method (Boeije, 2012). This will facilitate data reduction and conclusions by selecting, focusing, simplifying, abstracting and transforming the data. In grounded theory, inductive, systematic analytic strategies will be applied to qualitative data to conceptually analyse personal experiences. The constant comparative method involves continually comparing and contrasting concepts to inform relationships between phases and themes expressed by the study participants. Content analysis will be employed for free text responses and comments to identify emerging themes. Ranking will also used where applicable. Where consensus is being sought in a study, it will be defined in a variety of ways, such as the calculation of percentage levels regarding the agreement of the participants (Streiner et al., 2015).

## ETHICAL APPROVAL

This programme of research did not require the national research ethics committee approval. However, ethics approval was obtained from the University of Hertfordshire.

**SUMMARY**

- This chapter describes the rationale for this project as well as outlining the proposed studies to be undertaken in order to meet the research aim and objectives
- The study purpose was defined as mainly exploratory followed by additional descripto-explanatory studies where the descriptions gathered from decision-making studies will be used as a precursor to the explanation of possible results
- The research design was based on the 'research onion approach', where various options were appraised and the following were selected: pragmatic philosophy; inductive and deductive approach; experiment, survey, grounded theory, case study and action research as the main strategies; mixed-method choice and a cross-sectional and longitudinal time horizon
- Data sources were described for public domain data collection, whereas the selected sampling technique was non-probability purposive sampling based on characteristics of the population and the objective of the studies
- Data collection techniques were also appraised to meet the study objectives and the following were selected: narrative and systematic literature review; self-administered questionnaires (including QoDoS) as well as a focus group approach
- A detailed outline of questionnaire development and validation techniques were also provided as well as general steps in QoDoS studies
- Methodological choices related to data processing and data analyses were also described
- A detailed study plan and framework were outlined to demonstrate the relationship between the studies, chapters and the objectives of the research programme.

# Evaluation of the Quality of Regulatory Decision-Making Processes in Pharmaceutical Companies and Regulatory Authorities

## INTRODUCTION

Quality of decision-making processes throughout the lifecycle of medicines is critical for ensuring that they become available in a timely and efficient manner, with appropriate safeguards to the health of the public. Currently, regulatory authorities and pharmaceutical companies focus on the generation of data and the assessment of uncertainty regarding a medicine, but it is not always clear how the data is deliberated by individuals and organisations to determine whether it has the appropriate safety, efficacy and quality to be submitted for regulatory review and thereafter to be given marketing authorisation. The various decisions are nevertheless under constant scrutiny by regulatory authorities looking to improve their practices for reviewing medicines, pharmaceutical companies seeking to enhance the effectiveness of their go/no-go decision making, as well as patients seeking increased access to new medicines. Ultimately, quality and transparent decision making is an ambition for all stakeholders involved in the development and review of medicines in order to provide patients with confidence in the decisions that affect their access to medicines (Liberti et al., 2013; Cole et al., 2016).

Pharmaceutical companies and regulatory authorities make many decisions every day with regards to new medicines. Faced with an increasingly complex environment, both groups have been adopting various tools in order to make their decisions scientifically sound and transparent. Examples, as discussed in Chapter 1, include the implementation of various benefit-risk assessment methodologies by companies and authorities (Walker et al., 2014; Pignatti et al., 2015), introduction of GRevP by authorities (WHO, 2014) as well as specific frameworks and guidelines to formalise the decision-making process of various committees (EMA, 2007; FDA, 2008). Nevertheless, questions remain that go beyond the review process and the assessment of benefits and harms and would seek to understand what decision-making practices are built into the various regulatory processes from the point of view of the individual and the organisation to enable transparency, consistency and quality.

The science of decision making is well established both from a social and scientific viewpoint (Kahneman, 2011). Currently, what is lacking is research and insight into the decision-making practices and approaches for individuals and organisations involved in medicines development and the regulatory review. This study extends the concepts explored through a previous investigation into regulatory decision making, (Donelan et al., 2015) and intends to characterise regulatory processes within companies and authorities and to further assess the use of decision-making tools and frameworks. As many decisions are made by pharmaceutical companies and regulatory authorities every day, this study will focus on characterising the final process within a company to determine whether a submission of a new

medicine should be made to a regulatory authority; as well as the final process within the authority to decide on the approval of the medicine.

The aim of this study was to investigate decision-making behaviours and processes of pharmaceutical companies and regulatory authorities during medicines development and review.

The objectives were to:

- Identify current decision-making practices and procedures within their organisations
- Assess the use of different methodologies for measuring the quality of decision-making process
- Investigate views and challenges with regards to the various frameworks they are using for decision making.

## METHOD

### Design of the assessment tool

An assessment tool in the form of a questionnaire was designed based on previous research outcomes (Donelan et al., 2015) and following a review of the literature, which identified the key issues in decision making relating to the use of formal frameworks and techniques for structuring and measuring the quality of the decision-making process as well as the prevalence of biases and subjective influences, as described in Chapter 1.

Previous research (Leong et al., 2013) suggested that the decision-making process by which regulatory authorities and pharmaceutical companies make a decision can be classified into two systems, namely quantitative and qualitative (Table 3.1). In addition, free text was provided if the system deviated from the definitions, or if it was a combination of the two systems.

*Definition of a framework*

For the purpose of this study, the definition of a framework was derived from previous research in the area of benefit-risk assessment (Ferguson, 2008) and is defined as "a set of principles, guidelines and tools which provide a structured systematic approach to guide decision makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision".

**Table 3.1 Definitions of regulatory decision-making systems**

| System | Definition (companies) | Definition (authorities) |
|---|---|---|
| Qualitative | Our internal system for the final decision to submit a New Drug Application (NDA) is purely qualitative based on internal experts or management making a "gut decision". The final decision will be exercised based on Expert Judgment and company experience. | Our internal system for the final decision to approve or reject an NDA is purely qualitative based on internal experts making an intuitive decision ("gut decision"). The final decision will be exercised based on Expert Judgment and agency experience. |
| Quantitative | Our internal system for the final decision to submit an NDA is fully quantitative which brings together various key data for the decision (including Clinical ( Benefit-Risk), CMC (Manufacturing), Health Outcomes and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment. | Our internal system for the final decision to approve or reject an NDA is fully quantitative which brings together various key data for the decision (including Clinical (Benefit-Risk), CMC (Manufacturing), Health Outcomes and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment. |

Adapted from Leong et al., 2013

*Quality Decision-Making Practices*

In the absence of other validated criteria for evaluating quality decision making during medicines development and the regulatory review, Quality Decision-Making Practices (QDMPs) were proposed for evaluating the company and authority frameworks (Table 3.2). As previously described, the QDMPs were developed based on key issues in quality decision making identified through semi-structured interviews with 29 key opinion leaders from authorities and companies (Donelan et al., 2015).

*Biases*

The different types of cognitive biases that occur during decision making were also investigated. Four main groups of biases adapted from previous research (Lovallo and Sibony, 2010) (Table 3.3) were proposed for this study to underpin the evaluation of bias perception within companies and authorities. This typology was chosen as it focuses on those biases that occur most frequently and that have the largest impact on organisational and business decisions.

**Table 3.2 Quality Decision-Making Practices (QDMPs)**

| |
|---|
| 1. Have a systematic, structured approach to aid decision making (consistent and predictable) |
| 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) |
| 3. Consider uncertainty and examine alternative solutions |
| 4. Assign values and relative importance to decision criteria |
| 5. Re-evaluate as new information becomes available |
| 6. Evaluate both internal and external influences/biases |
| 7. Apply a structured approach to aid transparency and provide a record trail |
| 8. Perform impact analysis and effectively communicate the basis of the decision |

Adapted from Donelan et al., 2015

*Structure and content of the questionnaires*

The assessment tool was finalised into two questionnaires to evaluate the decision-making practices of international pharmaceutical companies and regulatory authorities, respectively. Since many decisions are made within such organisations on a daily basis, the questionnaires focused on the key high-level decisions during medicines development and review, namely that to submit a new drug application (NDA) for the company questionnaire and to approve or reject an NDA for the regulatory authority questionnaire.

The questionnaires were organised into four sections:

1. *Decision-making process:* this section included questions regarding the involvement of a committee, different decision-making practices and decision-making systems
2. *Decision-making frameworks:* this section included questions regarding the use of a framework and the practices incorporated
3. *Challenges:* this section consisted of questions focusing on biases
4. *Personal perceptions:* this section included questions regarding perceived hurdles and solutions for making quality decisions and measuring quality of decision making

**Table 3.3 Characteristics and definitions of biases**

| Bias type | Definition | Characteristics |
|---|---|---|
| Action-oriented | A bias that drives us to take action less thoughtfully than we should | • Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling |
| Interest | A bias that arises in the presence of conflicting incentives, including emotional ones | • Misaligned individual incentives<br>• Inappropriate attachments<br>• Misaligned perception of corporate goals/hierarchy |
| Pattern-recognition | A bias that leads us to recognise patterns even where there are none | • Confirmation bias to seek out information that supports a favoured decision<br>• Generalising based on examples that are recent or memorable<br>• Evaluating a plan or proposal based on the track record of the person presenting it, more than on the facts supporting it |
| Stability | A bias that creates a tendency toward inertia in the presence of uncertainty | • Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. |

Adapted from Lovallo and Sibony, 2010

The two questionnaires contained analogous questions where appropriate in order to allow a comparison between companies and regulatory authorities. The following issue was unique to the company questionnaire:

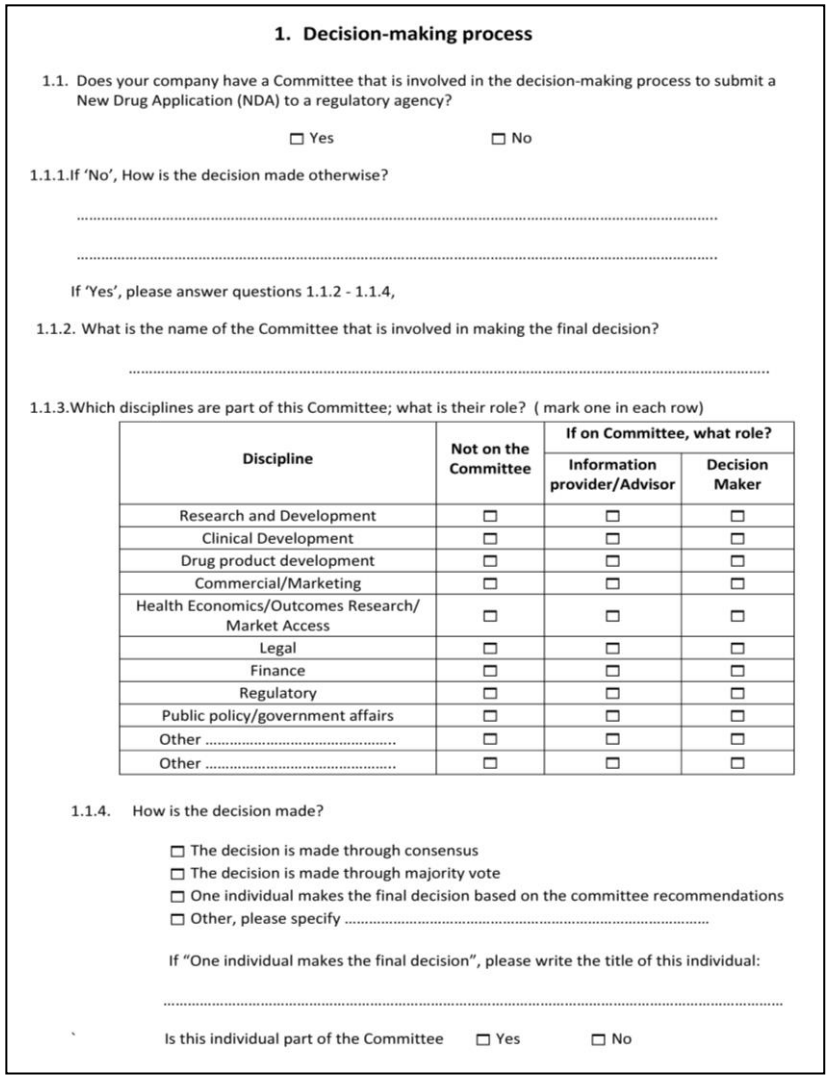
- Question 1.1.3 regarding the company departments and disciplines which are part of the final decision-making Committee as well as their role (information provider/advisor or decision maker)

The following issue was unique to the regulatory authority questionnaire:

- Question 1.3 regarding the measures that are in place to help build quality into this decision-making process

The company and regulatory authority questionnaires are shown in Figure 3.1 and Figure 3.2 respectively.

**Figure 3.1 The pharmaceutical company regulatory questionnaire**



## 1. Decision-making process

1.1. Does your company have a Committee that is involved in the decision-making process to submit a New Drug Application (NDA) to a regulatory agency?

☐ Yes ☐ No

1.1.1. If 'No', How is the decision made otherwise?

.....

.....

If 'Yes', please answer questions 1.1.2 - 1.1.4,

1.1.2. What is the name of the Committee that is involved in making the final decision?

.....

1.1.3. Which disciplines are part of this Committee; what is their role? ( mark one in each row)

| Discipline | Not on the Committee | If on Committee, what role? | |
|---|---|---|---|
| | | Information provider/Advisor | Decision Maker |
| Research and Development | ☐ | ☐ | ☐ |
| Clinical Development | ☐ | ☐ | ☐ |
| Drug product development | ☐ | ☐ | ☐ |
| Commercial/Marketing | ☐ | ☐ | ☐ |
| Health Economics/Outcomes Research/ Market Access | ☐ | ☐ | ☐ |
| Legal | ☐ | ☐ | ☐ |
| Finance | ☐ | ☐ | ☐ |
| Regulatory | ☐ | ☐ | ☐ |
| Public policy/government affairs | ☐ | ☐ | ☐ |
| Other ..... | ☐ | ☐ | ☐ |
| Other ..... | ☐ | ☐ | ☐ |

1.1.4. How is the decision made?

☐ The decision is made through consensus
☐ The decision is made through majority vote
☐ One individual makes the final decision based on the committee recommendations
☐ Other, please specify .....

If "One individual makes the final decision", please write the title of this individual:

.....

Is this individual part of the Committee ☐ Yes ☐ No

1.2. Which statement describes best the decision-making system at your company? (Mark one)

| System type | Mark if used |
|---|---|
| **Qualitative System:** Our internal system for the final decision to submit a NDA is a purely qualitative based on internal experts or management making a "gut decision". The final decision will be exercised based on Expert Judgment and company experience | ☐ |
| **Quantitative system:** Our internal system for the final decision to submit a NDA is a fully quantitative which brings together the various key data for the decision (including Clinical (BR), CMC (Manufacturing), Health Outcomes) and contributing opinions . The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment. | ☐ |
| **Other, please describe below:** ..... ..... | ☐ |

1.3. Are there formal assessments in place to periodically measure the quality of the decision-making process?

☐ Yes ☐ No ☐ Not sure

If 'Yes', please select which measures are used and who carries them out (tick all that apply)

| Measure of quality of the decision | Who is it measured by? | |
|---|---|---|
| | Internal team | External group |
| Audit of the decision process | ☐ | ☐ |
| Feedback from stakeholders on the decision-making process | ☐ | ☐ |
| Re-evaluation based on the outcome | ☐ | ☐ |
| Other, please specify..... | ☐ | ☐ |

## 2. Decision-making frameworks

*A Framework is a set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision.*

2.1. Do you have a framework in place that forms the basis of the decision to submit a NDA to a regulatory agency?

☐ Yes ☐ No

If "No", please answer 2.1.1-2.1.2

2.1.1. Why a formal framework is not used? (Mark all that apply)

- ☐ Lack of a validated framework
- ☐ Poor acceptance by staff
- ☐ Lack of knowledge/training on decision making in general
- ☐ Benefits of a framework not apparent
- ☐ Resource/administrative limitation
- ☐ Others, please specify……

2.1.2. Are there plans to adopt a formal framework in the next two years?

☐ Yes ☐ No ☐ Not sure

If 'Yes', please answer 2.1.3-2.1.4

2.1.3. Which statement best describes the nature of your framework?

- ☐ The framework has been formally defined and codified
- ☐ The framework is informal, by custom and practice (i.e. it has never been clearly agreed but over time has become the process)

If "The framework has been formally defined and codified", how has the formal framework been developed?

☐ Internally ☐ Externally

2.1.4. In your view, which practices of a Framework for Good Decision Making have been incorporated into your company's formal framework?

| Practice | Practice incorporated | Practice not incorporated | If 'not incorporated' tick if you consider it relevant |
|---|---|---|---|
| Have a systematic, structured approach to decision making | ☐ | ☐ | ☐ |
| Assign clear roles and responsibilities (decision makers, advisors, contributors) | ☐ | ☐ | ☐ |
| Consider uncertainty and examine alternative solutions | ☐ | ☐ | ☐ |
| Assign values and relative importance to decision criteria | ☐ | ☐ | ☐ |
| Re-evaluate as new information becomes available | ☐ | ☐ | ☐ |
| Evaluate both internal and external influences/biases | ☐ | ☐ | ☐ |
| Apply a structured approach to aid transparency and provide a record trail | ☐ | ☐ | ☐ |
| Perform impact analysis and effectively communicate the basis of the decision | ☐ | ☐ | ☐ |

2.2. Does your company use formal frameworks for other decisions-making processes listed below?

| Decision | Tick if a formal framework is used |
|---|---|
| Benefit-risk Assessment | ☐ |
| Product Portfolio (go/no-go decisions) | ☐ |
| Strategic Decisions | ☐ |
| Other…….. | ☐ |

## 3. Challenges

3.1. **In your opinion, how often do these biases occur at your organisation and/or influence the decision-making process** (tick one in each row)

| Bias | Degree of frequency | | | |
|---|---|---|---|---|
| | Never | Sometimes | Frequently | Always |
| **Action-oriented biases: drive us to take action less thoughtfully than we should. Characterised by:**<br>• Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling<br>• Planning without factoring in competitive responses | ☐ | ☐ | ☐ | ☐ |
| **Interest biases arise in the presence of conflicting incentives, including nonmonetary and even purely emotional ones. Characterised by:**<br>• Misaligned individual incentives<br>• Inappropriate attachments<br>• Misaligned perception of corporate goals/hierarchy | ☐ | ☐ | ☐ | ☐ |
| **Pattern-recognition biases lead us to recognize patterns even where there are none.**<br>• Confirmation bias to seek out information that supports a favoured decision<br>• Generalizing based on examples that are recent or memorable<br>• False analogies—especially, misleading experiences.<br>• Evaluating a plan or proposal based on the track record of the person presenting it, more than on the facts supporting it | ☐ | ☐ | ☐ | ☐ |
| **Stability biases create a tendency toward inertia in the presence of uncertainty.**<br>• Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. | ☐ | ☐ | ☐ | ☐ |

**Figure 3.2 The regulatory authority questionnaire**

### 4. Personal Perceptions

The following questions ask for your personal opinion. It is hoped that the responses will help generate ideas for discussions at the Syndicate Sessions at the CIRS Workshops **"Exploring Approaches to Decision Making"** in June 2015.

4.1. In your opinion, what are the top three hurdles for making a good quality decision? What are the possible solutions?

| Major Hurdle | Possible solutions |
|---|---|
| 1…… | 1…… |
| …… | …… |
| 2…… | 2…… |
| …… | …… |
| 3…… | 3…… |
| …… | …… |

4.2. Do you think that the decision-making process for submitting a dossier at your company could be improved?

☐ Yes ☐ No

4.3. Do you believe there are ways of measuring the quality of decision-making process?

☐ Yes ☐ No

If 'Yes', please describe:

……

……

4.4. Final Comments: Do you have any comments you would like to provide with regard to this topic or believe would be of value to discuss at the upcoming CIRS Workshop?

……

……

……

### 1. Decision-making process

1.1. Does your agency have a Committee that is involved in the decision-making process to approve or reject a New Drug Application (NDA)?

☐ Yes ☐ No ☐ Sometimes

1.1.1. If 'No' or 'Sometimes', How is the decision made otherwise?

……

……

If 'Yes', please answer questions 1.1.2 - 1.1.3,

1.1.2. What is the name of the Committee that is involved in making the final decision?

……

1.1.3. How is the decision made?

☐ The decision is made through consensus

☐ The decision is made through majority vote

☐ One individual makes the final decision based on the committee recommendations

☐ Other, please specify ……

If "One individual makes the final decision", please write the title of this individual:

……

Is this individual part of the Committee ☐ Yes ☐ No

1.2. Which statement describes best the decision-making system at your agency? (Mark one)

| System type | Mark if used |
|---|---|
| **Qualitative System:** Our internal system for the final decision to approve or reject a NDA is a purely qualitative based on internal experts making an intuitive decision ("gut decision"). The final decision will be exercised based on Expert Judgment and agency experience | ☐ |
| **Quantitative system:** Our internal system for the final decision to approve or reject a NDA is a fully quantitative which brings together the various key data for the decision (including Clinical (Benefit-Risk), CMC (Manufacturing), Health Outcomes) and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment. | ☐ |
| **Other, please describe below:** …… …… | ☐ |

1.3. What measures are in place to help build quality into this decision making process? (mark all that apply)

- ☐ Standard Operating Procedures
- ☐ External independent advisory committees
- ☐ Internal quality policy
- ☐ Internal peer review of decisions
- ☐ Dedicated quality department
- ☐ Other, please specify……

1.4. Are there formal assessments in place to periodically measure the quality of the decision-making process?

☐ Yes ☐ No ☐ Not sure

If 'Yes', please select which measures are used and who carries them out (mark all that apply)

| **Measure of quality of the decision** | **Who is it measured by?** | |
|---|---|---|
| | Internal team | External group |
| Audit of the decision process | ☐ | ☐ |
| Feedback from stakeholders on the decision-making process | ☐ | ☐ |
| Re-evaluation based on the outcome | ☐ | ☐ |
| Other, please specify…… | ☐ | ☐ |

## 2. Decision-making frameworks

*A Framework is a set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision.*

2.1. Do you have a framework in place that forms the basis of the decision to approve or reject a NDA?

☐ Yes ☐ No

If "No", please answer 2.1.1-2.1.2

2.1.1.Why a formal framework is not used? (Mark all that apply)

- ☐ Lack of a validated framework
- ☐ Poor acceptance by staff
- ☐ Lack of knowledge/training on decision making in general
- ☐ Benefits of a framework not apparent
- ☐ Resource/administrative limitation
- ☐ Others, please specify……

2.1.2. Are there plans to adopt a formal framework in the next two years?

☐ Yes ☐ No ☐ Not sure

If 'Yes' to question 2.1., please answer 2.1.3-2.1.4

2.1.3.Which statement best describes the nature of your framework?

- ☐ The framework has been formally defined and codified
- ☐ The framework is informal, by custom and practice (i.e. it has never been clearly agreed but over time has become the process)

If "The framework has been formally defined and codified", how has the formal framework been developed?

☐ Internally ☐ Externally

2.1.4. In your view, which practices of a Framework for Good Decision Making have been incorporated into your agency's formal framework?

| **Practice** | **Practice incorporated** | **Practice not incorporated** | **If 'not incorporated' tick if you consider it relevant** |
|---|---|---|---|
| Have a systematic, structured approach to aid decision making (consistent and predictable) | ☐ | ☐ | ☐ |
| Have a systematic, structured approach to aid transparency and provide a record trail | ☐ | ☐ | ☐ |
| Assign clear roles and responsibilities (decision makers, advisors, contributors) | ☐ | ☐ | ☐ |
| Consider uncertainty and examine alternative solutions | ☐ | ☐ | ☐ |
| Assign values and relative importance to decision criteria | ☐ | ☐ | ☐ |
| Re-evaluate as new information becomes available | ☐ | ☐ | ☐ |
| Evaluate both internal and external influences/biases | ☐ | ☐ | ☐ |
| Perform impact analysis and effectively communicate the basis of the decision | ☐ | ☐ | ☐ |

2.2. Does your agency use formal frameworks for other decisions-making processes listed below?

| **Decision** | **Tick if a formal framework is used** |
|---|---|
| Benefit-risk Assessment | ☐ |
| Post-approval changes to label/indication | ☐ |
| Clinical trial approvals | ☐ |
| Other…… | ☐ |

## 3. Challenges

3.1. **In your opinion, how often do these biases occur at your organisation and/or influence the decision-making process** (tick one in each row)

| Bias | Degree of frequency | | | |
|---|---|---|---|---|
| | Never | Sometimes | Frequently | Always |
| **Action-oriented biases: drive us to take action less thoughtfully than we should. Characterised by:**<br>• Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling | ☐ | ☐ | ☐ | ☐ |
| **Interest biases arise in the presence of conflicting incentives and even purely emotional ones. Characterised by:**<br>• Misaligned individual incentives<br>• Inappropriate attachments | ☐ | ☐ | ☐ | ☐ |
| **Pattern-recognition biases lead us to recognize patterns even where there are none.**<br>• Confirmation bias to seek out information that supports a favoured decision<br>• Generalizing based on examples that are recent or memorable<br>• False analogies—especially, misleading experiences. | ☐ | ☐ | ☐ | ☐ |
| **Stability biases create a tendency toward inertia in the presence of uncertainty.**<br>• Preference for the status quo in the absence of pressure to change it<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. | ☐ | ☐ | ☐ | ☐ |

## 4. Personal Perceptions

The following questions ask for your personal opinion. It is hoped that the responses will help generate ideas for discussions at the Syndicate Sessions at the CIRS Workshops **"Exploring Approaches to Decision Making"** in June 2015.

4.1. In your opinion, what are the top three hurdles for making a good quality decision? What are the possible solutions?

| Major Hurdle | Possible solutions |
|---|---|
| 1…… | 1…… |
| 2…… | 2…… |
| 3…… | 3…… |

4.2. Do you think that the decision-making process for approving or rejecting a NDA could be improved?

☐ Yes ☐ No

4.3. Do you believe there are ways of measuring the quality of decision-making process?

☐ Yes ☐ No

If 'Yes', please describe:

……

……

4.4. Final Comments: Do you have any comments you would like to provide with regard to this topic or believe would be of value to discuss at the upcoming CIRS Workshop?

……

……

……

……

**Study participants**

The study participants were selected based on experience and knowledge using purposive sampling, from those holding senior positions and having at least five years of experience in a managerial position within major international pharmaceutical companies and regulatory authorities. The finalised industry questionnaire was sent to senior management in 24 international pharmaceutical companies with large research and development (R&D) budget (>1bln USD), thereby reflecting their innovativeness and the number of submission decisions made (PharmExec, 2014). The 24 companies were selected based on being members of the Centre for Innovation in Regulatory Science (CIRS) research programmes to ensure timeliness and maximise the response rate (CIRS, 2018).

The finalised authority questionnaire was sent to senior executives within 14 major regulatory authorities. The focus was on major authorities, particularly those classified as Stringent Regulatory Authorities (SRAs) by the World Health Organisation (WHO) (2017) and which have a working relationship with CIRS (2018). To improve the representation of the sample, participants from various-sized organisations and geographical locations were invited including Australia, Asia, Europe and North America.

The study was designed as a cross-sectional study, aimed at collecting data during a period of two months to ensure an objective comparison of results. The study participants were contacted via e-mail in May 2015 and were invited to take part in the study and, if agreed, they were subsequently asked to complete the questionnaire and return by June 2015. The non-responders to the questionnaire were contacted via email, two weeks following the initial contact, in order to solicit further responses.

**Data processing and analysis**

The responses from each questionnaire were tabulated and analysed using descriptive statistics to draw a comparison between these two stakeholders. Data were expressed as percentage of number of responders for each question. All free text responses and comments were coded using processes guided by established methods, including grounded theory (Wertz, 2011) and constant comparison method (Boeije, 2012). In grounded theory, inductive, yet systematic analytic strategies are applied to qualitative data to conceptually analyse personal experiences. The constant comparative method involves constantly comparing and contrasting concepts to inform relationships between phrases and themes expressed by the study participants. Content analysis was employed for free text responses and comments to identify emerging themes. Ranking was used where applicable.

Due to confidentiality reasons, only aggregated results are shown and no data that indentifies an individual authority or company are reported. No statistical tests were planned or conducted as this study was designed to be exploratory with an aim to provide a qualitative assessment of the objectives as well as to generate premises for further research.

## RESULTS

This study focused on the final decision for companies to submit an NDA or for regulatory authorities to approve or reject an NDA. The key results are presented in four parts:

- Part I – Decision-making practices
- Part II – Decision-making frameworks
- Part III – Measures for assessing quality of decision making
- Part IV – Challenges and solutions for making quality decisions.

### Characteristics of the study participants

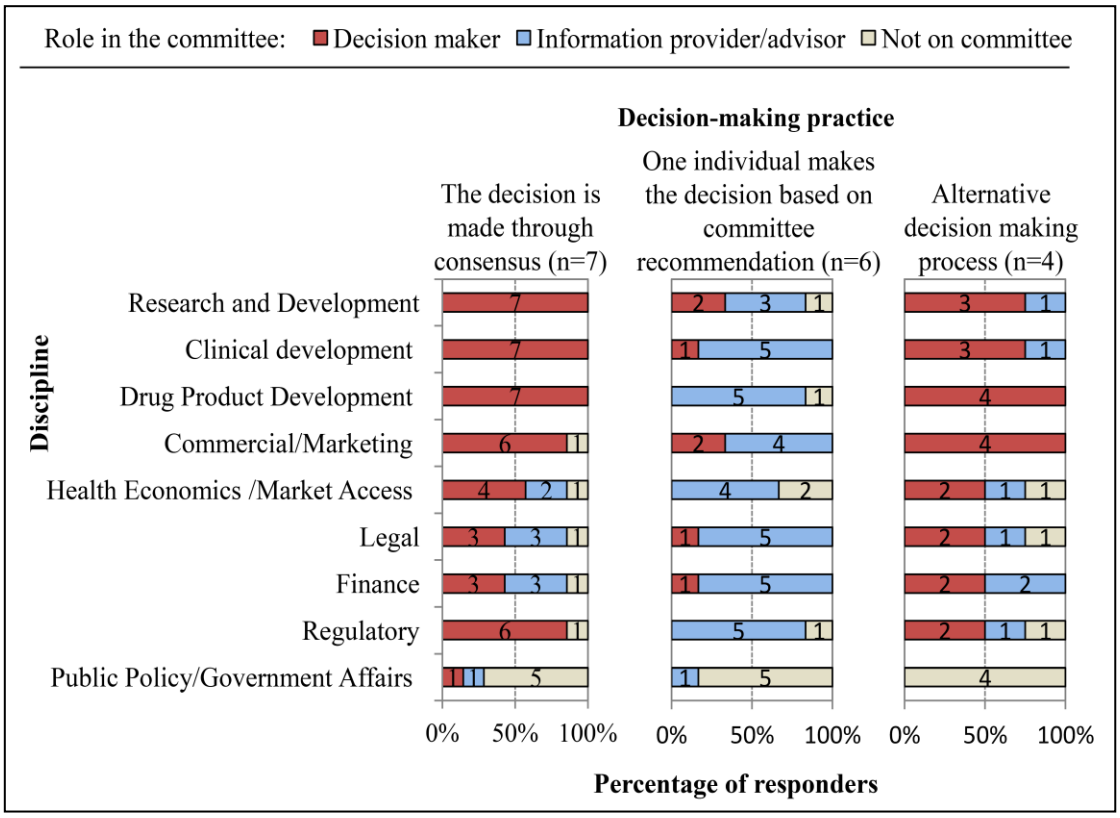
Seventeen out of 25 companies (68%) responded, namely Abbvie, Actelion, Astellas, AstraZeneca, Bayer, Biogen, Celgene, Daiichi Sankyo, Eisai, Eli Lilly, F. Hoffmann-La Roche, GlaxoSmithKline, Janssen, NovoNordisk, Pfizer, Sanofi Aventis and Takeda. Out of the 17, 15 (88%) were in the top 25 companies by R&D expenditure and all 17 had R&D budgets of more than 1bln USD (PharmExec, 2014). Ten out of the 14 regulatory authorities (71%) responded, with 8 out of the 10 being classified as SRAs and included the European Medicines Agency, national authorities from the European member states (Denmark, France, Sweden and UK using the national procedure; Netherlands using the centralised procedure), US Food and Drug Administration, Therapeutics Goods Administration of Australia, Health Canada and the Health Sciences Authority of Singapore. These regulatory authorities and pharmaceutical companies formed a diverse group, with representation from a mix of geographical locations and affiliations.

### Part I – Decision-making practices

All of the companies (17) indicated that they have a committee that is involved in decision making, but the way that the final decision is made varies. Seven companies reported that their decision-making process is through consensus, whereas for six companies an individual makes the final decision based on the committee's recommendations; for five out of six of the companies, this individual sits on the committee. Four companies indicated that a different practice was used, such as having the decision made by two co-chairs or employing two committees.

In considering the disciplines that are part of the committee and their role (Figure 3.3), the seven companies that made the decision through consensus all indicated that there were multiple decision makers on the committee. The most common decision maker disciplines were R&D, clinical development, drug/product development, commercial/marketing and regulatory. For the six companies in which one individual makes the decision based on the committee's recommendation, the majority of disciplines play the role of an information provider or advisor and the most frequent decision maker disciplines were R&D, commercial/marketing, legal, finance and clinical development. Ten companies specified a total of 14 other disciplines; for example statistics (2) and manufacturing (2) as information providers/advisors and presidents or Chief Executive Officer (CEO) (3) as decision makers.

**Figure 3.3 The decision-making committee and the disciplines within the 17 companies and their role by the type of the decision-making practice**




Similarly, most authorities (nine out of 10) utilised a committee in their decision making. For the nine authorities, four used an internal committee to inform all decisions and five used an external advisory committee to provide advice on specific questions arising during the review and to help inform this decision when requested. For the majority of authorities (six out of nine), the decision was made by one individual based on recommendations from the review team and advisory committee. Two authorities were found to make the decision through a majority vote and one authority indicated that the decision is reached through consensus.

Half of the companies (nine out of 17) reported that they were using a quantitative decision-making system, followed by qualitative system (4) and a combination of both (4). Among the authorities, the same number (4) were using a combination or a quantitative, followed by a qualitative system (2).

**Part II – Decision-making frameworks**

Most companies (11 out of 17) and regulatory authorities (8 out of 10) had a framework in place that formed the basis of the decision to submit or to approve or reject an NDA. Seven out of the 11 companies indicated that their framework has been formally defined and codified and in half of the cases (6) it has been developed internally. Four out of the 11 companies stated that the framework was informal, by custom and practice. All of the authorities that had a framework (8) indicated that it was formally defined and codified. Four of these developed their frameworks internally, two externally and two used a mixture of internal and external inputs.

Six companies and two authorities stated that they did not have a framework in place. The main reasons selected by companies were lack of a validated framework (4), benefits of a framework not apparent (4) and lack of knowledge on decision making in general (3). The two authorities that did not have a framework indicated that it was because the benefits of a framework were not apparent. Out of the six companies that did not have a framework, three indicated that they were not sure whether there were plans to adopt a framework in the next two years, whereas three companies indicated that there were no plans. Similarly, the two authorities without a framework also indicated that there were no plans to adopt one in the next two years.

The QDMPs selected by the seven companies and authorities with a formal framework are shown in Table 3.4. The practices that were less frequently incorporated by both groups were assigning values and relative importance to decision criteria; and performing impact analysis and effectively communicating the basis of the decision. The practice of evaluating both internal and external influences/biases produced the most disparity between authorities and companies, with companies having this practice more frequently incorporated and considered more relevant compared to authorities. Only three companies and none of the authorities indicated that they had all eight practices incorporated into their framework. Nevertheless, all the QDMPs which were not incorporated by the authorities and companies, were still considered relevant.

**Table 3.4 The Quality Decision-Making Practices (QDMPs) incorporated into formal regulatory frameworks**

| QDMP | QDMP incorporated into organisation's formal framework? | | If QDMP not incorporated, is it considered relevant? | |
|---|---|---|---|---|
| | Companies (n=7) | Authorities (n=8) | Companies | Authorities |
| 1. Have a systematic, structured approach to aid decision making (consistent and predictable) | 100% | 88% | - | 100% (n=1) |
| 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) | 86% | 100% | 100% (n=1) | - |
| 3. Consider uncertainty and examine alternative solutions | 100% | 100% | - | - |
| 4. Assign values and relative importance to decision criteria | 57% | 25% | 75% (n=4) | 83% (n=6) |
| 5. Re-evaluate as new information becomes available | 100% | 88% | - | 100% (n=1) |
| 6. Evaluate both internal and external influences/biases | 86% | 50% | 100% (n=1) | 75% (n=4) |
| 7. Apply a structured approach to aid transparency and provide a record trail | 100% | 100% | - | - |
| 8. Perform impact analysis and effectively communicate the basis of the decision | 57% | 38% | 75% (n=4) | 80% (n=5) |

Only companies and authorities that had a formal framework (as opposed to by "custom and practice") are included.
n = total number of responders

**Part III – Measures for assessing quality of decision making**

Interestingly, seven of 17 companies, but only two of 10 authorities reported that they had formal assessments in place to periodically measure the quality of their decision making. All of the companies (7) carried out a re-evaluation based on the outcome; five collected feedback from stakeholders and four carried out an audit of the decision making. The majority of these assessments (13) were carried out by an internal team while two were carried out by an external group. Conversely, of the two authorities that reported having formal assessments, both carried out an audit of the decision making and collected feedback from stakeholders and one carried out a re-evaluation based on the outcome. The assessments were carried out by a mix of external and internal groups, but only four companies and one authority carried out all three formal assessment activities.

All companies (17) and seven out of eight authorities (two did not respond) believed that there were ways of measuring the quality of decision making even though in general, these were not always incorporated. The companies suggested measures which related to both evaluating the actual practices but also the outcomes, whereas authorities identified measures relating to the practices of decision making only. The most frequent measure suggested by companies was assessing the outcomes, such as achieving the label that was expected at submission. Authorities quoted most frequently assessing adherence against validated standard or guideline for decision making (Table 3.5).

Finally, authorities indicated that they had other measures in place in order to help build quality into their decision-making process, such as standard operating procedures (9), internal peer review of decisions (8) external independent advisory committees (7), internal quality policy (6), as well as a GRevP system (3). Nevertheless, none of the authorities had a dedicated quality department.

**Part IV – Challenges and solutions for making quality decisions**

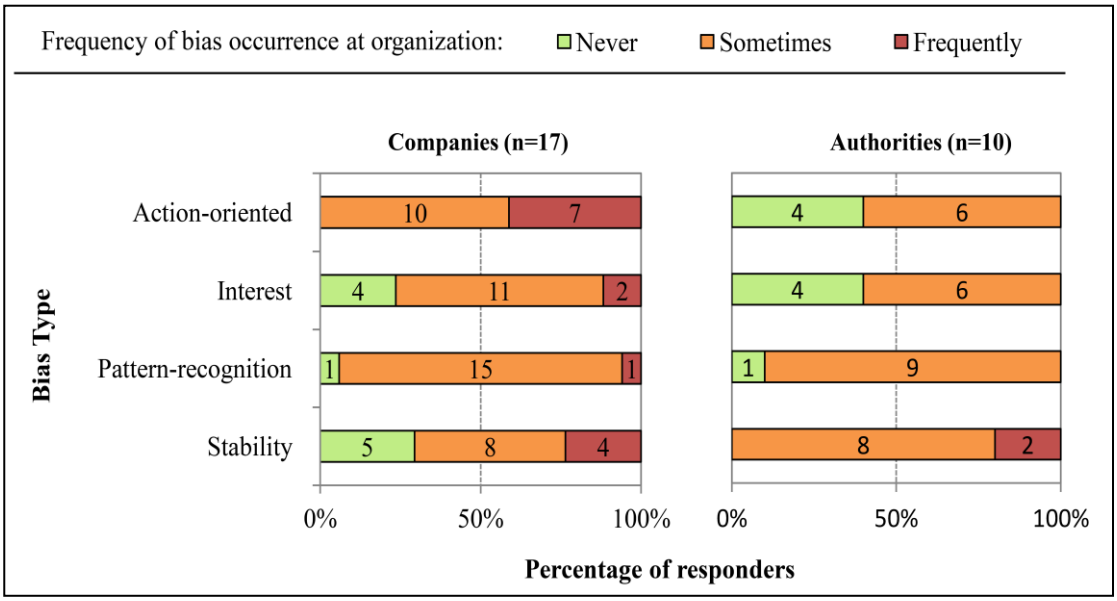
Both companies and authorities considered the occurrence of biases within their organisation or their influence on the decision making as pertinent. Nevertheless, the perceived frequency of their recognition varied for both groups according to the type of bias (Figure 3.4). For companies, the action-oriented bias, characterised by overconfidence and intuition, was perceived as the most frequently occurring (or influencing the decision making). For authorities, the action-oriented bias was considered less relevant and instead the stability bias, characterised by the preference for the status quo, was perceived as the most commonly occurring bias.

**Table 3.5 Key measures proposed by companies and regulatory authorities for assessing the quality of decision making**

| Companies (n=17) | Authorities (n=7) |
|---|---|
| 1. Assess the outcomes such as obtaining a first cycle approval, achieving a label decided at submission stage, short time to submission and approval (n=11) | 1. Assess adherence against validated standard or guideline for decision making (n=3) |
| 2. Receive formal feedback from internal and external stakeholder (n=6) | 2. Review the consistency of the decision-making practices within an organisation (n=2) |
| 3. Identify signs of bias (n=4) | 3. Assess the degree of clarity and transparency in decision making (n=2) |
| 4. Evaluate adherence to the decision-making practices (n=3) | 4. Review that all evidence (positive and negative) has been considered (n=2) |
| 5. Review lessons learned including best practices and project insights (n=4) | 5. Formally assess internal stakeholders' evaluation practices (n=1) |

n = number of responders

**Figure 3.4 Types of biases and the perceived frequency at which they occur within a company or regulatory authority during their decision making**

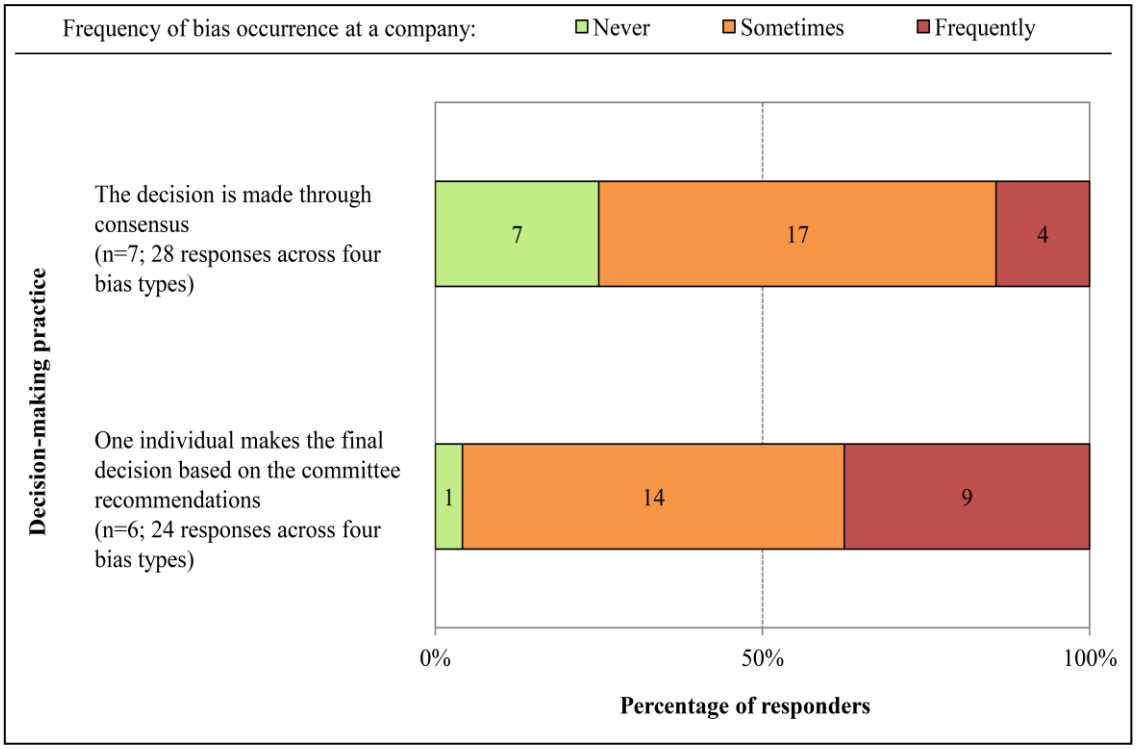



n = number of responders

The occurrence or influence of biases also varied depending on the type of the decision-making practice within a company, where having one individual make the decision increased the perceived frequency of bias compared to consensus decision making (Figure 3.5). Similarly, not having a framework or having an informal framework correlated with increased reporting of biases, compared to having a formally defined and codified framework (Figure 3.6). Nevertheless, these differences were not observed for authorities, which may be due to the low 'n' numbers in the 'consensus/majority group' (3) as well as 'informal framework group' (1).

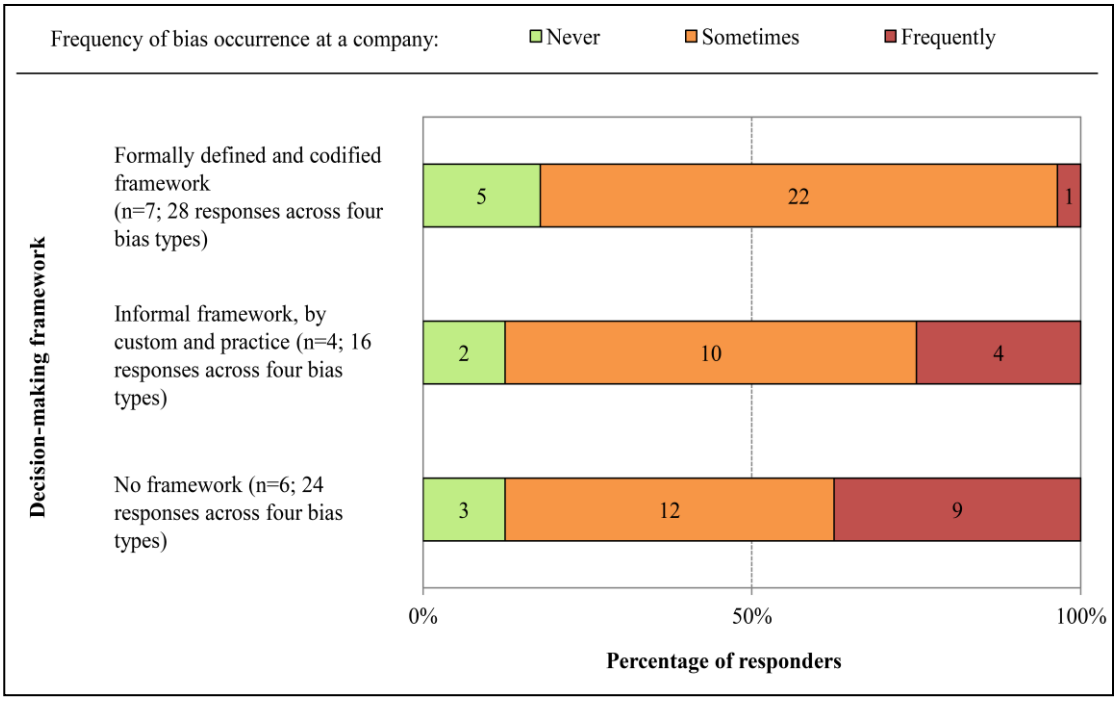
Interestingly, all companies (17) and most regulatory authorities (nine out of 10; one did not respond) believed that the decision making within their organisations could be improved. The major hurdle for making quality decisions identified by companies related to the presence of action oriented-biases such as excessive optimism and overconfidence. Similarly, the main barrier reported by authorities was the presence of internal and external biases, such as the stability bias (Table 3.6).

**Figure 3.5 The frequency at which biases (all four types consolidated) are perceived to occur within a company by the type of the decision-making practice**




n = number of responders

**Figure 3.6 The frequency at which biases (all four types consolidated) are perceived to occur within a company by the type of decision-making framework**




n = number of responders

**Table 3.6 Key hurdles for making quality regulatory decisions**

| Companies (n=17) | Authorities (n=10) |
|---|---|
| 1. Action oriented bias; excessive optimism and overconfidence (n=11) | 1. Internal and external biases (n=6) |
| 2. Difficult access to information or unavailability of data (n=10) | 2. Inconsistent review or evaluation practices/tools (n=5) |
| 3. Internal misalignment in organisation and the presence of competing interests (n=9) | 3. Difficult access to information or unavailability of data (n=4) |
| 4. Lack of a validated framework for decision making (n=7) | 4. Time pressure (n=4) |
| 5. Poor assessment of uncertainty and strength of evidence (n=7) | 5. Lack of knowledge with regard to decision making concept (n=3) |
| 6. Time pressure (n=6) | 6. Reluctance to discuss uncertainties or value judgments (n=3) |
| 7. Historical bias resulting from previous experiences (n=5) | 7. Resource constraints (n=2) |

n = number of responders

The majority of the proposed solutions reported by companies related to establishing or implementing a structured decision-making framework or methodology that will require values, preferences and uncertainty to be made explicit (Table 3.7) as well as to incorporate the views from all the relevant stakeholders including patients. Authorities also recommended this solution, as well as ensuring transparency and information access.

**Table 3.7 Key solutions proposed by companies and authorities for overcoming the hurdles for making quality decisions**

| Companies (n=17) | Authorities (n=10) |
|---|---|
| 1. Establish or implement a structured decision-making framework or method that requires values/preferences/uncertainty to be made explicit (n=10) | 1. Ensure transparency and information access (n=5) |
| 2. Multi-stakeholder inclusion - incorporate the views from all the relevant stakeholders including patients (n=10) | 2. Establish or implement a structured decision-making framework or method that requires values/preferences/uncertainty to be made explicit (n=4) |
| 3. Create an environment that encourages dissenting opinions and challenging ideas (n=9) | 3. Education on decision-making concepts/theory (n=4) |
| 4. Ensure transparency and information access (n=6) | 4. More formal review of the decision-making practices as well as the decisions (both positive and negative) (n=4) |
| 5. Have a robust system which focuses on evidence and facts (n=5) | 5. Create an environment that encourages dissenting opinions and challenging ideas (n=2) |
| 6. Education on decision-making concepts/theory (n=3) | 6. Have a robust system which focuses on evidence and facts (n=2) |
| 7. More formal review of the decision-making practices as well as the decisions (both positive and negative) (n=2) | 7. Multi-stakeholder inclusion - incorporate the views from all the relevant stakeholders including patients (n=2) |

n = number of responders

**DISCUSSION**

Quality decision making is critical to successful development and the regulatory review to ensure patients' access to innovative medicines. The benefits of making quality choices have the potential of influencing all stakeholders and interestingly decision making has recently been linked to improving R&D productivity within pharmaceutical companies (Smietana et

al., 2014). This study investigated and identified the diversity of current regulatory authority and pharmaceutical company practices and perspectives regarding quality decision-making processes and measures.

**Decision-making systems and committees**

The results revealed that companies and authorities use a mixture of decision-making systems and while companies had a preference for a quantitative approach, authorities use a quantitative or a combination of methodologies. This finding may relate to the fact that many organisations are now moving towards quantitative or semi-quantitative models for other decision-making practices such as formalised benefit-risk assessment, (Walker et al., 2014; Pignatti et al., 2015) and may therefore suggest a general move towards more structured decision making.

All companies and most authorities utilise committees when making decisions. Whilst companies and authorities tend to utilise internal committees and external advisory committees respectively, these are important vehicles for supporting the decision making and ensuring that all stakeholders' viewpoints are included. Nevertheless, previous studies have shown that biases can potentially influence the robustness of decision making in a committee setting and these should be countered through structured deployment of de-biasing techniques (McIntyre et al., 2012; Marangi et al., 2014; Smietana et al., 2014). Further research into decision making within regulatory authorities and company committees could uncover additional insights as well as identifying ways for minimising the impact of biases on decision making.

Companies and authorities use different approaches to arrive at the final decision. The majority of companies use consensus decision making or have one person make the decision based on committee recommendation, whereas most authorities use individual decision-making approaches. Although each method has advantages, such as speed for individual decision making and inclusiveness for group decision making, this study showed that both are affected by varying degrees of bias. Indeed, company results showed that individual decision making correlated with a higher frequency of perceived bias compared to consensus decision making. Although this study only looked at the final decision-making practices to either submit or approve an NDA, the process that leads up to this decision is of equal importance. It is therefore crucial that a system of checks and balances exists to ensure that the decision making is robust and transparent all the way through, whilst accounting for all disciplines and helping to minimise the influence of biases on the final decision.

**Decision-making frameworks and practices**

Although most organisations studied have a decision-making framework in place, the majority of companies do not have a formally defined and codified framework, whereas authorities do. Nonetheless, most companies and authorities with a formal framework incorporated most of the QDMPs including: having a systematic, structured approach to aid decision making; assigning clear roles and responsibilities; considering uncertainty and examining alternative solutions; re-evaluating as new information becomes available; and applying a structured approach to aid transparency and provide a record trail.

The practice of evaluating both internal and external biases was incorporated more widely by companies than authorities. However, both authorities and companies listed the influence of biases as the biggest hurdle to quality decision making and consequently the wider incorporation of this practice through various de-biasing methods could help address this issue. Additionally, this study identified that different types of biases are more relevant to both groups, with action-oriented biases (characterised by overconfidence) perceived as more frequently occurring within companies and stability biases (characterised by the preference for status quo) arising most commonly within authorities, suggesting that the authorities are perhaps more conservative in their approach to decision making.

The two practices which were incorporated by the lowest number of companies and authorities were assigning values and relative importance to decision criteria and performing impact analysis and effectively communicating the basis of the decision. Interestingly, companies and authorities proposed making decision values, preferences and uncertainty more explicit as a top solution for overcoming the hurdles for making quality decisions and this solution could be implemented by incorporating the two above practices into the organisations' formal frameworks. Furthermore, all of the QDMPs which were not incorporated by the authorities and companies were generally considered relevant, thereby emphasising the appropriateness of the QDMPs as a basis for a framework for both authorities and companies. It should be nevertheless noted that although these eight QDMPs developed by Donelan and colleagues (2015), were considered fit for purpose, minor changes were made to the wording of the QDMPs as a result of the comments and discussions following the conduct of this study. This was to ensure the QDMPs are clear and relevant and to split QDMPs which contained two items (original QDMP 3 and 8). Changes were also made to the order, thereby ensuring the QDMPs are listed in an accurate chronological order relative to a decision-making process (Table 3.8).

**Table 3.8 Modifications made to the wording and order of the Quality Decision-Making Practices (QDMPs)**

| Original QDMPs | Revised QDMP |
|---|---|
| 1. Have a systematic, structured approach to aid decision making (consistent and predictable) | 1. Have a systematic, structured approach to aid decision making (consistent and predictable and timely) |
| 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) | 2. Assign clear roles and responsibilities (decision makers, advisors, information providers) |
| 3. Consider uncertainty and examine alternative solutions | 5. Examine alternative solutions<br>6. Consider uncertainty |
| 4. Assign values and relative importance to decision criteria | 3. Assign values and relative importance to decision criteria |
| 5. Re-evaluate as new information becomes available | 7. Re-evaluate as new information becomes available |
| 6. Evaluate both internal and external influences/biases | 4. Evaluate both internal and external influences/biases |
| 7. Apply a structured approach to aid transparency and provide a record trail | 9. Ensure transparency and provide a record trail |
| 8. Perform impact analysis and effectively communicate the basis of the decision | 8. Perform impact analysis of the decision<br>10. Effectively communicate the basis of the decision |

n = number of responders

By contrast, some companies have informal frameworks and a number of authorities and companies do not have a decision-making framework in place at all. Upon closer inspection, the companies that had informal frameworks or no framework felt that biases occurred or influenced their organisation's decision making more frequently, compared with those with a formal framework. It is important to note that all companies and almost all authorities believed that decision making in their organisations could be improved. Both groups suggested establishing or implementing a structured decision-making framework as a main solution. Consequently, there is a need for a universal framework that will incorporate all of the QDMPs in order to enable improved decision making for both the individual and the organisation.

It has been recognised that if a group wants to improve their decision making, it needs to measure itself internally and also be able to see whether improvements have had an impact on the quality of their decision making (Kahneman, 2011). Indeed, some organisations already try and measure the quality of their decision making, but these are often based on the outcome

rather than the practices, which should be considered separately. There is consequently a need to start using suggested techniques and methodologies in order to measure the quality of decision making and to determine whether structured decisions are being made, to help identify any bias and to improve current practices (Donelan et al., 2015).

Companies and authorities also suggested other solutions for improving decision making within organisations, such as the inclusion of views from all stakeholders with an emphasis on patients. Change in organisational culture in order to encourage dissenting opinions and challenging ideas is also key, although it is then crucial that individuals are also educated and trained on the concepts, science and practice of decision making.

**SUMMARY**

- The science of decision making is well established, but evidence to date showed that there is a lack of research into the decision-making process during medicines development and the regulatory review
- The objectives of this study were to determine the current decision-making practices and methodologies for structuring and measuring the quality of decision making and the hurdles and solutions for making quality decisions within pharmaceutical companies and regulatory authorities
- Two analogous questionnaires were developed for use in this study
- Fourteen authorities and 25 companies were asked to complete the questionnaire, assessing the company decision making for submitting and the regulatory authority process for approving a new drug application
- The 68% (17 out of 25) and 71% (10 out of 14) response rate from companies and authorities, respectively, suggests interest in this topic
- From the results it appears that only 41% (seven out of 17) companies and 80% (eight out of 10) authorities had a formally defined and codified framework for structuring their decision-making processes
- Only 41% (seven out of 17) companies and 20% (two out of 10) authorities undertake formal assessments of decision making quality, but all 17 companies and 90% (nine out of 10) authorities believed that this was possible to adopt
- Moreover, all companies and 90% of the authorities (nine out of 10) believed that decision making at their organisations could be improved.
- The findings of this study support the need to further characterise and assess the practices and behaviours of individuals and organisations through medicines development and the regulatory review.

# Evaluation of the Quality of Reimbursement Decision-Making Processes in Pharmaceutical Companies and Health Technology Assessment (HTA) Agencies

## INTRODUCTION

At present, pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies concentrate on the generation and assessment of evidence regarding a medicine to ensure quality outcomes. Nevertheless, another important aspect is the process of decision making and, at present, it is not always clear how decisions, which require human judgment and interpretation, are made around the data generated or reviewed (Cole et al., 2016; Liberti et al., 2017).

An assessment of regulatory authorities and pharmaceutical company departments (Chapter 3) demonstrated that although both groups considered the Quality Decision-Making Practices (QDMPs) as important and relevant, these best practices are not always incorporated into organsiational frameworks to support the submission or approval processes for new medicines. The study also identified the key challenges as well as potential solutions for improving the quality of decision making within those organisations. It is therefore of interest to explore these themes regarding the second hurdle following the regulatory approval, namely HTA, which is used to recommend the reimbursement of medicines. Such a study could focus on the two key stakeholders involved, namely HTA agencies as well as health economic and outcomes research (HEOR) company departments.

Health technology assessment is an essential process for ensuring efficient allocation of healthcare resources. However, the current global HTA environment is diverse and increasingly multidisciplinary. As a result, projects are underway across HTA agencies, most recently through the proposal of the European Commission for European cooperation of HTA agencies (European Commission, 2018). Other projects focus on aligning the HTA decision making in partnership with pharmaceutical companies as well as regulatory authorities to ensure a more timely, efficient and effective development of medicines (Breckenridge et al., 2010, McAuslane et al., 2016). Indeed, a number of projects have focused on the various ways to improve the HTA assessment and appraisal methodologies and practices (Daniels N, 2000; Wahlster, 2016), to standardise the HTA evidence criteria (EUnetHTA, 2016) and to formalise the appraisal processes within the various HTA committees (CADTH, 2012; NICE, 2015). Some HTA agencies also have been looking to align evidentiary requirements with regulatory authorities by carrying out parallel or joint scientific advice as well as to synchronise the timing of the assessment process with the regulatory review process in order to ensure more timely and aligned decision making between stakeholders (McAuslane et al., 2016; Wang et al., 2016; Tafuri, 2018). Within companies, frameworks have been developed in order to provide better structure around evidence generation during medicines development to capture the HTA and payer requirements as well as to try and put systems in place to better

align with regulatory requirements (Dunlop et al., 2016; McAuslane et al., 2016). Nevertheless, more transparency is needed to understand human judgements and interpretations made around the data (Cole et al., 2016).

Researchers in the field of decision making and the psychology of judgment have been advocating the use of more structured approaches to decision making as well as the need to periodically measure the quality of the decision-making process in order to identify areas for improvement (Hammond et al, 1999, Kahneman, 2011). The potential merits of having a more structured decision-making process are: higher probability of favourable outcomes, improved consistency across decisions, transparency to stakeholders including patients and taxpayers, as well as decision accountability and trust (Cole et al., 2016). Consequently, there is a need to explicitly evaluate the quality of the deliberative decision-making processes within companies and HTA agencies (McAuslane et al., 2014).

The aim of this study was therefore to investigate decision-making behaviours and processes, focusing on two key specific processes to support the reimbursement of medicines; firstly, the decision-making process for evidence generation by pharmaceutical companies as well as the technology appraisal process by HTA agencies of the data submitted by companies.

The objectives were to:

- Identify current decision-making practices and procedures within the organisations
- Assess the use of different methodologies for measuring the quality of decision-making process
- Investigate views and challenges with regards to the various frameworks used for decision making.

## METHOD

### Design of the assessment tool

An assessment tool in the form of a questionnaire was developed for evaluating the decision-making practices of international pharmaceutical companies and HTA agencies. The questions were adapted from the study described in Chapter 3 on regulatory decision making of companies and regulatory authorities in order to facilitate comparisons between the two studies. The questions were designed based on previous research outcomes (Donelan et al., 2015) and following a review of the literature, which identified the key issues in decision making relating to the use of formal frameworks and techniques for structuring and measuring

the quality of the decision-making process as well as the prevalence of biases and subjective influences, as described in Chapter 1. Classification of decision-making systems, namely qualitative, quantitative as well as mixed (Table 4.1) was derived based on the regulatory questionnaire (Chapter 3) and originally adapted from a previous study assessing the need for a benefit-risk framework (Leong et al., 2013).

**Table 4.1 Definitions of health technology assessment decision-making systems to support reimbursement**

| System | Definition (companies) | Definition (agencies) |
|---|---|---|
| Qualitative | Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is purely qualitative based on experts or management making a subjective decision. The final decision will be exercised based on Expert Judgment and experience. | Our internal system for the final decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement is purely qualitative based on experts making a subjective decision. The final recommendation decision will be exercised based on Expert Judgment and experience. |
| Quantitative | Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is quantitative which brings together the various key data for the decision (such as comparative effectiveness data) and contributing opinions. The conclusion is based on the cumulative outcome from this system. | Our internal system for the final decision-making process to recommend/ restrict or not to recommend a new medicine for reimbursement is fully quantitative which brings together the various key data for the recommendation decision (such as comparative effectiveness data) and contributing opinions. The conclusion is based on the cumulative outcome from this system. |
| Mixed | Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is mixed, which takes into account various quantitative and qualitative elements. | Our internal system for the final decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement is mixed, which takes into account various quantitative and qualitative elements. |

Adapted from Leong et al., 2013

*Definition of a framework*

The definition of a *framework* was also derived from the regulatory questionnaire (Chapter 3) and was initially adapted from previous research in the area of benefit-risk assessment (Ferguson, 2008) and was defined as "a set of principles, guidelines and tools which provide a structured systematic approach to guide decision makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision."

*Quality Decision-Making Practices*

The QDMPs proposed for this study were also utilised in the regulatory study (Chapter 3). The QDMPs were developed based on the key issues in quality decision making identified through semi-structured interviews with 29 key opinion leaders from authorities and companies (Donelan et al., 2015).

**Table 4.2 The ten Quality Decision-Making Practices (QDMPs)**

| |
|---|
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) |
| 2. Assign clear roles and responsibilities (decision makers, advisors, information providers) |
| 3. Assign values and relative importance to decision criteria |
| 4. Evaluate both internal and external influences/biases |
| 5. Examine alternative solutions |
| 6. Consider uncertainty |
| 7. Re-evaluate as new information becomes available |
| 8. Perform impact analysis of the decision |
| 9. Ensure transparency and provide a record trail |
| 10. Effectively communicate the basis of the decision |

Adapted from Donelan et al., 2015

*Biases*

The different types of cognitive biases that occur during decision making were also investigated. Four main groups of biases adapted from previous research (Lovallo and Sibony, 2010) (Table 4.3) were proposed for this study to underpin the evaluation of bias perception within companies and agencies. This typology was chosen previously for the regulatory study (Chapter 3) as it focuses on those biases that occur most frequently and that have the largest impact on organisational and business decisions.

*Pilot study*

A pilot phase was designed with the aim of content validation of the initial questionnaire. The pilot study was conducted with two invited companies and two HTA agencies that agreed to complete the questionnaire followed by a short feedback form. The following feedback questions were asked:

1. In general, how did you find the questionnaire?
2. Is the format of the questionnaire clear? (Yes/No) If no, please comment.
3. Is the language used in the questionnaire clear? (Yes/No) If no, please list any terms or questions which were unclear.
4. Are there any questions you found difficult to answer? (Yes/No) If yes, please provide the question number and comment.

**Table 4.3 Characteristics and definitions of biases**

| Bias type | Definition | Characteristics |
|---|---|---|
| Action-oriented | A bias that drives us to take action less thoughtfully than we should | • Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling |
| Interest | A bias that arises in the presence of conflicting incentives, including emotional ones | • Misaligned individual incentives<br>• Inappropriate attachments<br>• Misaligned perception of corporate goals/hierarchy |
| Pattern-recognition | A bias that leads us to recognise patterns even where there are none | • Confirmation bias to seek out information that supports a favoured decision<br>• Generalising based on examples that are recent or memorable<br>• Evaluating a plan or proposal based on the track record of the person presenting it, more than on the facts supporting it |
| Stability | A bias that creates a tendency toward inertia in the presence of uncertainty | • Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. |

Adapted from Lovallo and Sibony, 2010

*Structure and content of the questionnaires*

The assessment tool was finalised into two questionnaires to evaluate the decision-making practices of international pharmaceutical companies and HTA agencies, respectively. Since

many decisions are made within such organisations on a daily basis, these questionnaires focused on specific high-level decisions, namely the company process for evidence generation to support an HTA dossier for new medicines and the HTA agency appraisal decision-making process to recommend reimbursement of new medicines, restrict or reject it.

The questionnaires were organised into four sections:

1. *Decision-making process:* this section included questions regarding the involvement of a committee, different decision-making practices and decision-making systems
2. *Decision-making frameworks:* this section included questions regarding the use of a framework and the practices incorporated
3. *Challenges:* this section consisted of questions focusing on biases
4. *Personal perceptions:* this section included questions regarding perceived hurdles and solutions for making quality decisions and measuring quality decision making

The two questionnaires contained analogous questions where appropriate in order to allow a comparison between companies and agencies. The following issues were unique to the company questionnaire:

- Question 1.1.3 regarding the location of the committee
- Question 1.1.5 examining if the committee is also responsible for the decision-making process for evidence generation to seek regulatory approval
- Question 1.1.6 regarding the timing of the decision-making process with regards to the filing for regulatory approval
- Question 1.1.7 pertaining to other decisions made by the Committee

The following issue was unique to the agency questionnaire:

- Questions 1.1.4 regarding whether or not the committee is open or closed to external stakeholders
- Question 1.4 regarding whether or not the recommendation is legally binding
- Question 1.5 pertaining to the decision-making criteria that are defined explicitly by the agency's framework
- Question 1.6 regarding whether or not there are procedures in place for the recommendation decision to be formally challenged

The company and agency questionnaires are shown in Figure 4.1 and Figure 4.2 respectively.

**Figure 4.1 The pharmaceutical company reimbursement questionnaire**

## 1. Decision-making process

**1.1. Does your company have a committee (defined as a formal or informal decision-making group) that is involved in the decision-making process for evidence generation to support the reimbursement of new medicines via the relevant HTA agencies?**

[ ] Yes [ ] No

**1.1.1. If 'No', how is the decision made otherwise and by whom?**

.....

*If 'Yes' please answer questions 1.1.2 - 1.1.10, If 'No', please go to question 1.2*

**1.1.2. What is the name of this Committee?**

.....

**1.1.3. Where is the Committee based?**

[ ] Central (head office)
[ ] Local (country/region-specific)
[ ] Other.....

**1.1.4. Please specify the standard composition of the committee:**

**1.1.4.1. Total number of committee members.....**

**1.1.5. Is this Committee also responsible for the decision-making process for evidence generation to seek regulatory approval?**

[ ] Yes [ ] No

**1.1.5.1. If 'No', please write the name of the regulatory decision-making Committee. Please also comment how the two Committees interact/communicate.**

.....

.....

**1.1.6. When does the Committee decision-making process (for evidence generation to support the reimbursement of new medicines) occur with regards to the filing for regulatory approval? (Mark all that apply)**

[ ] Ahead of process to file NDA for regulatory approval
[ ] At the same time as filing NDA for regulatory approval
[ ] After the filing for NDA for regulatory approval
[ ] After the attainment of regulatory approval
[ ] Other.....

**1.1.7. What other decisions are made by this Committee? (Mark all that apply)**

[ ] Label/indication decision for reimbursement
[ ] Target population for reimbursement
[ ] Price setting
[ ] Other, please specify .....

**1.1.8. Which disciplines are part of the Committee that is involved in the decision-making process for evidence generation to support the reimbursement of new medicines via the relevant HTA agencies? (Mark one in each row)**

| Discipline | Not on the Committee | If on Committee, what role? | |
|---|---|---|---|
| | | Information provider/Advisor | Decision Maker |
| Research and Development | [ ] | [ ] | [ ] |
| Clinical Development/Medical affairs | [ ] | [ ] | [ ] |
| Drug product development | [ ] | [ ] | [ ] |
| Commercial/Marketing | [ ] | [ ] | [ ] |
| Health Economics/Outcomes Research/ | [ ] | [ ] | [ ] |
| Market Access/Pricing | [ ] | [ ] | [ ] |
| Legal | [ ] | [ ] | [ ] |
| Finance | [ ] | [ ] | [ ] |
| Regulatory | [ ] | [ ] | [ ] |
| Pharmacovigilance/Drug safety | [ ] | [ ] | [ ] |
| Public policy/government affairs | [ ] | [ ] | [ ] |
| Patient-reported outcome/patient engagement | [ ] | [ ] | [ ] |
| Senior management | [ ] | [ ] | [ ] |
| Chief Executive Officer | [ ] | [ ] | [ ] |
| Regional representatives from company | [ ] | [ ] | [ ] |
| Other ..... | [ ] | [ ] | [ ] |
| Other ..... | [ ] | [ ] | [ ] |

**1.1.9. In general, how are decisions made for evidence generation to support the reimbursement of new medicines via the relevant HTA agencies?**

[ ] By the Committee through consensus
[ ] By the Committee through majority vote
[ ] One individual makes the final decision based on the Committee discussions
[ ] Other, please specify .....

**1.1.9.1. If "majority vote", please specify the voting method:**

[ ] Secret ballot
[ ] Open voting
[ ] Other, please specify .....

**1.1.9.2. If "one individual makes the final decision", please provide the position of this individual (e.g. chairman of committee/CEO):**

.....

**Does this individual sit on the Committee?** [ ] Yes [ ] No

**1.1.10. Can one group/individual in the Committee veto the decision?**

[ ] Yes [ ] No

**1.1.10.1. If yes, please specify who**.....

**1.2. Which statement best describes the decision-making system for this decision? (Mark one)**

| System type | Mark one |
|---|---|
| **Qualitative System:** Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is a purely qualitative based on experts or management making a subjective decision. The final decision will be exercised based on Expert Judgment and experience. | [ ] |
| **Quantitative system:** Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is quantitative which brings together the various key data for the decision (such as comparative effectiveness data) and contributing opinions. The conclusion is based on the cumulative outcome from this system. | [ ] |
| **Mixed System:** Our internal system regarding the decision-making process to support the reimbursement of new medicines via the relevant HTA agencies is mixed, which takes into account various quantitative and qualitative elements. | [ ] |

**1.3. Are there evaluations in place to periodically measure the quality of the decision-making process regarding evidence generation to support the reimbursement of new medicines via the relevant HTA agencies?**

[ ] Yes [ ] No [ ] Not sure

**1.3.1. If 'Yes', please select which measures are used, who carries them out and how methodically (mark all that apply):**

| Formal evaluation to measure the quality of decision-making process | Who is it measured by? | | How methodically is it measured? | |
|---|---|---|---|---|
| | Internal team | External individual / group | Systematically | Ad hoc |
| Audit of the decision-making process | [ ] | [ ] | [ ] | [ ] |
| Feedback from stakeholders on the decision-making process | [ ] | [ ] | [ ] | [ ] |
| Examination of the actual outcome compared to expected outcome | [ ] | [ ] | [ ] | [ ] |
| Other, please specify ..... | [ ] | [ ] | [ ] | [ ] |

## 2. Decision-making frameworks

*A decision-making framework is a set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision.*

**2.1. Which statement best describes the nature of your company's framework (as defined above) that forms the basis of the decision-making process regarding evidence generation to support the reimbursement of new medicines via the relevant HTA agencies?**

[ ] Formally defined and codified framework

[ ] Informal framework, by custom and practice (validation by application) i.e. it has never been clearly agreed but over time has become practice

[ ] No framework in place – the decision is made ad hoc

***If "No framework" or "Informal framework, by custom and practice", please answer 2.1.1-2.1.2***

**2.1.1. Why a formal framework is not used? (Mark all that apply)**

[ ] Has not been considered
[ ] Time factor relating to the maturity of the organisation
[ ] Organisational structure/size of the company
[ ] Lack of a validated framework
[ ] Poor acceptance by staff
[ ] Lack of knowledge/training on decision making in general
[ ] Benefits of a framework not apparent
[ ] Resource/administrative limitation
[ ] Others, please specify.....

**2.1.2. Are there plans to adopt a formal framework in the next two years?**

[ ] Yes - in the next two years
[ ] Yes - in the next three to five years
[ ] No
[ ] Not sure

***If 'Formally defined and codified framework' or 'Informal framework, by custom and practice', please answer 2.1.3-2.1.6***

**2.1.3. How has the framework been developed?**

[ ] Internally [ ] Externally [ ] Mixed internal and external input

**2.1.4. Please provide the title of the framework and describe briefly:**

.....

.....

.....

**2.1.5. Has the framework been published?**

[ ] Yes [ ] No

**2.1.5.1. If 'No', would you be willing to share it with CIRS?**

[ ] Yes [ ] No

**2.1.6. In your view, which practices of a Framework for Quality Decision Making[2] are relevant or have been incorporated into your company's framework? (Mark one in each row)**

| Practice | Practice incorporated | Practice not incorporated but considered relevant | Practice not incorporated and not considered relevant |
|---|---|---|---|
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) | [ ] | [ ] | [ ] |
| 2. Assign clear roles and responsibilities (decision makers, advisors, information providers) | [ ] | [ ] | [ ] |
| 3. Consider uncertainty regarding the process (risks and unknowns) | [ ] | [ ] | [ ] |
| 4. Examine alternative solutions (scenario planning) | [ ] | [ ] | [ ] |
| 5. Assign values and relative importance to decision criteria | [ ] | [ ] | [ ] |
| 6. Re-evaluate as new information becomes available | [ ] | [ ] | [ ] |
| 7. Evaluate both internal and external influences/biases (*please see next page for more details regarding biases*) | [ ] | [ ] | [ ] |
| 8. Ensure transparency and provide a record trail | [ ] | [ ] | [ ] |
| 9. Perform impact analysis of the outcome | [ ] | [ ] | [ ] |
| 10. Effectively communicate the basis of the decision | [ ] | [ ] | [ ] |

[2] Developed based on thematic analysis of semi-structured interviews with 29 key opinion leaders from regulatory agencies, pharmaceutical companies and contract research organizations. Donelan R, Walker S, Salek S. Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiol Drug Safety.* 2015;24:319–328.

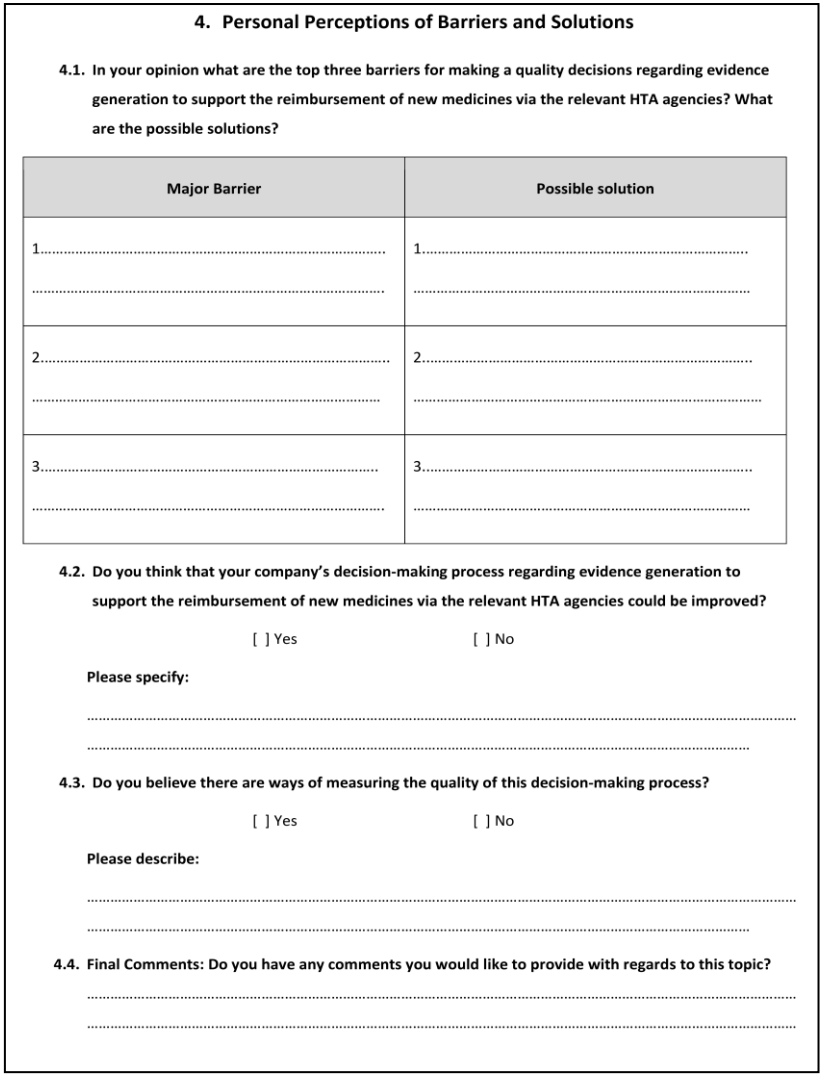
## 3. Challenges/Biases

**3.1. In your opinion, how often do the challenges/biases listed below occur at your organisation and/or influence the decision-making process regarding evidence generation to support the reimbursement of new medicines via the relevant HTA agencies? (Mark one in each row)**

| Challenge/Bias[3] | Degree of frequency | | | |
|---|---|---|---|---|
| | Never (0 in 4 decisions) | Sometimes (1 in 4 decisions) | Frequently (2 in 4 decisions) | Always (4 in 4 decisions) |
| **Action-oriented biases: drive us to take action less thoughtfully than we should. Characterised by:**<br>• Excessive optimism<br>• Overconfidence<br>• Intuition/gut-feeling | [ ] | [ ] | [ ] | [ ] |
| **Interest biases arise in the presence of conflicting incentives, including nonmonetary and even purely emotional ones. Characterised by:**<br>• Misaligned individual incentives<br>• Inappropriate attachments to people or products<br>• Misaligned perception of corporate goals/hierarchy | [ ] | [ ] | [ ] | [ ] |
| **Pattern-recognition biases lead us to recognize patterns even where there are none. Characterised by:**<br>• Confirmation bias to seek out information that supports a favoured decision<br>• Generalizing based on examples that are recent or memorable<br>• Evaluating a plan or proposal based on the track record of the person presenting it, more than on the facts supporting it | [ ] | [ ] | [ ] | [ ] |
| **Stability biases create a tendency toward inertia in the presence of uncertainty. Characterised by:**<br>• Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. | [ ] | [ ] | [ ] | [ ] |

[3] Lovallo D, Sibony O. The case of behavioral strategy. McKinsey Q. http://www.mckinsey.com/insights/strategy/the_case_for_behavioral_strategy. Published March 2010. Accessed April 15, 2015.

**Figure 4.2 The health technology assessment agency questionnaire**



**4. Personal Perceptions of Barriers and Solutions**

**4.1. In your opinion what are the top three barriers for making a quality decisions regarding evidence generation to support the reimbursement of new medicines via the relevant HTA agencies? What are the possible solutions?**

| Major Barrier | Possible solution |
|---|---|
| 1..... ..... | 1..... ..... |
| 2..... ..... | 2..... ..... |
| 3..... ..... | 3..... ..... |

**4.2. Do you think that your company's decision-making process regarding evidence generation to support the reimbursement of new medicines via the relevant HTA agencies could be improved?**

[ ] Yes [ ] No

**Please specify:**

.....

.....

**4.3. Do you believe there are ways of measuring the quality of this decision-making process?**

[ ] Yes [ ] No

**Please describe:**

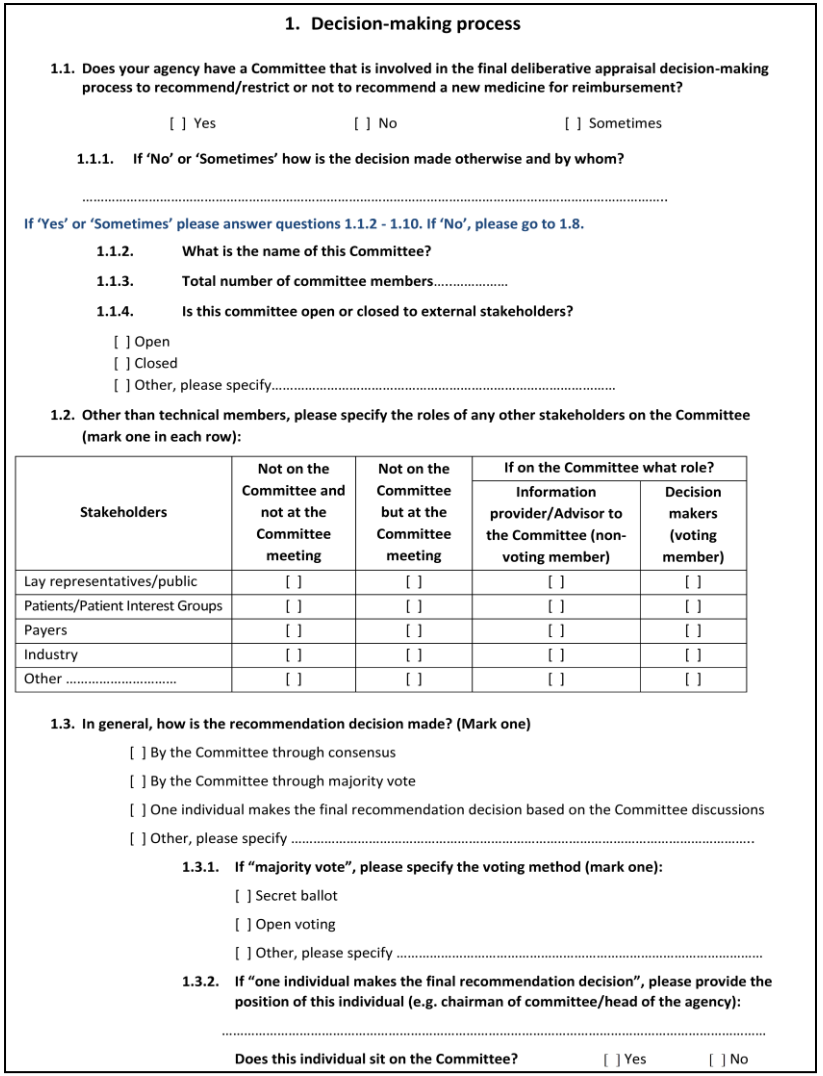
.....

.....

**4.4. Final Comments: Do you have any comments you would like to provide with regards to this topic?**

.....

.....



**1. Decision-making process**

**1.1. Does your agency have a Committee that is involved in the final deliberative appraisal decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement?**

[ ] Yes [ ] No [ ] Sometimes

**1.1.1. If 'No' or 'Sometimes' how is the decision made otherwise and by whom?**

.....

**If 'Yes' or 'Sometimes' please answer questions 1.1.2 - 1.10. If 'No', please go to 1.8.**

**1.1.2. What is the name of this Committee?**

**1.1.3. Total number of committee members**.....

**1.1.4. Is this committee open or closed to external stakeholders?**

[ ] Open
[ ] Closed
[ ] Other, please specify.....

**1.2. Other than technical members, please specify the roles of any other stakeholders on the Committee (mark one in each row):**

| Stakeholders | Not on the Committee and not at the Committee meeting | Not on the Committee but at the Committee meeting | If on the Committee what role? | |
|---|---|---|---|---|
| | | | Information provider/Advisor to the Committee (non-voting member) | Decision makers (voting member) |
| Lay representatives/public | [ ] | [ ] | [ ] | [ ] |
| Patients/Patient Interest Groups | [ ] | [ ] | [ ] | [ ] |
| Payers | [ ] | [ ] | [ ] | [ ] |
| Industry | [ ] | [ ] | [ ] | [ ] |
| Other ..... | [ ] | [ ] | [ ] | [ ] |

**1.3. In general, how is the recommendation decision made? (Mark one)**

[ ] By the Committee through consensus
[ ] By the Committee through majority vote
[ ] One individual makes the final recommendation decision based on the Committee discussions
[ ] Other, please specify .....

**1.3.1. If "majority vote", please specify the voting method (mark one):**

[ ] Secret ballot
[ ] Open voting
[ ] Other, please specify .....

**1.3.2. If "one individual makes the final recommendation decision", please provide the position of this individual (e.g. chairman of committee/head of the agency):**

.....

**Does this individual sit on the Committee?** [ ] Yes [ ] No

**1.4. Is the recommendation made by the HTA agency legally binding for adoption by payer bodies?**

[ ] Yes [ ] No

**1.5. Which of the following criteria apply in order to make the recommendation decision as defined explicitly by the agency's framework? (Mark all that apply)**

[ ] Cost-effectiveness (threshold/range)

[ ] Comparative effectiveness

[ ] Budget impact

[ ] Other.....

**1.6. Are there any procedures in place for the recommendation decision to be formally challenged?**

**Please describe** .....

.....

.....

**1.7. Can one group/individual in the Committee veto the recommendation?**

[ ] Yes [ ] No

**1.7.1. If yes, please specify who**.....

**1.8. Which statement best describes the system at your agency for the decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement? (Mark one)**

| System type | Mark one |
|---|---|
| **Qualitative System:** Our internal system for the final decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement is a purely qualitative based on experts making a subjective decision. The final recommendation decision will be exercised based on Expert Judgment and experience. | [ ] |
| **Quantitative system:** Our internal system for the final decision-making process to recommend/ restrict or not to recommend a new medicine for reimbursement is fully quantitative which brings together the various key data for the recommendation decision (such as comparative effectiveness data) and contributing opinions. The conclusion is based on the cumulative outcome from this system. | [ ] |
| **Mixed System:** Our internal system for the final decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement is mixed, which takes into account various quantitative and qualitative elements. | [ ] |

**1.9. What formal quality measures are in place to help build quality into this decision-making process? (Mark all that apply)**

[ ] Legal framework

[ ] Standard Operating Procedures

[ ] Systematic review of other countries' reimbursement recommendations

[ ] For EU: Transparency Directive (Council Directive 89/105/EEC)

[ ] Publication of the basis for the reimbursement recommendation

[ ] External independent advisory committees (please define.....)

[ ] Internal quality policy

[ ] Internal peer review of the recommendation decisions

[ ] Dedicated quality department

[ ] Stakeholder input (please specify: [ ] Patients/Patient Interest Groups [ ] Lay representatives/ public members [ ] Health care providers [ ] Industry [ ] Payers [ ] Other.....)

[ ] Other measures, please specify.....

**1.10. Are there evaluations in place to periodically measure the quality of this decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement?**

[ ] Yes [ ] No [ ] Not sure

**1.10.1. If 'Yes', please select which measures are used, who carries them out and how methodically (mark all that apply):**

| Formal evaluation to measure the quality of decision-making process | Who is it measured by? | | How methodically is it measured? | |
|---|---|---|---|---|
| | Internal team | External individual /group | Systematically | Ad hoc |
| Audit of the recommendation decision-making process | [ ] | [ ] | [ ] | [ ] |
| Feedback from stakeholders on the decision-making process: | [ ] | [ ] | [ ] | [ ] |
| Examination of the actual impact of the recommendation compared to what was anticipated at the time the recommendation decision was made | [ ] | [ ] | [ ] | [ ] |
| Other, please specify ..... | [ ] | [ ] | [ ] | [ ] |

## 2. Decision-making frameworks

*A decision-making framework is a set of principles, guidelines and tools which provide a structured systematic approach to guide decision-makers in selecting, organising, understanding and summarising subjective values and judgments that form the basis of a decision, as well as communicating the evidence relevant to the decision.*

**2.1. Which statement best describes the nature of your agency's framework (as defined above) that forms the basis of the decision to recommend/restrict or not to recommend a new medicine for reimbursement? (Mark one)**

[ ] Formally defined and codified framework

[ ] Informal framework, by custom and practice (validation by application) i.e. it has never been clearly agreed but over time has become the practice

[ ] No framework in place – the decision-making process is ad hoc

***If "No framework" or "Informal framework, by custom and practice", please answer 2.1.1-2.1.2***

**2.1.1. Why is a formal framework not used? (Mark all that apply)**

[ ] Has not been considered

[ ] Time factor relating to the maturity of the organisation

[ ] Organisational structure/size of the agency

[ ] Lack of a validated framework

[ ] Poor acceptance by staff

[ ] Lack of knowledge/training on decision making in general

[ ] Benefits of a framework not apparent

[ ] Resource/administrative limitation

[ ] Others, please specify.....

**2.1.2. Are there plans to adopt a formal framework?**

[ ] Yes - in the next two years

[ ] Yes - in the next three to five years

[ ] No

[ ] Not sure

***If 'Formally defined and codified framework' or 'Informal framework, by custom and practice', please answer 2.1.3-2.1.6***

**2.1.3. How has the framework been developed?**

[ ] Internally [ ] Externally [ ] Mixed internal and external input

**2.1.4. Please provide the title of the framework and describe briefly**

.....

.....

.....

**2.1.5. Has the framework been published?**

[ ] Yes [ ] No

**2.1.5.1. If 'No', would you be willing to share it with CIRS?**

[ ] Yes [ ] No

**2.1.6. In your view, which practices of a Framework for Quality Decision Making[2] are relevant or have been incorporated into your agency's framework? (Mark one in each row)**

| Practice | Practice incorporated | Practice not incorporated but considered relevant | Practice not incorporated and not considered relevant |
|---|---|---|---|
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) | [ ] | [ ] | [ ] |
| 2. Assign clear roles and responsibilities (decision makers, advisors, information providers) | [ ] | [ ] | [ ] |
| 3. Consider uncertainty regarding the process (risks and unknowns) | [ ] | [ ] | [ ] |
| 4. Examine alternative solutions | [ ] | [ ] | [ ] |
| 5. Assign values and relative importance to decision criteria (underpinning recommendation) | [ ] | [ ] | [ ] |
| 6. Re-evaluate as new information becomes available | [ ] | [ ] | [ ] |
| 7. Evaluate both internal and external influences/biases (*please see next page for more details regarding biases*) | [ ] | [ ] | [ ] |
| 8. Ensure transparency and provide a record trail | [ ] | [ ] | [ ] |
| 9. Perform impact analysis of the outcome (underpinning recommendation) | [ ] | [ ] | [ ] |
| 10. Effectively communicate the basis of the decision (underpinning recommendation) | [ ] | [ ] | [ ] |

[2] Developed based on thematic analysis of semi-structured interviews with 29 key opinion leaders from regulatory agencies, pharmaceutical companies and contract research organizations. Donelan R, Walker S, Salek S. Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiol Drug Safety.* 2015;24:319–328.

## 3. Challenges/Biases

**3.1. In your opinion how often do these challenges/biases occur at your organisation and/or influence the decision-making process to recommend/restrict or not to recommend a new medicine for reimbursement? (Mark one in each row)**

| Challenge/Bias[3] | Degree of frequency | | | |
|---|---|---|---|---|
| | Never (0 in 4 decisions) | Sometimes (1 in 4 decisions) | Frequently (2 in 4 decisions) | Always (4 in 4 decisions) |
| **Action-oriented biases drive us to take action less thoughtfully than we should. Characterised by:**<br>• Excessive optimism/pessimism<br>• Overconfidence<br>• Intuition/gut-feeling | [ ] | [ ] | [ ] | [ ] |
| **Interest biases arise in the presence of conflicting incentives and even purely emotional ones. Characterised by:**<br>• Misaligned individual incentives<br>• Inappropriate attachments to products | [ ] | [ ] | [ ] | [ ] |
| **Pattern-recognition biases lead us to recognize patterns even where there are none. Characterised by:**<br>• Confirmation bias to seek out information that supports a favoured decision<br>• Generalizing based on examples that are recent or memorable<br>• Evaluating a plan based on the track record of the person presenting it, more than on the facts supporting it | [ ] | [ ] | [ ] | [ ] |
| **Stability biases create a tendency toward inertia in the presence of uncertainty. Characterised by :**<br>• Preference for the status quo in the absence of pressure to change it<br>• The tendency to feel losses more acutely than gains of the same amount<br>• Rooting oneself to an initial value, leading to insufficient adjustments of subsequent estimates. | [ ] | [ ] | [ ] | [ ] |

[3] Lovallo D, Sibony O. The case of behavioral strategy. McKinsey Q. http://www.mckinsey.com/insights/strategy/the_case_for_behavioral_strategy. Published March 2010. Accessed April 15, 2015.

## 4. Personal Perceptions of Barriers and Solutions

**4.1. In your opinion what are the top three barriers for making a quality decision regarding the decision-making process to recommend a new medicine for reimbursement? What are the possible solutions?**

| Major Barrier | Possible solutions |
|---|---|
| 1.....<br>..... | 1.....<br>..... |
| 2.....<br>..... | 2.....<br>..... |
| 3.....<br>..... | 3.....<br>..... |

**4.2. Do you think that your agency's decision-making process for recommending the reimbursement of a new medicine could be improved?**

[ ] Yes [ ] No

**Please specify:**

.....

.....

**4.3. Do you believe there are ways of measuring the quality of this decision-making process?**

[ ] Yes [ ] No

Please describe:

.....

.....

**4.4. Final Comments: Do you have any comments you would like to provide with regards to this topic?**

.....

.....

**Study participants**

Similarly to the approach described in the regulatory study in Chapter 3, the study participants were selected based on experience and knowledge using purposive sampling, from those holding senior positions and having at least five years experience in a managerial position within major international pharmaceutical companies and HTA agencies. The finalised industry questionnaire was sent to executives within HEOR departments at 24 international pharmaceutical companies with large R&D budget (>1bln USD), thereby reflecting their innovativeness and the number of decisions made (PharmExec, 2016). The 24 companies were selected based on being members of Centre for Innovation in Regulatory Science (CIRS) research programme to ensure timeliness and maximise the response rate (CIRS, 2018).

The finalised agency questionnaire was sent to senior executives within 16 major HTA agencies. The focus was on major HTA agencies, which are part of the International Network of Agencies for Health Technology Assessment (INAHTA, 2018) or European network for health technology assessment (EUnetHTA, 2018) and which have a working relationship with CIRS (2018). To improve the representation of the sample, participants from various-sized organisations and geographical locations were invited including Australia, Asia, Europe and North America.

The study was designed as a cross-sectional study and the participants were invited via e-mail in January 2017 and were invited to take part in the study and if agreed were subsequently asked to complete the questionnaire and return by February 2017. The non-responders to the questionnaire were subsequently contacted via email in order to solicit further responses and the last response was received in July 2017.

**Data processing and analysis**

The responses from each questionnaire were tabulated and analysed using descriptive statistics to draw a comparison between the companies and the HTA agencies. Data were expressed as percentage of number of responders for each item. All free text responses and comments were coded using processes guided by established methods, including grounded theory (Wertz, 2011) and constant comparison method (Boeije, 2012). In grounded theory, inductive, yet systematic analytic strategies are applied to qualitative data to conceptually analyse personal experiences. The constant comparative method involves constantly comparing and contrasting concepts to inform relationships between phrases and themes expressed by the study participants. Content analysis was employed for free text responses and comments to identify emerging themes. Ranking was used where applicable.

Due to confidentiality reasons, only aggregated results are shown and no data that indentifies an individual agency or company are reported. No statistical tests were planned or conducted as this study was designed to be exploratory with an aim to provide a qualitative assessment of the objectives as well as to generate premises for further research.

## RESULTS

This study focused on the decision-making practices of pharmaceutical companies for evidence generation to support an HTA dossier for new medicines and HTA agencies' appraisal recommendation process**.** The key results are presented in five parts:

- Part I – Pilot study results
- Part II – Decision-making practices
- Part III – Decision-making frameworks
- Part IV – Measures for assessing quality of decision making
- Part V – Challenges and solutions for making quality decisions

### Characteristics of the study participants

Responses were received from 12 out of the 24 executives from company HEOR departments recruited into the study (50%), where 1 declined to complete the questionnaire due to the inability to meet the deadline. Eleven out of 24 (46%) gave positive responses which were used in the analysis, namely Abbvie, Bayer, Biogen, Eisai, Eli Lilly, F. Hoffmann-La Roche, Merck, Novartis, Pfizer, Sanofi Aventis and UCB. Nine out of the 11 companies were in the top 25 in terms of their R&D expenditure in 2016 and all 11 had R&D budget greater than 1bln USD (PharmExec, 2016).

As for the agencies, 11 (69%) out of the 16 provided responses, which included the national agencies from Australia (Pharmaceutical Benefits Advisory Committee), Belgium (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering), Brazil (Comissao Nacional de Incorporaca de Technologias), Canada national agency (Canadian Agency for Drugs and Technologies in Health), Canada Quebec province (Institut national d'excellence en santé et en services sociaux), England (The National Institute for Health and Care Excellence), Netherlands (Zorginstituut Nederland), Poland (Agencja Oceny Technologii Medycznych i Taryfikacji), Scotland (Scottish Medicines Consortium), Spain Basque region (Servicio de Evaluación de Tecnologías Sanitarias) and Sweden (Tandvårds- och läkemedelsförmånsverket). The companies and HTA agencies represented a diverse mix of geographical locations and affiliations and all belonged to either INAHTA (2018) or EUnetHTA (2018), demonstrating that these agencies have established HTA systems in place.

**Part I – Pilot study results**

The questionnaire was piloted among two companies and two agencies. The two agencies judged the questionnaire as 'straightforward', 'thorough' and 'detailed'. Both agencies considered the format and language used as clear and did not think that any questions should be removed as a result of being irrelevant or repetitive. One question was considered as unclear by one agency, which resulted in a word revision from 'In your opinion what are the top three hurdles for making a quality decision' to 'In your opinion what are the top three barriers for making a quality decision'. Two questions were added as a result of a suggestion from one agency, namely 'Is the recommendation made by the HTA agency legally binding for adoption by payer bodies?' and 'Which of the following criteria apply in order to make the recommendation decision as defined explicitly by the agency's framework?'.

The two companies rated the language used as clear, but one company found the format unclear in terms of separation between questions and answers, which resulted in the question text made bold. Questions regarding 'committee' were found difficult to answer which lead to a definition added, namely 'a formal or informal decision-making group'. In addition, the wording of one question was found unclear by a company and was subsequently changed from 'How are the decisions made by this Committee relating to evidence generation to seek reimbursement of new medicines' to 'In general, how are decisions made for evidence generation to support the reimbursement of new medicines via the relevant HTA agencies?'. None of the companies thought that questions should be removed as a result of being irrelevant or repetitive and no further questions were suggested.

**Part II – Decision-making practices**

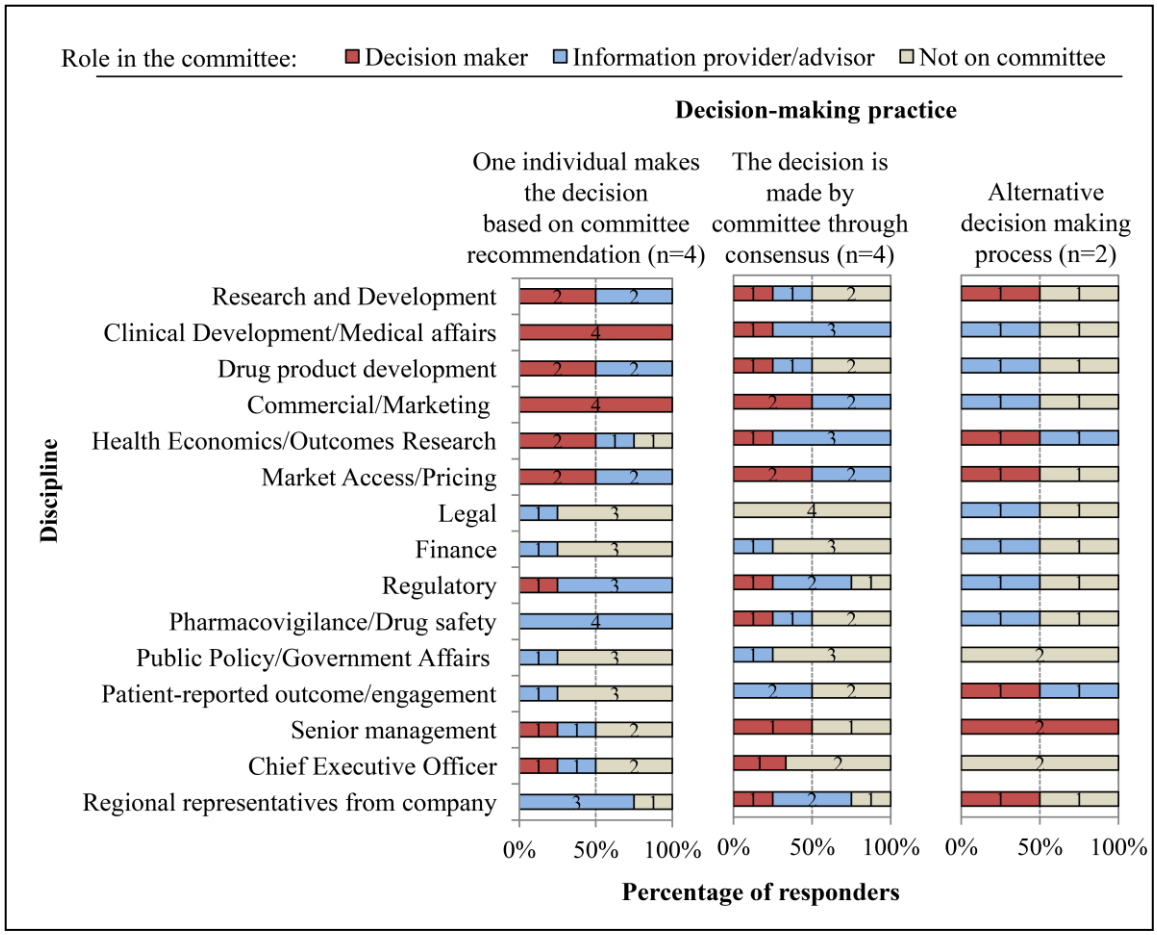
*A comparison of committees and systems*

Almost all of the companies (10 out of 11) and HTA agencies (10 out of 11) reported that they have a committee that is involved in the decision-making processes for the generation of evidence to support the reimbursement of medicines. The number of company committee members ranged from six to 20 and this number also varied within a company for example depending on the product. The mean for the agency committee members was 20, with a range from nine to 31 members. Both groups adopted mixed decision-making systems. For companies, an individual made the ultimate decision based on the respective committee's recommendation (4), the decision was made by consensus (4) or a different process was adopted (2). None of the companies used a majority vote system. Agencies utilised a majority vote (5; where three used open voting and two used a secret ballot), consensus (4; where two used a majority vote if consensus could not be reached) or an individual makes the decision (1). Almost all the companies (8) and agencies (9) utilised a mixed internal decision-making

system (which takes into account various quantitative and qualitative elements), as opposed to a purely qualitative or quantitative system.

Regarding the disciplines that were represented in the committee, the majority of companies had representatives from research and development, clinical development/medical affairs, drug/product development, commercial/marketing, health economics/outcomes, market access/pricing, regulatory, pharmacovigilance/drug safety, senior management and regional representatives (Figure 4.3). Overall, the most common decision makers were clinical development/medical affairs, commercial/marketing and market access/pricing and only minor differences were observed by type of decision-making practice (i.e. whether the decision is made by an individual, consensus or other). The group was split as to whether or not an individual member of the committee could veto the decision, with four stating this could be done, usually by the chair and the other four reported that it was not done. Other decisions made by the committee included label/indication for reimbursement (9), target population for (8) and price setting (4).

**Figure 4.3 The decision-making committee and the disciplines within the ten companies and their role by the type of the decision-making practice**



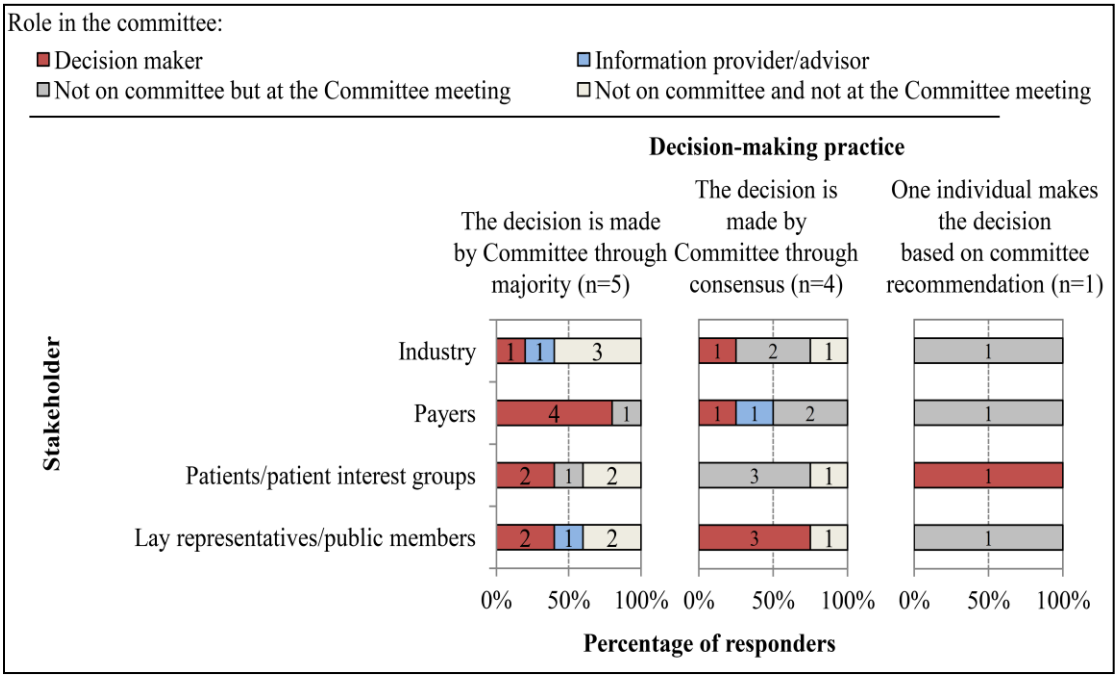

n = number of responders

For agencies, other than technical members, a number of stakeholders attended appraisal committee meetings, namely the industry, payers, patient/patient interest groups and lay representatives/public members. For committees where a decision is made through majority, the most common decision-making group (other than technical members) were payers, whereas for consensus-style committees, it was the lay representatives/public members (Figure 4.4). An individual in the committee could veto the decision in only one agency, but in most cases (10) the decision could be challenged by external stakeholders, primarily through legal procedures.

*Company-specific characteristics*

The majority of companies (8) reported that the committees were based centrally in the head office. In addition, companies were mixed as to the process timing with regards to the filing for regulatory approval, where, in most cases, the HTA committee process occurred either immediately ahead of process to file for regulatory approval (5) or as an iterative process before, during and post filing (4) or at the same time (1). For half of the companies (5), this committee was also responsible for generating evidence for seeking regulatory approval. For the companies where this was not the case (5), the majority (3) stated that the committees interacted by ensuring that there was an overlap of members on both committees.

**Figure 4.4 Stakeholders in the committee (other than the technical agency members) within the ten agencies and their role by the type of the decision-making practice**




n = number of responders

*Agency-specific characteristics*

In terms of the criteria used by each committee to make the recommendation decision as defined explicitly by the agency's framework: all agencies (11) utilised cost-effectiveness threshold/range and almost all used comparative effectiveness (10) and budget impact (8), whereas 8 specified other criteria, including burden of disease and unmet need. For the majority of the agencies (7) the committee recommendation was non-binding, for three agencies it was binding and in 1 case it would only be binding if it was a negative recommendation.

**Part III – Decision-making frameworks**

The majority of companies (9) had a framework that formed the basis of the decision-making process for evidence generation to support the reimbursement of medicines, where 6 were formally defined and codified and three were informal by "custom and practice"; that is, the framework had never been clearly agreed but over time had become the practice. The majority of companies (6) developed the framework internally and 2 used mixed internal and external input (1 did not respond). For the companies that did not have a framework (2), the reasons for this were mixed, including the time factor relating to the maturity of the organisation, organisational structure or size of the company, the lack of a validated framework and the fact that the benefits of a framework were not apparent. One company indicated that it had plans to adopt a framework in the next two years whereas one indicated that there were no plans.

All 11 agencies had a framework, where seven were formally defined and codified and 4 had an informal framework by "custom and practice". The majority of agencies (6) developed the framework using mixed internal and external input, whereas for two, development was internal (3 did not respond).

The incorporation of the ten QDMPs into company and agency formal frameworks is shown in Table 4.4. In general, the majority of the ten QDMPs were incorporated into the company and agency formal frameworks. QDMP 3 (assign values and relative importance to decision criteria) and QDMP 4 (evaluate both internal and external influences/biases) were least incorporated by the two groups. QDMP 5 (examine alternative solutions) was incorporated by all the companies, but only four out of seven agencies, whereas QDMP 8 (perform impact analysis of the decision) was incorporated by the majority of agencies, but only one out of the six companies. Only two agencies and none of the companies indicated that they had all ten QDMPs incorporated into their framework. Nevertheless, all the QDMPs that were least

incorporated into agency and company frameworks were generally considered as relevant by both groups.

**Table 4.4 The Quality Decision-Making Practices (QDMPs) incorporated into organisations' formal frameworks**

| Quality decision-making practices (QDMPs) | QDMP incorporated into organisation's formal framework? | | If QDMP not incorporated, is it considered relevant? | |
|---|---|---|---|---|
| | **Companies (n=6)** | **Agencies (n=7)** | **Companies** | **Agencies** |
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) | 67% | 100% | 100% (n=2) | - |
| 2. Assign clear roles and responsibilities (decision makers, advisors, information providers) | 100% | 100% | - | - |
| 3. Assign values and relative importance to decision criteria | 50% | 43% | 100% (n=3) | 75% (n=4) |
| 4. Evaluate both internal and external influences/biases | 33% | 43% | 100% (n=4) | 100% (n=4) |
| 5. Examine alternative solutions | 100% | 57% | | 67% (n=3) |
| 6. Consider uncertainty | 100% | 71% | - | 100% (n=2) |
| 7. Re-evaluate as new information becomes available | 100% | 86% | - | 100% (n=1) |
| 8. Perform impact analysis of the decision | 17% | 86% | 80% (n=5) | 100% (n=1) |
| 9. Ensure transparency and provide a record trail | 83% | 86% | 100% (n=1) | 100% (n=1) |
| 10. Effectively communicate the basis of the decision | 67% | 86% | 100% (n=2) | 100% (n=1) |

* Only companies and agencies that had a formal framework (as opposed to by "custom and practice") are included.
n = total number of responders.

**Part IV - Measures for assessing quality of decision making**

The majority of companies and agencies did not have formal assessments in place to measure the quality of decision making. For the 4 companies and 6 agencies that had formal assessments, most obtained formal feedback from internal and external stakeholders, followed by examining the actual outcome compared with expected outcome, but only two companies and three agencies reported that they audited their decision-making process. The assessments were generally carried out on a systematic basis, by internal groups for companies and a mix of internal and external groups for agencies. Interestingly, most companies (9 out of 11) and agencies (7 out of 11) believed that there were ways of measuring the quality of decision-making process. Moreover, companies and agencies primarily suggested measures for assessing the process, although currently the majority of organisations only assess outcomes (Table 4.5).

**Table 4.5 Key measures proposed by pharmaceutical companies and health technology assessment agencies for assessing the quality of decision making**

| Companies (n=7) | Agencies (n=6) |
|---|---|
| 1.Formal assessment of the internal decision-making process including decision transparency and communication (n=3) | 1. External benchmarking of decision-making processes and outcomes compared to other jurisdictions (n=4) |
| 2. Incorporation of milestones and indicators into process to verify if key factors at each stage are addressed by internal stakeholders (n=2) | 2. Internal assessment of the decision-making process (structure; use of committees and frameworks) (n=3) |
| 3. Evaluation of HTA success compared to the evidence generated (n=2) | 3. Degree of participation and engagement with stakeholders (n=2) |
| 4. Analysis of the actual decision and its foundation including the evidence considered and other influencing factors (n=2) | 4. Formal feedback from internal and external stakeholders regarding decision making (n=2) |

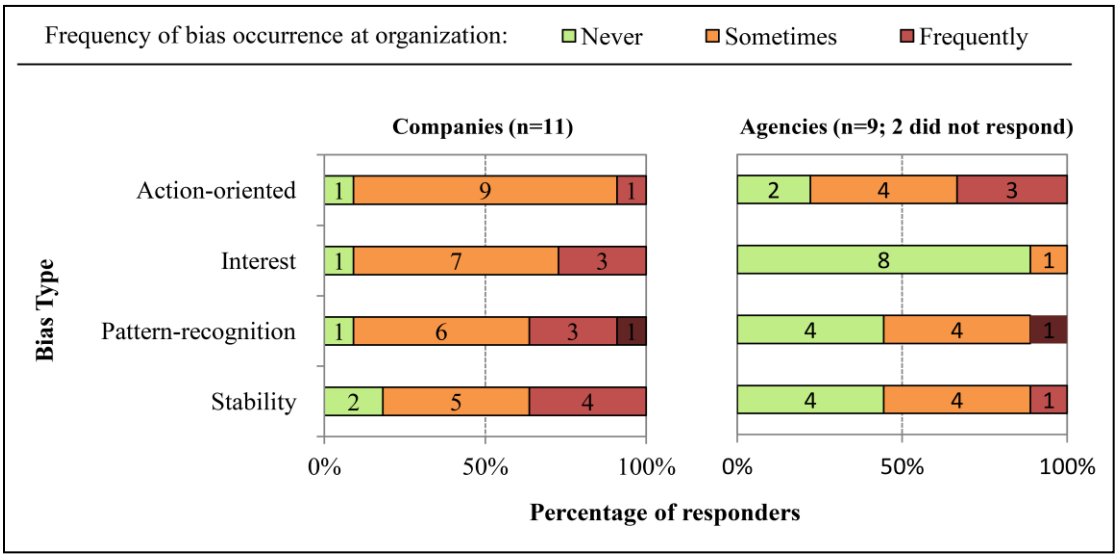
n = number of responders

**Part V - Challenges and solutions for making quality decisions**

In general, both agencies and particularly companies considered the occurrence of biases within their organisation or their influence on the decision making as pertinent. Nevertheless, the perceived frequency of their recognition varied for both groups according to the type of bias (Figure 4.5). In general, action-oriented bias (for example, overconfidence or intuition leading individuals to take action less thoughtfully) was perceived as most influential and

interest bias; that is, bias arising in the presence of conflicting incentives was perceived as the least pertinent for agencies, whereas for companies it was mixed.

**Figure 4.5 Types of biases and the perceived frequency at which they occur within pharmaceutical companies or health technology assessment agencies during their decision making**




n = number of responders

Almost all the companies (9 out of 11; 2 did not respond) and agencies (9 out of 11) believed that decision making within their organisations could be improved. Both groups identified barriers (Table 4.6) and possible solutions (Table 4.7) for making a quality decision. For agencies, the major barrier was regarding poor quality of evidence submitted as well as high uncertainty around the information. It was suggested that this could be addressed through the use of improved methodologies for clinical study design, economic modelling and price setting, as well as increased reliance on real world evidence/data. Nevertheless, agencies also highlighted lack of knowledge and frameworks for decision making as well as the presence of biases and time pressures. This in turn could be addressed by defining an internationally agreed decision-making framework and providing training on the topic of quality decision making, as suggested by the agencies. Companies reported challenges due to misalignment and competing interests, particularly externally, relating to divergent HTA agency decision-making processes, requirements and standards, as well as internal conflicts within companies, namely between HTA and regulatory functions and requirements (focus primarily on registration). Respondents suggested that this could be addressed by incentivising internal systems to align as well as encouraging external engagement with stakeholders. Resource and time constraints as well as lack of knowledge and experience with regard to HTA and reimbursement decision making were also highlighted as a key barrier. Companies suggested

that improvements could be made by increasing awareness of decision-making concepts within companies and by carrying out a more formal review of their decision-making processes and respective outcomes.

**Table 4.6 Key barriers identified by pharmaceutical companies and health technology assessment agencies for quality decision making**

| Companies (n=9) | Agencies (n=10) |
|---|---|
| 1. Lack of alignment relating to decision-making processes, requirements and HTA standards (e.g. local vs. global; HTA vs. regulatory) (n=10) | 1. Poor quality of evidence submitted by companies (n=10) |
| 2. Resource and time constraints – need to decide quickly and reluctance to start early (n=6) | 2. Limited data and high levels of uncertainty around the information (n=6) |
| 3. Internal decision-making misalignment between HTA and regulatory functions and requirements for evidence generation (n=5) | 3. Lack of knowledge and frameworks with regard to decision making (n=4) |
| 4. Lack of in-house knowledge and experience with regard to HTA and reimbursement decision making (n=4) | 4. Internal and external biases, trust issues and political pressures (n=3) |
| 5. No feedback loop in identifying the impact of decisions made (n=2) | 5. Time available to make the decision (n=2) |

n = number of responders

**Table 4.7 Key solutions proposed by companies and health technology assessment agencies for overcoming the barriers for making quality decisions**

| Companies (n=9) | Agencies (n=10) |
|---|---|
| 1. Incentivise internal systems to align and facilitate cross-functional collaborations (HTA-regulatory) early in the process (n=7) | 1. Improved methodologies for clinical study design, economic modelling and price setting (n=8) |
| 2. Education, capacity building and international engagement with external stakeholders (regulatory and HTA) (n=7) | 2. Increased reliance on real world evidence/data during decision making (n=6) |
| 3. More formal review of decision-making process, outcomes and feedback from stakeholders (n=4) | 3. Education, capacity building and international engagement (n=5) |
| 4. Lobby for a more predictable and harmonised HTA environment (n=4) | 4. Define an international framework to enable more structured decision making (n=3) |

n = number of responders

## DISCUSSION

Having a structured decision-making processes in place with appropriate frameworks and incorporating all ten QDMPs is imperative to ensuring transparency and increasing the probability of favourable outcomes regarding the reimbursement of new medicines. This study aimed to evaluate the decision-making processes within pharmaceutical company HEOR departments during medicines development for evidence generation to support an HTA dossier for new medicines and the HTA agency appraisal decision-making process to recommend reimbursement restriction or rejection of new medicines. The results provide a unique insight into the organisational practices within companies and agencies, their views of the occurrence of biases and the potential barriers and solutions for quality decision-making processes.

As this analysis has already been carried out for regulatory authorities and pharmaceutical companies regarding the decision-making processes for regulatory submission and review (Chapter 3), the results of the two studies are discussed to identify the areas of common strength as well as divergence. Such a comparison aims to promote future improvement and alignment of best practices for building quality into decision-making practices during medicines development, regulatory review and HTA. Indeed, ensuring the quality of decision-making practices for all organisations involved throughout the lifecycle of medicines is key to increase the probability of better outcomes.

Other initiatives have been carried out to characterise jurisdictional regulatory and HTA decision-making systems (Franken et al., 2012; Allen et al., 2013) and practices (Wang et al., 2015; Oortwijn et al., 2017), as well as to compare the evidentiary requirements from regulatory authorities and HTA agencies. Nevertheless, these studies do not take into account the various approaches organisations have been implementing to ensure a quality decision-making process. Nor do the studies attempt to clarify how decisions, which require human judgment and interpretation, are made around the data by the various committees in companies and agencies. Consequently, this study has moved beyond simply characterising the stepwise processes within organisations and aimed to determine the use of frameworks for decision making, the incorporation of best practices into those frameworks and the use of tools for evaluating the quality of decision making within those organisations.

### Decision-making systems and committees

This study evaluated firstly the process characteristics across companies and HTA agencies, namely the use of committees; types of decision-making processes (consensus; majority vote or one individual makes the decision based on committee recommendation) and types of

decision-making systems (qualitative, which is based on expert or management opinion; quantitative primarily based on data and computing or mixed).

Some similarities exist between the decision-making processes of pharmaceutical companies and HTA agencies, such as the use of committees and having a primarily internal decision-making system. Nevertheless, the results also indicate that different organisations use diverse processes to arrive at the final decision, where companies primarily make decisions via one individual or consensus whereas agencies also use a majority vote system. This may be due to the difference in the purpose of the decision made by an agency as opposed to a company, as well as to other factors such as differences in scope, political pressures or cultural differences between the various organisations.

Divergences in HTA decision-making processes, as well as internal decision-making systems, are consistent with the findings from the study with regulatory authorities and pharmaceutical companies (Chapter 3). It should be noted that differences in processes are not generally an issue and each method has its advantages, such as speed for individual decision making and inclusiveness as well as objectivity for group (majority or consensus) decision making. These differences nevertheless pose potential challenges faced by regulatory authorities and HTA agencies in trying to align practices and certain evidentiary requirements during the regulatory review and HTA recommendation processes. However, if attained, such alignment, both within and across regulatory authorities and HTA agencies, could increase decision consistency as well as enable potential reliance by one agency on the assessment of data by another (McAuslane et al., 2016).

**Decision-making frameworks and practices**

Secondly, the study evaluated the use of frameworks to structure the decision-making processes within companies and agencies. It was revealed that the majority of HTA agencies and companies have a framework that forms the basis of their decision making, but that is not always formally defined and codified, particularly within companies. Nevertheless, most agencies and companies with formal frameworks have incorporated the majority of the ten QDMPs. This is consistent with the results from the regulatory questionnaire (Chapter 3).

The QDMP that was least incorporated into company and HTA agency frameworks were QDMPs 3 (assign values and relative importance to decision criteria) and 4 (evaluate both internal and external influences/biases). This is also in line with the results of the previously reported regulatory study (Chapter 3).

Regarding QDMP 3 (assign values and relative importance to decision criteria), this has been emphasised through other research on HTA agency decision making, which uncovered that the role and implementation of decision criteria during HTA decision making is not always clear and should therefore be better defined (Franken et al., 2012). In addition, companies need to be more explicit in the criteria used for evidence generation to support their HTA dossier, as well as the timing of this process with respect to regulatory-evidence generation, where the two processes should be better aligned to increase the probability of favourable outcomes. The lack of incorporation of QDMP 4 (evaluate both internal and external influences/biases) is consistent with the perception that biases systematically affect decision-making processes within companies and agencies alike; this will be discussed in more detail in the next section.

Finally, QDMP 5 (examine alternative solutions) and QDMP 8 (perform impact analysis of the decision) was specifically not incorporated by HTA agencies only, which was also the case for the regulatory questionnaire but in this case this was for both the companies and regulatory authorities alike. This may be due to the perceived narrow frame of the decision where, despite its importance, generation of alternatives and impact analysis may not be considered as essential steps when the decision appears to be a yes/no. Nevertheless, those QDMPs which were least incorporated into company, regulatory and HTA agency frameworks were generally considered relevant and should therefore be implemented by such organisations to maximise decision quality.

**Biases, challenges and solutions**

Any decision with an element of risk is subject to universal human biases such as over-optimism and loss aversion (tendency to prefer avoiding losses to acquiring equivalent gain). Key, strategic decisions are also susceptible to biases, particularly when the incentives of certain individuals are not aligned with the rest of the organisation. Consequently, the different types of cognitive biases that occur during decision making were also investigated. Indeed, almost all the companies and HTA agencies perceived that decision making within their organisation was influenced by biases. The type of bias, nevertheless, varied according to organisation type.

For companies, the results were mixed, but in general, companies perceived a higher influence of biases on their decision making compared to agencies, which again was similar to regulatory department results (Chapter 3). Action-oriented bias (e.g., overconfidence or intuition leading individuals to take action less thoughtfully) was seen as most influential for HTA agencies, compared to stability bias (creating a tendency towards inertia in the presence

of uncertainty) within regulatory authorities (Chapter 3). In general, interest bias (arising in the presence of conflicting incentives) was perceived as the least influential by both HTA and also regulatory authorities (Chapter 3), which may be due to strict conflict of interest rules within the various committees at both organisations.

Companies and agencies identified challenges and potential solutions to quality decision making. Firstly, pharmaceutical companies highlighted the misalignment of international HTA requirements. Company respondents also emphasised the need for internal alignment, where HTA company functions are not always fully integrated with regulatory functions in the evidence-generation processes and are therefore not consistently involved in decision making during medicines development, as described previously by McAuslane and colleagues (2016). As a result, the company submission may not incorporate the necessary evidence to support an HTA dossier in addition to regulatory approval. Potential solutions to these challenges would be to incentivise the alignment of internal systems within companies during medicines development through improved methodologies for decision making and to promote external harmonisation of the HTA environment through various international initiatives, such as early scientific advice (EUnetHTA, 2017).

In addition, barriers for decision making identified by HTA agencies centred on the assessment of data rather than on decision making per se, highlighting the current focus on the generation of good-quality information rather than on how decisions should be made around that information (Cole et al., 2016). Here, focused education, training and capacity building (such as through creation of teams focusing on decision quality) were highlighted by companies and HTA agencies to develop internal decision-making capabilities.

**Decision-making assessments**

The only way organisations can learn how to make better decisions is by first evaluating the quality of their decision making (Kahneman, 2011). Consequently, companies and agencies were asked whether and how decision making should be measured. The majority of company departments and HTA agencies believe that the quality of decision-making processes can and should be measured and this was also the case regarding the perceptions of company regulatory departments and regulatory authorities (Chapter 3). Respondents suggested internal assessments of decision transparency and structure, as well as external benchmarking as possible areas of assessment in their decision making.

Nevertheless, despite this belief that measuring decision making is key, the majority of organisations do not currently perform such assessments and if they do perform them, it is

primarily to assess outcomes rather than process. Consequently, more effort is needed to increase the awareness of assessing and improving the quality of the process to increase the probability of good outcomes.

Currently it seems that organisations involved in the HTA of medicines focus mainly on the data and uncertainty when making decisions but insufficient attention is paid to the deliberative decision-making process itself when appraising the information. Although most participants recognised the occurrence of biases within their organisation as well as the need to improve the quality of their decision-making process, the majority do not currently perform any such formal assessments, but believe that it can and should be done. The findings of this study demonstrate the relevance of the ten QDMPs for ensuring quality decision making by companies, regulatory authorities and HTA agencies. Furthermore, they support the need to implement formal decision-making frameworks within organisations and to evaluate the practical implementation of the QDMPs throughout medicines development, regulatory review and health technology assessment. This could be achieved by formally evaluating the quality decision-making process within companies and regulatory and HTA agencies using the appropriate available techniques, as discussed in the next chapter. Such research could help increase awareness of the importance of quality decision making as well as uncover areas for improvement within companies and agencies in order to promote consistency and transparency to be built into the critical decisions during the lifecycle of medicines. Finally, such research would aim to improve internal as well as external decision-making accountability to ultimately ensure that the public understand and trust the decisions made by companies and agencies.

**SUMMARY**

- Currently, pharmaceutical companies and health technology assessment (HTA) agencies concentrate on evidence, but studies have shown that it is not always clear how decisions, which require human judgment and interpretation, are made around the data to support the reimbursement of new medicines
- The aims of this study were to determine the current decision-making practices and methodologies for structuring and measuring the quality of decision making and the barriers and solutions for making quality decisions within pharmaceutical companies and HTA agencies
- Two analogous questionnaires were developed for use in this study
- Sixteen agencies and 24 companies were asked to complete the questionnaire, assessing the company decision making for evidence generation to support an HTA dossier for new medicines and the HTA agency appraisal decision-making process to recommend, restrict or reject the reimbursement of new medicines
- Responses were obtained from 11 companies (50% response rate) and 11 HTA agencies (69%)
- Some similarities were identified between the decision-making processes of companies and agencies, such as the use of committees, having a primarily mixed (qualitative/quantitative) internal decision-making system, as well as the lack of systematic assessments of quality decision making and the relatively infrequent use of formal decision-making frameworks
- Nevertheless, the results indicate differences as companies and agencies use diverse processes to arrive at the final decision either through consensus, majority vote or an individual making the decision
- The majority of companies and agencies believe that the quality of decision making can and should be measured; moreover, organisations considered the occurrence of biases within their organisation as pertinent
- Finally, almost all the participants felt that there was room for improvement for their organisation's quality of decision making
- These findings are consistent with a published study on regulatory processes and support the need for more consistent and predictable decision-making processes during the lifecycle of medicines
- This could be achieved through capacity building, systematically evaluating the quality of decision-making and encouraging utilisation of formal decision-making frameworks within companies and agencies.

# Systematic Review of Techniques for Evaluating the Ten Quality Decision-Making Practices (QDMPs)

## INTRODUCTION

The literature on decision making stretches back over several centuries and encompasses a wide range of academic disciplines—from philosophy and history to mathematics (Buchanan and O'Connell, 2006). More recently, the science and art of decision making have been established regarding the psychology of judgment, decision-making styles, as well as behavioural economics to enable quality decision making (Thaler and Sustein, 2009; Lovallo and Sibony, 2010; Kahneman, 2011).

However, research on decision making to enable a quality process during medicines development, regulatory review and health technology assessment (HTA) is less well-articulated and it is not certain how it is being applied by organisations and individuals in companies and agencies. This may be because there is limited awareness regarding the science of decision making in this area, as well as limited training and education (Chapters 3 and 4). In addition, the current frameworks utilised by pharmaceutical companies, regulatory authorities and HTA agencies do not often account for the subjective elements, such as behaviours and influences that affect the process with which individuals and organisations arrive at the final decision.

In order to address this gap, a previous review of recent research on decision making has resulted in the development of ten QDMPs to enable quality decision making. These QDMPs were considered as relevant best practices by pharmaceutical companies, regulatory authorities and HTA agencies for incorporation into decision-making frameworks (Chapter 3 and 4). Moreover, the key frameworks used during medicines development, particularly in the area of benefit-risk assessment (Leong et al., 2015), as well as the science of decision making (Matheson and Matheson, 1998; Hammond et al., 1999; Blenko et al., 2010; SDG, 2011) are underpinned by this set of holistic practices.

Routine assessment of the quality of the decision-making processes (as opposed to just measuring outcomes) has been recognised as key for identifying areas of strength and weakness across the best practices in order to provide a basis for improvement to ultimately increase the productivity in decision making (Kahneman, 2011). This literature review aims to identify current techniques, including tools, questionnaires, surveys as well as studies that measure the quality of the decision-making process within regulatory authorities, HTA agencies and pharmaceutical companies.

The objectives were to

- Compare the existing techniques
- Assess their measurement properties
- Identify research gaps and recommend the way forward

Of interest would be to identify a technique that is applicable to all three stakeholders in order to have a common platform for discussing, sharing and comparing issues in quality decision making throughout the lifecycle of medicines.

## METHOD

A systematic review of the literature was undertaken to identify current approaches for assessing quality decision making in medicines development, regulatory review and HTA.

### Data Sources

The following databases were searched: MEDLINE (using PubMed), Web of Knowledge, Google Scholar and Open Access theses and dissertations. Gray literature was also searched using Google. This review was limited to English-language articles and covered the period from 1996 to 2017, which reflects the proliferation of publications in this area.

### Search Terms

Initially, an exploratory search was undertaken using basic terms as key words including quality, decision making, techniques, instruments, tools, measurement, regulatory review, medicines development and HTA. These were also used to search gray literature. The following structured search terms were constructed using PubMed guidelines and Medical Subject Headings (MeSH) terms and these were used in database searches *(Decision* OR "decision mak*" OR preference*) AND ("health technology" OR HTA OR reimbursement OR coverage OR regulat* OR R&D OR "research and development" OR development OR medicine*) AND (agency OR committee OR assessor* OR reviewer* "pharmaceutical compan*" OR industry) AND (measur* or metric* OR evaluat* OR assess* OR apprais* OR analys*) AND (technique OR checklist OR tool OR scale OR feedback OR survey OR questionnaire OR instrument)*.

### Selection Procedure

The titles and abstracts resulting from this search were screened for relevance and duplication. The full text studies were obtained for all titles/abstracts that appeared to meet the inclusion/exclusion criteria or where there was any uncertainty. The full text articles were

then screened and literature was also obtained by checking the references of the included articles as well as by searching the gray literature.

**Selection Criteria**

Included were: (1) All articles which identified a technique (tool, instrument, or questionnaire) for evaluating quality of decision making applicable to the area of medicines development, regulatory, or HTA including generic tools (e.g. where sample or audience were unspecified); (2) Techniques evaluating the decision, the decision-making process or key aspect(s) of the process and associated preferences, influences and behaviours; (3) Studies that assess the performance of the technique by evaluating hypothetical or real (historical) decisions, vignettes, or a reflection of individual style or approach.

Excluded were (1) General discussions on decision making and quality within the area of medicines development, review and HTA; (2) Techniques for measuring quality of decision making used specifically in disciplines other than medicines development, regulatory review and HTA (such as other industries including unrelated health organisations); (3) Frameworks for structuring and documenting decision-making processes and for enabling quality to be built into decision making.

**Data Extraction and Synthesis**

The following extracted information was recorded: title of the technique, decision area (e.g., regulatory advisory committee or medicines R&D), study subject (e.g., regulatory authority, HTA agency or industry), subject type (organisations or individuals) and method.

**Assessment of the Techniques**

In the absence of an alternative evaluation criteria system that captures issues relevant to the areas of medicines development, review and HTA assessment, the ten QDMPs were used to evaluate the techniques identified in this review to ensure that each technique is evaluating all key aspects of quality decision making. The ten QDMPs were developed based on results from semi-structured interview with 29 key opinion leaders from regulatory authorities and pharmaceutical companies to investigate and identify the important issues that influence decision making (Donelan et al., 2015). In addition, the key decision-making frameworks (Hammond et al., 1999; Blenko et al., 2010; SDG, 2011) as well as benefit-risk assessment methodologies (Leong et al., 2015; Pignatti et al., 2015) are also underpinned by these practices. In a subsequent review, these QDMPs were presented to major pharmaceutical companies, regulatory authorities and HTA agencies were considered as relevant (Chapters 3 and 4).

In addition, the measurement properties of each technique were assessed in terms of:

- Theoretical underpinning (development of a technique was based on a well-described methodological framework);
- Psychometric properties (content validity, internal consistency was demonstrated);
- Psychometric evaluations (reliability, relevance and sensitivity of the tool was demonstrated);
- Demonstrated practicality (the technique was applied to target population through pilot studies);
- Generalisability (the technique can be used across industry, regulatory and HTA); and
- Applicability (the technique is applicable to evaluating individuals and organisations), which were considered as the key properties that need to be considered when evaluating such instruments (McDowell, 2006; Streiner et al., 2015).

**Secondary Review**

An independent secondary reviewer was involved in the development of the search strategy and selection criteria, as well as article selection and data extraction. Secondary screening was carried out as follows: Magda Bujar (MB) selected at random 25% of the full text papers (10 out of 38), which were re-assessed for inclusion/exclusion by the secondary reviewer against the criteria. Disagreements were resolved through discussion, where MB and secondary reviewer disagreed regarding the inclusion of one paper. This was resolved by refining the inclusion criteria to make them more specific. Following this modification, 100% concordance was reached regarding the included papers. Secondary reviewer also independently carried out data extraction and a small number of disagreements were resolved through discussions until full agreement was reached.

**RESULTS**

For the purpose of clarity, the key results are presented in three parts:

• Part I: Selected articles for review

• Part II: Identified techniques for evaluating quality of decision making

• Part III: Measurement properties of the techniques.

**Part I: Selected Articles for Review**

Of 4,782 records, 785 were removed as duplicates and 3,959 were excluded following screening of titles and abstracts. Out of the 38 full text articles identified, 29 articles were excluded and an additional four articles were identified from references or gray literature (Figure 5.1). A total of 13 articles met the inclusion/exclusion criteria, each describing a technique for evaluating quality of decision making and assessing a total sample of

approximately 2,500 subjects (individuals, organisations, or medicines). These are summarised in Table 5.1 and described in greater detail below.

**Figure 5.1 Flow diagram of article selection**

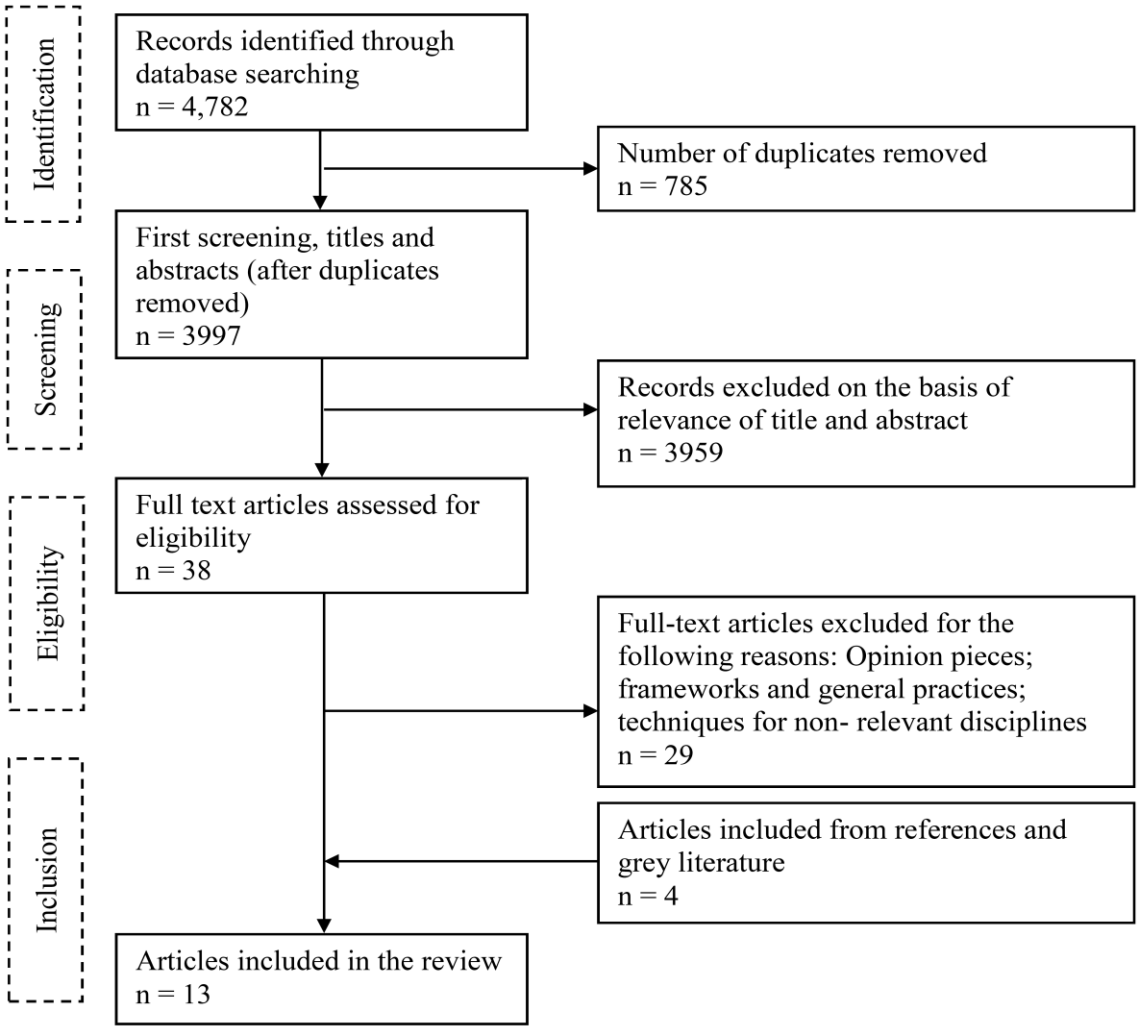


**Table 5.1 Summary characteristics of the 13 techniques for assessing quality decision making listed in descending order of total Quality Decision-Making Practices (QDMPs) evaluated by the technique**

| No. | Ref. | Title | Decision Area | Study subject | Subject type | Method | QDMPs evaluated | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1 | Matheson D & Matheson J, 1998 | Organisational IQ test | Corporate | Industry (including pharm.) | Org. | 45-item questionnaire assessing nine principles for strategic decision making in an organisation (N = 100s) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2 | Donelan et al., 2016 | Quality of Decision Making Orientation Scheme (QoDoS) instrument | Medicines R&D/Reg. Review | Regulatory authority + pharm. industry | Org. + Ind. | Questionnaire with 47 items assessing organisational decision making culture and approach, as well as individual competence and style (N = 76) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3 | Mindtools, 2013 | 'How Good Are Your Decision-Making Skills?' Questionnaire | General | ND | Ind. | Questionnaire, 'How Good Are Your Decision-Making Skills?' containing 18 items (N = ND) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| 4 | Garbuio et al., 2015 | Survey on strategic decision making | Corporate | Industry (including pharm.) | Org. | Survey (28 items) assessing relationship between robustness of analysis, dialogue and decision-making effectiveness (N = 634) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | ✓ |
| 5 | Open University, 2013 | Decision making Questionnaire | General | ND | Org. + Ind. | Questionnaire containing 12 items in three areas: decision-making process, psychological perspective and the role of social influences (N = ND) | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| 6 | Fischer et al., 2011 | A structured tool to analyse coverage decision making | HTA | HTA agencies | Med. | Ten indicators for a structured empirical comparison of coverage decisions with corresponding ordinal rankings (N = 6) | ✓ | ✓ | ✓ | | | | | ✓ | ✓ | ✓ |
| 7 | Wood, 2012 | Study exploring individual differences in decision-making styles as predictors of good decision making | General | University students | Ind. | Three-part study: 1. General Decision-Making Style measure (25 items) 2. The BFI personality test (50 items) 3. Peer ratings of decision-making quality (26 items) (N = 315) | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | | |
| 8 | Blenko et al., 2010 | Decision and organisational scorecard | General | ND | Org. | Two web-based questionnaires, with 4 and 10 items respectively assessing decision effectiveness and organisational drivers (N = 1,065) | ✓ | ✓ | | | | | | | | ✓ |

**(continued) Table 5.1 Summary characteristics of the 13 techniques for assessing quality decision making listed in descending order of total Quality Decision-Making Practices (QDMPs) evaluated by the technique**

| No. | Ref. | Title | Decision Area | Study subject | Subject type | Method | QDMPs evaluated | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 9 | Cowlrick et al., 2011 | Questionnaire for assessing perception of risk through phases of medicine R&D | Medicines R&D | Pharm. industry | Ind. | Questionnaire with 5 sets of judgment statements to assess case studies for 4 medicines (N = 52) | | | | ✓ | | ✓ | ✓ | | | |
| 10 | McIntyre et al., 2012 | Questionnaire for assessing how US FDA Advisory Committee Members prepare and what influences them | Regulatory Advisory Committee | Regulatory authority (US FDA) | Ind. | 26-item questionnaire assessing US FDA committees' preparatory practices, influencers and preferences (N =101) | | | | ✓ | ✓ | | ✓ | | | |
| 11 | Marangi et al., 2014 | Survey of the Italian Medicines Agency (AIFA) 2013 | Regulatory Advisory Committee | Regulatory authority (AIFA) | Ind. | Questionnaire, 'Survey AIFA 2013' consisting of 17 questions, 4 regarding participant information and 13 assessing influences on AIFA committees (N = 72) | | | | ✓ | ✓ | | ✓ | | | |
| 12 | Beyer et al., 2015 | A field study using the Domain Specific Risk Taking (DOSPERT) scale and the Big Five Jackson Inventory (BFI) scale | Reg. review | Regulatory authority (EU) | Ind. | Three-part questionnaire:<br>1. Demographic data and DOSPERT scale; 2. Medicine case Study;<br>3. The BFI personality test consisting of 44 items to assess risk perceptions of assessors (N = 75) | | | | ✓ | | ✓ | | | | |
| 13 | Salek et al. 2012 | Scorecards to assess the quality of a regulatory submission and its review | Reg. submission and review | Reg. authorities + pharm. industry | Med. | Two scorecards containing 50 items grouped into 7 domains: application format, content of the dossier, labelling, scientific advice, conduct of the review, communication and overall assessment (N = 4) | ✓ | | | | | | | | | |

Where: US FDA = Food and Drug Administration, HTA = health technology assessment; ind.=individual; med. = medicine; N = sample subject size used in testing; ND = not defined; org.=organisation; pharm.= pharmaceutical; QDMP = quality decision-making practice; reg. = regulatory; R&D = research and development; ✓ = QDMP evaluated by the technique; the QDMPs are: 1=Have a systematic, structured approach to aid decision making (consistent, predictable and timely); 2=Assign clear roles and responsibilities (decision makers, advisors, contributors); 3=Assign values and relative importance to decision criteria; 4=Evaluate both internal and external influences/biases; 5=Examine alternative solutions; 6=Consider uncertainty; 7=Re-evaluate as new information becomes available; 8=Perform impact analysis of decision; 9=Ensure transparency and provide a record trail; 10=Effectively communicate the basis of the decision

**Part II: Identified Techniques for Evaluating Quality of Decision Making**

Out of the 13 techniques identified in this review, seven were developed specifically to assess decision making in the area of medicines development, regulatory review or HTA; two examined corporate decision making and four were regarding general decision making. An examination of subject type demonstrated that the largest proportion of the techniques (6, 46%) assessed decision making of individuals, followed by the perception of individuals regarding the decision making of the organisation (3, 23%) and then the decision making regarding the medicine itself (2, 15%). Only two techniques (15%) evaluated both the decision making of individuals and organisations.

Regarding the ability for each technique to evaluate the ten QDMPs, the 13 techniques assessed a median of six QDMPs, with a mode of three QDMPs and only two techniques accounted for all ten QDMPs. An examination of the two most commonly assessed practices indicated that ten techniques assessed QDMP 4 (Evaluate both internal and external influences/biases), whereas nine techniques evaluated QDMP 1 (Have a systematic, structured approach to aid decision making). The two practices that were least evaluated were QDMP 9 (Ensure transparency and provide a record trail) and QDMP 10 (Effectively communicate the basis of the decision), with four and five approaches, respectively.

The 13 techniques are listed in Table 5.1 in descending order of total number of QDMPs evaluated by the technique, followed by the year of publication. They are then described in more detail based on published information.

*1. Organisational IQ Test (Matheson and Matheson, 1998)*

This test measures an R&D organisation's adherence to the nine principles of a smart organisation: value creation culture, creative alternatives, continual learning, embracing uncertainty, outside-in strategic perspective, systems thinking, open information flow, alignment and empowerment as well as disciplined decision making. The aim of this test is to benchmark “organisational intelligence” (i.e., the strategic decision-making abilities of an organisation), identify barriers to decision quality and prioritise the principles an organisation must focus on to increase its performance (Matheson and Matheson, 1998).

The nine principles were developed based on previous studies of decision quality and best practices, which were conducted in five well-described phases, namely: brief survey to identify organisations that exemplified high quality R&D decision making; in depth interviews with 22 companies to identify 45 best practices; questionnaire to create statistical benchmarks for practices; validation through conformational studies with other companies;

and extension of results to develop the principles. Subsequently, the test was developed and it consists of 45 questions, with five questions on each of the nine principles (Matheson and Matheson, 1998) These 45 questions can be used to evaluate all ten QDMPs from the point of view of an organisation.

The tool has now been used to assess approximately a hundred corporations from the point of view of thousands of individuals regarding their organisation's decision making and the results show that a strong IQ profile correlates positively with the financial performance of organisations, thereby demonstrating the applicability of the tool (Matheson and Matheson, 2011). The sensitivity or reproducibility of the tool has not been described. Although the tool evaluates the full spectrum of organisational-level QDMPs, the practices of an individual are not evaluated. Furthermore, the test is specific to R&D organisations and possesses generalisability to be applied within different departments in companies including the pharmaceutical industry, but its design did not involve input from regulatory authorities or HTA agencies and consequently, it does not assess the issues specific to those stakeholders.

In summary, the Organisational IQ, which was developed through studies with a range of R&D organisations, is a 45-item test that measures corporate decision making across all ten QDMPs from an organisational point of view only; it has been assessed in over a hundred companies, but it has not been developed or validated within agencies.

*2. Quality of Decision Making Orientation Scheme (QoDoS; Donelan et al., 2016)*

QoDoS (see Appendix 1) is a generic instrument for assessing the quality of decision making. Its aim is to evaluate the quality of decision making of individuals and organisations in order to promote awareness of best practices and biases in decision making. This should facilitate a clearer understanding of strengths and areas for improvement and ultimately encourage a better decision-making process for both companies and agencies (Donelan et al., 2016).

The tool was developed and validated using a standardised approach with both qualitative and quantitative techniques. The qualitative phase involved semi-structured interviews with 29 key opinion leaders from the pharmaceutical industry (10), regulatory authorities (9) and contract research organisations (10) (Donelan et al., 2015). This was followed by content validity testing, using a panel of experts for language clarity, completeness, relevance and scaling, resulting in a favourable agreement by panel members with an intra-class correlation coefficient value of 0.89 (95% confidence interval = 0.56, 0.99). The quantitative phase of factor analysis produced a 47-item tool with four domains: Part I = Organisational—Decision-Making Approach and Decision-Making Culture; Part II = Individual—Decision-

Making Competence and Decision-Making Style. QoDoS showed high internal consistency ($n$ = 120, Cronbach's alpha = 0.89), high reproducibility ($n$ = 20, intra-class correlation = 0.77) and a mean completion time of ten min (Donelan et al., 2016). Most importantly, QoDoS items can be mapped to assess the full spectrum of the ten QDMPs across different decision points from both the perspective of an organisation and an individual.

The applicability of the tool in a regulatory authority and pharmaceutical company setting was confirmed through a study with 76 participants (50% from regulatory authorities and 50% from pharmaceutical companies). The findings of this pilot study demonstrate that QoDoS has the practicality to identify differences in decision making between individuals and their organisation as well as between companies and regulatory authorities across all ten QDMPs (Bujar et al., 2016). Moreover, QoDoS possesses strong psychometric properties, is easy to understand and can be completed in a short time frame. Nevertheless, the tool needs to be further tested in terms of its reliability and relevance (Chapter 6) and sensitivity (outside the scope of this study). Moreover, although the initial practicality of QoDoS has been demonstrated, it would be of value to carry out in depth studies to further demonstrate the practicality of the instrument for assessing QDMPs in specific teams and departments within pharmaceutical companies, regulatory authorities and HTA agencies (Chapter 7).

To summarise, the QoDoS is a 47-item test that measures quality decision making across all ten QDMPs from an organisational and individual point of view. It was developed through studies with the population it was intended for (i.e., both the pharmaceutical industry and regulatory authorities); its applicability has been assessed with 76 participants with more testing planned in the future.

*3."How Good Are Your Decision-Making Skills?" Questionnaire (Mindtools, 2013)*

The aim of this generic web-based questionnaire was to assess individual decision-making skills and practices. It is composed of 18 questions that relate to six essential steps in any decision-making process: establishing a positive decision-making environment, generating potential solutions, evaluating the solutions, deciding, checking the decision and communicating and implementing (Mindtools, 2013).

The method used in the development or validation was not published, nor any results that were collected from participants. Overall, this questionnaire assesses nine QDMPs from the point of view of an individual, but nevertheless does not assess QDMP 10 regarding communication of the decision and it does not assess the personal perceptions regarding organisational decision making. This tool possesses generalisability to other decision areas

and subjects, but it lacks published data on its method used in development or validity testing to determine its practicality and robustness.

In summary, this questionnaire is a generic 18-item test that measures decision making across nine QDMPs from an individual point of view only; its origin and testing were not described.

*4. Survey on Strategic Decision Making (Garbuio et al., 2015)*

The aim of this survey was to assess strategic decision making amongst international companies, including the pharmaceutical industry. It was used in a study to test three hypotheses regarding the effect of two dimensions, namely the analysis performed on the decision and strategic conversations about the decision (coined "disinterested dialogue") on decision-making effectiveness (Garbuio et al., 2015).

The development of the survey was based on a literature review, previous scholarly works in this area (Dean and Sharfman, 1996) and interviews with 29 executives from large corporations. The survey assesses an individual's perception of decision making and contains a total of 28 questions focusing on a key strategic decision made in the past five years: eight on demographic characteristics of the respondents, six variables measuring robustness of analysis performed, six on disinterested dialogue, four on strategic decision effectiveness and four control variables. The Cronbach's alpha coefficient for strategic decision effectiveness, robustness of analysis and disinterested dialogue were 0.886, 0.793 and 0.716, respectively, which indicates the survey was appropriately formulated and suitable for the analysis (Garbuio et al., 2015). These survey items can be mapped to eight out of the ten QDMPs from the point of view of an individual, mainly regarding "Structure and Approach" (QDMP 1, 2), "Evaluation" (QDMPs 3, 4, 5 and 6), "Impact" (QDMP 8) as well as communication of the decision (QDMP 10). It nevertheless does not assess QDMP 7 regarding re-evaluating the decision with new information, as well as QDMPs 9 regarding ensuring transparency and providing a record trail.

The survey was completed by 634 executives from a global range of industries, regions and functional specialties. The response rate was 45%, which may be due to the lengthy method used in the study. Exploratory and confirmatory factor analysis was used to test the hypotheses (Garbuio et al., 2015). Overall, this survey provided a good overview of some of the perceptions of organisational-level QDMPs in companies. Nevertheless, the survey does not evaluate two of the QDMPs and it does not assess the individual level decision-making practices, which could have provided further key insights regarding decision making in companies. The survey possesses generalisability to be used in various teams and departments

in pharmaceutical companies, but would need to be validated further in terms of its sensitivity and reproducibility. Nevertheless, it is not appropriate for use in regulatory authorities and HTA agencies due to the specific nature of the technique.

To summarise, this technique is a 28-item survey that assesses corporate strategic decision making from the point of view of an organisation. Consequently, it was developed through studies with companies only (some of which were pharmaceutical) and subsequently tested with 634 subjects across eight QDMPs; it is not relevant to agencies.

*5. Open University Decision-Making Questionnaire (Open University, 2013)*

This test was administered as part of a postgraduate course in Business at the Open University, UK. The aim of the questionnaire was to help an individual develop greater insight into their personal decision-making processes (Open University, 2013).

The development or testing of the tool was not published. The questionnaire is composed of 12 questions assessing decision making in a recent major decision concentrating on three areas: formal rational decision-making process; psychological perspective and focus on the tendency to rely on "heuristics" (i.e., subjective judgments); and the role of social influences on decision making. The 12 questions can be mapped to seven out of the ten QDMPs from the point of view of an individual (though a small number of questions are applicable to organisations too), excluding QDMP 2 regarding roles and responsibilities and QDMPs 9 and 10 regarding transparency and communication.

In summary, this technique is a 12-item questionnaire that assesses decision making from the point of view of an individual or an organisation. Due to its generic nature, it may be applicable to companies and agencies alike, though this would require practicality testing and validation. Nevertheless, the development and testing of the tool were not described and the questionnaire assessed seven out of ten QDMPs.

*6. A Structured Tool to Analyse Coverage Decisions (Fischer et al., 2011)*

This study presents a structured tool that aims to analyse coverage decision-making processes and drivers. Its purpose was to compare country-specific reimbursement systems to inform a number of stakeholder including HTA agencies, manufacturers, policy-makers, patients and the public (Fischer et al., 2011).

The tool was developed based on the published conceptual framework of Rogowski et al. (2008) that identified seven key components in deciding on the reimbursement of a new

technology. Fifteen semi-structured interviews were conducted to apply this framework to specific case studies in the area of cancer prevention with participants from decision-making institutions from Austria, Sweden and Lithuania; data were further validated with publicly available documentation. From the case studies, the structured scheme describing the components of reimbursement decision processes and a proposal of ordinal rankings were deduced and validated through consultations with experts. The developed scheme contains eight reimbursement decision-making steps namely: trigger; participation, publication, assessment, appraisal, reimbursement, management and impact (Fischer et al., 2011). Overall, the tool evaluates six of the QDMPs covering all practices relating to "Structure and approach," "Impact," and "Transparency and Communication," but only one QDMP regarding "Evaluation," namely QDMP 3 (assign values and relative importance to decision criteria).

This method was applied to case scenarios with six medicines and it generated a scheme for structured and consistent comparison of a large variety of procedural aspects of reimbursement decision processes. The study met its purpose and a robust method was used to develop the scheme. Nevertheless, the semi-structured phone interviews were considered time consuming and the scope for interpretation of questions during interviews was wide. Further validation of the structured scheme and indicators as well as development of a web-based tool for more efficient large-scale empirical studies is still needed (Fischer et al., 2011). Moreover, the scheme does not explicitly assess QDMPs relating to evaluation, which if incorporated, would perhaps give more rationale for some of the heterogeneity seen in the decision outcomes.

In summary, this technique, which was designed based on a conceptual framework, is a structured tool to analyse coverage decision making of medicines using ten indicators across six QDMPs. Nevertheless, the tool is specific to evaluating certain decisions regarding technologies in HTA agencies and was not designed to assess general organisational or individual practices or decision making within companies and regulatory authorities.

*7. Study Exploring Individual Differences in Decision-Making Styles as Predictors of Good Decision Making (Wood, 2012)*

The aim of this study was to examine the relationship between decision-making styles and subjective self- and peer-ratings of decision quality. The second purpose of the study was to evaluate the incremental validity of decision styles and personality traits for predicting decision quality (Wood, 2012).

The method involved three phases. Decision style was measured using Scott and Bruce (1995) General Decision-Making Style measure; the Big Five Jackson Inventory (BFI) personality test (50 items) was conducted using the International Personality Item Pool short scales (Goldberg, 1999; Goldberg et al., 2006) and peer ratings of decision-making quality were collected using a scale where peers were asked to evaluate their friends' decision making by rating their habits in four sections. The first two measures were developed and validated previously; the third was created for the purpose of this study through factor analysis and psychometric tests for internal consistency. Overall, this technique can be used to assess six out of ten QDMPs, including all five QDMPs relating to evaluation, as well as QDMP 1 regarding having a structured approach. The technique can be used to assess the decision making of individuals only, but uniquely, the assessment can be conducted from the point of view of the participants as well as the perception of peers regarding the ratees' decision-making habits.

Three hundred and fifteen target participants from undergraduate courses at a public university in the Midwestern United States took part in phases 1 and 2 of the study, using an online survey administration and data collection system. In addition, 168 peer raters completed phase 3 of the study regarding decision-making habits of the target participants. However, the completion time was not specified and there are limitations to the use of the peer rating system, as indicated by a relatively low response rate (53% of phase 1 and 2 participants participated in phase 3). Furthermore, this technique does not assess organisational-level QDMPs or individual practices regarding roles and responsibilities, decision impact, transparency and communication, as specified by QDMPs 2, 8, 9 and 10, respectively.

To summarise, this three-part study, which aimed to assess differences in decision-making styles, was designed to be global in nature and consequently it may be applicable to any decision areas as well as be used by any subjects. Nevertheless, it assessed only six QDMPs and the method would require testing and validation in pharmaceutical companies, regulatory authorities and HTA agencies.

*8. Decision Effectiveness and Organisational Scorecards (Blenko et al., 2010)*

The aims of the scorecards were to give a high-level assessment of decision making within organisations, help identify the most pertinent issues and guide prioritisation of actions on specific decisions and broader organisation enablers. The two scorecards represent step 1, namely “Score your organisation,” with a sequence of five steps to improve decision making (Blenko et al., 2010).

The method used in the development of the two scorecards was not published. The decision effectiveness scorecard is composed of four items assessing quality, speed, yield and effort of the decision making-process. The organisational scorecard has ten items and it is used to assess drivers of decision effectiveness in an organisation, namely context, alignment, accountability, structure, process, information, tools, skills and capabilities, leadership and culture. Overall, the two scorecards look beyond decision making as a marker of an effective organisation and consequently assess three out of ten organisational-level QDMPs, namely QDMP 1 (structure), 2 (roles and responsibilities) and ten (communication of the decision). The scorecards were used to assess 1,065 organisations including large multinational corporations, entrepreneurial ventures, research universities and non-profit institutions, thereby highlighting the generalisability of this method (Blenko et al., 2010).

To summarise, this two-part scorecard is generic in nature and can be used to assess decision making of organisations. Nevertheless, the approach used in the development and validation of the scorecards was not described and none of the individual-level QDMPs and only three organisational-level practices can be assessed.

*9. Questionnaire for Assessing Perception of Risk through Phases of Medicine R&D (Cowlrick et al., 2011)*

This questionnaire was designed to assess risk perceptions in the pharmaceutical industry and allied healthcare sectors and is analogous to the Beyer regulatory authority study (Beyer et al., 2015) described later in this chapter. The aim is to investigate go/no-go judgments in discovery and medicine development in order to evaluate the influence of personality, experience as well as demographic traits on decision making (Cowlrick et al., 2011).

The method consists of a web-based questionnaire where respondents were asked to make five sets of judgment within case studies regarding four medicines derived from real scenarios. These five judgments were derived from 18 non-discrete steps relating to the regulatory requirements as set by the European Medicines Agency (EMA) and the US Food and Drug Administration (US FDA) and were related to major key disciplines in medicines R&D, namely target selection/ pharmacology; toxicology; biopharmacy and galenics; and clinical development/market introduction. In addition, the study assessed to what extent the individual judgments given by the respondents were influenced by demographics, experience, or their perceived entrepreneurial character. Paradigms of entrepreneurial behaviour were selected based on previous research, although the exact process for question design was not described (Cowlrick et al., 2011). The completion of the questionnaire takes ~10 min. Overall, the tool assesses only three of the ten QDMPs relating to evaluation, namely QDMP

4 (evaluate internal/external influences/biases), 6 (consider uncertainty) and 7 (re-evaluate as new information becomes available). Due to the stepwise nature of the cases, this tool offers the potential to understand whether individuals re-evaluated their decision making with new information, which was not possible in the single step decision study by Beyer et al. (2015).

The questionnaire was completed by 52 participants, a response rate of 62%, which indicated moderate acceptability (Cowlrick et al., 2011). The authors did not describe how the method used was developed, compared with the Beyer et al. (2015) study in which validated tools were used, but nevertheless, this technique was less time intensive.

In summary, this questionnaire was used to assess decision making during medicines R&D across three QDMPs from the point of view of an individual only. The design of the questionnaire is unknown. Furthermore, the questions are generalisable to other stakeholders, whereas the case studies are specific to the pharmaceutical industry and would require major modifications and further validation if to be used in regulatory authorities and HTA agencies.

*10. Questionnaire for Assessing How US FDA Advisory Committee Members Prepare and What Influences Them (McIntyre et al., 2012)*

This qualitative study was carried out to understand preparatory practices, influencers and preferences of US FDA advisory committees regarding materials provided by the sponsor and the FDA, advisory committee presentations and question and answer (Q&A) sessions. The goal was to understand what advisory committee members want from sponsors to enable their informed participation in the meetings (McIntyre et al., 2012).

It consisted of a web-based survey composed of 26 questions, with a target completion time of ten min. The method used in the design and validation of the questions was not described. This survey assesses a limited set of decision-making practices, namely QDMP 4, 5 and 7 regarding evaluation of influences/biases, examination of alternatives and re-evaluation with new information respectively from the point of view of an individual only.

The qualitative questionnaire was administered to 101 current or former members of one of the US FDA public biomedical advisory committees. The advantages are a short completion time and that the questionnaire captured the relevant individual practices and influences regarding evaluation of material for committee meetings (McIntyre et al., 2012). Moreover, the survey does not evaluate seven out of the ten individual practices, or what the individuals think about the practices of the organisation (in this case, the committee). This is likely due to the fact that this was outside the scope of this study.

In summary, this 26-item questionnaire was used to assess decision making by the US FDA Advisory Committee across three QDMPs from the point of view of an individual only. Nevertheless, the development and validation of the questions were not published. Although this questionnaire could be adopted for other regulatory bodies, the questions are specific to committee decision making and have limited transferability to other regulatory areas as well as stakeholders such as industry and HTA agencies.

*11. Survey of the Italian Medicines Agency (AIFA) 2013 (Marangi et al., 2014)*

A questionnaire that was analogous to US FDA's was undertaken by AIFA in 2013 to assess the influences on agency committees and secretariats' opinions and decisions. This study was part of an initiative to enhance a transparency-oriented policy and improve information exchange as well as decision making with stakeholders (Marangi et al., 2014).

The study was a web-based questionnaire with a completion time of seven min and a total of 17 questions assessing the demographics, professional qualifications and committee experiences, followed by questions regarding internal and external influences on committees and secretariat member opinions. The method used in the design of the questions was not described. Similar to the US FDA study, the questions are specific to AIFA advisory committee meetings and the survey assesses a narrow set of individual QDMPs relating to decision-making evaluation practices only (QDMP 4, 5 and 7). A total of 72 participants from AIFA committees, secretariats and subcommission members took part in the study (Marangi et al., 2014). This qualitative survey can be completed in a short timeframe, but the development of the questions was not described.

To summarise, this 17-item questionnaire was used to assess decision making by the AIFA Advisory Committee across three QDMPs from the point of view of an individual only. Moreover, the origin of the questionnaire has not been published. Although the questionnaire meets its objectives, it is not transferable outside the regulatory advisory committee setting to industry and HTA agencies.

*12. A Field Study Using the Domain-Specific Risk Taking (DOSPERT) Scale and the Big Five Jackson Inventory (BFI) Scale (Beyer et al., 2015)*

This set of tests aimed to assess the influence of risk attitudes and personality traits on clinical decision making of expert regulators. The two main objectives of the study were to describe the distribution of risk attitudes among medical assessors within EMA and to measure their personality traits and cross-domain risk attitudes (Beyer et al., 2015).

This study was implemented as a web-based questionnaire and was composed of three well-defined phases using validated tests; phase 1: demographic data and 30-item DOSPERT scale to measure risk appetite; phase 2: medicine case study using mock "clinical dossiers" for three medicines and eight rating scales on benefit-risk dimensions; and phase 3: The BFI 44-item personality test. Ordinal regression models were used to evaluate the relationships between the variables regarding risk taking, personality as well as the assessment of benefit and risk of a medicine (Beyer et al., 2015). Although the study evaluates the relationship between perception of uncertainty and personal influences as defined by QDMP 4 and 6, it does not evaluate any of the practices relating to decision making "structure and approach," "impact," or "transparency and communication" of decision making. Indeed, other individual as well as organisational decision-making practices should be explored in order to understand the broader context of these findings.

This technique was used to assess 75 assessors from European regulatory authorities. It utilises validated methods and it meets its purpose of assessing risk attitudes in medical assessors (Beyer et al., 2015). It generalisable to other agencies, but would need to be adapted for companies and HTA agencies with some modifications to phase 2 (medicine case study). A major drawback of this technique is that it is resource and time intensive for both the assessors and researchers.

To summarise, this three-part questionnaire was used to assess decision making of regulatory assessors. The development of the study was well-described, but it can only be used to assess two out of ten QDMPs and it does not evaluate the perceptions of the individuals regarding their organisation.

*13. Scorecards to Assess the Quality of a Regulatory Submission and Its Review (Salek et al., 2012)*

Two scorecards were developed to enable companies to assess the quality of the regulatory review and for regulatory authorities to assess the quality of submission relating to a specific product. This allows for a unique comparison of the quality of the submission compared to review, as well as inter-product, company, or agency cross-evaluations (Salek et al., 2012).

The scorecards were developed through a structured and well-described process of conceptualisation (expert discussions; bibliography review), item generation (literature review; expert input) and reduction (qualitative reduction; content validation). Each scorecard includes more than 50 items that are grouped into seven domains (application format, content,

labelling, scientific advice, conduct of the review, communication and overall assessment). The two scorecards enable a quantitative assessment of the quality of the information and communication specific to dossiers and go beyond just decision making as a marker of quality (Salek et al., 2012). As a consequence they evaluate whether a structured approach was taken (QDMP 1), but do not evaluate the roles and responsibilities of an individual/organisation (QDMP 2) or the quality of individual and organisational decision making as outlined in QDMP 3, 4, 5, 6 and 7, which are related to the evaluation practices as well as preferences, or QDMP 8, 9 and 10 which assess decision-making transparency and decision communication.

The scorecards were tested by three major regulatory authorities and four international pharmaceutical companies based on the same four products. The majority of respondents agreed that the scorecards covered all critical factors that affect the quality of the dossier and the review. A number of modifications were made following a pilot study, particularly the inclusion of definitions for each rating response option, which further added to the robustness of the scorecards (Salek et al., 2012).

The high response rate as well as positive feedback indicated their practicality, clarity and applicability, whilst the method used was well-described. The scorecards can be used for different regulatory procedures and across different teams and can be therefore applied to optimise the regulatory authority and company processes. Importantly, this technique encourages open internal and external dialogue. Although the scorecards meet their purpose of assessing the quality of review and submission, it can be argued that aspects specific to decision making, other than having a structured approach (QDMP 1), need to also be addressed to ensure that companies and agencies are not only embedding good review and submission practices, but are also making quality decisions (Liberti et al., 2013).

In summary, the scorecards can be used to assess the quality of regulatory submission and review and were developed using a well-defined framework using input from regulatory authorities and companies. Nevertheless, they only assess one QDMP and are outside the scope of HTA agencies; a separate set of scorecards would need to be developed and validated for this purpose.

**Part III: Measurement Properties of the Techniques for Evaluating Quality of Decision Making**

The 13 techniques were evaluated in terms of their measurement properties, according to six key criteria (McDowell, 2006; Streiner et al., 2015), namely theoretical underpinning (development technique was based on a well-described methodological framework); psychometric properties (development of technique involved psychometric tests, content validity and internal consistency); psychometric evaluations (reliability, relevance and sensitivity of the tool was demonstrated); demonstrated practicality (the technique was applied to target population through pilot studies); generalisability (the technique can be used across industry, regulatory and HTA); and applicability (the technique is applicable to evaluating individuals and organisations). The techniques were listed in a descending order by total number of criteria met, followed by year of publication (Table 5.2). Only five properties are shown in Table 5.2, as none of the techniques underwent psychometric evaluations.

Out of the 13 articles, only one met all criteria described in Table 5.2. Eleven (85%) of the techniques met at least two criteria, namely demonstrated practicality, followed by theoretical underpinning (8, 62%). On the other hand, the criteria that were met by the minority of the techniques were generalisability of study subjects (5, 38%); psychometric properties (3, 23%); and applicability to both assessing individuals and organisations (2, 15%). None of the 13 techniques met the criteria of psychometric evaluations regarding the demonstration of sensitivity/responsiveness (detecting change over time), reliability (producing similar results under consistent conditions) and relevance (being practical to the target audience) and were consequently not illustrated in Table 5.2.

**Table 5.2 Measurement properties of the 13 techniques for assessing quality decision making in descending order of total properties met, followed by year of publication**

| No. | Ref. | Title | **Theoretical underpinning** | **Psychometric properties** | **Demonstrated practicality** | **Generalisability** | **Applicability** |
|---|---|---|---|---|---|---|---|
| | | | *Development technique was based on a well described methodological framework* | *Content validity, internal consistency was demonstrated* | *The technique was applied to target population through pilot studies* | *The technique can be used across industry, regulatory and HTA* | *The technique is applicable to evaluating individuals and organisations* |
| 1 | Donelan et al., 2016 | Quality of Decision Making Orientation Scheme (QoDoS) instrument | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2 | Wood, 2012 | Study exploring individual differences in decision-making styles as predictors of good decision making | ✓ | ✓ | ✓ | ✓ | |
| 3 | Garbuio et al., 2015 | Survey on strategic decision making | ✓ | ✓ | ✓ | | |
| 4 | Matheson D & Matheson J, 1998 | Organisational IQ test | ✓ | | ✓ | | |
| 5 | Blenko et al., 2010 | Decision and Organisational Scorecard | | | ✓ | ✓ | |
| 6 | Fischer et al., 2011 | A structured tool to analyse coverage decision making | ✓ | | ✓ | | |
| 7 | Cowlrick et al., 2011 | Questionnaire for assessing perception of risk through phases of medicine R&D | ✓ | | ✓ | | |

**(continued) Table 5.2 Measurement properties of the 13 techniques for assessing quality decision making in descending order of total properties met, followed by year of publication**

| No. | Ref. | Title | Theoretical underpinning | Psychometric properties | Demonstrated practicality | Generalisability | Applicability |
|---|---|---|---|---|---|---|---|
| | | | *Development technique was based on a well described methodological framework* | *Content validity, internal consistency was demonstrated* | *The technique was applied to target population through pilot studies* | *The technique can be used across industry, regulatory and HTA* | *The technique is applicable to evaluating individuals and organisations* |
| 8 | Salek et al. 2012 | Scorecards to assess the quality of a regulatory submission and its review | ✓ | | ✓ | | |
| 9 | Open University, 2013 | Decision making Questionnaire | | | | ✓ | ✓ |
| 10 | Beyer et al., 2015 | A field study using the Domain Specific Risk Taking (DOSPERT) scale and the Big Five Jackson Inventory (BFI) scale | ✓ | | ✓ | | |
| 11 | McIntyre et al., 2012 | Questionnaire for assessing how US FDA Advisory Committee Members Prepare and What Influences Them | | | ✓ | | |
| 12 | Mindtools, 2013 | 'How Good Are Your Decision-Making Skills?' Questionnaire | | | | ✓ | |
| 13 | Marangi et al., 2014 | Survey of the Italian Medicines Agency (AIFA) 2013 | | | ✓ | | |

## DISCUSSION

This is the first literature review that has identified techniques for evaluating the quality of the decision-making process in medicines development, regulatory review and HTA. The objectives were to compare the existing techniques, assess their properties, identify research gaps and recommend the next steps. This literature review has demonstrated that the area of quality decision making has been explored to a certain extent during the medicines research and development, but in a fragmented way, where studies have been independent, few have been replicated and there is no overarching mutually agreed framework for quality decision making.

This is consistent with previous research which has identified that the majority of pharmaceutical companies, regulatory authorities and HTA agencies do not have formal assessments in place to periodically measure the quality of their decision making (Chapter 3 and 4) and this could be partially explained by the fact that very few appropriate techniques exist to enable this to be done. Nevertheless, both of these stakeholders believe that such measurements of quality decision making would be possible and would improve practices for individuals and organisations, which could be achieved by utilising the best techniques currently available (Chapter 3 and 4). Consequently, there is a need to identify a technique that is relevant, robust and can be applied to pharmaceutical companies, regulatory authorities and HTA agencies.

It should be noted that most of the techniques are suitably robust to be used in the area they were created for and therefore should be utilised for their specific purposes despite not having the applicability across all three stakeholders. Nevertheless, an advantage of having a tool valid across all three stakeholders would be the ability to discuss, share and compare challenges in decision making using a common terminology. Already companies, regulatory and HTA agencies have been collaborating regarding topics such as parallel scientific advice (EMA, 2016), real world evidence generation as well as parallel regulatory and HTA reviews (McAuslane et al., 2016) and it would be of interest to align best practices in decision making across the three groups.

### Key Trends and Features of Existing Techniques

This review identified 13 techniques for evaluating the quality of decision-making process in medicines development, regulatory review and HTA. This is a relatively low number, considering the increasing pressure on pharmaceutical companies, regulatory authorities and HTA agencies to make the best-quality decisions (Liberti et al., 2013). Moreover, routine assessment of the quality of the decision-making process (as opposed to just measuring

outcomes) has been recognised as key for improving the productivity of any organisation (Kahneman, 2011).

Out of the 13 techniques, 1, the Organisational IQ, was developed in 1998 and 12 were published from 2010 onward. This indicates that although some initial work was done early on and stands ahead of its time, it is only in more recent years that measuring decision making or understanding decision-making styles and approaches has become of interest in this arena. The 13 techniques have unique aims as well as strengths and weaknesses based on their origin and the methods that were used in their development and testing. Furthermore, they can be classified into three groups described below.

**Group 1: Seven Specific Research Techniques for Assessing the Quality of the Decision Making-Process in Medicines Development, Regulatory Review, or HTA**

An examination of the seven techniques developed specifically to assess decision making in the area of medicines development, regulatory review, or HTA demonstrated that a number of were developed to meet the needs of a particular organisation, for example to increase transparency of regulatory advisory committee meetings within AIFA and US FDA (McIntyre et al., 2012; Marangi et al., 2014). Nevertheless, although these two surveys are practical for their purpose and are characterised by low resource intensity, their design was not described and their latitude for generalisability and measurement against the QDMPs is limited due to their specific scope.

Other techniques, as exemplified by the work of Beyer et al. (2015) and Cowlrick et al. (2011) were developed as research tools to measure the effect of risk attitudes and personality traits on decision making regarding medicines development and review. These studies developed and tested a number of interesting hypotheses, but are resource intensive and are limited to the specific decision area as well as to the subjects they were designed to assess. Finally, a number of techniques evaluate more than just decision making as a marker of quality, such as the "Scorecards to Assess the Quality of Regulatory Submission and Review" (Salek et al., 2012) and the "Structural tool to analyse coverage decision making" (Fischer et al., 2011) and may represent promising techniques to study the general area of quality to assess the effectiveness of an organisation or an outcome (Fischer et al., 2011; Salek et al., 2012).

The last technique in this group "Survey on strategic decision making" (Garbuio et al., 2015) looked specifically at corporate decision making, which is applicable to pharmaceutical companies (i.e., medicines development). Although the tool was developed based on a well-

designed methodological framework and demonstrated practicality in companies, it is resource intensive and does not possess the generalisability to allow its application to other subjects such as regulatory authorities or HTA agencies or to individuals (as opposed to just organisations) due to the specific nature of the questions. It is important to note that, all seven of these techniques were used primarily for research or as one-off studies, but they have not been systematically adopted for use by companies, regulatory authorities or HTA agencies. Overall, none of these seven techniques are appropriate to measure decision making quality due to low generalisability as well as an inability to measure all ten QDMPs.

**Group 2: Four Educational or Consulting Techniques for Assessing the Quality of the Decision-Making Process**

Four of the techniques were either developed for educational purposes or by consulting groups to assess decision making in general (Blenko et al., 2010; Wood, 2012; Mindtools, 2013; Open University, 2013). Consequently, although all four possess good generalisability to be applied to industry, regulatory authorities and HTA agencies, only one of the techniques has published information regarding its design and psychometric properties (Wood, 2012), while only two have demonstrated practicality through pilot studies (Blenko et al., 2010; Wood, 2012). As well as that, only one of the techniques has the applicability to measure decision making in both individuals and organisations (Open University, 2013). Consequently, these may be useful generic tools for informal assessments of decision making, but due to lack of published data regarding their design and measurement properties, as well as a lack of applicability to individuals and organisations across the ten QDMPS, these techniques lack robustness to formally evaluate quality decision making in companies, regulatory authorities and HTA agencies.

**Group 3: The Two Most Promising Techniques for Assessing the Quality of the Decision-Making Process**

Only two of the 13 techniques evaluated the full spectrum of the ten QDMPs, namely the Organisational IQ (Matheson and Matheson, 1998) and QoDoS (see Appendix 1; Donelan et al., 2016). Incidentally, the two instruments possess a similar number of items (45 for Organisational IQ and 47 for QoDoS) and can therefore be completed in a short timeframe. Both techniques were designed based on a well-hypothesised conceptual and well-described methodological framework and demonstrated practicality in the target populations, but only QoDoS underwent psychometric testing during its design, namely content validity and internal consistency. It is nevertheless interesting and significant that these two most promising techniques for quality decision making were developed independently, with a 20-year time gap between them and both resulted in similar key features.

The second area of disparity is that the Organisational IQ test, unlike QoDoS, does not assess the practices of both individuals and organisations, but just the latter. Although it could be argued that this is sufficient as individuals make up an organisation, assessing individuals is also key as people tend to score themselves more favourably but be more critical of an organisation (Bujar et al., 2016). While this could be a potential sign of bias, areas of disparity between the individuals and organisations could also indicate deficiencies in practices within companies, agencies and committees, as changes in individuals could translate into better organisational practices. Consequently, assessment with QoDoS gives a unique perspective of both groups which helps to identify areas for improvement.

In the third area of divergence between the two techniques, the development of the Organisational IQ test was based on research among R&D organisations and consequently the factors in decision making specific to regulatory authorities and HTA agencies were not incorporated into the instrument. Nevertheless, the Organisational IQ test represents a practical approach and possibly a gold standard for measuring decision making of pharmaceutical and other companies. In contrast, QoDoS was developed specifically to look at decision making in the area of medicines development and regulatory review, based on interviews with key opinion leaders from agencies and companies. It is therefore a more appropriate tool compared with the Organisational IQ test to measure quality decision making in pharmaceutical companies, regulatory authorities and HTA agencies and moreover it can be applied to identify commonalities and differences between the various stakeholders as well as strengths and areas for improvement (Chapters 3 and 4). Most importantly, it can increase an awareness of the biases and influences that need to be considered when making decisions, as well as the best practices that should be incorporated into a decision-making framework. Although the psychometric evaluation of QoDoS has been partially established, further testing would seek to demonstrate its practicality through in depth case studies, as described in Chapter 7, as well as to assess its reliability and relevance (Chapter 6) and sensitivity (outside the scope of this research programme).

**Emerging Research Themes**

A secondary outcome of this review has been the identification of research themes and hypotheses regarding decision-making preferences and influences. These have been derived from the pilot studies conducted using the identified techniques and instruments. A selection of the findings is described below.

The research themes identified through the work of Beyer et al. (2015) as well as Cowlrick et al. (2011) relate to the impact of personality traits, functional role, education and gender on

decision making of individuals within pharmaceutical companies and regulatory authorities. Both studies demonstrate that these factors can explain the variability in judgments and decision-making techniques within organisations. Moreover, the study by Beyer et al. (2015) demonstrated that "conscientiousness" (being thorough and careful) predicted an increase in the perception of a medicine's benefits; whereas extraverted disposition was predictive of seeing fewer risks and interestingly, male assessors gave higher scores for a medicine's benefit ratings than did female assessors. Importantly, these research findings are in line with general research on decision making and risk taking (Thaler and Sustein, 2009; Lovallo and Sibony, 2010; Kahneman, 2011; SDG, 2011) and emphasise that despite sound scientific knowledge and experience, individuals within agencies and companies are equally prone to biases and reliance on emotional judgments when compared with lay people. Moreover, individuals are likely to rate their performance as superior to their organisation (Bujar et al., 2016). This has already been emphasised in a number of recent studies, which have discussed the role of informal factors in decision making, relating to biases and behaviours, which influence the decision-making processes during the delivery of dossiers for regulatory submissions as well as during the medicine evaluation process (Tafuri, 2013; Cook et al., 2014; Donelan et al., 2015). Furthermore, the occurrence of biases within organisations or their influence on decision making was perceived by regulatory authorities and pharmaceutical companies as one of the major barriers to ensuring quality decision making. This emphasises the importance of implementing a decision-making framework and incorporating the ten QDMPs, particularly making decision values, preferences and uncertainty more explicit, as suggested by pharmaceutical companies, regulatory authorities and HTA agencies in order to ensure that quality decisions are made throughout the life cycle of medicines (Chapters 3 and 4).

The two surveys described by McIntyre et al. (2012) and Marangi et al. (2014), which studied the decision making of the US FDA and the Italian AIFA Advisory Committees regarding how the members prepare for meetings and what influences their decision-making, interestingly both concluded a number of similar findings. Those included a diverse range of practices utilised by the members as well as potential biases that influence the decision making that may subsequently need closer monitoring. Both studies identified that a large proportion of individuals attend committee meetings having already decided how to vote. As well as that, the members are seldom influenced by external stakeholders such as healthcare professionals, patients and sponsors, despite finding their input important. On the other hand, the members are frequently influenced by internal committee members, particularly colleagues or the committee chair. Both studies suggest that in addition to already minimising biases due to conflicts of interest, the agencies should consider measuring the impact of the

so-called intellectual bias on decision making during meetings, which may lead the committee members believing information which appears more favourable or familiar. Moreover, better practices could be achieved by implementing the ten QDMPs into agency processes that promote having a structured approach to decision making (QDMP 1), assigning values to decision criteria (QDMP 3), evaluating different alternatives (QDMP 5) and new information (QDMP 7) and more importantly, evaluating different influences and biases (QDMP 4) to ensure that structured decisions are made during the review of medicines. It would be of interest to widen the scope of such studies to other regulatory authorities, as well as HTA committees in order to address the uncertainty surrounding the process for appraising whether or not medicines should be recommended for reimbursement (Calnan et al., 2017).

Finally, the research by Garbuio et al. (2015) assessed decision making amongst international companies through a study of 634 outcomes made by executives across multiple industries, including the pharmaceutical industry. This study demonstrated first of all that strategic decision making is important for decision effectiveness. Secondly, the study found that robust analysis of data and strategic conversations and communication during decision making around the data ("disinterested dialogue") have a significant positive relationship with decision-making effectiveness. Moreover, the findings demonstrated that the strategic conversations have in fact more impact on decision effectiveness than analysis of data. This is consistent with previous research in this area, such as that by Westley (1990) where managers were interviewed regarding challenges on strategic making; for example the difficulties in not being included in strategic meetings but being given lengthy reports instead, as expressed by one of the interviewees: "just looking at the numbers doesn't give me the insights. It does not give me to total picture. I don't know how they (executives) are interpreting those numbers."

This emphasises the importance of QDMP 10 regarding communication during decision making, as well as QDMP 9 to ensure transparency and provide a record trail of the process through which the decision was made. Despite its apparent importance, QDMPs 9 and 10 were the least assessed practices by the 13 decision-making techniques identified in this review. Consequently, these practices may require closer evaluation and better incorporation into the decision-making practices of individuals and organisations to ensure decision effectiveness.

This systematic literature review identified a general paucity of research in the area of decision making in medicines development and review, but particularly in the area of HTA regarding the development as well as the systematic application of techniques for evaluating quality decision making and lack of consensus around a gold standard.

This review found 13 techniques that can be used to assess the quality of decision making by pharmaceutical companies, regulatory authorities and HTA agencies in order to ultimately enable a more consistent and transparent process. Although some of these techniques are scientifically sound and have been developed and tested using robust methodologies, the majority do not possess generalisability to be applied across companies, regulatory authorities and HTA agencies, whereas only a proportion have demonstrated practicality and applicability to measure decision making in individuals and organisations against all ten QDMPs. Indeed, assessing the quality of decision making using a common technique can provide a basis for clear dialogue of issues in decision making within the three stakeholders and ultimately build trust and understanding of what issues are common and which are specific to the three stakeholders. There is also a need to develop more transparency around how some of the existing techniques and instruments were developed, as well as more testing and routine application for the most promising techniques. Furthermore, such measurements of quality will enable trust, consistency, transparency and timeliness to be built into critical decisions in medicines development, regulatory review and HTA.

**SUMMARY**

- Routine assessment of the quality of the decision-making process (as opposed to just measuring outcomes) has been recognised as key for improving the productivity of any organisation
- This systematic review of literature aimed to identify current techniques, including tools, questionnaires, surveys as well as studies that measure the quality of the decision-making process within regulatory authorities, HTA agencies and pharmaceutical companies
- Major databases were searched in addition to gray literature covering the period from 1996 to 2017
- A systematic approach was used using search terms, defined selection procedure and criteria and well as extraction of data and a secondary review was carried out to validate this
- Each technique was evaluated according to its ability to assess quality of decision making according to the ten QDMPs; the measurement properties of each technique were also assessed
- This systematic literature review identified a general paucity of research in the area of decision making in medicines development, regulatory review and HTA
- Out of the 13 techniques reviewed, two, Organisational IQ and QoDoS, have been identified as the most promising, as they assess all ten QDMPs
- Nevertheless, the Organisational IQ can only be applied to the pharmaceutical industry from an organisational point of view, whereas QoDoS has the potential to capture the issues of companies and agencies alike, as well as evaluating both individuals and their perception of their organisations
- This could render QoDoS as the most appropriate measure relative to the other techniques identified
- The next steps would be to test the relevance and reliability (Chapter 6) as well as sensitivity of QoDoS (not undertaken as part of this research project) and to further demonstrate its practicality across the relevant stakeholders (Chapter 7)
- The review also identified a number of interesting themes, such as the roles of personality traits, gender in decision making, as well as the importance of bias awareness and dialogue during the decision-making process
- The overall benefit of systematically assessing the quality of decision making with QoDoS is to enable an increased awareness of biases and best practices but also provide the ability to measure change over time in order to determine the impact of improvement initiative.

# Assessment of the Reliability and Relevance of the Quality of Decision-Making Orientation Scheme (QoDoS)

## INTRODUCTION

In the absence of a validated instrument for measuring quality of the decision-making processes throughout the lifecycle of medicines, the Quality of Decision-Making Orientation Scheme (QoDoS) was developed using a standardised, established approach for the design and evaluation of such measures. QoDoS already possesses certain psychometric properties including validity, which refers to the fact that a tool measures what it purports to measure. A number of validity aspects of QoDoS have already been demonstrated by Donelan and colleagues (2016), namely face validity (instrument assesses desired qualities), content validity (instrument includes a representative set of items) and construct validity (the results obtained from the use of a measure fit the theoretical foundations from which it is designed) (Trochim, 2006; Streiner et al., 2015). In addition, QoDoS is easy to understand and can be completed in a short time frame (Donelan et al., 2015; 2016). The practicality of the tool in a regulatory authority and pharmaceutical company setting was confirmed through a study with 76 participants (50% from regulatory authorities and 50% from pharmaceutical companies). The findings of this pilot study as well as the results of a recent literature review (Chapter 5) demonstrate that QoDoS is the most promising instrument for evaluating quality of the decision-making process during medicines research, development and assessment, identifying differences between stakeholders and raising awareness of the issues in quality decision making across individuals and within organisations. The challenge is how to ensure that QoDoS, in addition to the above described capabilities, produces reliable results.

The relevance of the instrument can be evaluated by applying cognitive debriefing, a technique of actively testing the tool among representatives of the target population. The aim will be to determine the perception of the participants regarding the relevance, language clarity and completeness of the QoDoS items (Brod et al., 2009; Streiner et al., 2015). Reliability, on the other hand, reflects the scale's ability to differentiate among participants, despite measurement error. It can be demonstrated in two ways, firstly through internal consistency, based on a single administration of the measure, which represents the average of the correlations among all the items in the measure (Streiner et al., 2015). Cronbach's alpha determinations were already used to measure this by Donelan and colleagues (2016) and QoDoS showed high internal consistency (n = 120, Cronbach's alpha = 0.89), which will be re-examined through this study. Secondly, where an assessment instrument is used over time, reliability can be determined by the reproducibility of the scores on different occasions. This can be demonstrated with test-retest reliability by evaluating whether an instrument yields the same scores over time with multiple administrations, assuming subject stability (Streiner et al., 2015), namely that the decision-making practices of the individuals and the perception of their organisation has not changed

The aim of this study was to further test the psychometric properties of the QoDoS tool with the target audience, namely pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies. The objectives across the three stakeholders were to:

- Confirm the internal consistency of the scores for QoDoS individual and organisational parts of the scale; and the overall scale score
- Assess the test-retest reliability of QoDoS items; the scores for the QoDoS individual and organisational parts of the scale; and the overall scale score
- Apply cognitive debriefing to evaluate the relevance, language clarity and completeness of QoDoS items; the clarity of the scaling as well as spontaneity responding to the questionnaire.

## METHOD

### Design of the study

This study was designed as a longitudinal study with participants assessed on two different occasions, firstly at baseline ('test 1') and then seven days after initial application ('test 2'). A period of seven days has been recommended to ensure that participants do not remember their responses following the first administration of such a test. The aim is therefore to minimise 'confounding factors' (i.e. third variables) that may impact the retest, yet on the other hand, to ensure that the condition of the participants should have remained stable (Paiva et al., 2014). In addition, internal consistency of the scores was determined for both 'test 1' and 'test 2' and relevance of the questionnaire was evaluated for 'test 1'.

### Assessment tool

This study utilised the Quality of Decision-Making Orientation Scheme (QoDoS) (See Appendix 1). The 47-item QoDoS has two parts, where 'Part 1' relates to the 'Organisation', which has two domains ('Approach', items 1-12; and 'Culture', items 13-23) and 'Part 2' relates to the 'Individual' with two domains ('Competence', items 24-37; and 'Style', items 38-47). As many decisions are made by individuals every day, the participants were asked to complete the instrument relating to their views on their personal and their organisation's decision-making processes for major strategic choices within their organisation.

The 47 QoDoS items were rated as either favourable or unfavourable using an expert panel (Table 6.1); for example, item 2 'My organisation's decision making is transparent' represents a favourable practice, whereas item 13 'My organisation has suffered a negative outcome due to slow decision making' represents unfavourable practice. Based on this, the Likert scale response options were quantified by assigning scores to each of the response

scale. For QoDoS items considered as favourable practice, the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items considered as unfavourable practice, the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0 (Table 6.1). In addition, four background questions were used to collect data on gender, job title, professional experience and organisation type.

In addition, respondents for 'test 1' were asked to complete five questions to assess the following properties: relevance, where each item should reflect an aspect of importance regarding decision making to the target population; language clarity, where sentences should be clear, understandable, straightforward and simple; scaling, where the format of the categories must be clear and fit with the items and the construct; comprehensiveness to ensure that no items are believed to be missing or as seen as repetitive and spontaneity to ensure that QoDoS can be completed efficiently without prompting or rethink, thereby maximising response rate and minimising errors or undesirable response behaviour. The following questions were developed for the purpose of this study (Brod et al., 2009; Streiner et al., 2015):

- Question 1: Did you find the QoDoS items relevant? (yes/no) If no please specify item number.
- Question 2: Did you find the QoDoS items easy to understand? (yes/no) If no please specify item number.
- Question 3: Did you find the response options easy to understand? (yes/no) If no please specify.
- Question 4: Were you able to respond to the QoDoS spontaneously? (yes/no)
- Question 5: Any items that you believe should be deleted or added (yes/no) If yes please specify.

**Table 6.1 Quality of Decision-Making Orientation Scheme (QoDoS) items assigned as either favourable or unfavourable practice**

| Assignment | QoDoS item number |
|---|---|
| Favourable practice | 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 37 |
| Unfavourable practice | 5, 13, 14, 15, 16, 17, 18, 19, 20, 21, 36, 38, 39, 40, 41, 42, 43, 45, 46, 47 |

**Study participants**

The focus groups were organised as part of an international workshop on quality decision making (CIRS, 2017). The study participants were recruited based on experience using purposive sampling, from those holding senior positions having at least five years of experience in a managerial position within major international pharmaceutical companies, regulatory authorities, HTA agencies as well as relevant academic institutions. A sample size of at least 30 individuals for 'test 1' and 'test 2' was required (Paiva et al., 2014).

**Study procedure**

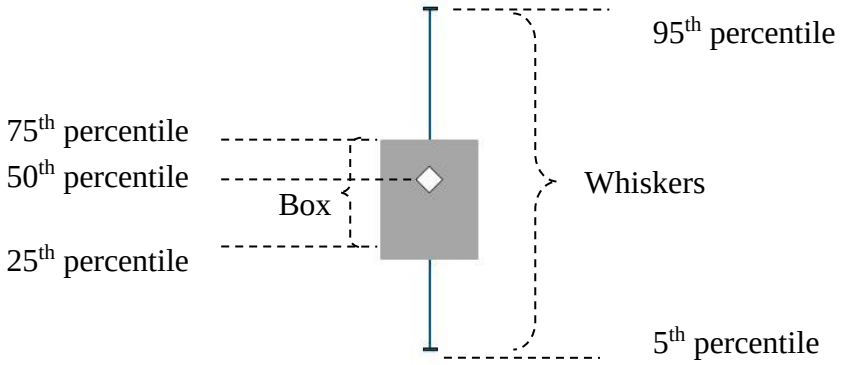
Participants were invited in May 2017, with the study planned to take place in June 2017. Prior to the 'test 1', participants were subject to a one-day training course on quality decision making in order to ensure that their baseline knowledge of decision making is the same and to minimise 'learning effect' occurring between the initial and second completion of the questionnaire. As a result, it was assumed that the decision-making practices of the individuals and the perception of their organisation has not changed and therefore that the participants' circumstances are stable. Following completion of the first assessment, participants received a second copy of the QoDoS with a unique identification number, contact information and a note with the completion date indicated (seven days from the initial assessment). They were also informed that they would receive a reminder for the follow-up questionnaire. On the sixth day following their initial assessment the participants were sent a reminder email regarding the completion of the retest the following day; on the seventh day, they were sent an electronic copy of the QoDoS for completion. All the respondents who completed 'tests 1 and 2' within a seven- and eight-day interval were included in the analysis.

**Data processing and analysis**

Information was gathered manually into an Excel database for the completed questionnaires and subsequently cleaned and coded. The questionnaires were paired based on the unique identification numbers assigned to each copy of the instrument. The analysis was carried out on the 47 QoDoS items using Excel and Statistical Package for the Social Sciences (SPSS) version 23. Initially, the responses were plotted as a 'box-and-whisker' graph, which indicates the $25^{th}$ and $75^{th}$ percentile (box), the $5^{th}$ and $95^{th}$ percentile (whiskers) as well as the median (diamond) in order to explore variance within each item as well as when comparing 'test 1' with 'test 2' (Figure 6.1). Internal consistency of QoDoS was assessed using the Cronbach alpha coefficient for the inter-item correlation, where a value of 0.7-0.9 was required based on the number of items in the instrument. A value that is too low signifies that some items are not representative whereas a value that is too high may reflect redundancy amongst items (Streiner et al., 2015). Test-retest reliability was assessed using the Intraclass Correlation

Coefficient (ICC), which shows absolute agreement between two scores where a value of >0.7 was required. The ICC also accounts for systematic error and it is based on analysis of variance in scores (Paiva et al., 2014; Streiner et al., 2015). For the purpose of this study where the rater is the same (intra-rater reliability) a 'two-way mixed effects' model was chosen and the definition of relationship was considered as 'absolute agreement' (Koo and Li, 2016). Responses to the five questions regarding the relevance were analysed using Excel and the comments were codified and combined where applicable. Due to confidentiality reasons, only aggregated results are shown and no data that indentifies an individual or a specific organisation were reported.

**Figure 6.1 Guide to interpreting a 'box-and-whisker' plot**




**RESULTS**

This study focussed on relevance and reliability testing (internal consistency and test-re-test reliability) of the QoDoS instrument in the target population, namely individuals involved throughout medicines development, regulatory review and reimbursement of medicines. For the purpose of clarity, the key results are presented in three parts:

- Part I – Internal consistency testing
- Part II – Test-retest reliability
- Part II – Relevance testing

**Characteristics of the study participants**

The initial 'test 1' was completed by 44 individuals from 55 contacted (80% response rate), where 24 (55%) were from pharmaceutical companies, 12 (27%) from regulatory authorities, three (7%) from HTA agencies and five (11%) from a range of relevant academic institutions. In terms of gender, 20 (45%) were male, 22 (50%) female and two individuals did not specify (5%). The individuals had a median of 21 years of work experience, with a range of five to 38 years and titles ranging from manager to organisational head and professor in the case of

academia (Table 6.2). The re-test ('test 2') was completed by 32 out of the 44 individuals who had completed 'test 1', resulting in a 73% response rate. In this case, 13 individuals were from companies (41%), 11 from regulatory authorities (34%), three (9%) from HTA agencies, five (16%) from academia. In terms of gender, 15 were male (47%) and 17 female (53%) with a median of 18 years of professional experience ranging from seven to 38 years and titles varying from manager to organisational head and professor in the case of academia (Table 6.2).

**Part I – Internal consistency testing**

*Variance in QoDoS scores*

Initially, the variance within each item for 'test 1' and 'test 2' was illustrated with a 'box-and whisker' plot for the organisational and individual QoDoS parts (Figure 6.2) across all the responders. The variance was reported in terms of 5$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$ and 95$^{th}$ percentiles. Overall, each item had a considerable variance around the median, generally a difference of two points in the 25$^{th}$ and 75$^{th}$ percentile box.

**Table 6.2 Demographic characteristics of the study participants for tests 1 and 2**

| Test | Total number of respondents | Number of respondents by organisation | | | | Number of respondents by gender | | |
|---|---|---|---|---|---|---|---|---|
| | | Pharmaceutical companies | Regulatory authorities | HTA agencies | Academia | Male | Female | Not specified |
| 1 | 44 | 24 | 12 | 3 | 5 | 20 | 22 | 2 |
| 2 | 32 | 13 | 11 | 3 | 5 | 15 | 17 | 0 |

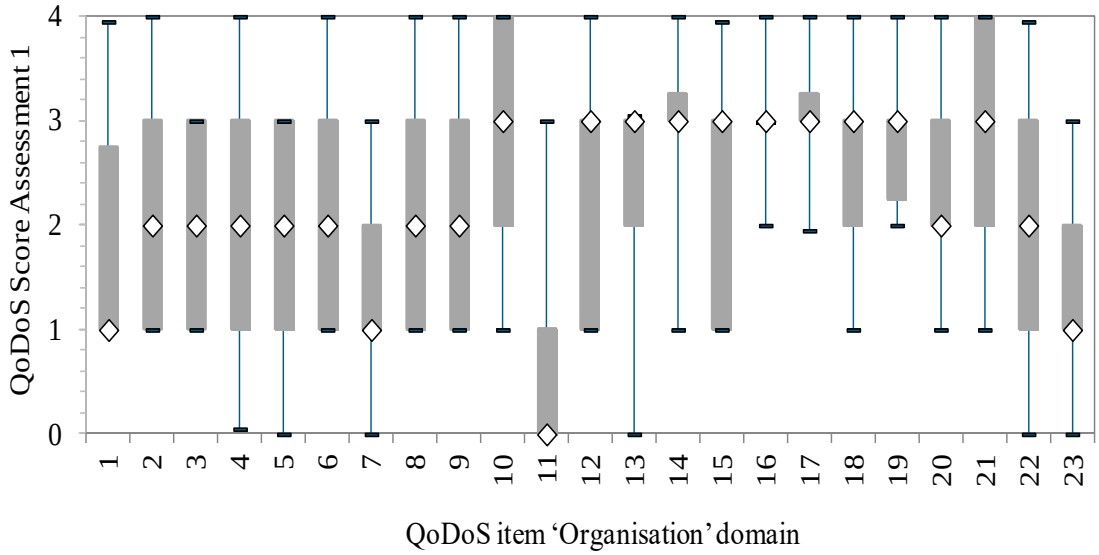
For 'test 1', the organisational items with smallest variance in terms of the length of the 25$^{th}$ and 75$^{th}$ percentile box were items 14 ('My organisation's culture has resulted in its inability to make a decision'), 16 ('My organisation's decision making results in making the same mistake as in the past') and 17 ('My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest)'). The items with the biggest variance were 4 ('My organisation uses a structured approach in its decision making) and 22 ('My organisation effectively communicates the decisions it makes') according to the largest difference between the 5$^{th}$ and 95$^{th}$ percentiles (whiskers). The 'test 1' individual items with the smallest variance were items 31 ('I understand the importance of the decisions I make'), 38 ('Emotion is part of my decision making'), 40 ('I have experienced a negative outcome by a decision not being made') and 42 ('Recent or dramatic events greatly impact my decision making'), whereas the largest variance was for item 33 ('I assign qualitative values to its decision-making criteria'). In general, these differences were also reflected in 'test 2',

although the variance was somehow smaller for a number of items in ‘test 2’ compared to ‘test 1’ due to smaller sample size.

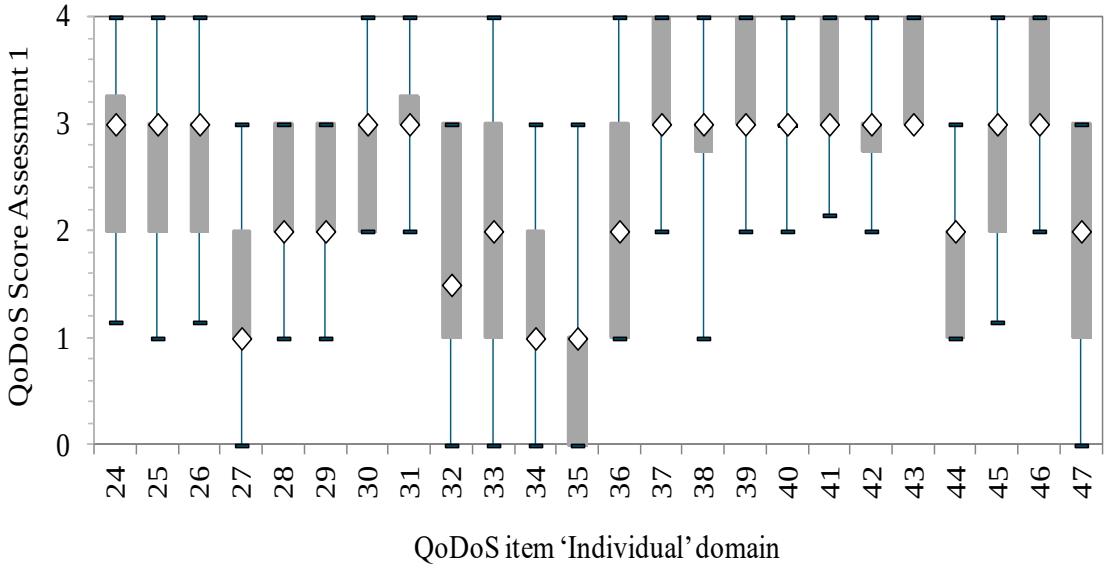
**Figure 6.2 Quality of Decision-Making Orientation Scheme (QoDoS) scores; where whiskers indicate 95th and 5th percentile, the 75th and 25th percentile and the white diamond is the median**

**a) Test 1; n = 44**

i) ‘Organisational’ items 1-23 (‘Approach’, items 1-12; and ‘Culture’, items 13-23)



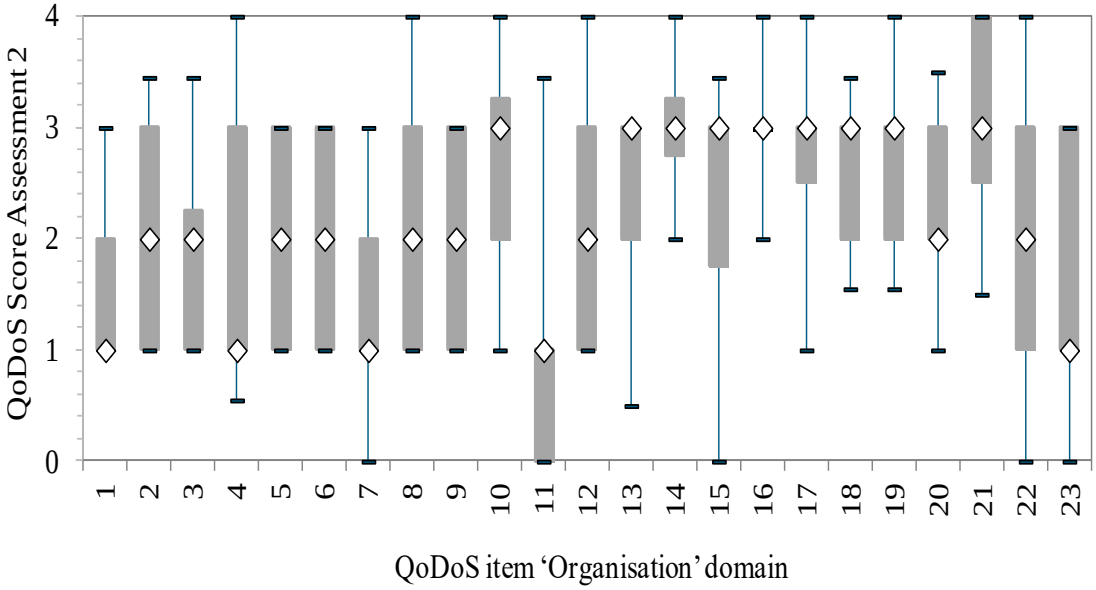

ii) Individual’ items 24-47 (‘Competence’, items 24-37; and ‘Style’, items 38-47)



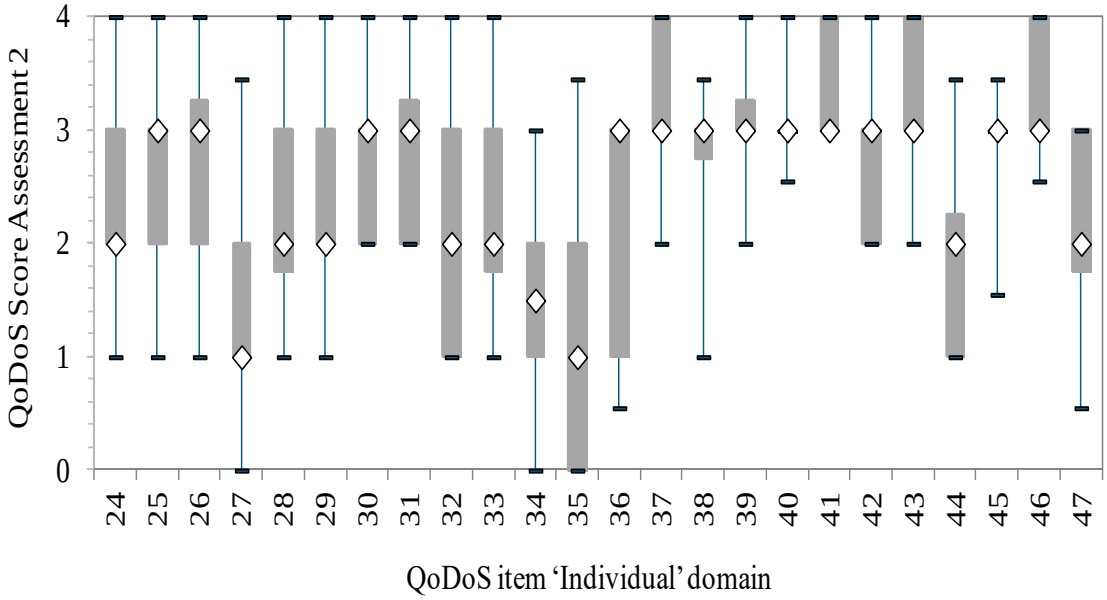
**(continued) Figure 6.2 Quality of Decision-Making Orientation Scheme scores (QoDoS); where whiskers indicate 95th and 5th percentile, the 75th and 25th percentile and the white diamond is the median**

**b) Test 2; n = 32**

i) 'Organisational' items 1-23 ('Approach', items 1-12; and 'Culture', items 13-23)




ii) Individual' items 24-47 ('Competence', items 24-37; and 'Style', items 38-47)




*Cronbach Alpha Coefficient*

Internal consistency of the QoDoS scores was assessed in terms of the Cronbach alpha coefficient both for the 'test 1' and 'test 2' across the pooled sample (Table 6.3). The assessment was carried out for each of the four QoDoS domains, namely organisational

decision-making approach and culture as well as individual decision-making competence and style. Cronbach alpha coefficient was greater than 0.7 across all the QoDoS domains for 'test 1' and 'test 2', ranging from 0.713 to 0.792., indicating 'good' consistency (Streiner et al., 2015). For the overall score across all 47 items, the coefficient was 0.805 for 'test 1' and 0.861 for 'test 2' which is considered as 'very good' (Streiner et al., 2015).

**Table 6.3 Internal consistency Cronbach's alpha coefficient for Quality of Decision-Making Orientation Scheme (QoDoS) domains**

| QoDoS domain | Test 1 (n=44) | Test 2 (n=32) |
|---|---|---|
| Organisational decision-making approach (12 items) | .767 | .792 |
| Organisational decision-making culture (11 items) | .715 | .787 |
| Individual decision-making competence (14 items) | .757 | .848 |
| Individual decision-making style (10 items) | .713 | .703 |
| Overall (47 items) | .805 | .861 |

**Part II: Test-retest reliability**

The external consistency (reproducibility) of the QoDoS scores for two completions was assessed. For 'Test 2', 32 individuals returned their responses out of the 44 included in 'test 1' (73%). Interestingly, from the 12 individuals who did not provide responses to the re-test, 11 were from pharmaceutical companies. ICC estimates and their 95% confident intervals were calculated based on absolute agreement, 2-way mixed-effects model. The four QoDoS domains showed moderate to strong reproducibility (ICC range 0.626-0.857). The ICC was lower for the two individual domains (0.626 for competence and 0.721 for style) compared to the two organisational domains (0.857 for approach and 0.821 for culture). The QoDoS had an overall ICC of 0.871 (Table 6.4).

**Part III: Relevance testing**

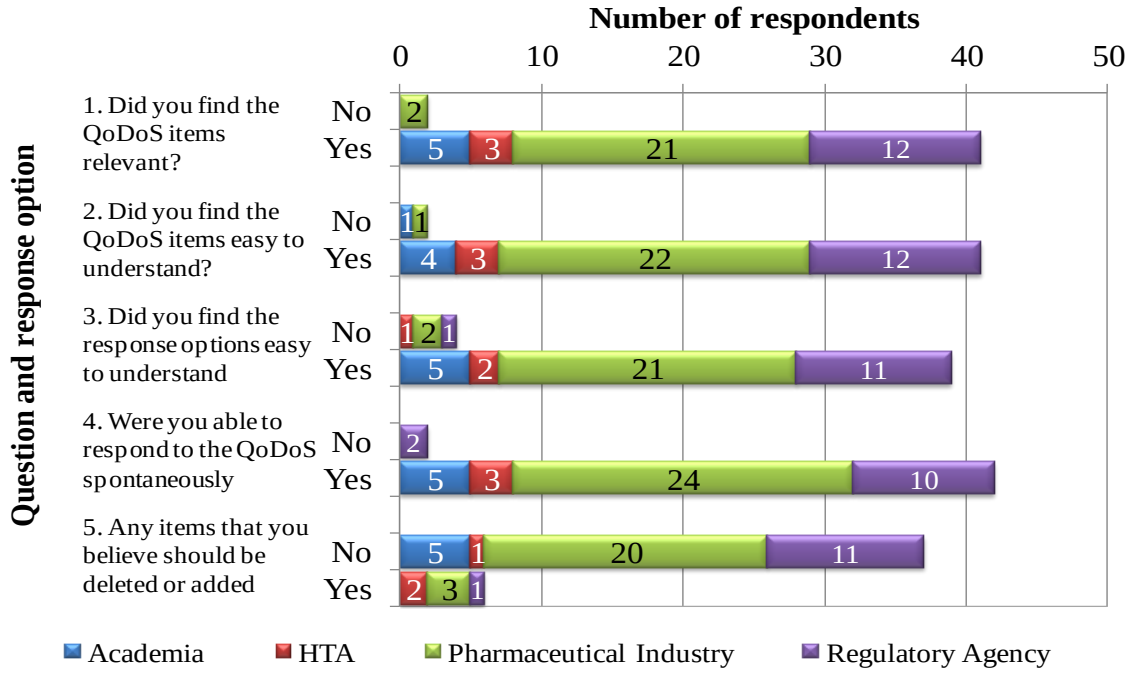
Cognitive debriefing was applied to test the relevance of the QoDoS questionnaire. The five feedback questions included in 'test 1' of the study were completed by 43 out of the 44 participants, where one individual from a pharmaceutical company did not provide responses (Figure 6.3). Overall, 41 out of 43 (95%) of the participants considered the QoDoS items relevant, easy to understand and spontaneous to answer based on responses to questions 1, 2 and 4 respectively. For question 3 regarding the response options, 91% of individuals agreed that the response options are easy to understand, whereas 86% of the participants believed

QoDoS tool to be complete and that that no additional items should be added or deleted. The comments provided by the diverging individuals are summarised in Table 6.5.

**Table 6.4 Test-retest reliability of Quality of Decision-Making Orientation Scheme (QoDoS) domains with 32 participants**

| QoDoS domain | ICC | 95% CI | | Significance |
|---|---|---|---|---|
| | | Lower Bound | Upper Bound | |
| Organisational decision-making approach (12 items) | .857 | .724 | .928 | .0001 |
| Organisational decision-making culture (11 items) | .820 | .665 | .908 | .0001 |
| Individual decision-making competence (14 items) | .721 | .504 | .853 | .0001 |
| Individual decision-making style (10 items) | .626 | .359 | .798 | .0001 |
| Overall (47 items) | .871 | .753 | .935 | .0001 |

**Figure 6.3 Responses to the five 'cognitive debriefing' questions to establish the Quality of Decision-Making Orientations Scheme (QoDoS) relevance**




n=number of participants

**Table 6.5 Comments from participants regarding 'cognitive debriefing' to establish Quality of Decision-Making Orientation Scheme (QoDoS) relevance**

| Question | Comment |
|---|---|
| 1. Did you find the QoDoS items relevant (yes/no)? If no please specify item number. | • Don't think all the items should be equally weighed (n=1)<br>• Many questions were repetitive (n=3) |
| 2. Did you find the QoDoS items easy to understand? (yes/no) If no please specify item number. | • Need to clarify context further (i.e. development process) (n=1)<br>• Unclear whether to respond as an individual versus for the organisation (n=1)<br>• Item 6: my organisation assigns qualitative values to its decision-making criteria (n=1) |
| 3. Did you find the response options easy to understand? (yes/no) If no please specify. | • Need to differentiate between frequently/often (n=3)<br>• Could benefit from yes/no instead of current answers (n=2) |
| 5. Any items that you believe should be deleted or added? (yes/no) If yes please specify. | • Availability of tools to support decision making (n=1)<br>• Instructions why tool is required (n=1) |

n=number of participants

**DISCUSSION**

A recent literature review has demonstrated that QoDoS is the most promising available technique for assessing decision making in the lifecycle of medicines (Chapter 5). The overall benefit of systematically assessing the quality of decision making with QoDoS is to enable an increased awareness of biases and best practices but also provide the ability to measure change over time in order to determine the impact of improvement initiatives. One of the literature review recommendations was therefore to further test the reliability of the QoDoS, this being a fundamental property of any subjective measure of such type, in order to ensure that the results produced are precise, reliable and reproducible over time, which is particularly important when using QoDoS in longitudinal studies. Consequently, this study aimed to demonstrate the relevance and reliability (internal consistency and test-retest reliability) of the QoDoS instrument and thereby provide confidence of its robustness in evaluating quality of decision making during the research and development of medicines.

The variance around the QoDoS scores, particularly for 'test 1' and also for 'test 2', was considerable, which reflects the ability of the tool to differentiate between participants regarding their perception of their own decision making as well as that of their organisation. The items with the smallest variance, such as 16 ('My organisation's culture has resulted in its inability to make a decision') or 40 (I have experienced a negative outcome by a decision

not being made'), should also be further evaluated in future QoDoS studies. Perhaps for these two items, both referring to timeliness, the scores might have been narrow and generally positive due to the fact that companies and agencies have to make key decisions within a specified time limit (either legislated timelines by regulatory authorities/HTA agencies or business decisions dictated by companies). The rationale and differences in the items with the largest variance should also be explored in future studies with organisations.

The reliability of the QoDoS was assessed for the total scale as well as the four domains (organisational decision-making approach; organisational decision-making culture; individual decision-making competence and individual decision-making style). The results confirmed acceptable internal consistency according to Cronbach's alpha for the overall instrument and the domains, as compared to the internal consistency of QoDoS evaluated by Donelan and colleagues (2016). This demonstrates that the domains and the overall instrument are well defined and homogenous in terms of tapping into the appropriate aspects of the same construct (quality decision-making).

The reproducibility of the QoDoS was also established using test-retest reliability with a 7 days period between the two assessments. Interestingly, almost all the participants who completed 'test 1' but not 'test 2' where from pharmaceutical companies, which suggests that individuals from industry may not recognise the importance of such an exercise or that they are less accustomed to being engaged in these kinds of studies compared to agencies and academia. The results from the test-retest demonstrate a strong level of agreement between the initial and second assessment across the four domains and for the overall QoDoS score. Interestingly, the ICC was lower for the two individual domains of QoDoS compared to those of the organisation. This may be due to the fact that the opinion of an individual regarding their own decision making is less stable as an individual's perception of their own abilities may be subject to mood changes or personal circumstances at the time of completion, as opposed to being more objective regarding their assessment of their organisation. Another explanation may be that individuals might have adjusted their decision making during the seven days following the training session received on the day of the 'test 1' completion. Nevertheless, the overall ICC score was more than 0.8 for the instrument indicating that QoDoS generates results that are precise and objective despite the subjective nature of the topic the scale assesses.

This study also demonstrated the relevance of QoDoS in target participants, where the feedback from the respondents confirmed the relevance, language clarity and completeness of the QoDoS items; the clarity of the scaling as well as spontaneity to the response process. The

comments received by the individuals have also been reviewed. Regarding question 1 (relevance of items), individuals commented that items should be equally weighed and that questions were repetitive. Nevertheless, it should be noted that QoDoS items have already been reduced using factor analysis to enable mean completion time of 10 minutes, whereas item deletion may result in loss of information regarding certain key areas of the construct. Secondly, although the 47 items are equally weighted, the items can be assigned to ten QDMPs, where each QDMP, according to its relative importance, has a different number of QoDoS items, thereby resulting in partial weighting of results (Donelan et al., 2016).

Regarding the clarity of the items (question 2), individuals provided comments regarding the need to clarify the decision context beyond just stating 'key strategic decisions'. Nevertheless, this was not possible for the purpose of this study due to the wide range of participants and therefore decisions they make, but will be taken into account in future studies with similar organisations or individuals. In addition, item 6 was highlighted as unclear ('my organisation assigns qualitative values to its decision-making criteria') and this should be explored further, though noting that only one respondent highlighted this issue. Finally, the lack of clarity regarding the distinction between organisational and individual level questions was noted and this could be addressed by making the difference between the QoDoS tables for 'part 1' and 'part 2' more apparent (see Appendix).

For the response options (question 3), individuals reflected that they do not see the difference between 'frequently' and 'often'. Nevertheless, the weighing of the response options has been clearly defined in the instrument, i.e. "Assume that Not at all = 0% of time; Sometimes = 25% of time; Frequently = 50% of time; Often = 75% of time; Always = 100% of time" and perhaps this sentence should be further highlighted in the questionnaire or the percentages should be noted in the actual table containing the 47 questions. In addition, two individuals recommended changing the options to 'yes' and 'no', but this may result in loss of information, where intermediate options may be required by respondents.

Finally, in question 5 regarding completeness of the tool, participants highlighted that an item could be added regarding 'availability of tools to support decision making as well as adding 'instructions why tool is required'. This could be addressed by creating a supplementary 'Questions and Answers' document for future QoDoS studies. For the former comment, QoDoS already provides insight into the aspects of tool availability to support decision making through item 27 regarding the use of Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis. This could be addressed further by revising item 27 ('I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making') to ('I

utilise decision making tools such as Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making').

The feedback received will be taken into account during future QoDoS studies in order to further ensure the objectiveness and precision of the results obtained. Future studies would also concentrate on establishing the differences between the reliability of QoDoS across the three groups, pharmaceutical companies, regulatory authorities and HTA agencies, which would require a larger sample. In conclusion, the results of this study provide a strong support for the relevance and reliability of QoDoS for longitudinal and cross-sectional application of the instrument when evaluating quality of decision making across participants involved in the R&D of medicines.

**SUMMARY**

- This study aimed to evaluate reliability (internal consistency and test-re-test reliability) and relevance (using cognitive debriefing) of the QoDoS instrument in the target population
- Participants included individuals from pharmaceutical companies, regulatory authorities, HTA agencies and academia
- The initial 'test 1' was completed by 44 individuals from 55 contacted (80% response rate) and the re-test ('test 2') was completed by 32 out of the 44 individuals who completed 'test 1', resulting in a 73% response rate
- Variance within each QoDoS item for 'test 1' and 'test 2' was evaluated with a 'box-and whisker' plot for the organisational and individual QoDoS parts across all the responders; the variance was reported in terms of $5^{th}$, $25^{th}$, $50^{th}$, $75^{th}$ and $95^{th}$ percentiles.
- The internal consistency was assessed with Cronbach's alpha and the test-retest was evaluated using the ICC for the four QoDoS domains (organisational decision-making approach; organisational decision-making culture; individual decision-making competence and individual decision-making style)
- Cronbach alpha coefficient was greater than 0.7 across all the domains for 'test 1' and 'test 2', ranging from 0.713 to 0.792., indicating 'good' consistency (Streiner et al., 2015)
- For the overall score across all 47 items, the Cronbach alpha coefficient was .805 for 'test 1' and .861 for 'test 2' which is 'very good' (Streiner et al., 2015)
- ICC estimates and their 95% confidence intervals were calculated based on absolute agreement, 2 way mixed-effects model.
- The four QoDoS domains showed moderate to strong reproducibility (ICC range 0.626-0.857) with an overall ICC of 0.871
- The relevance of QoDoS was evaluated by applying cognitive debriefing using five short feedback questions following 'test 1'
- The feedback from the 43 respondents (98% response rate) confirmed the relevance (95% agreement), language clarity (95%) and completeness of items (86%); the clarity of the scaling (91%) as well as spontaneity to the response process (95%)
- The results of this study provide a strong support for the relevance and reliability of QoDoS, which are key properties for future for longitudinal and cross-sectional application of the instrument when evaluating quality of decision making across participants involved in the lifecycle of medicines.

# Assessment of the Ten Quality Decision-Making Practices (QDMPs) in a Pharmaceutical Company, a Regulatory Authority and a Health Technology Assessment (HTA) Agencies Agency with the Quality of Decision-Making Orientation Scheme (QoDoS)

## INTRODUCTION

In order for organisations to determine their status quo regarding the incorporation of the ten Quality Decision-Making Practices (QDMPs) into key decision-making processes, the Quality of Decision-Making Orientation Scheme (QoDoS) was developed (Donelan et al., 2015, Donelan et al., 2016) and was deemed as the most promising available technique for such assessments (Chapter 5). A pilot study with a mixed group of participants from pharmaceutical companies and regulatory authorities demonstrated the initial practicality of QoDoS in assessing the strengths and weaknesses as well as similarities and differences in decision-making practices across the individuals, as well as their perception of the organisation (Bujar et al., 2016). Furthermore, Chapter 6 demonstrated the reliability and relevance of QoDoS in pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies. These two properties are crucial for any future applications of the instrument, particularly longitudinal studies in order to ensure that a potential change in decision-making practices is a result of modified organisational processes, as opposed to being due to measurement error (Streiner et al., 2015).

The next step is to apply QoDoS in pharmaceutical companies, regulatory authorities and HTA agencies, in order to determine whether the instrument has the ability to assess the level of implementation of the ten QDMPs within the three distinct stakeholder groups. This could be achieved by carrying out in-depth studies with participants from specific teams, committees or departments from across the three types of organisations. Such studies could be used to determine the factors that influence decision making within organisations, including favourable practices and those that may require improvement, as well as to identify common themes in quality decision making across the organisations, such as decision-making preferences as a result of gender, as initially discussed in Chapter 5. This chapter will consequently describe an initial set of such case studies with organisations, which will be used to illustrate the above properties.

Importantly, the data obtained from QoDoS studies could provide a basis for internal dialogue (within an organisation) and, where applicable, external discussions (across organisations) to explore the rationale for the responses and increase the awareness of the QDMPs and other key considerations during decision making across the individuals (McAuslane et al., 2011). Organisations could also utilise the data and the discussion points gathered through such a study to promote best practices across their organisation to ensure consistency, as well as to address the least favourable practices by incorporating them more effectively into decision-making frameworks. This could ultimately improve the R&D productivity of pharmaceutical companies (Smietana et al., 2014) and ensure that regulatory authorities and HTA agencies are not only undertaking good-quality assessments, but are also making quality decisions (McAuslane et al., 2011).

The aim of this study was to evaluate the practicality of QoDoS in identifying the incorporation of the ten QDMPs in three types of organisations through illustrative case studies, with a pharmaceutical company, a regulatory authority and an HTA agency. The objectives were to:

- Evaluate the quality of the decision-making practices of the individuals and their perception of their organisation's decision making
- Identify favourable and unfavourable practices across the ten QDMPs
- Assess consistency of the QDMPs within each organisation according to pre-specified sub-groups as well as pertaining to the group demographics (work experience and gender)
- Evaluate the feasibility and the perceived benefits of the study method based on feedback discussions as well as lessons learned.

## METHOD

### Design of the study

This study was designed in the form of three case studies, with a pharmaceutical company, a regulatory authority and an HTA agency, where participants were asked to complete the QoDoS instrument (see Appendix 1). Each study was planned as a cross-sectional assessment, where the data was collected at one point in time. The purpose of each study was to examine the organisation as a whole and, where possible to assess a number of logical sub-units, such as departments, within each organisation.

### Assessment technique

This study utilised QoDoS (see Appendix 1) with 47-item and two parts, where 'Part 1' relating to the 'Organisation' has two domains ('Approach', items 1-12; and 'Culture', items 13-23) and 'Part 2' relates to the 'Individual' with two domains ('Competence', items 24-37; and 'Style', items 38-47). In addition four background questions were used to collect data on gender, job title, professional experience and organisation type. The 47 QoDoS individual and organisational items can be grouped according to the ten QDMPs based on each QoDoS item representing either favourable or unfavourable practice (Table 7.1). The QoDoS Likert scale response options were also quantified by assigning scores to each of the response scale, according to whether a QoDoS item describes favourable or unfavourable practice, as shown in Table 7.1. For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable', the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0.

**Table 7.1 Quality of Decision-Making Orientation Scheme (QoDoS) items mapped to the ten Quality Decision-Making Practices (QDMPs)**

| Ten Quality Decision-Making Practices | QDMP short name | 24 QoDoS individual items | 23 QoDoS organisational items |
|---|---|---|---|
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) | Structure | *24, 25, 27, 30, 32, 35, 36, 39, 40, 43* | *3, 4, 11, 13, 14* |
| 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) | Roles | *37* | *15, 23* |
| 3. Assign values and relative importance to decision criteria | Criteria | *33, 34, 44* | *6, 7* |
| 4. Evaluate both internal and external influences/biases | Bias | *38, 42* | *5, 17, 20, 21* |
| 5. Examine alternative solutions | Alternatives | *28* | *8, 9* |
| 6. Consider uncertainty | Uncertainty | *26, 45* | *10, 18* |
| 7. Re-evaluate as new information becomes available | New information | *46* | *12, 19* |
| 8. Perform impact analysis of the decision | Impact | *31, 47* | *1* |
| 9. Ensure transparency and provide a record trail | Transparency | *29, 41* | *2, 16* |
| 10. Effectively communicate the basis of the decision | Communication | | *22* |

Underlined items indicate those that correspond to 'unfavourable practice', whereas non-underlined items indicate those which represent 'favourable practice'.

**Study participants**

*Selection process*

Four pharmaceutical companies, four regulatory authorities and four HTA agencies were initially invited to take part in this study with the aim of identifying one from each type of organisation. The 12 organisations were selected using purposive sampling from across the members of the Centre for Innovation in Regulatory Science (CIRS) research programmes or from those organisations which have a working relationship with CIRS to help ensure the timeliness of the study completion and to maximise the response rate (CIRS, 2018). This sampling process was considered appropriate as the aim was to produce illustrative pilot case studies as opposed to generating company, regulatory authority or HTA agency aggregated trends.

The selected companies had large R&D expenditure (>1bln USD) (PharmExec, 2017) thereby reflecting their innovativeness and the number of decisions made. The four regulatory authorities were all classified as Stringent Regulatory Authority (SRA) as defined by the

WHO (2017). Lastly, the four HTA agencies were selected based on size and maturity from those organisations which are part of the INAHTA (2018) or EUnetHTA (2018). This was to ensure that the organisations involved in the studies have well established decision-making systems in place in order to be able to complete the QoDoS.

Senior executives from the 12 organisations were selected based on their past involvement in other studies as part of this research programme (Chapters 3 and 4) as well as perceived interest, which was estimated from the questionnaires as well as personal interactions. A detailed study protocol was sent to the potential study participants by email, which outlined the purpose and objectives of the study, the proposed method and project timeliness. The relevance of this study was also highlighted by sharing a copy of research and development Briefing (Bujar et al., 2017; see Appendix 2) covering the outcomes of the other research studies undertaken as part of this programme.

Positive responses were obtained from two pharmaceutical companies, two regulatory authorities and one HTA agency. Teleconferences were subsequently organised with each organisation to further investigate their willingness and suitability to participate. The criteria for selection for the study were: availability of resources in terms of staff and time as well as cohort size, where a larger group with sub-groups was preferred. This would enable calculation of the response variance as well as sub-group analysis on the dataset to identify differences and similarities and the consistency of implementation of the ten QDMPs.

Out of the two companies and two regulatory authorities which provided positive responses, all were appropriate in terms of resource and willingness to participate; but only one was selected from each to take part in the study based superior group size. More specifically, for the company, one organisation proposed 12 individuals from one group, compared to the selected company where 31 participants across 4 groups were proposed to take part in the study. One of the regulatory authorities proposed a study with nine individuals from one group compared with the selected regulatory authority which suggested involving 47 individuals from across two groups. The HTA agency which agreed to participate proposed a group with a cohort size of 28.

*Selected study participants*

The pharmaceutical company cohort consisted of 31 individuals from across the leadership team (LT), which focuses on ensuring regulatory, quality and safety aspects of medicines for the purpose of submission of the dossier to a regulatory authority; as well as three sub-teams (STs) which develop the data for the leadership committee, where two STs focus on

regulatory affairs' aspects and one ST focuses on medicines' safety aspects. For the selected agency, the 47 participants were all assessors who review the regulatory dossier prior to the issuance of the marketing authorisation of a medicine (pre-market assessors) as well as assessors who re-evaluate the marketing authorisation status of a medicine based on new information to determine whether or not to modify the marketing authorisation (post-market assessors). The HTA agency participants were members of the agency's appraisal committee which recommends whether or not a new medicine should be reimbursed under the national health system. The members were all external experts not directly employed by the agency.

**Decision-making process**

As many decisions are made on a daily basis, each organisation selected a key strategic decision-making process of interest to them (Table 7.2) and this was described in the QoDoS questionnaire. It should be noted that for the pharmaceutical company, the RA LT was asked to assess their decision making relating to submitting a new drug application (NDA) to a regulatory authority, whereas the three STs assessed both their perception of their own decision making as well as how they believe the RA LT makes decisions, thereby facilitating comparisons. For the regulatory authority and the HTA agency, the decision-making processes focussed on the review and appraisal of new medicines respectively, assessing both how the individuals believe they make decisions as well as how they believe their organisation (the regulatory authority and the HTA agency) makes decisions.

**Study procedure**

Once the participants and the decision point were selected, the steps and timelines for each of the studies were agreed. Each study followed the same format as described below to ensure process consistency.

1. Initially, the participants were given a 60 min presentation on the study background and the importance of decision making, as well as being provided with a study protocol that included the study aim, objectives and method as described in this chapter.
2. Following the introduction session, the participants were given a copy of the QoDoS questionnaire and were asked to complete this immediately following the presentation. The three studies were completed by February 2018.
3. The responses were analysed within a month and a report of the results was shared with the participants.

4. Initial feedback discussions were organised with the cohort leaders in order to discuss the relevance and clarity of the results as well as initial perception of the study method feasibility and benefits.
5. Formal feedback discussions have been planned for the second part of 2018 with each group in order to:
    - Discuss the suitability of the method used in each study
    - Discuss the rationale for the results obtained particularly where there was variance or identification of an unfavourable practice
    - Establish the benefits of completing QoDoS as well as having feedback discussions
    - Establish areas of best practice and consider the lessons learned and any next steps, particularly where areas for improvement were identified.

**Table 7.2 Decision-making processes assessed with the Quality of Decision-Making Orientation Scheme (QoDoS) across the three case studies**

| Study | Subject | Decision-making process specified for completing QoDoS | |
|---|---|---|---|
| | | **Part 1 (organisation)** | **Part 2 (individual)** |
| **Pharmaceutical company** | Leadership team (LT) | LT process to submit a New Drug Application to a regulatory authority | |
| | Sub-teams (STs): two regulatory and one safety | LT's decision making to submit a New Drug Application to a regulatory authority | ST process to present an emerging risk to a regulatory authority |
| **Regulatory authority** | Pre-market assessors | Pre-market process to approve or reject a New Drug Application | |
| | Post-market assessors | Post-market process to modify (or not) the marketing authorisation of a new medicine based on new information | |
| **HTA agency** | Appraisal committee members | Committee's process to recommend/restrict or not to recommend reimbursement of a new medicine, focusing on single technology assessment of pharmaceutical products. | |

**Data processing and analysis**

Information was processed manually into an Excel database for the completed questionnaires and subsequently cleaned and coded. The scores for the individual QoDoS items were codified based on the categorisation in Table 7.1. This was then used to calculate the overall score for each QDMP by taking a median across the relevant QoDoS item scores. Due to confidentiality reasons, only aggregated results were shown and no data that indentifies an

individual or a specific organisation was reported. No statistical tests were planned or conducted as this study was designed to be illustrative, with an aim of providing a qualitative assessment of the objectives as well as to generate premises for further research.

The data were analysed using descriptive statistics, including calculation of median ($50^{th}$ percentile) and variance ($25^{th}$ and $75^{th}$ percentiles). The results relating to the ten QDMPs (individual and organisation) were plotted in the form of box plots as well as spider diagrams using Excel. The box plots were used to illustrate the $25^{th}$ and $75^{th}$ percentiles for the QDMP scores as well as the median (diamond), whereas the spider diagrams showed the median for each QDMP. The following traffic light colour coding was utilised according to the overall QDMP score, where

- score <1 = 'unfavourable practice' = red;
- score >1 and <3 = 'needs improvement' = yellow
- score >3 = 'favourable practice' = green.

An analysis of the items which are the same for Part 1 and Part 2 within the QoDoS was also carried for the regulatory authority and the HTA agency (as the decision-making processes were the same for Part 1 and Part 2; Table 7.2) for the following ten item pairs:

- 3 and 25 - Consistent decision making
- 4 and 32- Apply a structured approach to decision making
- 11 and 35 - Provide/receive training in decision making
- 6 and 33 - Assign qualitative values to decision-making criteria
- 7 and 34 - Assign quantitative values to decision-making criteria
- 10 and 26 - Consider uncertainty in decision making
- 18 and 45 - Underestimate problems that adversely impact decision making
- 19 and 46 - Continue with projects/products which should be terminated earlier
- 2 and 29 - Transparent decision making
- 16 and 41 - Make the same mistake as in the past

**RESULTS**

This study focussed on the assessment of the implementation of the ten QDMPs using QoDoS through three cross-sectional case studies with a pharmaceutical company, a regulatory authority and an HTA agency. For the purpose of clarity, the results are presented in five parts:

- Part I – Pharmaceutical company
- Part II – Regulatory authority

- Part III – HTA agency
- Part IV – Demographic breakdown
- Part V – Initial feedback

**Characteristics of the study participants**

The three QoDoS studies were completed by a total of 31 individuals from across the four teams from the company, 40 individuals from the regulatory authority and 25 from the HTA agency. The response rate was 100% for the company (31 individuals), for the regulatory authority it was 78% for the pre-market assessors (25 out of 32 individuals contacted) and 100% for the post-market assessors (15 individuals) and for the HTA agency it was 89% (25 out of 28 individuals). Both studies were generally balanced in terms of gender, whereas the median work experience was 20 years for the combined data set for the company, 15 years for the regulatory authority and 24 years for the HTA agency as shown in Table 7.3.

**Table 7.3 Demographic characteristics of the study participants**

| Cohort | Subject | Total number of respondents | Number of respondents by gender | | | Work experience | | |
|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Not specified | Median | Max | Min |
| ***Pharma-ceutical company*** | Leadership team | 5 | 2 | 3 | 0 | 20 | 36 | 13 |
| | Sub-team 1 (regulatory) | 6 | 1 | 3 | 2 | 25 | 37 | 14 |
| | Sub-team 2 (regulatory) | 11 | 6 | 3 | 2 | 20 | 32 | 8 |
| | Sub-team 3 (safety) | 9 | 3 | 6 | 0 | 20 | 33 | 11 |
| | *Combined company* | *31* | *12* | *15* | *4* | *20* | *37* | *8* |
| ***Regulatory authority*** | Pre-market assessors | 25 | 11 | 11 | 3 | 20 | 32 | 2 |
| | Post-market assessors | 15 | 5 | 9 | 1 | 6 | 37 | 1 |
| | *Combined authority* | *40* | *16* | *20* | *4* | *15* | *37* | *1* |
| ***HTA agency*** | Appraisal Committee members | 25 | 15 | 6 | 4 | 24 | 35 | 2.5 |
| ***Combined (all cohorts)*** | ***All subjects*** | **96** | **43** | **41** | **12** | **21** | **37** | **1** |

**Part I – Pharmaceutical company**

*Assessment of individual practices*

This study demonstrated that overall, the individual-level QDMPs of the company participants are generally favourable, namely regarding how the individuals within the three sub-teams perceive their decision-making process for presenting an emerging risk to a regulatory authority as well as how the individuals within the leadership team perceive their process for submitting an NDA to a regulatory authority (Figure 7.1).

Interestingly, an analysis of the QDMP median scores for the three STs uncovered that the individual practices were identical and generally favourable for ST1 and ST 2, thereby suggesting more consistency across the two regulatory sub-teams compared to the safety sub-team (ST 3) where there were some differences that should be explored with the participants. One practice that was not favourable for ST 1 and 2 was QDMP 3 (assign values and relative importance to decision criteria), which received a median score of two. The practices for the safety group (ST 3) were also generally favourable and differed from ST1 and ST2 regarding QDMP 3 (criteria) and 6 (consider uncertainty) with higher scores for ST3 compared to ST 1 and ST 2, whereas QDMP 9 (ensure transparency and provide a record trail) received a lower score for the safety group compared to the two regulatory STs.

The main differences between the practices of the three STs and the LT were QDMP 2 (assign clear roles and responsibilities), where the practices of the leadership team were less favourable by one point; similarly QDMP 5 (examine alternative solutions), where the LT scored in the area of 'needing improvement' and finally QDMP 9 (transparency) was also less favourable for the LT compared to the three STs.

The variance in the scores was also explored (Figure 7.2) and demonstrated that despite some differences in medians, the overlap between the scores was considerable, for example for QDMP 2 (roles) where the median score was between 3 and 4 for the three STs, whereas the $25^{th}$-$75^{th}$ median range was also between 3 and 4, demonstrating that generally the individual practices are relatively consistent and favourable. On the other hand, some differences in variance exist for practices with the same median, for example QDMP 1 (have a systematic, structured approach to aid decision making), where the $25^{th}$-$75^{th}$ box was in the area of 'favourable practice' for ST3, but suggests a potential need for improvement for the LT and ST2. The practice with the most variance across the group was QDMP 3 (criteria), indicating that this practice is not consistently applied across the individuals within the teams.

**Figure 7.1 Ten Quality Decision-Making Practices (QDMPs) for individual's decision making (QoDoS Part 2) for pharmaceutical company leadership team and the three sub-teams**

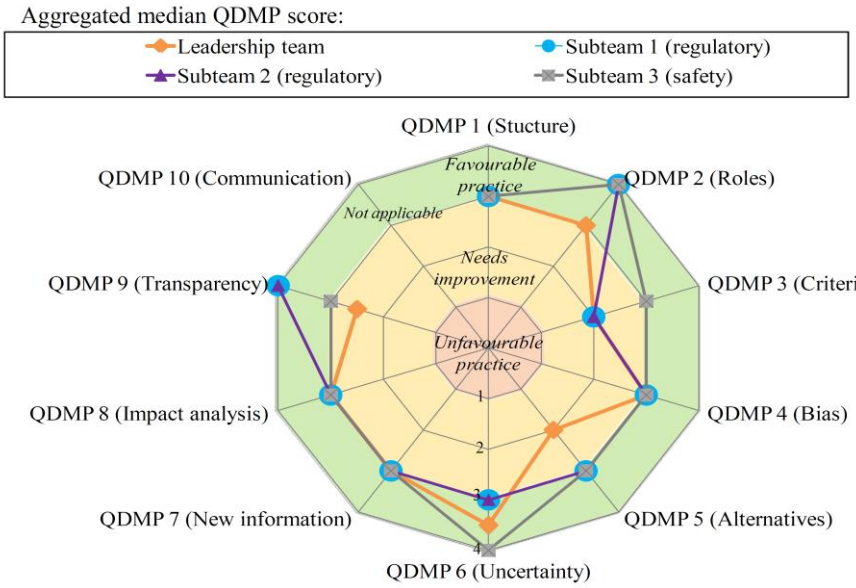
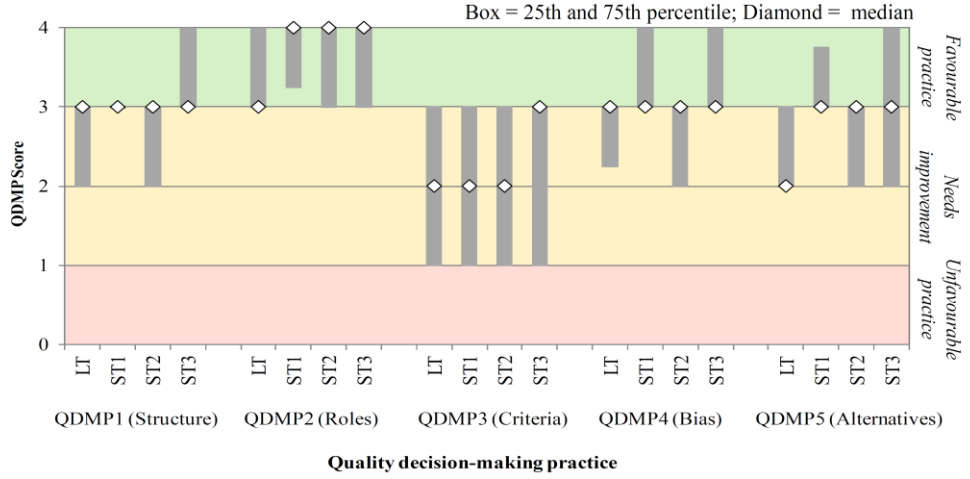
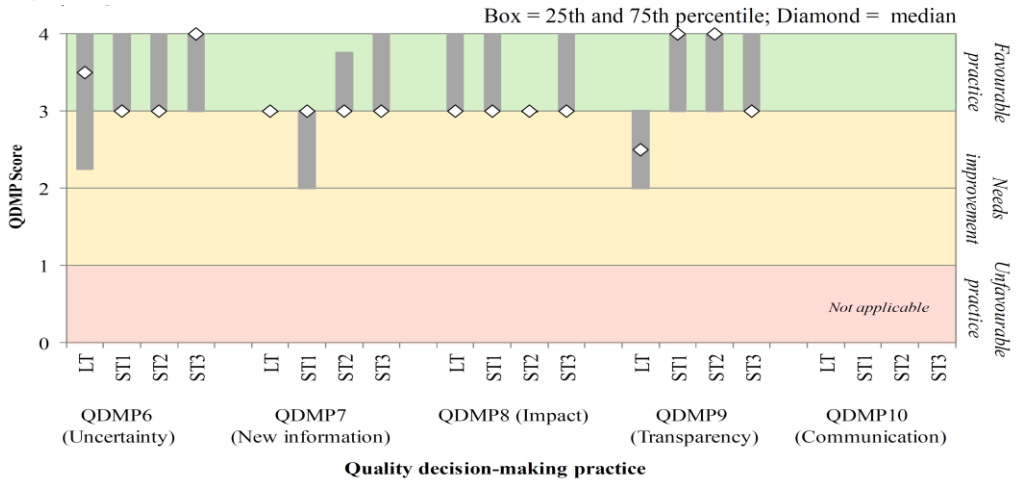



**Figure 7.2 Variance in the Quality Decision-Making Practice (QDMP) scores for individual's decision making (QoDoS Part 2) for pharmaceutical company leadership team and the three sub-teams**

**a) QDMPs 1-5**




**b) QDMPs 6-10**



*Assessment of organisational practices*

The individuals from the three STs also evaluated their perception of the decision making of the LT for submitting an NDA to a regulatory authority, which was compared to the results of the leadership team assessing their own decision making for that same decision-making process (Figure 7.3). The results suggest the three STs perceive a number of practices of the LT as favourable, namely QDMP 6 (consider uncertainty), 7 (re-evaluate as new information becomes available), 8 (perform impact analysis of the decision) and 10 (effectively communicate the basis of the decision).

On the other hand, there were some differences in the median scores across the three STs (relating how they each perceive the LT) for QDMP 1 (have a systematic, structured approach to aid decision making), 2 (assign clear roles and responsibilities), 3 (assign values and relative importance to decision criteria), 4 (evaluate both internal and external influences/biases), 5 (examine alternative solutions) and 9 (ensure transparency and provide a record trail), thereby indicating a need to discuss this difference in perception and any need for improvement in practice. Of particular interest would be to discuss the ST2 responses which were the largest outliers in terms of median value.

The results from the three STs were generally similar to those obtained directly from the LT, where one of the main differences was regarding QDMP 10 (effectively communicate the basis of the decision), where the three STs generally agreed that this practice was favourable for the LT, whereas the leadership team perceived this practice as 'needing improvement'. As with the assessment of the individual practices, the perceived incorporation of the ten QDMPs into LT's decision making was also characterised by considerable variance, for example for QDMP 1 (structure), 2 (roles), 3 (criteria) and 4 (bias) (Figure 7.4).

**Figure 7.3 Ten Quality Decision-Making Practices (QDMPs) for organisation's decision making (QoDoS Part 1) for pharmaceutical company leadership team and the three sub-teams**

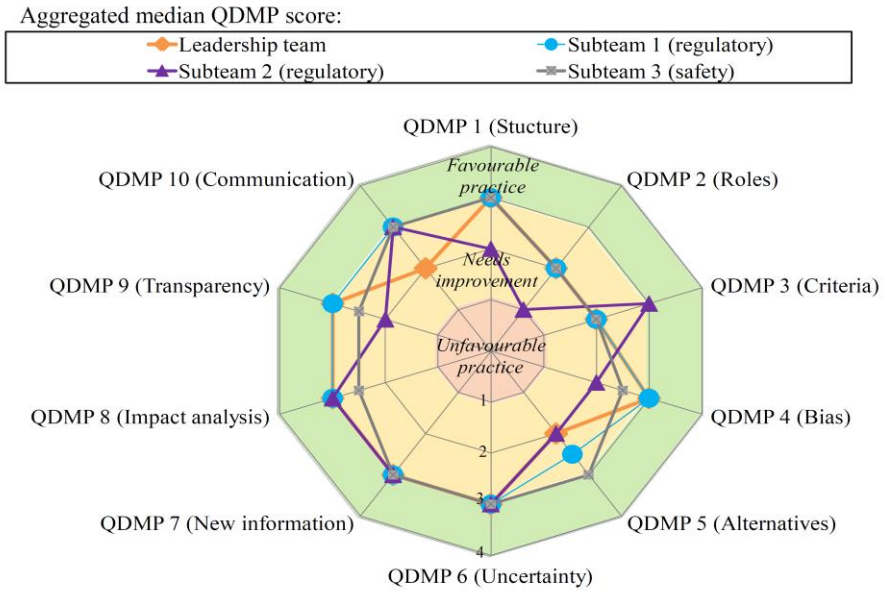
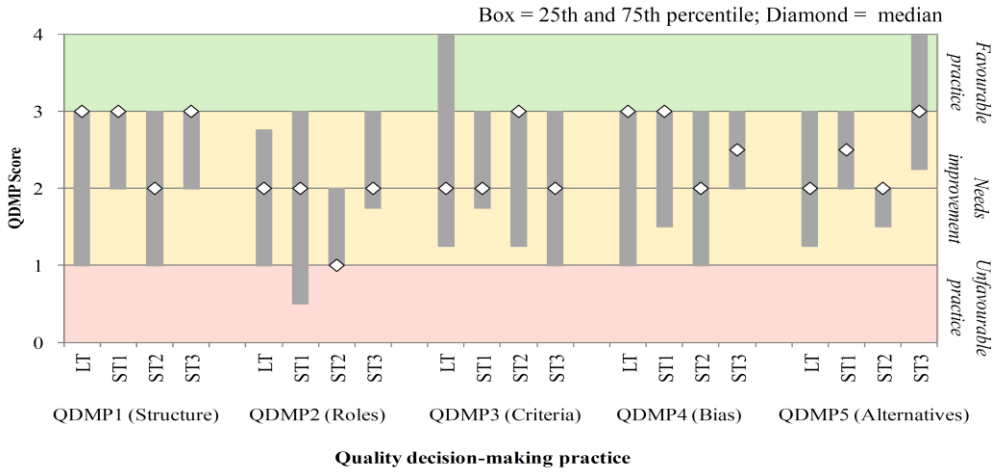
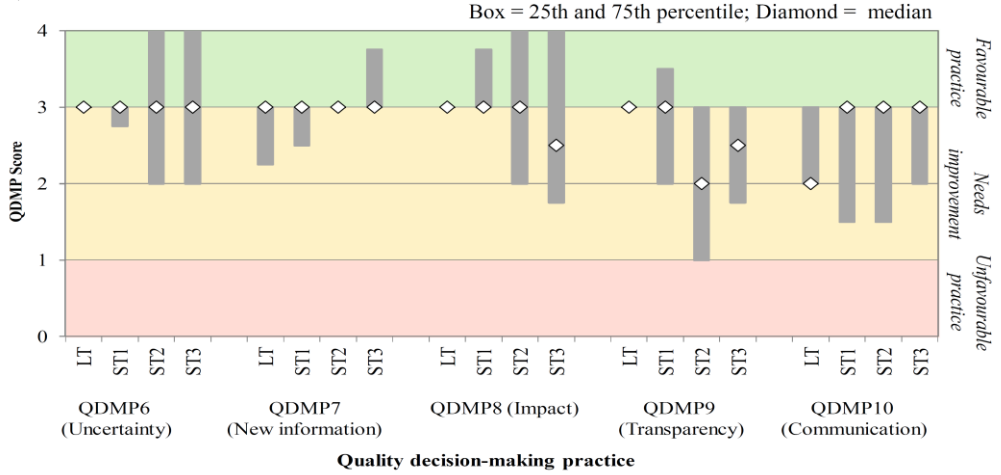



**Figure 7.4 Variance in the Quality Decision-Making Practice (QDMP) scores for organisation's decision making (QoDoS Part 1) for pharmaceutical company leadership team and the three sub-teams**

**a) QDMPs 1-5**




**b) QDMPs 6-10**



*QDMP breakdown by QoDoS items*

A breakdown of each QDMP according to the corresponding QoDoS items, relating both to the individual (Table 7.4) and organisational (Table 7.5) decision making, provides further insight into the company responses. Interestingly, the majority of the responses were relatively consistent across the four teams in terms of median (min-max difference in median). For individual decision making (Table 7.4), the item with most variance (min-max difference = 2) was item 34 ('I assign quantitative values to its decision-making criteria') and 44 ('my decision making could be improved by assigning relative importance to decision criteria'), which suggests that this practice is not consistently applied by all the teams.

The large variance in items 34 and 44 (Table 7.4) was reflected in the considerable variance for QDMP 3 in Figure 7.2. Consequently, the individual QoDoS items can be used to better understand the rationale for the QDMP median responses and variance. In addition, item 29, relating to transparent decision making in individuals, also received disparate QoDoS scores across the four teams, where the individuals on the LT felt their decision making was less transparent compared to the other groups.

Regarding the organisation (Table 7.5), items 15 and 20, relating to decision making being influenced by politics and incentives or penalty payments, were characterised by the most variance (min-max difference = 1.5). Here, ST2 was the outlier in their rating, perceiving that these influences (relating to LT's decision making) occurred more frequently compared to other teams. Finally, training in decision making (item 35 in Table 7.4; item 11 in Table 7.5) was generally provided and/or received on a "sometimes" basis.

**Table 7.4 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); individual's decision making (QoDoS Part 2) for company leadership team (LT) and the three sub-teams (STs)**

| QDMP | QoDoS item | Median | | | | Min-max difference in median |
|---|---|---|---|---|---|---|
| | | LT | ST1 | ST2 | ST3 | |
| QDMP1 (Structure) | 24. My decision making is knowledge based | 3 | 4 | 3 | 4 | 1 |
| | 25. My decision making is consistent | 3 | 3 | 3 | 3 | 0 |
| | 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | 2 | 1 | 1 | 2 | 1 |
| | 30. I understand the context of the decision I am being asked to make | 3 | 3 | 3 | 3 | 0 |
| | 32. I use a structured approach in my decision making | 2 | 3 | 2 | 3 | 1 |
| | 35. I receive training in the science of decision making | 1 | 0.5 | 0 | 1 | 1 |
| | *36. I use intuition or "gut-feeling" in my decision making | 3 | 3 | 2 | 3 | 1 |
| | *39. I have experienced "paralysis by analysis" caused by my slow decision making | 3 | 3 | 3 | 4 | 1 |
| | *40. I have experienced a negative outcome by a decision not being made | 3 | 3 | 3 | 3 | 0 |
| | *43. My procrastination has resulted in a negative outcome | 3 | 4 | 4 | 4 | 1 |
| QDMP2 (Roles) | 37. My professional experience is important when having to make challenging decisions | 3 | 4 | 4 | 4 | 1 |
| QDMP3 (Criteria) | 33. I assign qualitative values to its decision-making criteria | 2 | 3 | 3 | 3 | 1 |
| | 34. I assign quantitative values to its decision-making criteria | 1 | 1.5 | 1.5 | 3 | 2 |
| | 44. My decision making could be improved by assigning relative importance to decision criteria | 3 | 1 | 1 | 1 | 2 |
| QDMP4 (Bias) | *38. Emotion is part of my decision making | 3 | 3.5 | 3 | 3 | 0.5 |
| | *42. Recent or dramatic events greatly impact my decision making | 3 | 3 | 2 | 3 | 1 |
| QDMP5 (Alternatives) | 28. I present contingencies or achievable options as part of my decision making | 2 | 3 | 3 | 3 | 1 |
| QDMP6 (Uncertainty) | 26. I consider uncertainty and unknowns in my decision-making approach | 3 | 4 | 3 | 4 | 1 |
| | *45. I underestimate problems which adversely impact my decision making | 4 | 3 | 3 | 4 | 1 |
| QDMP7 (New information) | *46. I continue with projects/products which should be terminated at an early stage | 3 | 3 | 3 | 3 | 0 |
| QDMP8 (Impact) | 31. I understand the importance of the decisions I make | 4 | 4 | 3 | 4 | 1 |
| | *47. I feel that I could make better quality decisions | 3 | 3 | 3 | 3 | 0 |
| QDMP9 (Transparency) | 29. My decision making is transparent | 2 | 4 | 4 | 3 | 2 |
| | *41. In my decision making, I make the same mistakes as in the past | 3 | 4 | 4 | 3 | 1 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0. Red highlight shows median difference ≥ 1.5

**Table 7.5 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); organisation's decision making (QoDoS Part 1) for company leadership team (LT) and the three sub-teams (STs)**

| QDMP | QoDoS item | Median | | | | Min-max difference in median |
|---|---|---|---|---|---|---|
| | | LT | ST1 | ST2 | ST3 | |
| QDMP1 (Structure) | 3. My organisation's decision making is consistent | 3 | 3 | 2 | 2 | 1 |
| | 4. My organisation uses a structured approach in its decision making | 3 | 3 | 3 | 3 | 0 |
| | 11. My organisation provides training in the science of decision making | 1 | 1 | 1 | 2 | 1 |
| | *13. My organisation has suffered a negative outcome due to slow decision making | 3 | 3 | 3 | 3 | 0 |
| | *14. My organisation's culture has resulted in its inability to make a decision | 3 | 3 | 2 | 3 | 1 |
| QDMP2 (Roles) | *15. My organisation's decision making is influenced by organisational politics | 2 | 2 | 1 | 2.5 | 1.5 |
| | 23. My organisation provides clear and unambiguous instructions for decision making | 2 | 1.5 | 1 | 2 | 1 |
| QDMP3 (Criteria) | 6. My organisation assigns qualitative values to its decision-making criteria | 2 | 2 | 3 | 2.5 | 1 |
| | 7. My organisation assigns quantitative values to its decision-making criteria | 2 | 2.5 | 3 | 2 | 1 |
| QDMP4 (Bias) | *5. My organisation's decision making is influenced by external stakeholder's demands | 1 | 1 | 1 | 1 | 0 |
| | *17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | 3 | 3 | 3 | 3.5 | 0.5 |
| | *20. My organisation's decision making is influenced by similar organisations or competitors | 2 | 3 | 2 | 2 | 1 |
| | *21. My organisation's decision making is influenced by incentives or penalty payments | 3 | 4 | 2 | 3 | 2 |
| QDMP5 (Alternatives) | 8. My organisation is open to using better alternatives in its decision making | 2 | 2.5 | 2 | 3 | 1 |
| | 9. My organisation encourages innovative decision making | 2 | 2.5 | 2 | 3 | 1 |
| QDMP6 (Uncertainty) | 10. My organisation considers uncertainties in relation to its decision making | 3 | 3 | 3 | 3 | 0 |
| | *18. My organisation underestimates problems which adversely impact its own decisions | 3 | 3 | 3 | 3 | 0 |
| QDMP7 (New information) | 12. My organisation re-examines its decision making as new information becomes available | 2 | 3 | 3 | 3 | 1 |
| | *19. My organisation continues with projects/products which should be terminated at an earlier stage | 3 | 3 | 3 | 3 | 0 |
| QDMP8 (Impact) | 1. My organisation evaluates the impact of the decisions it makes | 3 | 3 | 3 | 2.5 | 0.5 |
| QDMP9 (Transparency) | 2. My organisation's decision making is transparent | 3 | 2.5 | 2 | 2 | 1 |
| | *16. My organisation's decision making results in making the same mistake as in the past | 3 | 3 | 3 | 3 | 0 |
| QDMP10 (Communication) | 22. My organisation effectively communicates the decisions it makes | 2 | 3 | 3 | 3 | 1 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0. Red highlight shows median difference ≥ 1.5

**Part II – Regulatory authority**

*Assessment of individual practices*

An analysis of the decision-making practices across the 40 assessors indicated that both pre-market and post-market assessors perceive their practices as generally 'favourable' across all ten QDMPs (Figure 7.5). The only QDMP in the area of 'needing improvement', according to the median, was QDMP 5 (examine alternative solutions) for the post-market assessors.

In terms of median, the practices were consistent between pre and post-market staff, whereas notable differences in median (one-point difference) were observed for QDMP 1 (have a systematic, structured approach to aid decision making), 4 (evaluate both internal and external influences/biases), 5 (examine alternative solutions) and 6 (consider uncertainty) (Figure 7.5). Nevertheless, the variance around the median for each of those QDMP (Figure 7.6) suggests that there are considerable differences around certain practices. For example, despite QDMP 3 (assign values and relative importance to decision criteria) having a median corresponding to 'favourable practice', the variance ($25^{th}$-$75^{th}$ percentile) was in the area of 'needing improvement', particularly for pre-market assessors, indicating that this practice should be further explored.

*Assessment of organisational practices*

The perception of organisational QDMPs by the assessors was also in the area of 'favourable practice' and the QDMP scores were similar for pre- and post-market assessors (Figure 7.7). Interestingly, there was more consistency between responses from pre- and post-market assessors on their perception of their organisation (Figure 7.7) compared to perception of own decision making (Figure 7.5). In terms of median, the only differences between pre- and post-market assessors in Figure 7.7 were for QDMP 2 (assign clear roles and responsibilities), where pre-market responses resulted in 'favourable practice' compared to 'needing improvement' for post-market staff; on the other hand, QDMP 8 (perform impact analysis of the decision), was rated by pre-market assessors as 'unfavourable practice' and as 'needing improvement' by post-market assessors. Nevertheless, there was also considerable variance for a number of the QDMPs, such as QDMP 3 (criteria) and QDMP 5 (alternatives) for pre-market assessors and QDMP 4 (bias) for post-market assesses (Figure 7.8).

**Figure 7.5 Ten Quality Decision-Making Practices (QDMPs) for individual's decision making (QoDoS Part 2) for regulatory authority pre- and post-market assessors**

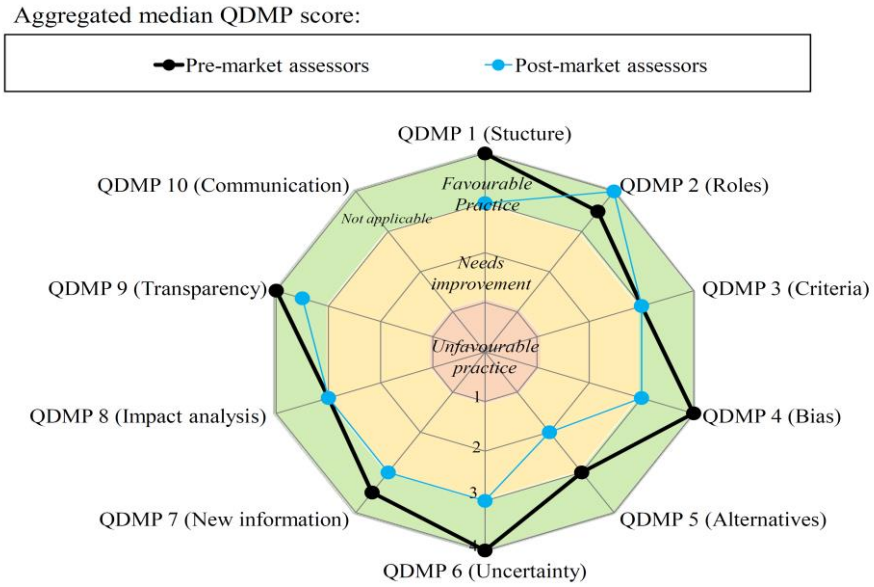
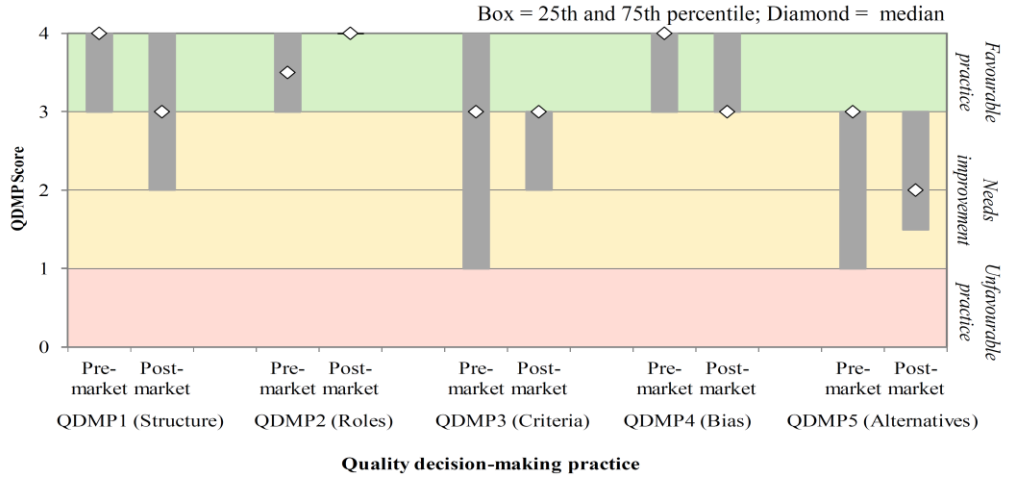



**Figure 7.6 Variance in the Quality Decision-Making Practice (QDMP) scores for individual's decision making (QoDoS Part 2) for regulatory authority pre- and post-market assessors**

**a) QDMPs 1-5**




**b) QDMPs 6-10**

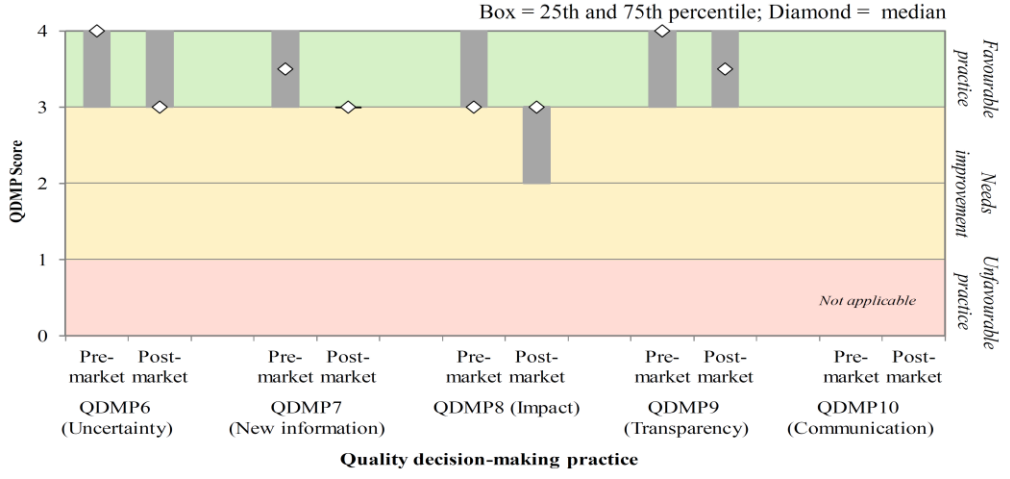


**Figure 7.7 Ten Quality Decision-Making Practices (QDMPs) for organisation's decision making (QoDoS Part 1) for regulatory authority pre- and post-market assessors**

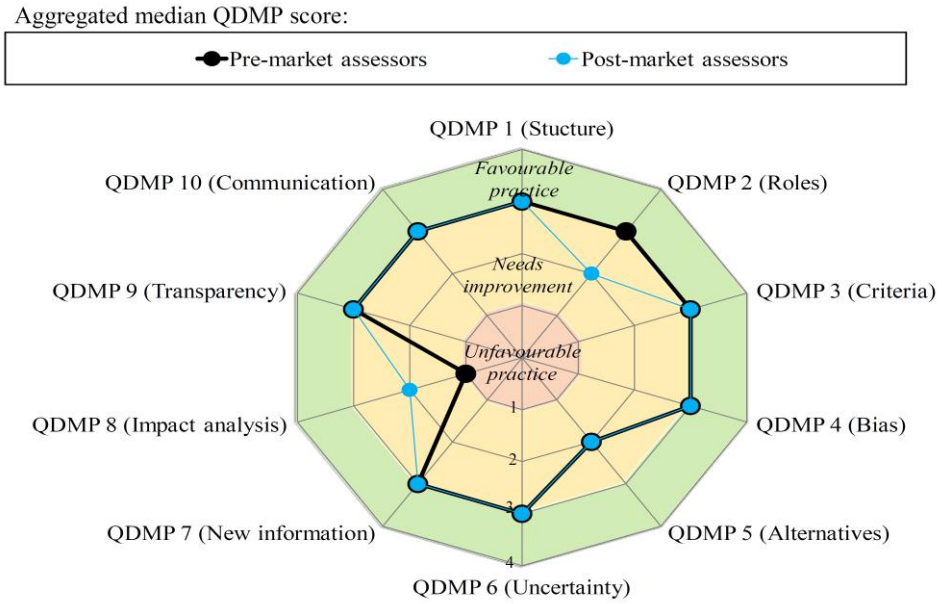
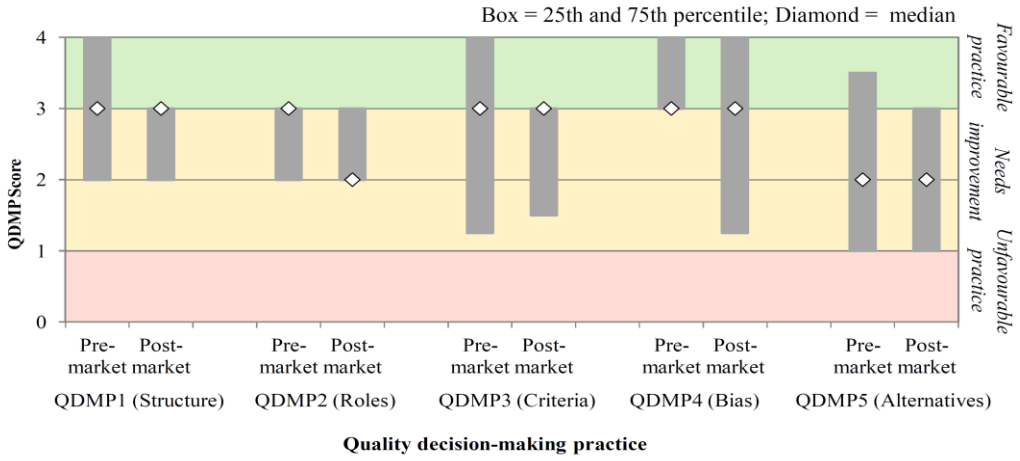
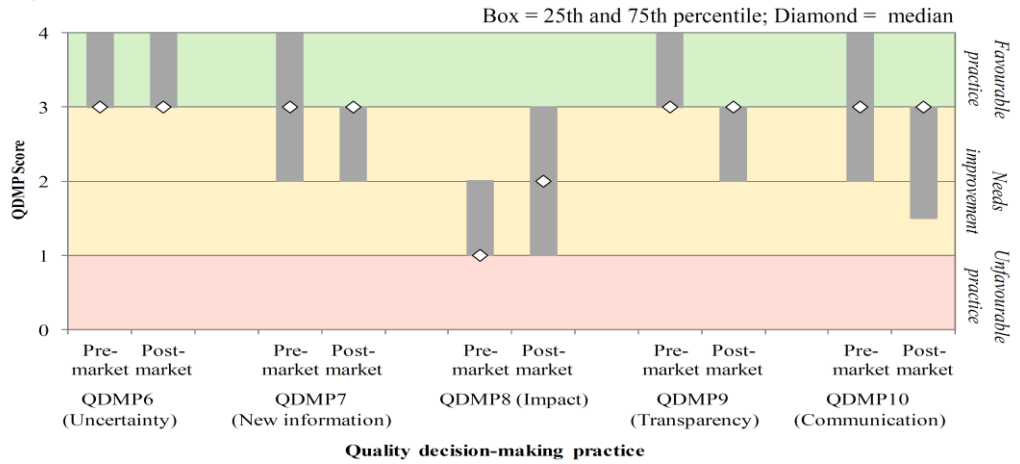



**Figure 7.8 Variance in the Quality Decision-Making Practice (QDMP) scores for organisation's decision making (QoDoS Part 1) for regulatory authority pre- and post-market assessors**

**a) QDMPs 1-5**




**b) QDMPs 6-10**



*QDMP breakdown by QoDoS items*

The QoDoS item scores were generally consistent, where the difference in median between the pre- and post-market assessors was one point (mix-max difference) or less as indicated in Tables 7.6 and 7.7. In addition, an analysis of the QoDoS items can be used to determine what drives the various median QDMP scores in Figure 7.5 and 7.7, as well as what is the rationale for the variance in QDMP scores in Figures 7.6 and 7.8.

For example, for QDMP 1 (have a systematic, structured approach to aid decision making) the median score and the variance reflecting individual practice was more favourable for the pre-market assessors compared to post-market assessors (Figure 7.6), which in turn can be explained by individual QoDoS items in Table 7.6. Here, on average (median), the pre-market assessors used SWOT analyses during their decision making (item 27) more frequently compared to post-market assessors and always understood the decision context (30) as well as based their decision on their knowledge (24), which was carried out less frequently by the post-market assessors. Conversely, pre-market assessors seemed to be less influenced by potential biases and other subjective influences (and hence had higher scores compared to post-market assessors) as a result of intuition (item 36) or being unable to make a decision due to over-analysis of the situation (item 39) or experiencing a negative outcome due to slow decision making (40). The overall median across these individual QoDoS item scores, which were all higher for the pre-market compared to post-market assessors, resulted in a more favourable QDMP 1 for pre-market compared to post-market assessors.

There are ten sets of identical QoDoS items for part 1 (Organisation) and part 2 (Individual) of QoDoS, as described in the method. An analysis of these pairs of items revealed that, for all ten cases, individuals scored themselves the same or more highly compared to the organisation for the regulatory authority. Individuals scored themselves more favourably regarding having a structured approach (item 32 in Table 7.6 and item 4 in Table 7.7); assigning quantitative values to decision-making criteria (item 34 in Table 7.6 and item 7 in Table 7.7), considering uncertainty in decision making (item 26 in Table 7.6 and item 10 in Table 7.7) and making the same mistake as in the past (item 41 in Table 7.6 and 16 in Table 7.7). Finally, in terms of training in decision making, this was provided at organisational level and received on an individual level on a “sometimes” basis by both pre-market and post-market assessors, which is similar to the company result.

**Table 7.6 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); individual's decision making (QoDoS Part 2) for regulatory authority pre- and post-market assessors**

| QDMP | QoDoS item | Median | | Difference in median |
|---|---|---|---|---|
| | | Pre-market assessors | Post-market assessors | |
| QDMP1 (Structure) | 24. My decision making is knowledge based | 4 | 3 | 1 |
| | 25. My decision making is consistent | 3 | 3 | 0 |
| | 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | 2 | 1 | 1 |
| | 30. I understand the context of the decision I am being asked to make | 4 | 3 | 1 |
| | 32. I use a structured approach in my decision making | 4 | 4 | 0 |
| | 35. I receive training in the science of decision making | 1 | 1 | 0 |
| | *36. I use intuition or "gut-feeling" in my decision making | 4 | 3 | 1 |
| | *39. I have experienced "paralysis by analysis" caused by my slow decision making | 4 | 3 | 1 |
| | *40. I have experienced a negative outcome by a decision not being made | 4 | 3 | 1 |
| | *43. My procrastination has resulted in a negative outcome | 4 | 4 | 0 |
| QDMP2 (Roles) | 37. My professional experience is important when having to make challenging decisions | 3.5 | 4 | 0.5 |
| QDMP3 (Criteria) | 33. I assign qualitative values to its decision-making criteria | 3 | 2.5 | 0.5 |
| | 34. I assign quantitative values to its decision-making criteria | 3 | 3 | 0 |
| | 44. My decision making could be improved by assigning relative importance to decision criteria | 1 | 2 | 1 |
| QDMP4 (Bias) | *38. Emotion is part of my decision making | 4 | 4 | 0 |
| | *42. Recent or dramatic events greatly impact my decision making | 3.5 | 3 | 0.5 |
| QDMP5 (Alternatives) | 28. I present contingencies or achievable options as part of my decision making | 3 | 2 | 1 |
| QDMP6 (Uncertainty) | 26. I consider uncertainty and unknowns in my decision-making approach | 4 | 4 | 0 |
| | *45. I underestimate problems which adversely impact my decision making | 3 | 3 | 0 |
| QDMP7 (New information) | *46. I continue with projects/products which should be terminated at an early stage | 3.5 | 3 | 0.5 |
| QDMP8 (Impact) | 31. I understand the importance of the decisions I make | 4 | 3 | 1 |
| | *47. I feel that I could make better quality decisions | 3 | 3 | 0 |
| QDMP9 (Transparency) | 29. My decision making is transparent | 3.5 | 3 | 0.5 |
| | *41. In my decision making, I make the same mistakes as in the past | 4 | 4 | 0 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0.

**Table 7.7 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); organisation's decision making (QoDoS Part 1) for regulatory authority pre- and post-market assessors**

| QDMP | QoDoS item | Median | | Difference in median |
|---|---|---|---|---|
| | | Pre-market assessors | Post-market assessors | |
| QDMP1 (Structure) | 3. My organisation's decision making is consistent | 3 | 3 | 0 |
| | 4. My organisation uses a structured approach in its decision making | 3 | 3 | 0 |
| | 11. My organisation provides training in the science of decision making | 1 | 1 | 0 |
| | *13. My organisation has suffered a negative outcome due to slow decision making | 3 | 3 | 0 |
| | *14. My organisation's culture has resulted in its inability to make a decision | 4 | 3.5 | 0.5 |
| QDMP2 (Roles) | *15. My organisation's decision making is influenced by organisational politics | 3 | 3 | 0 |
| | 23. My organisation provides clear and unambiguous instructions for decision making | 2 | 2 | 0 |
| QDMP3 (Criteria) | 6. My organisation assigns qualitative values to its decision-making criteria | 3 | 3 | 0 |
| | 7. My organisation assigns quantitative values to its decision-making criteria | 2 | 2.5 | 0.5 |
| QDMP4 (Bias) | *5. My organisation's decision making is influenced by external stakeholder's demands | 3 | 3 | 0 |
| | *17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | 4 | 4 | 0 |
| | *20. My organisation's decision making is influenced by similar organisations or competitors | 2 | 1 | 1 |
| | *21. My organisation's decision making is influenced by incentives or penalty payments | 4 | 4 | 0 |
| QDMP5 (Alternatives) | 8. My organisation is open to using better alternatives in its decision making | 3 | 2 | 1 |
| | 9. My organisation encourages innovative decision making | 1 | 2 | 1 |
| QDMP6 (Uncertainty) | 10. My organisation considers uncertainties in relation to its decision making | 3 | 3 | 0 |
| | *18. My organisation underestimates problems which adversely impact its own decisions | 3 | 3 | 0 |
| QDMP7 (New information) | 12. My organisation re-examines its decision making as new information becomes available | 2 | 3 | 1 |
| | *19. My organisation continues with projects/products which should be terminated at an earlier stage | 3 | 3 | 0 |
| QDMP8 (Impact) | 1. My organisation evaluates the impact of the decisions it makes | 1 | 2 | 1 |
| QDMP9 (Transparency) | 2. My organisation's decision making is transparent | 3 | 3 | 0 |
| | *16. My organisation's decision making results in making the same mistake as in the past | 3 | 3 | 0 |
| QDMP10 (Communication) | 22. My organisation effectively communicates the decisions it makes | 3 | 3 | 0 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0.

**Part III – HTA agency**

*Assessment of individual and organisational practices*

The combined results across the 25 individuals from the HTA agency indicate that the appraisal committee members perceive their own decision-making practices as generally 'favourable', both in terms of how the members perceive themselves as well as the organisation (Figure 7.9). The practices with unfavourable or 'needing improvement' medians were QDMP 3 (assign values and relative importance to decision criteria), QDMP 5 (examine alternative solutions) and QDMP 8 (perform impact analysis of the decision), which is interestingly similar to the results from the regulatory authority. A number of QDMPs with medians close to 'favourable practice' were characterised by considerable variance in the 'needing improvement' area, for example QDMP 2 (assign clear roles and responsibilities) and QDMP 7 (re-evaluate as new information becomes available) regarding the individuals' perception of the organisation's decision making (Figure 7.10).

*QDMP breakdown by QoDoS item*

Interestingly, for the HTA agency responses, an assessment of the items which are identical for the organisation and the individual revealed that the median scores were either the same or had higher organisational score compared to individual for almost all the item pairs (nine out of ten) (Tables 7.8 and 7.9). The exception was regarding continuing with projects/products which should be terminated at an early stage (item 46 in Table 7.8 and item 19 in Table 7.9) where the minimal difference was 0.5 in favour of the individual. This was a contrast compared to the regulatory authority results. Finally, the participants indicated that they receive training in quality decision on a 'sometimes' basis, which is consistent with results from the company and regulatory authority.

**Figure 7.9 Ten Quality Decision-Making Practices (QDMPs) for individual's and organisation's decision making (QoDoS Part 2 and 1 respectively) for HTA appraisal committee members**

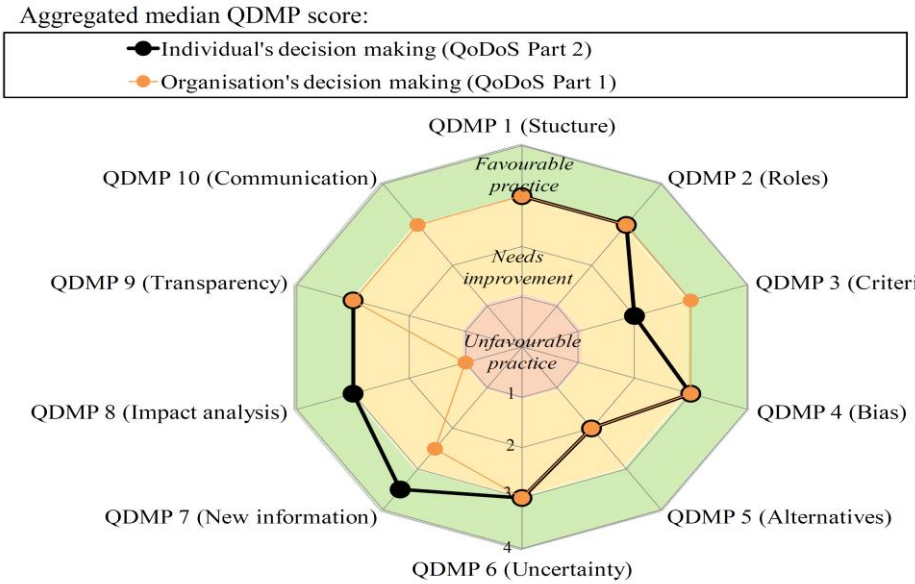
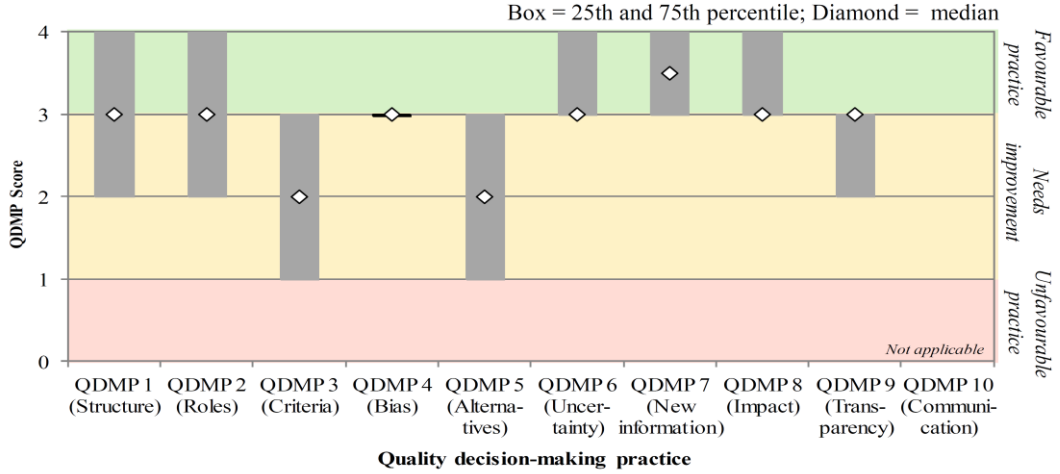



**Figure 7.10 Variance in the Quality Decision-Making Practice (QDMP) scores for HTA appraisal committee members**

**a) Individual's decision making (QoDoS Part 2)**




**b) Organisation's decision making (QoDoS Part 1)**

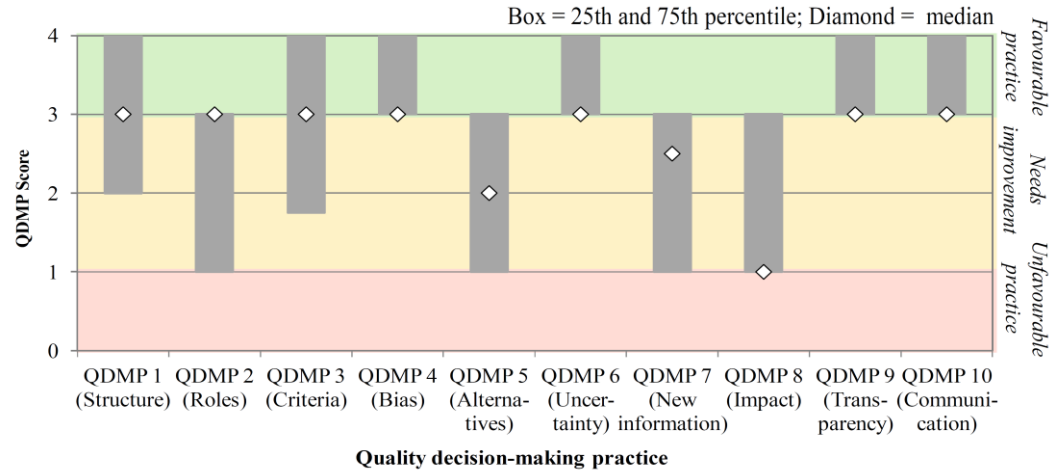


**Table 7.8 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); individual's decision making (QoDoS Part 2) for HTA appraisal committee members**

| QDMP | QoDoS item | Appraisal Committee Median |
|---|---|---|
| QDMP1 (Structure) | 24. My decision making is knowledge based | 3 |
| | 25. My decision making is consistent | 3 |
| | 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | 0 |
| | 30. I understand the context of the decision I am being asked to make | 4 |
| | 32. I use a structured approach in my decision making | 3 |
| | 35. I receive training in the science of decision making | 0 |
| | *36. I use intuition or "gut-feeling" in my decision making | 2 |
| | *39. I have experienced "paralysis by analysis" caused by my slow decision making | 3 |
| | *40. I have experienced a negative outcome by a decision not being made | 4 |
| | *43. My procrastination has resulted in a negative outcome | 4 |
| QDMP2 (Roles) | 37. My professional experience is important when having to make challenging decisions | 3 |
| QDMP3 (Criteria) | 33. I assign qualitative values to its decision-making criteria | 2 |
| | 34. I assign quantitative values to its decision-making criteria | 2.5 |
| | 44. My decision making could be improved by assigning relative importance to decision criteria | 2 |
| QDMP4 (Bias) | *38. Emotion is part of my decision making | 3 |
| | *42. Recent or dramatic events greatly impact my decision making | 3 |
| QDMP5 (Alternatives) | 28. I present contingencies or achievable options as part of my decision making | 2 |
| QDMP6 (Uncertainty) | 26. I consider uncertainty and unknowns in my decision-making approach | 4 |
| | *45. I underestimate problems which adversely impact my decision making | 3 |
| QDMP7 (New information) | *46. I continue with projects/products which should be terminated at an early stage | 3.5 |
| QDMP8 (Impact) | 31. I understand the importance of the decisions I make | 4 |
| | *47. I feel that I could make better quality decisions | 3 |
| QDMP9 (Transparency) | 29. My decision making is transparent | 2.5 |
| | *41. In my decision making, I make the same mistakes as in the past | 3 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0.

**Table 7.9 Quality of Decision-Making Orientation Scheme (QoDoS) item median scores for each Quality Decision-Making Practice (QDMP); organisation's decision making (QoDoS Part 1) for HTA appraisal committee members**

| QDMP | QoDoS item | Appraisal Committee Median |
|---|---|---|
| QDMP1 (Structure) | 3. My organisation's decision making is consistent | 3 |
| | 4. My organisation uses a structured approach in its decision making | 4 |
| | 11. My organisation provides training in the science of decision making | 1 |
| | *13. My organisation has suffered a negative outcome due to slow decision making | 3 |
| | *14. My organisation's culture has resulted in its inability to make a decision | 4 |
| QDMP2 (Roles) | *15. My organisation's decision making is influenced by organisational politics | 3 |
| | 23. My organisation provides clear and unambiguous instructions for decision making | 2 |
| QDMP3 (Criteria) | 6. My organisation assigns qualitative values to its decision-making criteria | 2.5 |
| | 7. My organisation assigns quantitative values to its decision-making criteria | 3 |
| QDMP4 (Bias) | *5. My organisation's decision making is influenced by external stakeholder's demands | 3 |
| | *17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | 4 |
| | *20. My organisation's decision making is influenced by similar organisations or competitors | 3 |
| | *21. My organisation's decision making is influenced by incentives or penalty payments | 4 |
| QDMP5 (Alternatives) | 8. My organisation is open to using better alternatives in its decision making | 2 |
| | 9. My organisation encourages innovative decision making | 1 |
| QDMP6 (Uncertainty) | 10. My organisation considers uncertainties in relation to its decision making | 4 |
| | *18. My organisation underestimates problems which adversely impact its own decisions | 3 |
| QDMP7 (New information) | 12. My organisation re-examines its decision making as new information becomes available | 1 |
| | *19. My organisation continues with projects/products which should be terminated at an earlier stage | 3 |
| QDMP8 (Impact) | 1. My organisation evaluates the impact of the decisions it makes | 1 |
| QDMP9 (Transparency) | 2. My organisation's decision making is transparent | 3 |
| | *16. My organisation's decision making results in making the same mistake as in the past | 3 |
| QDMP10 (Communication) | 22. My organisation effectively communicates the decisions it makes | 3 |

For QoDoS items corresponding to 'favourable practice', the following scores were assigned where 'Not at all' = 0, 'Sometimes' = 1, 'Frequently' = 2, 'Often' = 3, 'Always' = 4. For QoDoS items categorised as 'unfavourable practice' (*), the reverse scores were assigned where 'Not at all' = 4, 'Sometimes' = 3, 'Frequently' = 2, 'Often' = 1, 'Always' = 0.

**Part IV – Demographic breakdown**

The demographic characteristics of the respondents were used to analyse the perception of the individual's decision making according to gender and work experience for the combined dataset across the pharmaceutical company, regulatory authority and HTA agency. Interestingly, an analysis of the medians by gender indicated that the practices for males and females are generally consistent (Figure 7.11). Differences were seen for QDMP 3 (assign values and relative importance to decision criteria) and QDMP 5 (examine alternative solutions), although with considerable overlap in variance (Figure 7.12). On the other hand, the variance for QDMP 4 (evaluate both internal and external influences/biases) and QDMP 7 (re-evaluate as new information becomes available) was larger and tending towards needing improvement for males compared to females.

A breakdown by the number of years of experience (Figure 7.13), 1-12 years; 13-24 years and 25-37 years, indicated a consistency in median across a number of QDMPs, namely 1 (have a systematic, structured approach to aid decision making), 2 (assign clear roles and responsibilities), 4 (bias), 7 (new information) and 8 (perform impact analysis of the decision). Differences in median were noted for QDMP 3 (criteria), 5 (alternatives) and QDMP 6 (uncertainty) and QDMP 9 (ensure transparency and provide a record trail), where the cohort with 25-37 years of experience was characterised by the highest proportion of 'favourable practice'. Nevertheless, there was considerable variance that differed across the three groups (Figure 7.14).

**Figure 7.11 Ten Quality Decision-Making Practices (QDMPs) for individual's decision making (QoDoS Part 2) for males and females for combined study cohorts**

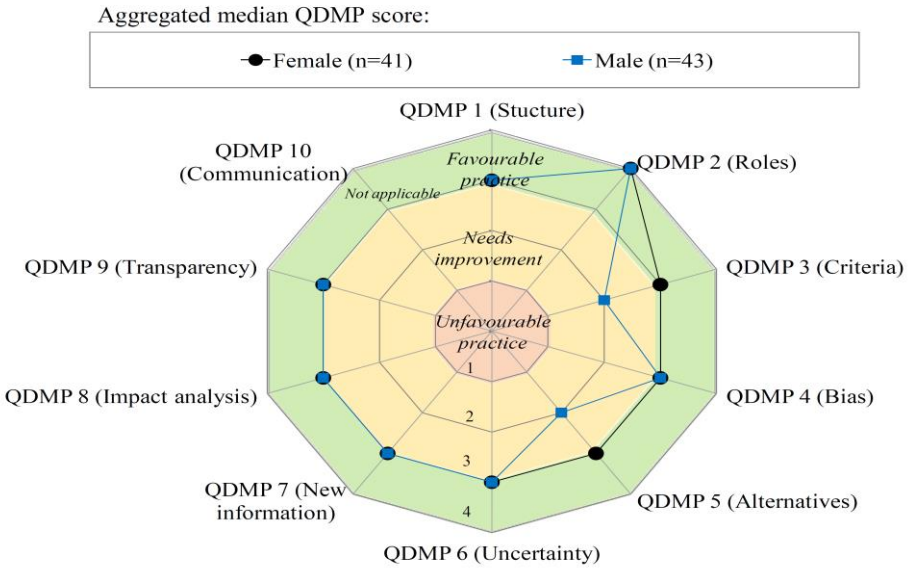
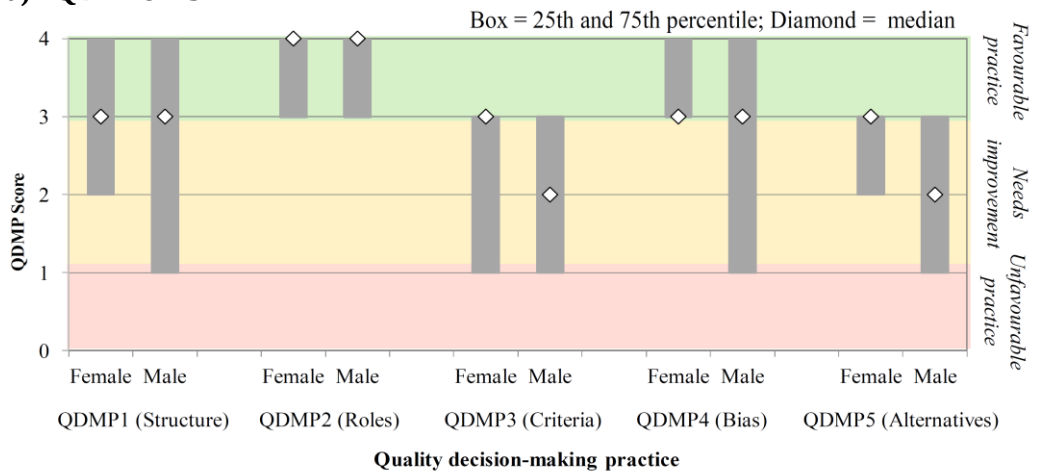



**Figure 7.12 Variance in the Quality Decision-Making Practice (QDMP) scores for individual's decision making (QoDoS Part 2) for males and females for combined study cohorts**

**a) QDMPs 1-5**




**b) QDMPs 6-10**

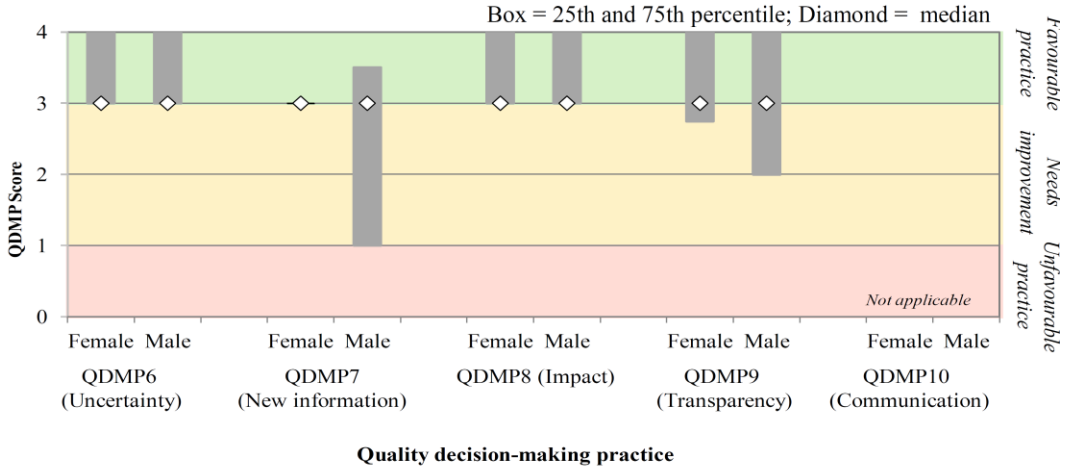


**Figure 7.13 Ten Quality Decision-Making Practices (QDMPs) for individual's decision making (QoDoS Part 2) by the number of years of work experience**

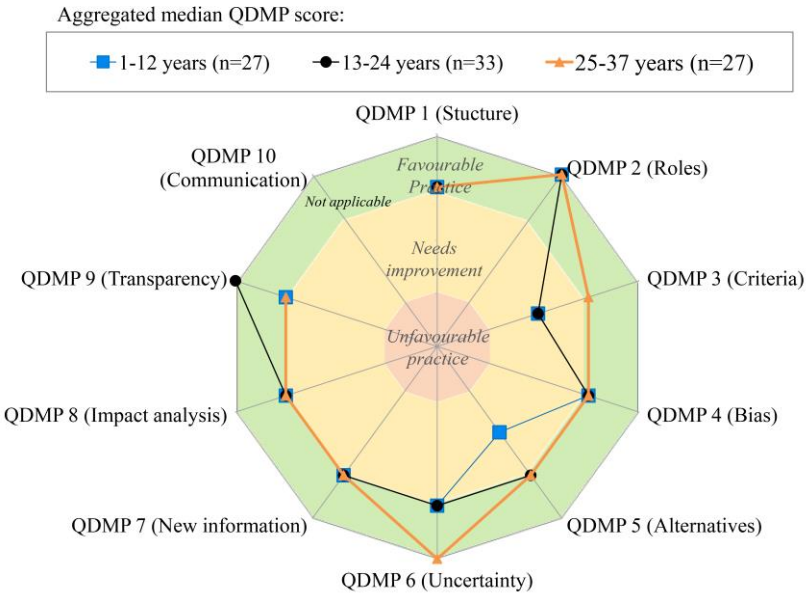
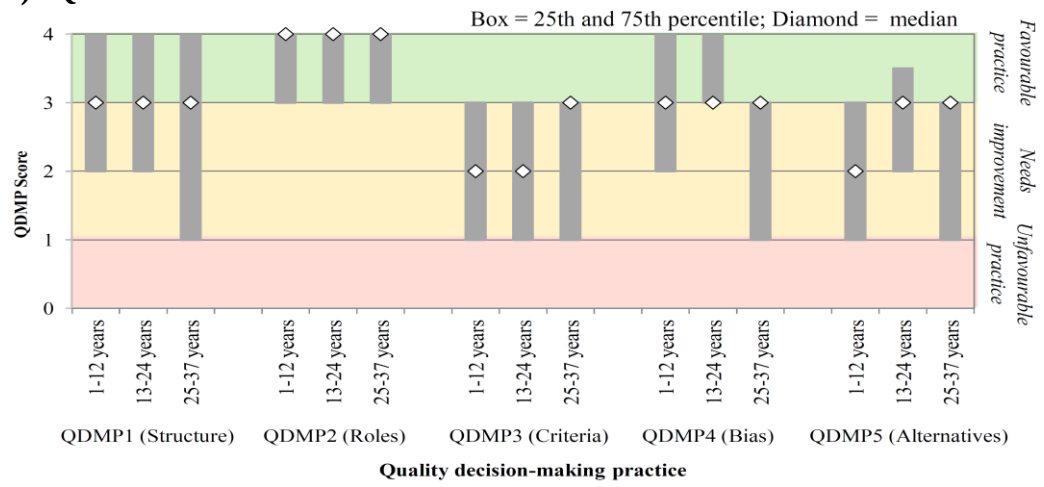
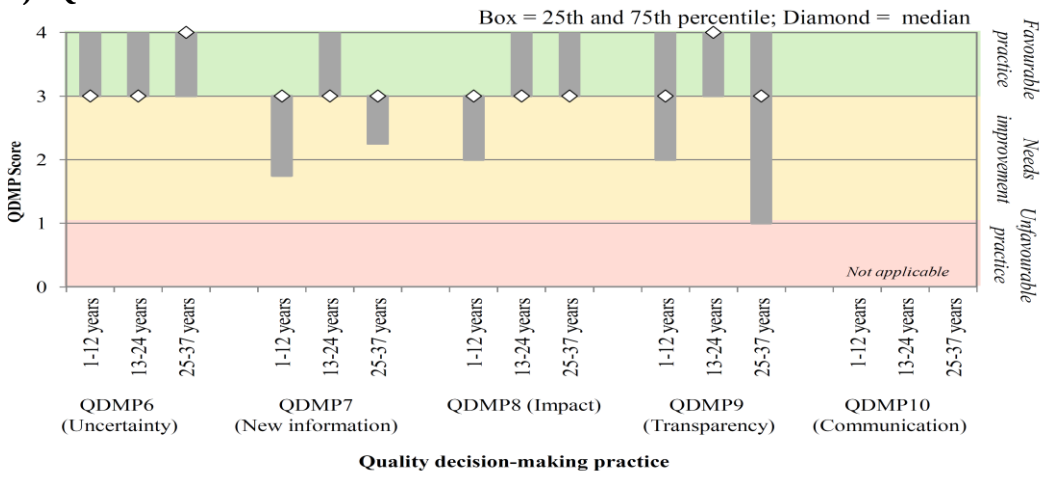



**Figure 7.14 Variance in the Quality Decision-Making Practice (QDMP) scores for individual's decision making (QoDoS Part 2) by the number of years of work experience**

**a) QDMPs 1-5**




**b) QDMPs 6-10**



**Part V – Feedback from participants**

Informal feedback discussions were organised with the group leaders from each study. These confirmed the feasibility of the study method as well as initial benefits of the approach, including raising awareness of biases and best practices in decision making, gaining a basis for discussion of the issues in decision making as well as making recommendations for improving the lowest scoring or least consistent practices. The discussions also helped to uncover rationale for some differences in responses across sub-groups or when comparing individual and organisational perception.

For example, the pharmaceutical company study uncovered that the median score for QDMP 10 (effectively communicate the basis of the decision) regarding the decision making of the leadership team was more favourable regarding how this is perceived by the three STs compared to the median obtained from the LT directly (Figure 7.3). A potential explanation received during the initial feedback session was that this may be a result of efficient and clear communication of LT's decisions by the sub-team managers to their direct reports in ST1, ST2 and ST3; this was highlighted as key to informing the day-to-day activities of the three STs. This difference as well as others will be explored during the formal feedback discussions with the study participants from each study cohort, which are planned for the second part of 2018. In addition, these discussions will seek to determine the perceived benefits of the study (including completion QoDoS as well as the feedback discussions), the lessons learned as well as the next steps that each organisation would like to undertake as part of the project.

The initial feedback discussions also facilitated a discussion on the weighting of the QoDoS items (favourable vs. unfavourable), for example the fact that item 5 ('my organisation's decision making is influenced by external stakeholder's demands') and item 36 ('I use intuition or "gut-feeling" in my decision making') are considered as unfavourable practices. Indeed, previous research has shown that sometimes individuals are better off with making a quick decision based on their 'expert intuition'. Nevertheless, successful decision making relies on a balance between deliberate and instinctive thinking. Consequently, individuals need to be aware of gut feeling or intuition and need to understand what is behind their quick judgment and first impression. Moreover, individuals need to be prepared to logically and objectively explain as to why they feel a certain way or make a particular decision in order to minimise the chance of being biased (Kahneman, 2011). As a result, the weightings of the QoDoS scores will be reviewed before pursuing future studies in order to ensure relevance and clarity.

## DISCUSSION

### Advancing the field of quality decision making

Although there is an increasing use of framework-based simulation and modelling to aid decision making within the lifecycle of medicines, the various decision-making processes are subjective in nature and should be further explored to identify areas of best practice as well as those that may need improvement in order to increase process quality, consistency and transparency (Walker et al., 2012). Other methodologies have been utilised to measure quality decision making in individuals and organisations as described in Chapter 5. Nevertheless, these are either brief in terms of number of items (Blenko et al., 2010); go beyond decision making as just one aspect of quality (Salek et al., 2012); assess only some of the QDMPs (McKinsey 2008; Cowlrick et al., 2011; Fischer et al., 2011; McIntyre et al., 2012; Open University, 2013; Marangi et al., 2014); or focus only on how individuals make decisions without taking into account how they perceive their organisation (Wood, 2012; Mindtools, 2013; Beyer et al., 2015). In addition, in terms of a target audience, the majority of the techniques are either tailored to meet specific organisational needs, or are designed for commercial organisations only and are therefore not generalisable with respect to agencies (Matheson and Matheson, 1998). The QoDoS, however, differs from these initiatives as it can be used across different groups involved in the development and review of medicines as well as for any decision process of interest in order to assess the incorporation of all ten QDMPs, both regarding individual practices as well as those of the organisation as perceived by the individuals.

### Key outcomes from the three case studies

This chapter described three illustrative case studies where QoDoS was used to assess the incorporation of the ten QDMPs in a company, a regulatory authority and an HTA agency. The three studies demonstrated the practicality of QoDoS to identify favourable and unfavourable practices as well as to assess their consistency and transparency within each organisation. Importantly, this study was the first application of QoDoS in an in-depth organisational setting and the results confirmed the initial feasibility of the proposed method. All three case studies demonstrated generally favourable results across the QDMPs, where overall, all three organisations have incorporated the majority of the ten QDMPs. This may not be surprising, as the organisations that were selected for the three pilots have established decision-making systems based on their size and multinational status (for the company) and maturity level (in case of agencies).

The three studies differed in terms of cohort type and decision point as described below, in order to demonstrate the different ways in which QoDoS can be applied. The pharmaceutical

company study was used to assess the decision making across four groups, where the QoDoS questions relating to the individual were answered regarding a decision-making processes specific to each group, whereas the questions relating to individual's perception of the organisation were used to assess the leadership team. This demonstrated certain differences, first of all across the individual practices for the three STs and in comparison to the LT; as well as differences and similarities in how the three STs perceive the LT compared to the LT itself.

Secondly, the regulatory authority study was used to demonstrate differences in individual practices and perception of the organisation by two different sub-groups as part of the same organisation for two specific decision-making processes (pre- and post-market approval). In this case, the QoDoS responses demonstrated that the perception of the organisation is relatively consistent for the two groups and certain differences were identified in how the individuals make decisions, which may be due to the different processes in place for the pre- and post-market process. Nevertheless, an assessment of the QoDoS items which are the same for the individual and organisation demonstrated that individuals generally perceive themselves more favourably compared to the organisation which is consistent with findings from a previous pilot study with a mix of participants from companies and agencies (Bujar et al., 2016). This could relate to factors such as an individual being more accountable at a micro level for the decisions they make as compared to an organisation on a macro level. On the other hand, as individuals make up the organisation, large differences could indicate bias or lack of understanding of organisational practices, areas of disparity could therefore help identify room for improvement to ensure that best practice is consistently applied.

Lastly, the HTA case study involved one group, the appraisal committee, where the individuals assessed themselves and their organisation for the same decision point, where the results demonstrated general consistency. Nevertheless, in this case, the perception of the individuals regarding their own decision making compared to their organisation for the ten QoDoS item pairs was similar and in favour of the organisation, which is contrary to the regulatory agency. This may because the HTA committee members are all external i.e. not being employed on a daily basis by the agency (as opposed to being internal employees for the regulatory authority). This could result in the committee members perceiving the organisation more objectively as a result of not being so involved in the process.

Interestingly, the QoDoS demonstrated the need for improvement across a number of practices, where some similarities were identified, such as the need for better assignment of values and relative importance of decision criteria (QDMP 3) as well as the evaluation of

alternatives (QDMP 5) for the three organisations and the need for a better impact analysis for the regulatory and the HTA agency (QDMP 8). Interestingly, both QDMP 3 and QDMP 8 were seen as generally not incorporated into company and agency frameworks during medicines regulatory submission, review and HTA processes as per Chapters 3 and 4. As these practices were nevertheless seen as relevant by the respondents, QDMP 3 should be addressed through the incorporation of more formal frameworks, such as a benefit-risk framework during regulatory decision making (Leong et al., 2013), as well as having standardised evidence criteria for HTA (EUnetHTA, 2016). In addition, impact analysis (QDMP 8) could be incorporated within authority and agency frameworks in two ways; firstly, through an assessment of linked decisions as well as relevant precedents, including decisions previously made by the organisation or other relevant stakeholders; secondly such an assessment should focus on the impact of this decision on the present and future processes and this should address relevant stakeholders including patients. For example, for a regulatory authority, impact analysis ahead of issuing a marketing authorisation would firstly assess how other similar medicines were reviewed within this jurisdiction as well as other regulatory agencies; secondly the reviewer should aim to understand the impact of the decision on other processes, such as HTA, as well as the ultimate impact on patients, including the approved label (indication) for the medicine.

Whilst it was recognised that both agencies and companies felt that their decision making could be somehow improved, training in this area was rarely provided. This may be because there is limited awareness of the science of decision making which has been applied in other disciplines outside the regulatory environment (Phillips and Stock, 2003; Morton et al., 2009). Consequently, there is a need to promote education and the provision of training by the organisations to raise awareness of the issues in decision making and promote best practice so that individuals know how they can improve.

Another key finding was the general variance ($25^{th}$-$75^{th}$ percentile) around the responses obtained from the three groups for the incorporation of the ten QDMPs. It is important to note that variation is not perceived as a shortcoming as QoDoS assesses a process that is subjective in nature and aims to capture differences in perceptions that can then be explored through feedback discussions. Variance can also be investigated by evaluating the QoDoS item scores corresponding to each QDMP to determine the rationale of the overall QDMP scores. Differences in scores may be a result of a mixture of factors: inconsistencies in individual practices and differences in the perception of the organisation due to poor transparency and documentation of the practices or different experiences within the organisation.

Furthermore, analysis of the responses according to gender and years of experience suggests further rationale for the variation in the individual QoDoS responses and the ten QDMPs based on differences in the characterises of the group. Some differences according to median were uncovered such as better incorporation of QDMP 3 (criteria) and QDMP 5 (alternatives) by females compared to males as well as by more experienced individuals compared to those with less experience; QDMP 7 (uncertainty) was also incorporated better by more experienced individuals compared to individuals with less experience. This therefore builds on the research of Beyer et al. (2015) as well as Cowlrick et al. (2011) who evaluated the correlation between personality traits, functional role, education as well as gender and the decision making of individuals within pharmaceutical companies and regulatory authorities. Both studies demonstrate that these factors can explain the variability in judgments and decision-making techniques within organisations. Consequently, there may be other confounding factors, other than work experience or gender characteristics currently captured by QoDoS, such as personality traits, cultural differences and careers paths as well as differences due to training or exposure to research on decision making, which may also be important drivers of the differences in QDMP incorporation; this should be explored further.

**Next steps for improving the practices of individuals and organisations**

Structured feedback discussions are planned to take place with the study participants in order to further investigate the feasibility of the method used in the study, the perceived benefits as well as lessons learned and next steps. The initial discussions with the cohort leaders gave an early indication of a QoDoS study benefits, as described following a previous practicality study (Bujar et al, 2016). First, simply completing the QoDoS instrument can increase an awareness of the biases and influences that need to be considered when making decisions, as well as the best practices (QDMPs) that should be incorporated into a decision-making framework of organisations. Second, the QoDoS can be used to internally monitor and visualise an organisation's decision making within and across different teams and divisions to provide a basis for discussions to build trust and to provide factual information on where improvements are needed in terms of the least favourable or least consistent practices. In addition, routine assessments using QoDoS has the ability to measure change over time in order to determine the impact of any improvement initiatives. The ongoing use of quality systems for making decisions will also reduce uncertainty around decision making and will result in more predictable and favourable outcomes. Finally, QoDoS can be utilised to externally benchmark an organisation's decision-making practices and performance and compare it to those of other organisations. This in turn could be used for external discussions with stakeholders to identify and promote best practice as well as to build trust into key

strategic decisions made by organisations during medicines development, the regulatory review and HTA.

It would be of interest to initiate similar studies with additional teams and groups to assess consistency of QDMPs within each of the three organisations. It would also be of value to involve other organisations, including smaller companies or agencies with less established systems, to determine how QDMPs are built into those organisations, compared to larger companies and agencies. It would also be of value to explore the research findings and themes identified above to determine their generalisability in other similar organisations. Of particular interest would be also to initiate more studies with HTA agencies. This chapter describes the first major application of QoDoS in an HTA setting and it would be important to continue testing the practicality of QoDoS in HTA agencies.

Finally, as QoDoS represents a subjective assessment of decision making, it would be of interest to develop an additional instrument, which could take the form of a checklist, to objectively audit the results of a QoDoS study. For example if an organisation received a low score regarding QDMP 2 (assign clear roles and responsibilities), it would be expected that the organisation does not have clear SOPs and guidelines in place to establish the decision maker, advisor and information provider at the start of the decision-making process. Secondly, if indeed areas of improvement were identified, QoDoS does not currently offer suggestions on how to address the least favourable practices. This could also be could be addressed by the checklist, which would include a set of measures and markers that agencies and companies could put in place to improve processes, such as the above example for QDMP 2. Such an approach will be explored in Chapter 8.

**SUMMARY**

- This study was designed in the form of three cross-sectional case studies, with a pharmaceutical company, a regulatory authority and an HTA agency, where participants were asked to complete the QoDoS instrument to evaluate decision-making practices for pre-specified decision points; sub-group analysis was also carried out for the company and regulatory authority responses
- These studies aimed to demonstrate the practicality of QoDoS in identifying the incorporation of the ten QDMPs in three types of organisations as well as identifying favourable and unfavourable practices and assessing the consistency and transparency of the ten QDMPs within each organisation, both regarding the individual practices and the perceived organisational practices
- QoDoS demonstrated generally favourable practices across the three groups as well as the need for improvement across a number of QDMPs where some similarities were identified, such as the need for better assignment of values and relative importance to decision criteria (QDMP 3) as well as evaluation of alternatives (QDMP 5) for the three organisations and the need for better impact analysis for the regulatory and HTA agency (QDMP 8)
- Variance around the responses may be a result of a mixture of factors: inconsistencies in individual practices and differences in the perception of the organisation due to lack of knowledge around organisational practices or poor transparency and documentation
- Analysis of responses according to gender and years of experience suggests some differences, but it is likely that there are other confounding factors, such as personality traits, cultural differences, careers paths as well as differences due to training or exposure to research on decision making, which may be also important drivers of differences in QDMP incorporation
- Initial feedback from participants confirmed the feasibility and benefits of the study method: raising awareness of biases and best practices in decision making, gaining a basis for discussion of the issues in decision making and making recommendations for improving an organisation's practice
- More formal discussions have been organised and will aim to determine from the entire study cohort the rationale for the responses, the perceived benefits of the study as well as lessons learned and next steps
- Other next steps would seek to organise additional QoDoS studies in additional organisations, including less mature or smaller organisations as well as HTA agencies
- In addition it would be of interest to develop a methodology to objectively audit the QoDoS results and thereby list the measures and markers and organisation could instigate to ensure the practical incorporation of the ten QDMPs, where a checklist approach will be explored in the next chapter.

# Development of Practical Approaches for Integrating Quality into Decision-Making Practices in Medicines Development, Regulatory Review and Health Technology Assessment (HTA)

## INTRODUCTION

Decisions, ranging from the mundane to the critically important, are constantly being made throughout the lifecycle of medicines. Those decisions, no matter the field, are taken under conditions of uncertainty (Eichler et al., 2008) and without an established process for accounting for people's subjective judgments in order to minimise bias. Lovallo and Sibony (2016) stated that, organisations "cannot afford to ignore the human factor in making strategic decisions. They can greatly improve their chances of making good ones by becoming more aware of the way cognitive biases can mislead them, by reviewing their decision-making processes and by establishing a culture of constructive debate."

Results from a survey of pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies (Chapter 3 and Chapter 4) indicated that less than half the companies (41%) and only 20% of the regulatory authorities have formal assessments in place to periodically measure the quality of their regulatory decision making, whereas regarding reimbursement processes, this was carried out by 36% of the health economics and outcomes research (HEOR) company departments and 55% of the HTA agencies. These assessments included re-evaluation based on the outcome, feedback from stakeholders and audits of decision making. In the same survey, respondents indicated that there are ways of measuring the quality of decision making, relating to evaluating the actual practices as well as the outcomes, although such measurements are not always incorporated into the organisations. Nevertheless, if the quality of the decision-making process is truly key to increasing the probability of making good decisions and in building trust in those decisions (Kahneman, 2011), then the challenges that stand in the way of the measurement of decision making should be determined and ways to meet those challenges proposed.

The Ten Quality Decision-Making Practices (QDMPs) were identified through empirical research to identify important issues that influence quality decision making (Donelan et al., 2015). The QDMPs have been organised into four areas, namely, 'Structure and Approach', 'Evaluation', 'Impact' and 'Transparency and Communication'. One way to measure decision making could be based on a pre-specified agreement regarding what a successful decision would look like, including an anticipated positive result. Indeed, one of the QDMPs specifies the performance of an impact analysis of the decision, but this may not be a good measure of the total decision-making process, as indeed a good decision-making process may lead to a bad outcome and *vice versa* due to uncertainty. However, despite the challenges to the direct measurement of quality decision making and its outcome, by understanding the components of quality decision-making practices, it may be possible to build a methodology to develop measures and markers against each practice to ensure that the practice is embedded within

organisational and individual processes. Such an approach could take the form of a checklist, already utilised widely in a number of industries and disciplines including medicine and aviation, in order to ensure a quality decision-making process (Gawande, 2011). The utilisation of a checklist during key strategic decision making by pharmaceutical companies, regulatory authorities and HTA agencies would ensure process quality, consistency and transparency both internally as well to external stakeholders to promote efficiency and build trust.

The aim of this study was to develop practical approaches for integrating quality into the decision-making processes during medicines development, regulatory review and HTA. The objectives were to:

- Identify the challenges and solutions to measuring the quality of decision making as defined by the ten QDMPs
- Explore the role of external assessment of decision-making processes and outcomes to eliminate inherent internal biases
- Examine how organisations should practically incorporate quality into their decision-making processes across the ten QDMPs
- Develop practical approaches for reducing biases in decision making
- Formulate the markers that organisations could instigate to ensure a quality decision-making process
- Investigate if these markers could ultimately be correlated to the outcome of the process
- Develop a checklist for the ten QDMPs by investigating how pharmaceutical companies, regulatory authorities and HTA agencies can integrate quality into their decision-making processes

## METHOD

### Design of the study

This study was designed in the form of focus groups in order to develop and generate ideas as well as explore issues of shared importance for building quality into decision making throughout medicines development, the regulatory review and HTA. Three sets of research questions were generated based on the findings from other studies described earlier (i.e. Chapters 3-7) in order to explore different aspects of decision making. The research questions were initially shared by email with a small group of experts from pharmaceutical companies, regulatory authorities and HTA agencies with at least 15 years of professional experience in order to ensure that the questions were relevant and clear. In summary, the comments were

positive and used to make minor wording changes to the questions. Subsequently, three focus groups were organised for the purpose of this study (Table 8.1).

**Table 8.1 Research questions across the three focus groups**

| Focus Group | Research questions |
|---|---|
| A | What are the practical challenges to measuring quality of decision making within a company and an agency/authority; what are the potential solutions and is there a role for external assessment of decision-making processes and outcome to eliminate inherent internal biases? |
| B | How should pharmaceutical companies, regulatory authorities and HTA agencies practically incorporate quality into their decision-making process as defined by the ten QDMPs and practical approaches for reducing biases in decision making? |
| C | What could be the markers that an organisation could instigate to ensure that a quality decision-making process is embedded and to know if an organisation has improved; how could these markers ultimately be correlated to the outcome of the decision? |

**Study participants**

The focus groups were organised as part of an international workshop on quality decision making (CIRS, 2017). Study participants were selected using purposive sampling from pharmaceutical companies, regulatory authorities, HTA agencies and academia based on their professional experience. They were all at a managerial or senior executive level within their respective organisations and therefore regarded as being key opinion leaders. Due to the complexity of the topic and a broad range of stakeholders involved, a target sample size of 20 individuals per group was sought, as opposed to the recommended size of four to 12 (Breen, 2006; Saunders et al., 2009). The three groups were set up in order to ensure that each was similar in terms of size and participant demographics (Table 8.2).

**Table 8.2 Demographic characteristics of the study participants**

| Focus Group | Total number of participants | Number of respondents by organisation | | | | Number of respondents by gender | |
|---|---|---|---|---|---|---|---|
| | | Pharmaceutical companies | Regulatory authorities | HTA agencies | Academia | Male | Female |
| A | 20 | 11 | 4 | 1 | 4 | 10 | 10 |
| B | 21 | 13 | 4 | 1 | 3 | 9 | 12 |
| C | 20 | 12 | 4 | 0 | 4 | 11 | 9 |

As recommended by Nagle and Williams (2013), each focus group was assigned a facilitator, based on professional experience and the willingness to participate, whose role was to moderate the group discussion and to ensure that the focus group functioned properly, namely that all members had an opportunity to actively participate, that all relevant matters were discussed and that effective conclusions and recommendations were made. In addition, each focus group was assigned a rapporteur, whose role was to record the output of the discussion and present it to the participants to ensure that all the relevant information has been captured. The session was not recorded to respect the confidentiality of the group and to encourage open communication as well as free exchange of ideas.

**Study procedure**

The focus groups were planned as three parallel sessions as part of an international workshop on quality decision making (CIRS, 2017). The steps carried out in order to plan and undertake the study are listed in Figure 8.1 and are in more detail described below. The planning phase was initiated approximately six months prior to the study to first define the purpose and research questions (Table 8.3). Approximately three months prior to the study, participants were invited to the workshop, which was organised in Washington DC, USA.

Approximately six weeks ahead of the study, the following items were developed:

1. The discussion notes, which firstly included definitions of a 'framework' (adopted from Chapters 3 and 4) as well as the list of ten QDMPs and secondly the background to the focus group discussion was described as per the introduction to this chapter;
2. The discussion prompts relating to the ten QDMPS, as outlined in Table 8.3.
3. Guidance notes for the facilitator and the rapporteur in order to clarify their role as described in the previous section (Nagle and Williams, 2013).

The notes were shared with the participants one week prior to the study.

The three focus groups were organised in June 2017 and were preceded by a half-day workshop session with opening presentations in order to set the scene and to introduce the participants to the area of quality decision making. Following this, each focus group was set-up in a separate room as a roundtable session and started with a 30 minute introduction of the participants and the reading of the discussion questions and prompts. During the main two-hour session, each group was requested to address the research questions with the aid of the discussion prompts (Table 8.3). Participants were also asked to make general recommendations in the area of measuring and incorporating quality decision-making practices.

The discussions were documented and then qualitatively summarised by the rapporteur and the summary was reviewed together with each focus group to ensure that all key discussions points, outcomes and recommendations were captured. Following the completion of the focus group sessions, the rapporteurs presented the results to the workshop participants across the three groups in the form of ten minute presentations and the topics were subsequently discussed by the combined workshop group.

**Figure 8.1 Focus group study procedure**

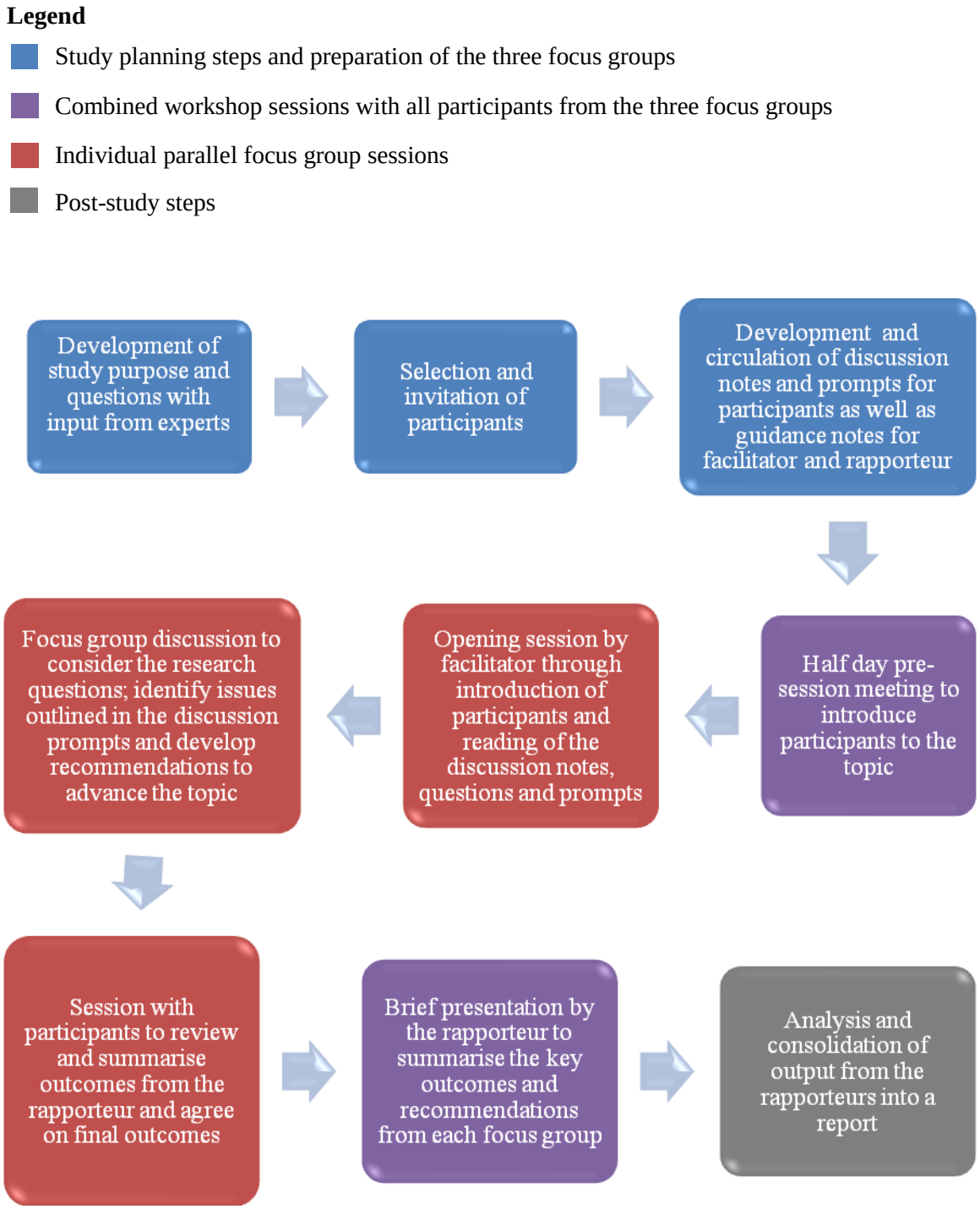


**Table 8.3 Discussion prompts relating to the ten Quality Decision-Making Practice (QDMP) for the three focus groups**

| | FOCUS GROUP A | | FOCUS GROUP B | FOCUS GROUP C | |
|---|---|---|---|---|---|
| Quality Decision-Making Practice | Practical challenges to these practices being measured | Potential internal or external solutions to overcome the challenges | Methods to ensure incorporation of practices and reduction of biases | Markers to ensure the practice is embedded into the process | Methods to ultimately correlate markers with the outcome of the decision |
| 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely) | | | | | |
| 2. Assign clear roles and responsibilities (decision makers, advisors, contributors) | | | | | |
| 3. Assign values and importance to decision criteria | | | | | |
| 4. Evaluate both internal and external influences/biases | | | | | |
| 5. Examine alternative solutions | | | | | |
| 6.Consider uncertainty | | | | | |
| 7. Re-evaluate as new information becomes available | | | | | |
| 8. Perform impact analysis of the decision | | | | | |
| 9. Ensure transparency and provide a record trail | | | | | |
| 10. Effectively communicate the basis of the decision | | | | | |

**Data processing and analysis**

Following the workshop, the output from each focus group was further reviewed in order to convert the findings from the rapporteur presentation and discussions notes into a report based summary. The report, as per the results and discussion sections of this chapter, was subsequently shared with the participants (Walker et al., 2017).

**Development of the checklist for incorporating the ten QDMPs**

The stakeholder perspectives and suggestions from the three focus groups were assessed in comparison with the outcomes of the other major studies undertaken as part of this research programme, namely:

1. Literature search (Chapter 1) and systematic literature review (Chapter 5)
2. Evaluation of the Quality of Regulatory Decision-Making Processes in Pharmaceutical Companies and Regulatory Authorities (Chapter 3)
3. Evaluation of the quality of Reimbursement Decision-Making Processes in Pharmaceutical Companies and HTA Agencies (Chapter 4)
4. Assessment of the ten QDMPs in a pharmaceutical company, a regulatory authority and an HTA agency with the Quality of Decision-Making Orientation Scheme (QoDoS) (Chapter 7)

A qualitative comparative analysis of these various outcomes highlighted the key challenges faced by the pharmaceutical companies, regulatory authorities and HTA agencies as a first step for making the necessary recommendations regarding how organisations can integrate quality decision making into their processes. These facilitated the proposal of a checklist for incorporating the ten QDMPs into the processes of the three stakeholders.

**RESULTS**

This study focused on identifying across the key stakeholders involved in the lifecycle of medicines: the challenges and solutions to measuring the quality of decision making; methods for incorporating the quality decision-making practices as well as markers to ensure practices are embedded within organisations and whether markers could correlate to the outcome of the decision**.** For the purpose of clarity the results are presented in four parts:

- Part I: Findings from focus group A
- Part II: Findings from focus group B
- Part III: Findings from focus group C
- Part IV: Recommendations from the three focus groups
- Part V: Development of a checklist for incorporating the ten QDMPs

**Part I: Findings from focus group A**

The aim of focus group A was to identify the practical challenges to measuring the quality of decision making within pharmaceutical companies, regulatory authorities or HTA agencies, as well as the potential solutions. In addition, the group was asked to discuss the role for the external assessment of decision-making processes and outcomes to eliminate internal biases.

*Practical challenges*

The practical challenges to measuring and ensuring quality decision making identified by the group are listed in Table 8.4. It should be noted that the participants also considered this in the wider context of developing an organisational programme in quality decision making. The participants discussed that in addition to the basic barrier of the natural human resistance to change, differing and sometimes clashing cultural perspectives and considerations regarding the decision-making process within and among organisations and geographic areas represent important challenges to measuring the quality of decision making. These cultural differences can include a disparity in the levels of organisational readiness for the increased transparency that is required to measure the quality of decision making. Organisations will also vary as to their ability or willingness to identify and implement objective measures to assess decision quality and the availability and acceptance of the tools and the training required to use them. There may even be a perception within an organisation that decision quality has already been achieved and therefore does not need to be evaluated (Spetzler et al., 2016).

**Table 8.4 Practical challenges to measuring quality of decision making and developing a quality decision-making programme within each organisation**

| **Practical challenges** |
|---|
| • Cultural perspective/considerations for decision-making process |
| • Opinion that quality decision making has already been achieved |
| • General resistance to change as part of human nature |
| • Need to link quality decision-making process to outcomes in order to gain buy-in |
| • Competing resources and priorities |
| • Administrative/bureaucratic burden to implement a quality decision-making process |
| • Management and communication of decision quality under crisis conditions only |
| • Complexity of implementation of quality decision making in a project matrix structure |
| • Organisational readiness for increased transparency not achieved |
| • Lack of availability and/or acceptance of decision tools and training |

It was discussed that even in organisations that recognise that quality decision making is important, quality processes may not be implemented because of many competing business priorities or because of the perception of the administrative or bureaucratic burden associated with implementing a quality decision-making programme. This may be particularly true when considering ongoing decision making within the complex project matrix structure that exists within most pharmaceutical companies. An additional challenge is that the communication and management of quality decision making is only prioritised under crisis conditions (such as rejection of a medicine by a regulatory authority), whereas it should be important regardless of the circumstances. Finally, despite knowledge of the fact that quality decision-making practices may not result in positive outcomes, the tendency for data-driven organisations to link outcomes to the quality of processes may need to be overcome.

*Potential solutions*

The potential solutions identified by the group are listed in Table 8.5, both regarding how to measure quality of decision making as well as for developing an organisational programme in quality decision making. Participants agreed that decision quality champions are required to overcome organisational resistance to change. Discussants emphasised that it is important to differentiate between a champion, who assumes ownership of a quality decision-making programme and strives to convince colleagues of its applicability and effectiveness and an external expert, who might be more objective. Whilst an external champion for quality decision making can be used, they would need to be combined with an internal champion at a managerial level who would have the influence to drive change. A combination of internal champions at the operational and managerial level, that is, a combined bottom-up and top-down approach, would seem the most effective in implementing quality decision making. Quality decision programmes may be adversely affected, however, with organisational shifts that result in the removal of the managerial champion.

To mitigate individual and organisational resistance, it is important for the programme champion to have a value proposition in place that includes the identification and highlighting dissatisfaction with the status quo as well as "selling points' for the quality decision programme's ability to increase predictability and efficiency in decision making. Clear communication regarding the necessary separation of the quality of the decision process from the decision outcome is essential, as is the establishment of clear decision-making roles and responsibilities and the use of an established decision-making framework. Managerial or organisational buy-in to decision making quality programmes should include the development of training and the integration of the training into the employee competencies managed by

human resource departments, including structured and scheduled "lessons-learned" exercises and non-conformity reports.

**Table 8.5 Potential solutions to measuring quality of decision making and success factors for developing a decision making quality programme**

| **Potential solutions and success factors** |
|---|
| • Independent teams to review quality decision making – internal peer review |
| • Quality decision making value proposition – selling points to mitigate resistance to decision quality<br>– Increase predictability in decision making<br>– Increase efficiency in decision making |
| • Champions for quality decision making – management commitment |
| • Training in quality decision making – integration into employee competencies |
| • Identify/highlight dissatisfaction with status quo |
| • Structured, regular lessons-learned exercises<br>– Integration of quality decision making into quality management system<br>– Consider external accreditation opportunities – ISO9001<br>– Change management<br>– Non-conformity reporting and assessment |
| • Benchmarking/comparative data<br>– In-industry<br>– Comparable industries |
| • Assessment of decision process – blind to the outcome |
| • Define clear roles and responsibilities in the decision-making process |

*External assessments*

Citing the peer review of decisions in place at the EMA (2010), discussants recommended the use of independent review teams within organisations to conduct separate evidence-based evaluations of those decisions (Table 8.5). Baseline decision-making data should be established through status quo analysis of individual organisations and data accrued for purposes of comparison, from both within industry and comparable business models. Case studies could be created for organisations that have already implemented quality decision-making programmes and external accreditation opportunities similar to ISO9001 (International Standards Organization; family of quality management systems standards) could also be considered. Any assessment of an organisation's decision process should be blind to the outcome of decisions.

**Part II: Findings from focus group B**

Focus group B was tasked with determining how pharmaceutical companies, regulatory authorities and HTA agencies should practically incorporate quality into their decision-making process as defined by the ten QDMPs, as well as with developing practical approaches for reducing biases in decision making.

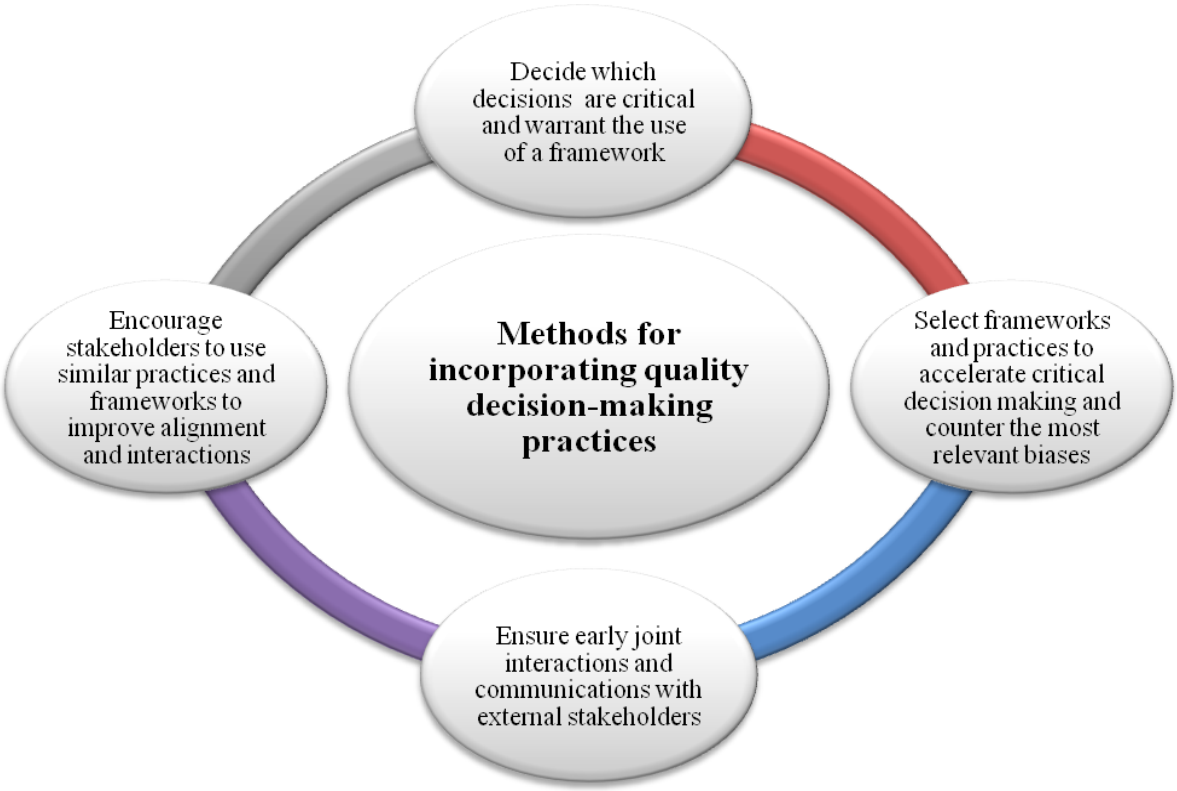
*Incorporation of the ten Quality Decision-Making Practices*

The discussants developed key methods for ensuring the incorporation of frameworks, consisting of the ten Quality Decision-Making Practices, into organisational processes (Figure 8.2). It was agreed that not all decisions require the use of a decision framework in its full context and, in addition, the development of a guide for use of the framework that explains the rationale for its application would be beneficial. Quality decision-making practices should play an important role throughout the life cycle of medicines and decision makers should be aware of the crucial decision points where their use may be of critical importance. An example of such a decision point would be when sponsors and investigators must decide what kind of human exposure a medicine can be given based on the data from nonclinical studies. It is also important to understand the potential of a framework and of QDMPs to accelerate critical decision making.

Discussants agreed that decision making relies not only on data, but also on additional factors, such as early interaction and communication among all stakeholders. In particular, pharmaceutical decision-making processes should incorporate the perspective of patients and payers as early in the life cycle as possible. In fact, patients should be considered as research partners throughout medicine's development, regulatory review and HTA and in addition to well-designed studies, patient-generated data from new technologies may be an important resource in this regard.

Likewise, to manage expectations before the submission of a marketing authorisation application, the sponsors of new medicines should request early consultations and ongoing meetings at key product developmental milestones with regulators as well as with health technology assessment agencies where possible. This approach to early, collaborative communication could facilitate organisations to better align their decision making, both externally between companies, regulatory authorities and HTA agencies as well as internally, for example between regulatory and HEOR departments within a pharmaceutical company. In addition, having different stakeholders using the QDMP-based framework could improve external and internal alignment and interactions.

**Figure 8.2 Methods for incorporating quality decision-making practices into pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies**




*Identifying and mitigating internal and external influences and biases*

Because the term *bias* has a negative connotation, it may be more helpful to consider the impact of internal and external behavioural influences on decision making. Practical approaches to mitigate these influences should be based on the objectives of individual decisions (Table 8.6). It was agreed that the grouping of biases/influences developed by Lovallo and Sibony (2010), namely action-oriented biases (e.g. having a tendency to take immediate action), interest biases (e.g. having a conflict of interest in committee setting), pattern-recognition biases (e.g. seeking evidence to support own views) and stability biases (e.g. tendency to do things as always), is appropriate and relevant in the context of medicines development, regulatory review and HTA. Furthermore, the categorisation introduces order to discussion around the behavioural influences within an organisation. Such discussions are key to raising awareness of these biases on the decision-making process of individuals and groups and eventually create an equilibrium in influencing the ultimate decision. Nevertheless, in addition to raising awareness, work is required to develop a model for mitigating biases within organisations.

**Table 8.6 Approaches to mitigate influences/biases in decision making and the goals of those approaches**

| Approaches to mitigate biases | Objectives of the approach |
|---|---|
| Discuss and categorise influences as per Lovallo and Sibony (2010) | To introduce order and awareness and potentially create equilibrium in the group |
| Openly state perspectives throughout the decision-making process | To establish trust and transparency needed for decision making |
| Examine and discuss the criteria for and documentation of decision making | To determine a clear scope and ensure incorporation of good practice in decision making |
| Establish committees, make decisions through consensus and re-examine negative decisions | To bring in internal views and introduce objectivity into decision making |

Because transparency underpins trust in decision making, stakeholders should openly state their perspectives at the beginning and throughout the process. In addition, decision makers need to examine and discuss the criteria for and documentation of decision making, establishing a clear scope and ensuring that good practices are incorporated. The establishment of decision committees will bring in external views and introduce objectivity into decision making. Finally, where possible, decisions should be made through consensus and unfavourable outcomes should be followed-up by a re-examination of the decision-making process.

**Part III: Findings from focus group C**

The remit of focus group C was to discuss markers that an organisation could instigate to ensure that a quality decision-making process is integrated with its culture and to know if it has improved its decision-making practices. In addition the group was asked to consider whether these markers of the decision-making process could be correlated to the outcome of the decision.

*Markers for a quality-decision-making process*

Participants discussed the categorisation of the ten QDMPs, currently organised into four groups, namely:

- Structure and Approach (QDMPs 1 and 2)
- Evaluation (QDMPs 3, 4, 5, 6 and 7)
- Impact (QDMP 8)
- Transparency and Communication (QDMPs 9 and 10).

The group participants proposed reorganising the four categories as follows:

- Establish who, why and how decisions are made (QDMPs 1,2 and 3),
- Ensure decision quality, relevance and importance (QDMPs 4, 6 and 7),
- Consider decision alternatives and impact (QDMPs 5 and 8) and
- Ensure decision transparency and communication (QDMPs 9 and 10).

Consequently, the key difference is the location of QDMP 3 (Roles and Responsibilities) and 5 (Alternatives). It appears that the new approach proposed by the focus groups is more logical, as roles should be considered at the start of decision-making process, whereas alternatives should be discussed in the context of impact (Table 8.7). In addition, the new grouping results in a more balanced division of the ten QDMPs, where each of the four categories consists of two to three practices (as opposed to previous approach where 'impact' consisted of one practice and 'evaluation' of five practices).

Participants further agreed that documentation is a key marker of quality decision making and specified that for practices 1,2 and 3, this should include documenting the decision-making framework utilised, the decision criteria as well as any weighting or ranking used, standard operating procedures (SOPs) and a list of participants including their roles and responsibilities (Table 8.7). The participants should be accountable for adherence to the SOPs and decisions should reflect their perspectives. Documentation of practises 4, 6 and 7 should include a summary of the approach used for evaluating biases, uncertainties that were considered and fully defined triggers for the re-evaluation of the decision. Documentation for practices 5 and 8 should include a list of the alternatives to the decision that were considered and the template that was used to perform an analysis of the impact of the decision. Finally, documentation for practices 9 and 10 should include a template to be used for the communication of the decision, both internally and externally.

*Correlating markers for quality decision-making process and outcomes*

It was discussed whether documentation as a marker for quality decision making facilitates linking the decision-making process and outcome, although indeed a quality process does not always guarantee a good outcome. By documenting the decision at the time it is made, including all the key markers outlined in Table 8.7, as well as documenting an expected outcome of the decision would provide a basis for comparison.

The ability to look back and evaluate the quality of past decision making can inform future decisions, but this typically occurs when there has been an unfavourable outcome such as a lack of regulatory approval or the withdrawal of a drug for safety concerns. Re-evaluation on

the other hand is less common when the outcome of a decision has been favourable or as anticipated, when such a discussion may be considered by some to be a waste of resources. Nevertheless, such evaluations and comparisons should occur over multiple points in time and regardless of whether the outcome is positive or negative. Moreover, it is important that lessons are learned not only from negative, but also from the positive outcomes in order to highlight the use of best practices.

**Table 8.7 Quality Decision-Making Practices (QDMPs) according to their goal and specified documentation as a clear marker of quality decision making**

| Quality Decision-Making Practices (QDMPs) | Goal of the practices | Documentation marker |
|---|---|---|
| 1. Have a systematic, structured approach to aid decision making<br>2. Assign clear roles and responsibilities (decision makers, advisors, contributors)<br>3. Assign values and importance to decision criteria | Establish who, how and why decision is made | • Rigorous process defined by SOPs<br>• Decision template with decision framework and weighting criteria<br>• List of participants and their perspectives |
| 4. Evaluate both internal and external influences/biases<br>6. Consider uncertainty<br>7. Re-evaluate as new information becomes available | Ensure information quality, relevance and importance | • Approach used to evaluate bias<br>• Uncertainties that were considered<br>• Clearly defined triggers for re-evaluation |
| 5. Examine alternative solutions<br>8. Perform impact analysis of the decision | Consider alternatives and impact | • Alternatives that were considered<br>• Template for impact analysis |
| 9. Ensure transparency and provide a record trail<br>10. Effectively communicate the basis of the decision | Communicate clearly and openly | • Template for decision communication internally and externally |

**Part IV: Recommendations from the focus groups**

Finally, the participants across the three focus groups A, B and C developed recommendations to advance progress in the area of measuring and incorporating good decision-making practices (Table 8.8). These recommendations have been categorised into three groups, namely recommendations relating to future research directions for building the evidence around quality decision-making practices; secondly recommendations for organisations regarding what may be the issues that need to be internally considered to build quality into the decision process and lastly relating to approaches for measuring the processes and outcomes within organisations.

**Table 8.8 Recommendations from the focus group discussions**

| Recommendation category | Recommendations from the Focus Groups |
|---|---|
| Future research directions for building the evidence around quality decision-making practices | • Accrue benchmarking data on organisational decision making quality for pharmaceutical companies, regulatory authorities and HTA agencies |
| | • Generate case studies of organisations where quality decision-making programmes have been implemented |
| | • Consider a controlled pilot in which agencies and companies compare the results of decision making with and without a structured framework and the ten QDMPs |
| | • Organise an exercise among agencies and companies to determine if using the ten QDMPs improves communication and interactions |
| | • Analyse joint venture decision-making processes e.g. parallel processes between regulatory authorities and HTA agencies; product acquisition between companies |
| | • Develop a new model of bias mitigation starting with a change in terminology to behavioural influences |
| Internal considerations for building quality into the decision process | • Clarify that as a result of uncertainty a quality decision-making process may result in either a positive outcome or an unfavourable outcome including project termination |
| | • Create a value proposition/business case for decision quality that includes the provision of clearer articulation of decisions |
| | • Define clear decision-making roles and responsibilities |
| | • Create appropriate motivational incentives and an environment to balance the internal and external influences |
| | • Conduct post-decision-making discussions between stakeholders |
| Internal considerations for measuring the processes and outcomes of decision making | • Perform status quo analysis of an organisation's decision-making process and continue to re-evaluate in future particularly with process improvement initiatives |
| | • Ensure the availability of documentation at the time of decision |
| | • Examine and highlight the importance of the rationale for quality decision making not just the methodology |
| | • Document the expected outcome at the time of the decision so there is a basis for comparison |
| | • Assess the quality of decision making across multiple decisions |

**Part V: Development of a checklist for incorporating the ten QDMPs**

A checklist approach was supported by the focus group participants as a way to outlining the practical steps for incorporating the ten QDMPs into an organisation. The participants highlighted, in line with previous research on checklists (Gawande, 2011) that such a

checklist should be clear, concise and user friendly. In order to generate the initial checklist items, the recommendations from the focus groups were qualitatively reviewed alongside other findings from the studies undertaken as part of this research programme (Figure 8.3), namely a review of literature as summarised in the thesis introduction and Chapter 5, as well as findings from other studies undertaken as part of this research project, specifically questionnaires undertaken with companies, regulatory authorities and HTA agencies described in Chapters 3 and 4 as well as decision-making studies with QoDoS summarised in Chapter 7. Interestingly, many overlaps were found, such as regarding the need to introduce approaches to bias mitigation, ensure clear communication of decision making through templates and ensure capacity building and education within organisations to minimise reluctance to quality decision making. The generated and revised items were then organised according to the ten QDMPs in order to outline the appropriate steps under each practice for incorporating quality into key strategic decision-making processes.

The findings from the literature review have demonstrated that there are two key aspects of incorporating quality into decision making: firstly ensuring that at the management level there are appropriate mechanisms in place, such as templates, guidelines and process steps, to build quality into an organisation's decision making (Hammond et al., 1999; Kahneman, 2011; Spetzler et al., 2016); secondly, as noted further by Spetzler and colleagues (2016), organisations need to ensure that these various mechanisms and steps are followed at the time of the decision making for any key strategic decisions. Consequently, a two part-checklist was developed (Table 8.9). The first part of the checklist should be therefore used by companies and agencies during general management or team meetings to prospectively plan how to integrate the QDMPs into its framework and project matrix structure, including key process steps, templates and documents that should be in place. In addition, in order to enable a quality process at the time of the actual decision making, part two of the checklist identifies process steps that organisations should establish and document in order to enable process quality, transparency and consistency for key strategic decisions. The development of a manual is beyond the scope of this study, but this could further facilitate and encourage the use of this checklist, including how and when it would completed and by whom.

**Figure 8.3 Study outcomes utilised in the development of the checklist for quality decision making**

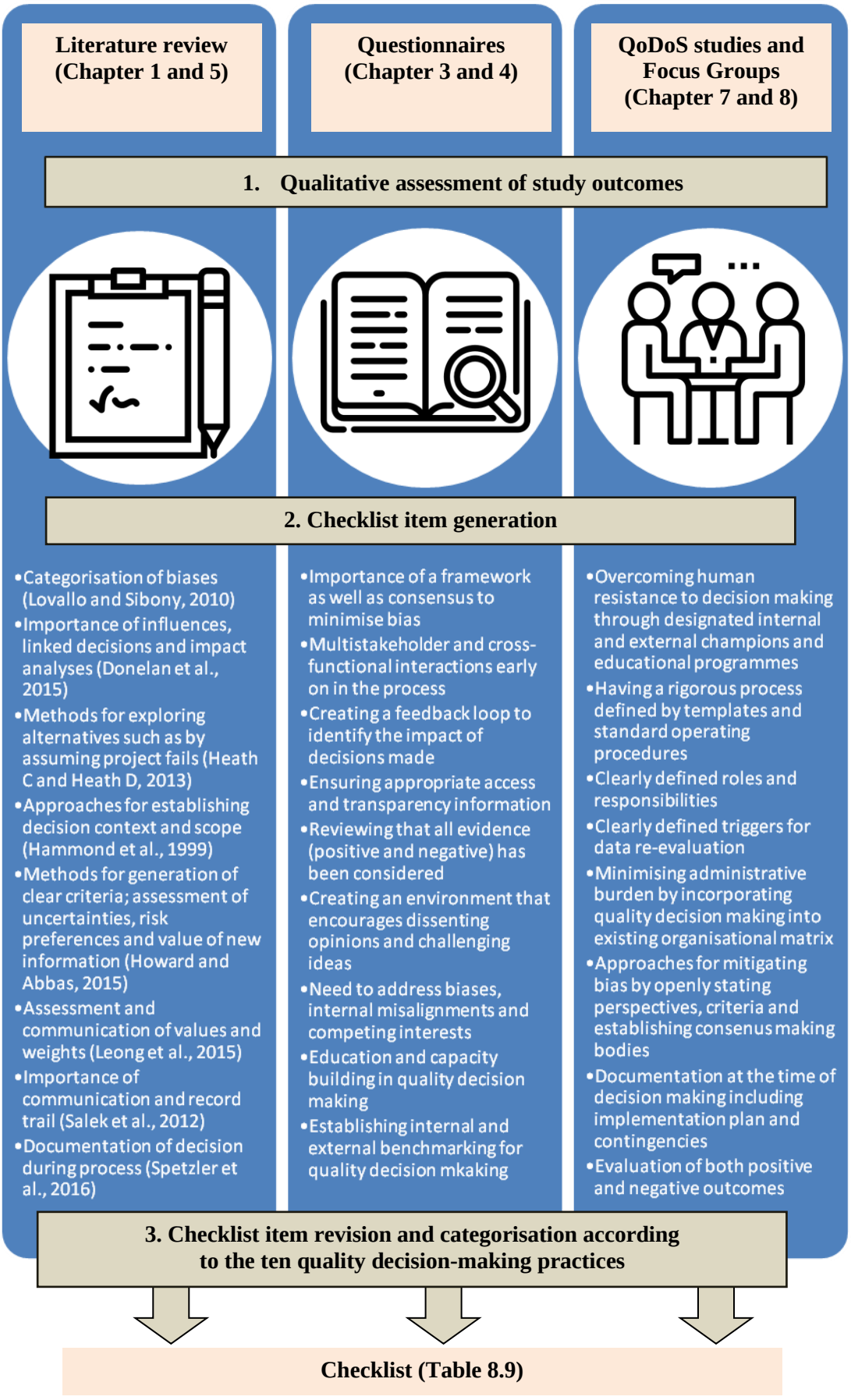


**Table 8.9 Checklist for the implementation of the ten Quality Decision-Making Practices (QDMPs)**

Part I: Steps to ensure that the practice is incorporated into the organisational framework before the decision-making process

| QUALITY DECISION-MAKING PRACTICE | IS THE ITEM IS IN PLACE AT YOUR ORGANISATION *AHEAD OF THE DECISION-MAKING PROCESS?* | YES | NO |
|---|---|---|---|
| 1. HAVE A SYSTEMATIC, STRUCTURED APPROACH TO AID DECISION MAKING | Guidelines for quality decision making | | |
| | Standard operating procedures | | |
| | Training programme for quality decision making | | |
| | Internal champion on quality decision making | | |
| | Collaboration with external experts in decision making quality | | |
| 2. ASSIGN CLEAR ROLES AND RESPONSIBILITIES | Documents for ensuring adherence to SOPs and guidelines by stakeholders | | |
| | Template for documenting participants involved in decision making and their roles and responsibilities | | |
| 3. ASSIGN VALUES AND IMPORTANCE TO DECISION CRITERIA | Template for defining decision criteria | | |
| | Template for assigning weights to criteria | | |
| 4. EVALUATE BOTH INTERNAL AND EXTERNAL INFLUENCES/BIASES | Approaches for minimising biases/influences | | |
| | Templates for documenting potential influences and conflicts of interest | | |
| | Staff training programmes for minimising biases/influences | | |
| 5. EXAMINE ALTERNATIVE SOLUTIONS | Procedure for exploring and generating multiple innovative alternatives against decision criteria | | |
| | Templates for assessing alternatives, their consequences and trade-offs | | |
| 6.CONSIDER UNCERTAINTY | Approach for assessing data limitations | | |
| | Sensitivity analysis models for assessment of risk regarding known events and unknowns | | |
| 7. RE-EVALUATE AS NEW INFORMATION BECOMES AVAILABLE | System for triggering re-evaluation of decision making | | |
| | Model for assessing value of new information (positive or negative) | | |
| 8. PERFORM IMPACT ANALYSIS OF THE DECISION | Approach for linking relevant or similar decisions | | |
| | Template for impact analysis | | |
| | Planning tool for decision implementation | | |
| | Approach for early interactions with key stakeholders | | |
| 9. ENSURE TRANSPARENCY AND PROVIDE A RECORD TRAIL | Template for recording decision at the time it was made | | |
| | Documents for internal and external audits | | |
| 10. EFFECTIVELY COMMUNICATE DECISION BASIS | Templates for internal and external communication of evidence, the deliberative process, consideration and uncertainties | | |

Part II: Steps to ensure that the practice is followed at the time of decision making for key strategic decisions

| QUALITY DECISION-MAKING PRACTICE | IS THE ITEM IS ESTABLISEHD AND DOCUMENTED *AT THE TIME OF DECISION-MAKING PROCESS?* | YES | NO |
|---|---|---|---|
| 1. HAVE A SYSTEMATIC, STRUCTURED APPROACH TO AID DECISION MAKING | Defined decision frame including objectives, scope and decision importance | | |
| | List of data requirements, key variables and assumptions and how they relate | | |
| | Defined process steps and timelines | | |
| 2. ASSIGN CLEAR ROLES AND RESPONSIBILITIES | Composition of the decision group including list of decision makers, advisors and information providers | | |
| | Clear decision-making instructions for stakeholders | | |
| 3. ASSIGN VALUES AND IMPORTANCE TO DECISION CRITERIA | Clear and distinct decision criteria | | |
| | Criteria evaluation through rating or ranking | | |
| 4. EVALUATE BOTH INTERNAL AND EXTERNAL INFLUENCES/BIASES | Appropriate input and participation from all relevant stakeholders | | |
| | Objective assessment of political/financial/competitor influences | | |
| | Debate and/or presence of "devil's advocate" | | |
| | Decision preference statement prior and post debate including explicit statement of conflict of interest | | |
| 5. EXAMINE ALTERNATIVE SOLUTIONS | Generation of at least two distinct options by different individuals | | |
| | Brainstorming of alternatives e.g. by assuming you cannot see any current options or by assuming that the project fails | | |
| | Assessment of consequences for each alternative and trade-off analysis | | |
| 6.CONSIDER UNCERTAINTY | Judgment of available data and limitations | | |
| | Risk preferences to reflect probability assessment of known and unknown events | | |
| | Sensitivity analysis of alternatives and against uncertainties | | |
| 7. RE-EVALUATE AS NEW INFORMATION BECOMES AVAILABLE | List of time or data triggers for re-evaluation of decision (positive or negative) | | |
| | Assessment of value of additional knowledge | | |
| | Feasibility of information gathering | | |
| 8. PERFORM IMPACT ANALYSIS OF THE DECISION | Assessment of linked or similar decisions | | |
| | Assessment of possible and expected outcomes now and in future | | |
| | Impact on internal and external stakeholders including Implementation and contingency plans | | |
| 9. ENSURE TRANSPARENCY AND PROVIDE A RECORD TRAIL | Defined decision basis and key drivers including a list of areas of disagreement | | |
| | Commitment to action plan through resource allocation | | |
| 10. EFFECTIVELY COMMUNICATE DECISION BASIS | List of relevant stakeholders to be informed | | |
| | Internal communication plan and timelines | | |
| | External communication plan and timelines | | |

**DISCUSSION**

The developed checklist, as a result of the study outcomes undertaken as part of this research programme (Chapters 3, 4 and 5), current and previous research on decision making (Hammond et al., 1999; Kahneman, 2011; Heath C and Heath D, 2013; Spetzler et al., 2016) as well as the focus group discussions, is an advancement in the field of quality decision making during the lifecycle of medicines. The checklist offers a new addition to the current decision quality toolbox, alongside of the ten QDMPs as well as the QoDoS (Donelan et al., 2016). Although, the ten QDMPs provide the structure in the form of best practices for decision making and the QoDoS tool identifies whether these best practices are followed or whether there are areas needing improvement, the checklist on the other hand provides a practical approach for ensuring that best practices are followed within an organisation, including process steps for embedding quality into an organisational structure ahead of decision making as well as what needs to be established or documented at the time of the actual decision-making process for key strategic decisions.

Similar approaches exist in the area of medicines development and regulatory review, such as scorecards for assessing the quality of the regulatory review and submissions (Salek et al., 2012) and templates for assessing the benefits and risks of a medicine during regulatory review (Leong et al., 2015). Nevertheless, the developed checklist proposes a novel approach for incorporating best practices into the broader decision-making processes within organisations for any key strategic decisions made by the stakeholders, beyond just regulatory review/submission and benefit-risk assessment. The development of a detailed manual for the use of the checklist was outside the scope of this study, but there is certainly a need to develop such a document as well as further evaluate the checklist with the target audience in order to establish its practicality, validity and relevance. Of need and interest would be to establish firstly the potential value compared to the burden of such as an approach, the clarity, relevance and user friendliness of the items (including any addition or reduction) and finally approaches for ensuring its utilisation and adherence.

The checklist was designed in part based on the issues raised and recommendations made for building and assessing quality decision making, developing bias mitigation techniques and decision quality documentation markers. Ultimately, documentation of the decision would facilitate re-evaluation of the process in order to build transparency and trust. There are already some opportunities to re-evaluate decision making during the regulatory review such as, is anticipated will occur in Australia, where provisional regulatory approvals that are scheduled to begin in 2018 will include a time-bound directive to re-examine decisions (Bootes, 2017). It is envisioned that building the requirement for re-examination into the

legislation for provisional approvals will ensure that labelling is as broad or restricted as appropriate and that post-marketing commitments are fulfilled. Re-evaluation of a decision can also be part of an appeal or dispute resolution process with a regulatory authority such as the US FDA when new or different information that may impact a decision has emerged (FDA, 2017). It may be valuable to examine a case in which a regulatory authority issued a different decision as the result of such an appeal. The re-evaluation of decision-making quality may prove more challenging around HTA where negotiation and advocacy are part of the decision-making process in addition to scientific evaluation. HTA bodies are also subject to additional economic and political external pressures that may affect decision making and add to the complexity of its evaluation. Finally, it should be recognised that the quality of decision making can rarely be isolated and evaluated as a single decision, but must be more typically considered as a continuum.

The key challenges for measuring the quality of decision making relating to organisational issues such as culture, resource allocation and organisational willingness have also been identified by the focus groups. Interestingly, one of the challenges identified in this study regarding identification of objective measures for assessing the quality of decision-making process has already been addressed through this research programme, namely a literature review evaluating available measures (Chapter 5). In addition, the methodology developed for benchmarking organisational decision making in order to build a business case for quality decision making has also been developed (Bujar et al., 2016) and has been applied through three case studies with a pharmaceutical company, a regulatory authority and an HTA agency (Chapter 7). Moreover, a number of solutions proposed by the focus groups, such as identifying champions, providing training and ensuring clear roles and responsibilities have been implemented into the QDMP checklist. The methods for ensuring incorporation of quality by firstly deciding which decisions are key and selecting and integrating appropriate practices are also consistent with the general recommendations developed by Lovallo and Sibony (2010) regarding the science of decision making. In addition, the approaches developed in this study include additional key considerations specific to the area of medicines, such as ensuring communication and alignment across companies, regulatory authorities, HTA agencies and patients in order to ensure favourable outcomes.

Nevertheless, it should be noted that perspectives differ as to whether individual decisions have been successful, which reinforces the argument that an analysis of outcomes has major limitations. Regulators may view their decisions as appropriate inasmuch as the outcomes of those decisions achieve the regulatory objectives of ensuring access to treatment and avoiding the release of less effective medicines into the marketplace. In fact, if regulatory decisions

achieve those objectives, regulators may consider them to be correct and not subject to challenge. This viewpoint may make some regulators resistant to changes in their decision-making practices. In evaluating the outcome of their decisions regarding medicines, industry asks if those decisions facilitated the approval of the label that was sought in a timely way; if the scope of that label was appropriate in terms of the designated population and dosage as well as if the post-marketing commitments and manufacturing specifications and limitations were as expected. The affordability of medicines as part of its HTA is also an important outcome of decision making that may not be considered as early or as often as necessary by all decision makers (Tafuri, 2013).

However, there is a shared desire among decision makers in the development, regulation and HTA of medicines for the ultimate overall outcome of their decision making to be the improvement of public health for patients (Liberti et al., 2013). Indeed, this has been noted by the focus group participants that patients should be seen as research partners and that decision-making processes should incorporate the perspective of patients as early in the life cycle as possible. Work is in progress to develop a universal framework for patient involvement industry-led medicines research and development, regulatory review, or market access decisions (Hoos et al., 2015; Boutin et al., 2016).

Finally, the use of the QDMPs and checklist approach in decision making by different stakeholders could improve alignment and interactions for the benefit of patients and build trust and transparency into the process through which medicines become available. The next steps would be to test and validate the checklist with pharmaceutical companies, regulatory authorities and HTA agencies to increase its user friendliness, clarity, relevance and applicability. A systematic literature review of other existing checklists, such as those utilised in medicine, aviation and other industries (Gawande, 2011) in order to learn from best practice in terms of checklist format and the procedure for utilising it (e.g. who should complete it). The validated checklist could then be utilised in a study to determine whether it increases the quality and consistency of decision making and its transparency to internal and external stakeholders. It is hoped that this checklist approach will ultimately gain wide acceptability by stakeholders and will become ‘‘standard practice’’ during the key decision-making processes throughout the research and development of medicines.

**SUMMARY**

- Despite the challenges to the direct measurement of quality decision making and its outcome, by understanding the components of QDMPs, it may be possible to build a checklist against each practice to ensure that it is embedded within organisational culture and individual processes
- The aim of this study was to develop practical approaches for incorporating quality into the decision-making processes during medicines development, regulatory review and HTA
- This study was designed in the form of three parallel focus groups (A, B and C) with individuals from pharmaceutical companies, regulatory authorities, HTA agencies and academia in order to develop and generate ideas as well as explore issues of shared importance for building quality into decision making throughout medicines development, regulatory review and HTA
- The focus group A discussion resulted in the development of key challenges and solutions to measuring the quality of decision making and considerations for external assessments of decision making; focus group B developed methods for incorporating quality decision making into organisational processes as well as practical approaches for reducing biases in decision making and focus group C formulated the markers organisations could instigate to ensure that a quality decision-making process is incorporated.
- All three focus groups developed recommendations regarding future research directions for building the evidence around quality decision-making practices, recommendations for organisations regarding what may be the issues that need to be internally considered to build quality into the decision process and lastly relating to approaches for measuring the processes and outcomes within organisations.
- Stakeholder perspectives and suggestions from the three focus groups were assessed in comparison with the outcomes of the other major studies undertaken as part of this research programme in order to develop a checklist for incorporating the ten Quality Decision-Making Practices.
- This checklist enables an organisation to incorporate these practices into its project matrix structure and lists process steps that need to be established and documented at the time of decision making in order to enable process quality, transparency and consistency.

# General Discussion

## INTRODUCTION

The research on decision making has been amplified over the past two decades through the work of Hammond and colleagues (1999), Thaler and Sustein (2009), Kahneman (2011) and Spetzler (2016). It would therefore seem obvious for the numerous industries, where decisions are made under conditions of uncertainty, to incorporate the various findings and recommendations into their operations to increase the efficiency and effectiveness of processes. Surprisingly, this has not been the case as intuition and gut reactions still prevail, though some progress has been made in applying the research, particularly in the areas of aviation, economics, environmental protection, clinical practice, nuclear safety and government affairs (Rafliff et al., 1999; Hunink et al., 2001; Dowding and Thompson, 2003; Morton et al., 2009; Gawande, 2011; Thaler and Sustein, 2009; Wagner, 2013; Avorn, 2018). The uptake of this research into the pharmaceutical industry, regulatory authorities and HTA agencies has been nevertheless been slow and occurring only in specific areas, such as the benefit and risk assessment and the portfolio management of medicines (Sharpe and Keelin, 1998; Cook et al., 2014; Pignatti et al., 2015). The gap was initially addressed through the research of Donelan and colleagues, which resulted in defining the best practices in decision making in the lifecycle of medicines, namely the ten Quality Decision-Making Practices (QDMPs), as well as the development of the Quality of Decision-Making Orientation Scheme (QoDoS) that can be used to measure the incorporation of these ten practices in companies and agencies (Donelan et al., 2015; 2016). However, the lack of application and implementation of these methods demonstrates that more work is needed to address the research gap. Indeed, despite pressures from the public to improve decision-making outcomes and accountability of companies and agencies, the focus so far has been on data generation and review, whereas it is not always certain how key strategic decisions, which involve subjective judgments and preferences, are made by individuals and organisations. For patients and other stakeholders, this process could resemble a “black box”, where only inputs and outputs are visible, so there is now an urgent need to address and improve the transparency of the process through which decisions are made around data.

Moreover, in the world of medicine development and review, decisions can be subjective, where the lack of approval of a medicine with high uncertainty can be perceived positively by regulators who protect public health, but negatively by patients who may not have access to the medicine, due to different levels of risk appetite (Breckenridge and Walley, 2008). High uncertainty also means that the rigour of the process does not always correlate to the perceived quality of outcomes. Therefore, organisations and individuals cannot always control the outcome, but they can influence the process to ensure clarity and transparency. This may ultimately increase the probability of best outcomes in the long term. Furthermore,

processes should be clearly documented to facilitate audits and lessons learned as well as transparent communication. The ultimate aim would be to increase public understanding of the decisions with an agreement from all stakeholders that this was the best possible course of action taken. For example, a regulator should be explicit about the rationale for a decision (e.g. if a medicine is not approved due to safety concerns), so that if a different decision about the same product is made later on by the same agency (due to more information emerging) or by a different agency (due to different legal or scientific considerations), it is clearly understood by patients (Breckenridge et al., 2011; Tafuri, 2013). Interestingly, a recent review of factors which influence regulatory outcomes revealed that in addition to technical factors (e.g., clinical trial study designs, clinical evidence of efficacy), there exist other social considerations (e.g. regulatory processes followed and influence of advisory committee recommendations) which could be used to predict regulatory outcomes (Liberti et al., 2017). These were also the least studied factors, compared to technical factors; this gap needs to be addressed to understand why organisations, such as two regulatory authorities, can arrive at different decisions if faced with the same data. Such differences could therefore be explained on the basis of benefits, harms and uncertainty, their relative importance, as well as the decision-making process used including the involvement of patients at the time of the decision (Tafuri, 2013).

These various considerations were highlighted at a recent Workshop on quality decision making, which brought together major companies, regulatory authorities and HTA agencies in order to make recommendations for advancing this relatively unexplored topic (Walker et al., 2017). Importantly, a presentation from Carl Spetzler from Strategic Decision Group (SDG) demonstrated that some progress has been made, with case studies from a couple of the major pharmaceutical companies, which have created decision quality departments to broaden the importance of the science of decision making during medicines R&D. Nevertheless, this has not yet transpired into the regulatory and Health Economics and Outcomes Research (HEOR) company departments and functions, or the other stakeholders, namely regulatory authorities and HTA agencies. All in all, the complexity and uncertainty regarding the development and assessment of medicines has created a need for new approaches and methodological tools as well as greater transparency of decision-making processes (Eichler et al., 2008). It is this idea that has fuelled the research described in this thesis, where a number of unique contributions have been made, culminating in an overarching roadmap for improving the quality decision-making processes for key decisions made during the medicines development, regulatory review and HTA that will be presented in this chapter.

**RESEARCH OUTCOMES AND CONTRIBUTIONS**

Despite interest in characterising the decision-making processes of pharmaceutical companies, regulatory authorities and HTA agencies, no studies have been undertaken to identify the use of frameworks for decision making, the incorporation of best practices into those frameworks, as well as the use of tools for evaluating the quality of decision making within those organisations. Structured questionnaires developed for the purpose of this research aimed to bridge that gap, as described in Chapters 3 and 4. The results uncovered that pharmaceutical companies (regulatory and HEOR departments), regulatory authorities and HTA agencies utilise different processes, for example through the use of committees or having a single decision maker, in order to make decisions regarding the submission and approval of information to support the marketing authorisation and reimbursement of medicines. These studies also uncovered the composition of the various decision-making groups or committees, which may be of interest to organisations setting up their management bodies, in order to help decide the stakeholders that should be involved. Nevertheless, although organisations may be using different processes, they could all benefit from the use of formal frameworks to ensure structured and consistent processes. Interestingly, the results demonstrated that formal frameworks are not always utilised by organisations. Moreover, even those organisations with established frameworks had not incorporated all ten QDMPs into their processes, particularly QDMP 3 (assign values and relative importance to decision criteria), which should be addressed as a priority by organisations by making criteria, values and preferences explicit to all decision makers, as well as recording this information for the purpose of communication and audit. Nevertheless, all ten QDMPs were generally considered as relevant by the participants, thereby emphasising their appropriateness as a basis for formal frameworks for companies and agencies.

The results from the questionnaires also revealed common challenges in decision making, including the influence of biases. Interestingly, the company results in the regulatory questionnaire suggest that consensus decision-making or the use of formal frameworks is associated with less bias compared to having one individual make the decision or not having a formal framework. Nevertheless, it has been appreciated that the term ‘bias’ has negative connotations, as explored by Kahneman (2011) and perhaps a different terminology, such as ‘subjective influences’ could be utilised in the future. Almost all the study participants felt that there was room for improvement in their organisation’s decision making and suggested a number of solutions, including better training, education and ensuring the use of structured processes.

The organisations also stated that they do not generally perform assessments of their quality decision-making processes, whereas assessments of outcomes are more frequent, despite the former being a key first step in identifying areas for improvement in the practices (Kahneman, 2011). In order to confirm and further understand this finding from the questionnaires, a systematic review of literature was undertaken to identify techniques from the public domain for assessing the ten QDMPs. The review identified a general paucity of research into this area, with 13 techniques identified in total, but only two (QoDoS and Organisational IQ) assessing all the QDMPs, where only QoDoS was relevant to both companies and agencies based on its questions. Consequently, the lack of formal assessments within organisations, as identified by the questionnaires, could be explained by the lack of available techniques revealed through the literature review.

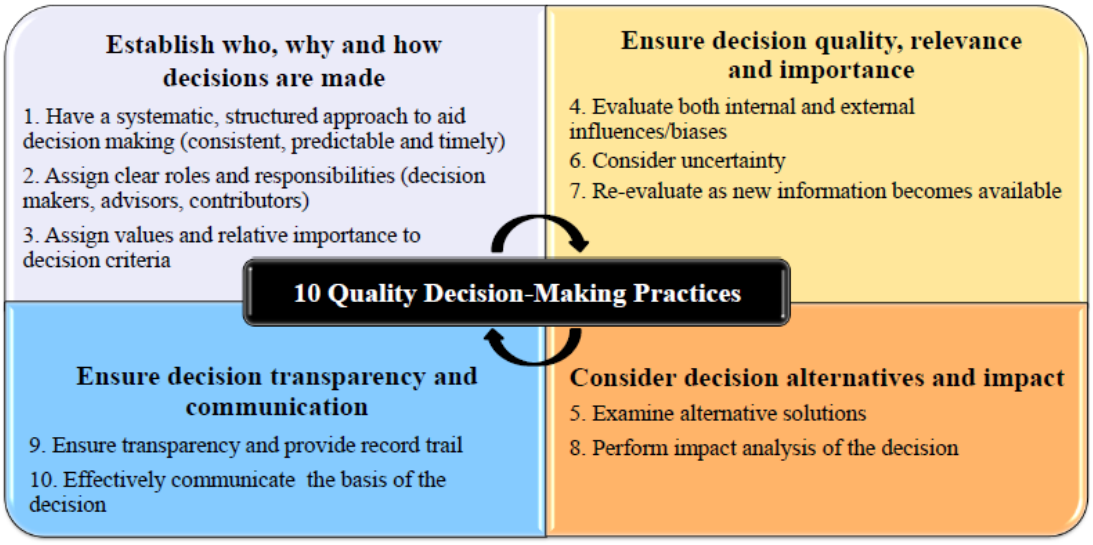
The QoDoS, aims to address companies' and agencies' need to assess the quality of their decision making with a structured and systematic approach that incorporates human awareness and provides the basis to achieve better practice (Donelan et al., 2015). Such evidence-based decision-making approach may lead to a shift to utilisation of formal frameworks and more systematic and structured processes for decision making. Although QoDoS already possesses a number of key psychometric properties, this programme of research further demonstrated the instrument's internal consistency, test-retest reliability as well as relevance in the target audiences, including language clarity and completeness of the QoDoS items. In addition, a number of small clarifications have been suggested to QoDoS, such as revising item 27 (I generate a Strengths-Weaknesses-Opportunities-Threats analysis in my decision making) to (I utilise decision making tools such as Strengths-Weaknesses-Opportunities-Threats analysis in my decision making), which will be taken account in future QoDoS studies.

Lastly, three illustrative case studies were carried out as first in-depth applications of QoDoS with selected groups within a company, a regulatory authority and an HTA agency. The studies resulted in identifying favourable and unfavourable practices, raising awareness across the individuals of the issues in decision making and enabling dialogue within organisations as a starting point for initiating a change in practice. Moreover, the case studies demonstrated the overall feasibility of this method as well as confirmed the practicality of QoDoS in assessing decision making in three different environments. This is indeed a major advantage, as assessments of different organisations with a common tool could facilitate external discussions as well as potential alignment of decision-making practices between companies, regulatory and HTA agencies. Studies described in Chapters 6 and 7 also illuminated the difficulty in assigning favourable or unfavourable scores to the QoDoS items, such as QoDoS

item 36 ('I use intuition or "gut-feeling" in my decision making'), which is scored as 'unfavourable practice', as indeed the overuse of intuition could lead to bias. Nevertheless, it should be noted that successful decision making relies on a balance between deliberate and instinctive thinking. The weighting of the QoDoS items should be therefore reviewed in the future with an expert panel, as well as how the QoDoS items are assigned to the ten QDMPs, to ensure the relevance and clarity of the results.

Finally, it was hypothesised that despite the challenges to the direct measurement of quality decision making and its outcome, by understanding the components of QDMPs, it may be possible to build a list of markers against each practice to ensure that each practice is embedded within organisational culture and individual processes. Consequently, a study with three focus groups from companies, agencies and academia aimed to develop practical approaches for incorporating quality into the decision-making processes during medicines development, regulatory review and HTA. All three focus groups developed recommendations, firstly regarding future research directions for building the evidence around quality decision-making practices, secondly relating to what may be the issues that need to be internally considered to build quality into the decision processes and lastly relating to approaches for measuring the processes and outcomes within organisations. One of the key outcomes of the focus groups has also been the reorganisation of the ten QDMPs under new subheadings and it is suggested that this new categorisation is taken forward in future studies (Figure 9.1).

**Figure 9.1 The re-organised ten Quality Decision-Making Practices**




Stakeholder perspectives and suggestions from the three focus groups were assessed in comparison with the outcomes of the other major studies undertaken as part of this research

programme in order to develop a checklist for incorporating the ten QDMPs. This checklist enables an organisation to incorporate these practices into its project matrix structure ahead of decision making (part 1) and lists process steps that need to be established and documented at the time of the decision-making process (part 2) in order to enable process quality, transparency and consistency. Next steps would seek to validate the checklist in -target audiences to increase its user friendliness, clarity, relevance and applicability. These objectives could also be achieved by appraising other existing checklists through a systematic review of the literature, which should also be undertaken.

A key challenge going forward is ensuring that this checklist is utilised and adhered to by organisations. Of major importance is ensuring that the roadmap is user friendly, clear and relevant, which is where future research could focus. Perhaps a starting point would be to utilise the validated checklist for training purposes using mock scenarios, so that organisations could understand in theory how to ensure a quality process through the incorporation of best practices, without creating too much strain on ongoing decision-making processes. Initial pilots could be used to generate case studies to demonstrate the advantages of such an approach. In addition, the checklist should be used primarily for important strategic decisions, as not every decision warrants such a detailed structured approach in order to balance burden compared to benefit (Kahneman, 2011). The development of a user manual would be essential to facilitate this.

**ROADMAP FOR IMPROVING QUALITY OF DECISION-MAKING PROCESSES**

It is important to note that the overall reactions to the studies carried out as part of this research programme have been very positive, perhaps due to this area being largely unexplored despite its importance, as highlighted at a recent Workshop (Walker et al., 2017). This therefore supported the idea of bringing together the various methods developed and utilised throughout this programme of research into an overarching roadmap for improving the quality of decision-making processes for key strategic decisions. The roadmap aims to encourage organisations to banish the “black box” decision-making systems which currently prevail. It consists of the following steps that organisations could undertake (Figure 9.2):

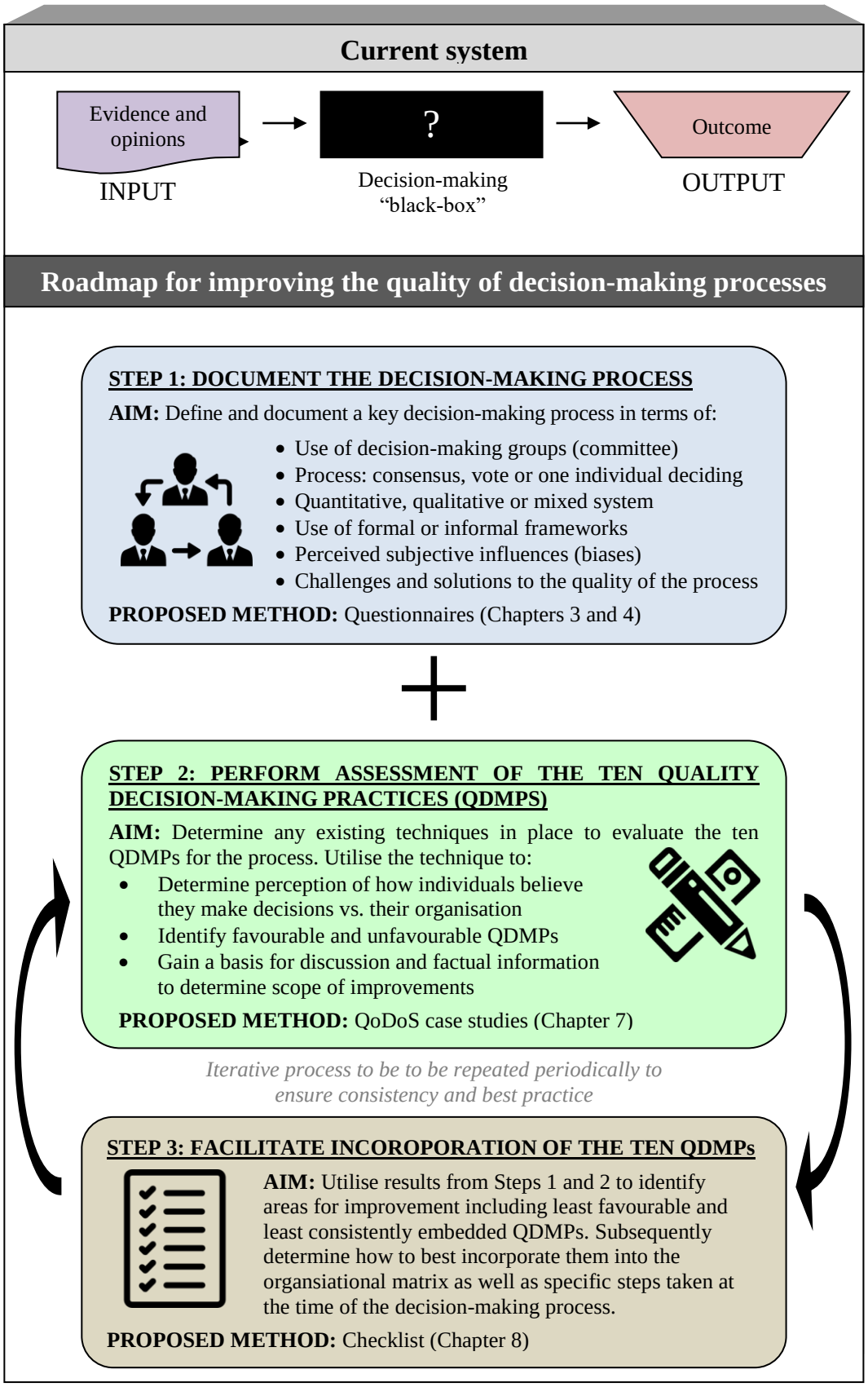
- **Step 1: Document the decision-making process.** For this initial step, questionnaires such as those utilised in Chapters 3 and 4 could be adapted and completed by management overseeing a specific decision-making process that would be the focus of improvements. This could either be a rare and key decision (for example reorganising a company) or a repetitive and high stake decision (initiating a clinical study phase by companies). Once the process is selected, the questionnaires could be applied to first

characterise the decision-making process (e.g. committee consensus process; one individual makes the decision etc.), the system (e.g. quantitative system using data and algorithm; qualitative system using expert judgment or a mixture), the use of frameworks (formal; informal) and whether or not the ten QDMPs have been theoretically incorporated into the framework. Of additional interest would be to determine whether it is perceived that the organisation is influenced by biases (subjective influences) (Lovallo and Sibony, 2010), as well as determining any perceived barriers and solutions to decision making.

- **Step 2: Perform Assessment of the ten QDMPs.** Once the process has been characterised, the next step would be to determine whether any techniques for evaluating the ten QDMPs are currently utilised by the organisation either systematically (e.g. every year) or on ad hoc basis. Following that, an evaluation would be proposed, where the use of QoDoS will be encouraged due to it being a relevant and reliable technique in assessing the ten practices as demonstrated in Chapters 5 and 6. This step would be in line with case studies described in Chapter 7, which has demonstrated the feasibility of this approach. QoDoS would therefore be used as a diagnostic test to evaluate the process selected in step 1. The aim would be to assess the decision-making competence and style of the individuals as well as how they perceive the decision-making approaches and culture of their group/team/organisation. The results could be used to identify favourable and unfavourable QDMPs as well as the key subjective influences (biases). In addition, the results would provide a basis for discussions within the group as well as obtaining factual information to initiate a change in practices.
- **Step 3: Facilitate incorporation of the ten QDMPs.** Finally, the results of steps 1 and 2 could be subsequently used to address the least favourable and least consistently embedded QDMPs. This step could utilise the checklist developed in Chapter 8. The aim would be to determine how to best incorporate them into the organsiational matrix (checklist part 1) as well as what specific actions need to be followed and documented at the time of the process (checklist part 2). Nevertheless, if improvements are made, the assessments described in steps 1 and 2 of the roadmap should be periodically repeated to ensure the effectiveness of implementation of any changes.

This roadmap therefore describes the steps an organisation could undertake to improve the quality of key decision-making processes, namely by first defining the decision, evaluating the ten QDMPs and subsequently better incorporating them into their organisational framework. It is based on the methods and tools developed and/or utilised and validated throughout this programme of work, namely the questionnaires (Chapters 3 and 4), the QoDoS (Chapter 5, 6 and 7) and the checklist (Chapter 8),

**Figure 9.2 The roadmap for improving the quality of decision-making processes for key strategic decisions made by pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies**



The implementation of the roadmap in companies, regulatory authorities and HTA agencies could also contribute to a better alignment between the various stakeholders, as the various methods outlined in steps 1-3 have been tested and were demonstrated as relevant to all three environments. Moreover, the roadmap could be used as a basis for communicating with the public, for example through annual company and agency reports to illustrate how well the organisational framework adheres to the ten QDMPs (Steps 1 and 2) as well as through public reports specific to the assessment of a medicine, where the checklist could be used as a basis for demonstrating the process utilised to arrive at a specific outcome (Step 3).

Nevertheless, the challenge is how to ensure the implementation of such a roadmap, as indeed the perceived burden may seem higher than the benefit. A key to success would be having internal and external decision-making champions within each organisation or creating departments whose role it would be to increase the awareness of quality decision making and facilitate a change in culture at the operational level, including the development of training programmes for all staff as well as international accreditation programmes, for example through ISO9001 (International Standards Organization; focus on Quality Management Principles). Indeed certain companies, such as Eli Lilly, have already undertaken such steps (Walker et al., 2017). Endorsement from management would be essential to enable and encourage changes; case studies could be developed for that purpose to demonstrate the importance of a quality decision-making process.

As many organisations are primarily interested in outcomes, it would be of key importance to ultimately demonstrate that the use of the ten QDMPs improves the probability of better outcomes, although this would be challenging due to the high uncertainty and multifactorial nature of the decision-making process. The focus could be initially placed on strategic management meetings as well as training and educational programmes to increase awareness of the important considerations in improving decision making, with the hope that with organisational buy-in, the QDMPs could also be used in time during real-life scenarios to demonstrate that they increase the overall probability of better outcomes. This approach , for example, could be used by company or agency decision-making committees when evaluating alternatives, both by mature organisations to set a benchmark, as well as by smaller or less mature companies and agencies in order to train staff and improve practices.

Of interest would be also to incorporate the ten QDMPs, as well as the roadmap, into the growing body of internationally accepted guidelines to help companies and agencies implement systems for making better decisions. For regulatory authorities and pharmaceutical companies, the ten QDMPs and the associated roadmap could be introduced through the

World Health Organisation (WHO), which already offers guidance relating to good review practices. For HTA agencies, it could be the European Network for Health Technology Assessment (EUnetHTA) or the International Network of Agencies for Health Technology Assessment (INAHTA), which facilitate European and international cooperation on HTA in Europe and globally and could incorporate the ten QDMPs into their tools and resources. The aim would be to ensure the use of the QDMPs and the roadmap at the international level and therefore facilitate alignment and convergence of best practices globally.

**STUDY LIMITATIONS**

As with any research there are a number of limitations including the following:

- For Chapter 3 (regulatory questionnaires), a pilot study was planned with companies and agencies in order to validate the acceptability and content of the questionnaires. However, this did not take place due to a lack of responses from the pilot participants despite repeated follow-ups with emails and phone calls. The questionnaire nevertheless went ahead as this was an exploratory, fact finding study and it was validated internally within the research team for format and language clarity.
- Whilst the regulatory and reimbursement questionnaires (Chapters 3 and 4) were international in nature, information was not obtained from agencies in certain key European jurisdictions, such as German or French HTA agencies or the Swiss regulatory authority, due to a lack of responses despite multiple attempts to contact those organisations. Whereas the response rate achieved for regulatory and HTA agencies as well as regulatory company departments were very good (~70%), this was only satisfactory for HEOR company departments (46%). This may be due to the lower level of maturity of those departments, which are generally newer compared with the regulatory departments, as well as due to the changing nature of the decision-making processes within companies to adapt to the dynamic HTA environment.
- The systematic literature review to identify techniques for assessing the quality of decision making presented in Chapter 5 was limited to articles in English language and covered a period from 1996 to 2017. Consequently, other techniques, if any, published in other languages and outside this timeframe were not identified. Nevertheless, the period identified reflects the proliferation of publications in this area, whereas the majority of the tools were published or translated into English due to their international importance.
- For Chapter 7, only one company, regulatory authority and HTA agency were selected to demonstrate the practicality of QoDoS for identifying the incorporation of the ten QDMPs and generally to demonstrate the feasibility of the method. This

sampling was considered nevertheless appropriate as the aim was to produce illustrative pilot case studies for testing the practical application of the methodology, as opposed to generating aggregated trends or extrapolating the results to other organisations. Furthermore, the formal feedback discussions with the study participants have not yet taken place, but are planned for the second part of 2018. The objectives would be to discuss the rationale for the results obtained as well as to establish the suitability and benefits of the study method.

**RECOMMENDATIONS**

As a result of this research, there are a number of recommendations:

- Pharmaceutical companies, regulatory authorities and HTA agencies should place greater emphasis on the quality aspects of decision making for key strategic processes, as specified by the ten QDMPs. This could be facilitated through the creation of quality decision-making departments, the involvement of champions and encouraging training and education in the science of decision making. The aim would be to raise awareness of the issues, biases and best practices in decision making.
- The QoDoS should be applied as a diagnostic instrument within teams, committees or departments in pharmaceutical companies, regulatory authorities and HTA agencies. The results could serve as a basis for identifying and discussing favourable and unfavourable practices and obtaining factual information underpinning a change within an organisation. Furthermore, the routine application of QoDoS has the potential to change the organisational culture and the individual's approach to decision making with an increased focus on process quality.
- The ten QDMPs should be incorporated into organisational frameworks within companies and agencies. The checklist could be further utilised to identify how each QDMP, especially if identified as unfavourable by QoDoS, could be incorporated into the organisational matrix structure as well as embedded during strategic decision-making processes. The ten practices, as well as the overarching roadmap, could be furthermore incorporated into recognised international guidelines (e.g. WHO) for companies and agencies to promote best practice and alignment of decision-making processes.

**FUTURE WORK**

- It would be of value to apply the questionnaires described in Chapters 3 and 4 to less mature regulatory authorities and HTA agencies, as well as small and medium enterprises (SMEs). This would aim to identify differences and similarities compared

to larger, more established organisations in terms of the decision-making processes, the use of frameworks as well as perceived challenges and solutions in decision making.

- Of interest would also be to further evaluate the importance and influence of biases during the lifecycle of medicines. Subsequently, the results could be used to develop a new model of bias mitigation, starting with a change in terminology to behavioural influences.
- Future QoDoS studies, as described in Chapter 7, should be organised with other mature and established organisations, including different committees, groups and departments. In addition, studies with less mature regulatory authorities and HTA agencies, as well as smaller companies, including SMEs could also be organised in order to identify further similarities and differences. One example could be a greater need for improvement across the QDMPs within maturing organisations or a bigger demand for accountability of the decisions made for smaller companies.
- Additional QoDoS studies could also be used to address the focus group recommendations (Chapter 7), such as to compare the results of QoDoS for organisations with and without a structured framework; to analyse joint venture decision-making processes e.g. parallel processes between regulatory authorities and HTA agencies or product acquisition between companies.
- Datasets from previous and future studies could be accrued to create a QoDoS benchmarking database. The aim would be to identify any trends in how companies and agencies make decisions, as well as other overarching themes, such as the differences in how individuals perceive themselves compared to their organisation, as well as the influence of gender and the number of years of experience on decision making.
- The checklist developed as a result of the study outcomes provides an initial list of items that need to be considered in implementing the ten QDMPs, once areas for improvement have been identified with QoDoS. The next steps would be to develop a user manual and subsequently validate the checklist with pharmaceutical companies, regulatory authorities and HTA agencies in order to establish its practicality, clarity and relevance; a systematic literature review of other checklists utilised in other industries would also be of interest. Once the checklist is validated, the QoDoS could then be utilised to determine whether a better implementation of the ten QDMPs with the checklist results in a more favourable QoDoS score, thereby demonstrating the sensitivity of QoDoS to detect a change in practice over time.

- Finally, of interest would be to pilot the checklist with an organisation over time, where it could be used for a number of similar decision-making processes. The organisation could complete the checklist for each decision, thereby documenting their process and subsequently this could be compared to the outcome of the decision once it emerges. The aim would be to perform an impact analysis in order to determine whether unfavourable outcomes could be tied to persistent deficiencies in the process, as documented by the checklist.

## CONCLUSION

This programme of research marks a milestone in addressing the gap between the well-recognised science of decision making with that addressed in the area of regulation and reimbursement of medicines. The studies undertaken have for the first time, using well-defined methods and techniques, evaluated both the decision-making practices as well as their implementation during the lifecycle of medicines. The overall outcome was the development of a roadmap for improving the quality of decision making for the key strategic processes undertaken by pharmaceutical companies, regulatory authorities and health technology assessment agencies. This has the potential to not only fundamentally change the culture within those organisations, but will ensure a greater emphasis on decision making as opposed to just evaluating the data. This could therefore revolutionise the way companies and agencies make decisions, which may ultimately increase the probability of favourable outcomes, with the final goal of building public trust and accountability into the key strategic decisions made by all three stakeholders.

## REFERENCES


Allen, N., Pichler, F., Wang, T., Patel, S. and Salek, S. (2013). Development of archetypes for non-ranking classification and comparison of European National Health Technology Assessment systems. *Health Policy*, 113(3), pp.305-312.

Avorn, J. (2018). The Psychology of Clinical Decision Making — Implications for Medication Use. *New England Journal of Medicine*, 378(8), pp.689-691.

Benson, B. (2016). *Cognitive bias cheat sheet – Better Humans*. [online] Better Humans. Available at: https://betterhumans.coach.me/cognitive-bias-cheat-sheet-55a472476b18 [Accessed 7 May 2018].

Beyer, A., Fasolo, B., de Graeff, P. and Hillege, H. (2015). Risk Attitudes and Personality Traits Predict Perceptions of Benefits and Risks for Medicinal Products: A Field Study of European Medical Assessors. *Value in Health*, 18(1), pp.91-99.

Blenko, M., Mankins, M. and Rogers, P. (2010). *Decide and deliver*. Boston, Mass: Harvard Business School Publishing.

Boeije, H. (2012). A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality Quantity*. 36 (4), pp.391–409.

Bootes, A. (2017). *Provisional approval pathway for prescription medicines*. [online] ARCS MMDR Webinar Series. Available at: https://www.tga.gov.au/sites/default/files/tga-presentation-provisional-approval-pathway-for-prescription-medicines-170426.pdf [Accessed 7 May 2018].

Boutin, M., Dewulf, L., Hoos, A., Geissler, J., Todaro, V., Schneider, R., Garzya, V., Garvey, A., Robinson, P., Saffer, T., Krug, S. and Sargeant, I. (2016). Culture and Process Change as a Priority for Patient Engagement in Medicines Development. *Therapeutic Innovation & Regulatory Science*, 51(1), pp.29-38.

Breckenridge, A. and Walley, T. (2008). Early Access to New Medicines. *Clinical Pharmacology & Therapeutics*, 84(1), pp.23-25.

Breckenridge, A., Feldschreiber, P., Gregor, S., Raine, J. and Mulcahy, L. (2011). Evolution of regulatory frameworks. *Nature Reviews Drug Discovery*, 10(1), pp.3-4.

Breckenridge, A., Woods, K. and Walley, T. (2010). Medicines Regulation and Health Technology Assessment. *Clinical Pharmacology & Therapeutics*, 87(2), pp.152-154.

Breen, R. (2006). A Practical Guide to Focus-Group Research. *Journal of Geography in Higher Education*, 30(3), pp.463-475.

Briggs, K., and Myers, I. (1987). *Myers-Briggs Type Indicator: Form G*. Palo Alto, CA: Consulting Psychology.

Brod, M., Tesler, L. and Christensen, T. (2009). Qualitative research and content validity:

developing best practices based on science and experience. *Quality of Life Research*, 18(9), pp.1263-1278.

Bryman, A. (2006). Integrating quantitative and qualitative research: how is it done?. *Qualitative Research*, 6(1), pp.97-113.

Buchanan, L., and O'Connell, A. (2006). A brief history of decision making. *Harv Bus Rev*. 84, pp.32–41.

Bujar, M., Donelan, R., McAuslane, N., Walker, S. and Salek, S. (2016). Assessing the Quality of Decision Making in the Development and Regulatory Review of Medicines. *Therapeutic Innovation & Regulatory Science*, 51(2), pp.250-256.

Bujar, M., McAuslane, N., Salek, S. and Walker, S. (2017). *CIRS R&D Briefing 61: Building Quality into Decision-Making Processes in Medicines' Development, Regulatory Review and Health Technology Assessment*. Centre for Innovation in Regulatory Science. [online] Available at: http://www.cirsci.org/wp-content/uploads/2017/01/CIRS-RD-Briefing-61-Decision-making.pdf [Accessed 7 May 2018].

Bunag, T., & Savenye, W. (2013). *Value of Delphi technique as an educational design research method: Building a model for the design of chemistry laboratory experiments for instruction*. In T. Plomp, & N. Nieveen (Eds.), Educational design research – Part B: Illustrative cases (pp. 1061-1078). Enschede, the Netherlands: SLO. [online] Available at: http://international.slo.nl/bestanden/Ch49.pdf/ [Accessed 7 May 2018].

Calnan, M., Hashem, F. and Brown, P. (2017). Still Elegantly Muddling Through? NICE and Uncertainty in Decision Making About the Rationing of Expensive Medicines in England. *International Journal of Health Services*, 47(3), pp.571-594.

Canadian Agency for Drugs and Technologies in Health (CADTH). (2012). *Common Drug Review Recommendations Options and Deliberative Framework*. [online] Available at: https://www.cadth.ca/media/cdr/cdr-pdf/CDEC_Deliberative_Framework_e.pdf [Accessed 7 May 2018].

Centre for Innovation in Regulatory Science (CIRS). (2017). *Building quality into the decision-making process – Does measuring decision making enable a better quality process for companies and regulatory and HTA agencies?* [online] Available at: http://www.cirsci.org/events/building-quality-into-the-decision-making-process-can-this-be-meaningfully-measured/ [Accessed 7 May 2018].

Centre for Innovation in Regulatory Science (CIRS). (2018). *CIRS Agenda*. [online] Available at: http://www.cirsci.org/wp-content/uploads/2018/02/REV-CIRS-2018-8-Page-agenda-for-print_230218_11.pdf [Accessed 7 May 2018].

Cherny, N., Sullivan, R., Dafni, U., Kerst, J., Sobrero, A., Zielinski, C., de Vries, E. and Piccart, M. (2016). A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Annals of Oncology*, 26 pp.1547–1573.

Cole, A., Marsden, G., Devlin, N., Grainger, D., Lee, E. K., and Oortwijn, W. (2016). *New Age Decision Making in HTA: Is It Applicable in Asia?* Report of the HTAi 2016 Panel Session, Tokyo, 10–14 May. [online] Available at: https://www.ohe.org/publications/%E2%80%9Cnew-age%E2%80%9D-decision-making-hta-it-applicable-asia [Accessed 7 May 2018].

Collis, J. (2009). *Business research: A practical guide for undergraduate and postgraduate students*. 3rd ed. London: Palgrave MacMillan.

Cook, D., Brown, D., Alexander, R., March, R., Morgan, P., Satterthwaite, G. and Pangalos, M. (2014). Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. *Nature Reviews Drug Discovery*, 13(6), pp.419-431.

Cook, D., Mulrow, D. and Haynes, R. (1997). Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions. *Annals of Internal Medicine*, 126(5), p.376.

Cowlrick, I., Hedner, T., Wolf, R., Olausson, M. and Klofsten, M. (2011). Decision-making in the pharmaceutical industry: analysis of entrepreneurial risk and attitude using uncertain information. *R&D Management*, 41(4), pp.321-336.

Daniels, N. (2000). Accountability for reasonableness. *BMJ*, 321(7272), pp.1300-1301.

Dean, J. and Sharfman, M. (1996). Does Decision Process Matter? A Study Of Strategic Decision-making Effectiveness. *Academy of Management Journal*, 39(2), pp.368-392.

Dicicco—Bloom, B., and Crabtree, B. (2006). The qualitative research interview. *Med. Educ* 40(4), pp.314-21.

Dodgson, J. S. 2009. *Multi-criteria analysis: a manual*. London: London School of Economics.

Donabedian, A. (1988). The Quality of Care. *JAMA*, 260(12), p.1743.

Donelan, R., Walker, S. and Salek, S. (2015). Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiology and Drug Safety*, 24(3), pp.319-328.

Donelan, R., Walker, S. and Salek, S. (2016). The Development and Validation of a Generic Instrument, QoDoS, for Assessing the Quality of Decision Making. *Frontiers in Pharmacology*, 7(180).

Dowding, D. and Thompson, C. (2003). Measuring the quality of judgement and decision-making in nursing. *Journal of Advanced Nursing*, 44(1), pp.49-57.

Dunlop, W., Mullins, C., Pirk, O., Goeree, R., Postma, M., Enstone, A. and Heron, L. (2016). BEACON: A Summary Framework to Overcome Potential Reimbursement Hurdles. *PharmacoEconomics*, 34(10), pp.1051-1065.

Edlavitch, S., Salmon, W.J. (2015). Towards an applied science of therapeutic regulatory decision-making. *J Pharmacovigilance*. doi: 10.4172/2329-6887.1000e137.

Eichler, H., Pignatti, F., Flamion, B., Leufkens, H. and Breckenridge, A. (2008). Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nature Reviews Drug Discovery*, 7(10), pp.818-826.

European Commission. (2018). *Proposal for a regulation of the European Parlimenta nd of the Council on health technology assessment (HTA) and amending Directice 2011/24/EU*. [online] Available at: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51_en.pdf

[Accessed 7 May 2018].

European Medicines Agency (EMA). (2007). *CHMP Rules of Procedure*. [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004628.pdf [Accessed 7 May 2018].

European Medicines Agency (EMA). (2010). *Experience of the CHMP Peer Review – A tool for quality assurance of the evaluation of a new marketing authorisation application in the Centralised Procedure*. [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/05/WC500091037.pdf [Accessed 7 May 2018].

European Medicines Agency (EMA). (2011). *Benefit-risk methodology project: Work package 3 report: Field tests*. [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112088.pdf

European Medicines Agency (EMA). (2016). *Report of the pilot on parallel regulatory-health technology assessment scientific advice.* [online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/03/WC500203945.pdf [Accessed 7 May 2018].

European network for health technology assessment (EUnetHTA). (2016). *HTA Core Model*. [online] Available at: https://meka.thl.fi/htacore/ViewHandbook.aspx [Accessed 7 May 2018].

European network for health technology assessment (EUnetHTA). (2017) *What is the added value of more HTA collaboration in Europe? EUnetHTA JA3 - more than a year later*. [online] Available at: https://redets.msssi.gob.es/IVJornadas/presentaciones/docs/WGoettsch.pdf [Accessed 7 May 2018].

European network for health technology assessment (EUnetHTA). (2018). *Our Organization*. [online] Available at: https://www.eunethta.eu/about-eunethta/organization/ [Accessed 7 May 2018].

Ferguson, J. (2008). *Prerequisites of a benefit-risk framework for the registration of a new medicine*. CMR International Institute for Regulatory Science Workshop Report. [online] Available at: http://cirsci.org/publications/June_2008.pdf [Accessed 7 May 2018].

Fischer, K., Leidl, R. and Rogowski, W. (2011). A structured tool to analyse coverage decisions: Development and feasibility test in the field of cancer screening and prevention. *Health Policy*, 101(3), pp.290-299.

Fisher, I. (1907). *The rate of interest; Its Nature, Determination and Relation to Economic Phenomena*. New York: The Macmillan Company.

Food and Drug Administration (FDA). (2008). *Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings*. [online] Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125641.pdf [Accessed 7 May 2018].

Food and Drug Administration (FDA). (2017). *U.S. Department of Health and Human Services Food and Drug Administration. 2017. Formal Dispute Resolution: Sponsor Appeals*

*Above the Division Level*. [online] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm343101.pdf [Accessed 7 May 2018].

Food and Drug Administration (FDA). (2018). *Benefit-risk assessment in drug regulatory decision-making; Draft PDUFA VI Implementation Plan (FY 2018-2022).* [online] Available at: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf [Accessed 7 May 2018].

Franken, M., le Polain, M., Cleemput, I. and Koopmanschap, M. (2012). Similarities and differences between five European drug reimbursement systems. *International Journal of Technology Assessment in Health Care*, 28(04), pp.349-357.

Freud, S. (1915). The Unconscious. *SE,* 14, pp.159-215.

Garbuio, M., Lovallo, D., and Sibony, O. (2015). Evidence doesn't argue for itself: the value of disinterested dialogue in strategic decision-making. *Long Range Plan*. 48, pp.361–380. doi: 10.1016/j.lrp.2015.09.002.

Gawande, A. (2011). *The checklist manifesto*. New York: Must Read Summaries.

Gill, P., Stewart, K., Treasure, E. and Chadwick, B. (2008). Methods of data collection in qualitative research: interviews and focus groups. *British Dental Journal*, 204(6), pp.291-295.

Glitz, B. (1997). The focus group technique in library research: an introduction. *Bulletin of the Medical Library Association*, 24(3), pp.208-15.

Goldberg, L. R. (1999). *International Personality Item Pool.* [online] Available at: https://ipip.ori.org/ [Accessed 7 May 2018].

Goldberg, L., Johnson, J., Eber, H., Hogan, R., Ashton, M., Cloninger, C. and Gough, H. (2006). The international personality item pool and the future of public-domain personality measures. *Journal of Research in Personality*, 40(1), pp.84-96.

Goodman, C. S. (2014). *HTA 101: Introduction to Health Technology Assessment. Bethesda, MD: National Library of Medicine (US)*. [online] Available at: https://www.nlm.nih.gov/nichsr/hta101/HTA_101_FINAL_7-23-14.pdf [Accessed 7 May 2018].

Gray, D. (2014). *Doing research in the real world*. 3rd ed. London: SAGE.

Guo, J., Pandey, S., Doyle, J., Bian, B., Lis, Y. and Raisch, D. (2010). A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy—Report of the ISPOR Risk–Benefit Management Working Group. *Value in Health*, 13(5), pp.657-666.

Hammond, K., Keeney, R., and Raiffa, H. (1999). Smart Choices: A Practical Guide to Making Better Decisions. New York: Harvard Business School.

Hassanzadeh, S., Gourc, D., Marmier, F., and Bougaret, S. (2011). *Decision-making in R&D projects, a framework based on fuzzy logic*. International Conference on Production Research, Stuttgart (Germany), France. pp.1, 2011.

Heath, C., and Heath D. (2013). *Decisive: How to Make Better Choices in Life and Work*. New York: Crown Business.

Hoos, A., Anderson, J., Boutin, M., Dewulf, L., Geissler, J., Johnston, G., Joos, A., Metcalf,

M., Regnante, J., Sargeant, I., Schneider, R., Todaro, V. and Tougas, G. (2015). Partnering With Patients in the Development and Lifecycle of Medicines. *Therapeutic Innovation & Regulatory Science*, 49(6), pp.929-939.

Howard, R., Abbas, A. and Howard, R. (2015). *Foundations of decision analysis*. 1st ed. Harlow: Pearson.

Hunink, M. and Weinstein, M. (2001). *Decision making in health and medicine*. 2nd ed. Cambridge: Cambridge University Press.

International Network of Agencies for Health Technology Assessment (INAHTA). (2018). *Members List.* [online] Available at: http://www.inahta.org/members/members_list/ [Accessed 7 May 2018].

J. Skulmoski, G., T. Hartman, F. and Krahn, J. (2007). The Delphi Method for Graduate Research. *Journal of Information Technology Education: Research*, 6, pp.001-021.

Jekunen, A. (2014). Decision-making in product portfolios of pharmaceutical research and development – managing streams of innovation in highly regulated markets. *Drug Des. Devel. Ther*. 8, pp.2009–2016. doi: 10.2147/DDDT.S68579.

Kahneman, D. (2011). *Thinking Fast and Slow*. London: Penguin Books.

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), pp.155–163. doi: 10.1016/j.jcm.2016.02.012

Leong, J., McAuslane, N., Walker, S. and Salek, S. (2013). Is there a need for a universal benefit-risk assessment framework for medicines? Regulatory and industry perspectives. *Pharmacoepidemiology and Drug Safety*, 22, pp.1104-1012.

Leong, J., Walker, S. and Salek, S. (2015). A practical approach to communicating benefit-risk decisions of medicines to stakeholders. *Frontiers in Pharmacology*, 6.

Liberti, L., Breckenridge, A., Hoekman, J., McAuslane, N., Stolk, P. and Leufkens, H. (2017). Factors related to drug approvals: predictors of outcome? *Drug Discovery Today*, 22(6), pp.937-946.

Liberti, L., McAuslane, N., Patel, P., Breckenridge, A., Eichler, H. and Peterson, R. (2013). Regulatory Review: How Do Agencies Ensure the Quality of Decision Making?. *Clinical Pharmacology & Therapeutics*, 94(3), pp.305-308.

Lovallo, D. and Sibony, O. 2016. *Distortions and deceptions in strategic decision.* McKinsey Quarterly February. [online] Available at: https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/distortions-and-deceptions-in-strategic-decisions [Accessed 7 May 2018].

Lovallo, D. and Sibony, O. 2010. *The case for behavioral strategy.* McKinsey Quarterly March. [online] Available at: https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/the-case-for-behavioral-strategy [Accessed 7 May 2018].

Lowy, A. and Hood, P. (2004). *The Power of the 2 x 2 Matrix: Using 2 x 2 Thinking to Solve Business Problems and Make Better Decisions*. San Francisco: Jossey-Bass.

Marangi, M., Cammarata, S. M., and Pani, L. (2014). Insights into the decision making of

advisory groups to the Italian Medicines Agency. *Ther. Innov. Reg. Sci*. 48, pp.696–701. doi: 10.1177/2168479014529571.

Matheson, D. and Matheson, J. (2001). Smart Organizations Perform Better. *Research-Technology Management*, 44(4), pp.49-54.

Matheson, D., and Matheson, J. (1998). *The Smart Organization: Creating value through Strategic R&D.* Boston, MA: Harvard Business Review Press.

McAuslane, N., Patel, P., Liberti, L., Connelly, P. (2011). *Centre for Innovation in Regulatory Science Workshop report: Evolving the Regulatory Review Process: What are the features that enable a transparent, timely, predictable and good-quality review?* [online] Available at: http://cirsci.org/publications/CIRS_December_2011_WS_Report.pdf [Accessed 7 May 2018].

McAuslane, N., Wang, T., Liberti, L., Connelly, P. (2016). *Centre for Innovation in Regulatory Science Workshop Summary: Commonality in evidentiary requirements across regulatory authorities and HTA stakeholders* [online] Available at: http://www.cirsci.org/wp-content/uploads/2017/02/CIRS-September-2016-Workshop-Synopsis_12Dec2016.pdf [Accessed 7 May 2018].

McDowell, I. (2006). *Measuring Health: A Guide to Rating Scales and Questionnaires*. New York, NY: Oxford University Press.

McIntyre, T. D., Pappas, M., and DiBiasi, J. J. (2012). How FDA Advisory Committee Members prepare and what influences them. *Drug Inform*. J. 47, pp. 32–40. doi: 10.1177/0092861512458096.

McKinsey (2008). *Global Survey results: Flaws in strategic decision making*. McKinsey Quarterly November. [online] Available at: http://www.mckinseyquarterly.com/Flaws_in_strategic_decision_making_McKinsey_Global_Survey_Results_2284 [Accessed 7 May 2018].

Medicines and Healthcare products Regulatory Agency (MHRA). (2013). *Report of the Expert Group on innovation in the regulation of healthcare.* [online] Available at: http://webarchive.nationalarchives.gov.uk/20141206100916/http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con336728.pdf [Accessed 7 May 2018].

Mindtools (2013). *Decision-Making* [online]. Available online at: https://www.mindtools.com/pages/article/newTED_79.htm [Accessed 7 May 2018].

Morton, A., Airoldi, M., and Phillips, L. D. (2009). Nuclear risk management on stage: a decision analysis perspective on the UK's committee on radioactive waste management. *Risk Anal.* 29, pp.764–779. doi: 10.1111/j.1539-6924.2008.01192.x

Nagle, B., Williamsm N. (2013). *Methodology Brief: Introduction to Focus Groups by the Center for Assessment, Planning and Accountability*. [online] Available at: http://www.mmgconnect.com/projects/userfiles/file/focusgroupbrief.pdf [Accessed 7 May 2018].

National Institute for Health and Care Excellence (NICE). (2015). *Technology Appraisals Committee Terms of Reference and Standing Orders*. [online] Available at: https://www.nice.org.uk/Media/Default/Get-involved/Meetings-In-Public/Technology-appraisal-committee/TAC-terms-of-reference-standing-orders.pdf [Accessed 7 May 2018].

Needham, M.D. and Vaske, J.J. (2008). *Chapter 7: Survey implementation, sampling, and weighting data*. Philadelphia, PA: Venture Publishing. doi: 10.1016/j.jval.2017.03.011.

Nunnally, J.C., Bernstein, I.H. (1994). *Psychometric theory*. New York: McGraw-Hill.

Oortwijn, W., Determann, D., Schiffers, K., Tan, S.S., van der Tuin, J. (2017) Towards Integrated Health Technology Assessment for Improving Decision Making in Selected Countries. *Value in Health*, 20(8), pp.1121-1130.

Open University. (2013). *Making Decisions*. [online] Available at: http://www.open.edu/openlearn/ocw/pluginfile.php/58757/mod_oucontent/oucontent_download/epub/83f9b136c23c9909cf9191212ebf0098eb118ebb/making_decisions.epub [Accessed 7 May 2018].

Paiva, C. E., Barroso, E. M., Carneseca, E. C., de Padua Souza, C., Dos Santos, F. T., Mendoza Lopez, R. V., et al. (2014). A critical analysis of test-retest reliability in instrument validation studies of cancer patients under palliative care: A systematic review. *BMC Medical Research Methodology*, 14(1), 8. doi:10. 1186/1471-2288-14-8.

Patel, P., McAuslane, N., Liberti, L., Connelly, P. (2016). *Centre for Innovation in Regulatory Science Workshop report: What are the key performance metrics that agencies and companies should use to measure the regulatory process and practices to facilitate the licensing of new medicine.* [online] Available at: http://www.cirsci.org/wp-content/uploads/2017/02/CIRS_February_2016_Workshop_Final_15Aug_high.pdf [Accessed 7 May 2018].

Peters, W.S. (1987). *Counting for Something: Statistical Principles and Personalities*. New York: Springer Texts in Statistics.

Pharmaceutical Executive (PharmExec). (2014). *Pharm Excec's Pharma 50 companies 2014*. [online] Available at: http://www.pharmexec.com/pharm-execs-pharma-50-2014 [Accessed 7 May 2018].

Pharmaceutical Executive (PharmExec). (2016). *Pharm Excec's Pharma 50 companies 2016*. [online] Available at: http://www.pharmexec.com/2016-pharm-exec-50 [Accessed 7 May 2018].

Pharmaceutical Executive (PharmExec). (2017). *Pharm Excec's Pharma 50 companies 2017*. [online] Available at: http://www.pharmexec.com/pharm-execs-top-50-companies-2017 [Accessed 7 May 2018].

Pharmaceutical Research and Manufacturers of America (PhRMA). (2015). *Biopharmaceutical Research & Development: The Process Behind New Medicines*. PhRMA, Washington, DC. [online] Available at: http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf [Accessed 7 May 2018].

Phillips, L.D. (2006). *Decision conferencing Operational Research working papers, LSEOR 06.85*. Operational Research Group, Department of Management, London School of Economics and Political Science, London, UK. [online] Available at: http://eprints.lse.ac.uk/22712/ [Accessed 7 May 2018].

Phillips, L.D and Stock, A. (2003). *Use of multi-criteria decision analysis in air quality policy*. Department for Environment, Food and Rural Affairs, London, UK. [online] Available at: https://uk-air.defra.gov.uk/assets/documents/reports/cat09/0711231556_MCDA_Final.pdf

[Accessed 7 May 2018].

Pichler, F., Allen, N., Salek, S. and Liberti, L. (2010). Development of systematic process maps to enable comparison between different HTA and decision making systems: the first step to benchmarking. *Value in Health*, 13(7), p.A409.

Pignatti, F., Ashby, D., Brass, E., Eichler, H., Frey, P., Hillege, H., Hori, A., Levitan, B., Liberti, L., Löfstedt, R., McAuslane, N., Micaleff, A., Noel, R., Postmus, D., Renn, O., Sabourin, B., Salmonson, T. and Walker, S. (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), pp.522-533.

Pritchard, J., Jurima-Romet, M., Reimer, M., Mortimer, E., Rolfe, B. and Cayen, M. (2003). Making Better Drugs: Decision Gates in Non-Clinical Drug Development. *Nature Reviews Drug Discovery*, 2(7), pp.542-553.

Ratliff, A., Angell, M., Dow, R. W., Kuppermann, M., Nease, R., Fisher, R., et al. (1999). What is a good decision? *Effect. Clin. Pract*. 2, pp.185–197.

Robson, C. (2002). *Real world research*. 2nd ed. Malden, MA: Blackwell.

Rogowski, W., Hartz, S. and John, J. (2008). Clearing up the hazy road from bench to bedside: A framework for integrating the fourth hurdle into translational medicine. *BMC Health Services Research*, 8(1).

Salant, P., & Dillman, D. A. (1994). *How to conduct your own survey*. Wiley. US: New York.

Salek, S., Mallia-Milanes, A., McAuslane, N., and Walker, S. (2012). Development and application of scorecards to assess the quality of a regulatory submission and its review. *Ther. Innov. Reg. Sci*. pp.46, 73–83. doi: 10.1177/0092861511427694.

Saunders, M., Lewis, P. and Thornhill, A. (2009). *Research methods for business students*. 5th ed. Harlow: Pearson Education.

Schnipper, L., Davidson, N., Wollins, D., Tyne, C., Blayney, D., Blum, D., Dicker, A., Ganz, P., Hoverman, J., Langdon, R., Lyman, G., Meropol, N., Mulvey, T., Newcomer, L., Peppercorn, J., Polite, B., Raghavan, D., Rossi, G., Saltz, L., Schrag, D., Smith, T., Yu, P., Hudis, C. and Schilsky, R. (2015). American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options. *Journal of Clinical Oncology*, 33(23), pp.2563-2577.

Scott, S. G., and Bruce, R. A. (1995). Decision-making style: the development and assessment of a new measure. *Educ. Psychol. Meas*. 55, pp.818–831.

Sharpe, P., and Keelin, T. (1998). How Smithkline Beecham makes better resource-allocation decisions. *Harvard Business Rev*. 76, pp.45–57.

Smietana, K., Ekstrom, L., Jeffery, B. and Møller, M. (2015). Improving R&D productivity. *Nature Reviews Drug Discovery*, 14(7), pp.455-456.

Spetzler, C., Winter, H. and Meyer, J. (n.d.). *Decision Quality*. 1st ed. NJ, US: Wiley.

Steele, K. and Stefánsson, H.O. (2015). *Decision Theory: The Stanford Encyclopedia of*

*Philosophy*. [online] Available at: http://plato.stanford.edu/archives/win2015/entries/decision-theory [Accessed 7 May 2018].

Strategic Decision Group (SDG) (2011). *Decision Quality Webinar: The Art and Science of Good Decision Makin*g. University of Stanford.

Streiner, D. L., Norman, G., and Cairney, J. (2015*). Health Measurement Scales: A Practical Guide to Their Development and Use*, 5th ed. Oxford: Oxford University Press.

Tafuri, G. (2013). *Exploring the Regulatory Decision-making Process for Medicines*. Ph.D. University of Utrecht.

Tafuri, G., Lucas, I., Estevão, S., Moseley, J., d'Andon, A., Bruehl, H., Gajraj, E., Garcia, S., Hedberg, N., Massari, M., Molina, A., Obach, M., Osipenko, L., Petavy, F., Petschulies, M., Pontes, C., Russo, P., Schiel, A., Van de Casteele, M., Zebedin-Brandl, E., Rasi, G. and Vamvakas, S. (2018). The impact of parallel regulatory-health technology assessment scientific advice on clinical development. Assessing the uptake of regulatory and health technology assessment recommendations. *British Journal of Clinical Pharmacology*, 84(5), pp.1013-1019.

Thaler, R. H., and Sustein, C. R. (2009). *Nudge: Improving Decisions About Health, Wealth and Happines*s. New Haven, CT: Yale University Press.

Trewatha, R. and Newport, G. (1982). *Management Functions and Behavior*. Business Publications; Subsequent edition. The University of Virginia, VA, US.

Trochim, W. (2006). *Research methods knowledge base*. Mason (Ohio): Atomic Dog Publishing Inc.

Tufts Center for the Study of Drug Development (CSDD). (2014). *Briefing: Cost of Developing a New Drug*. [online] Available at: http://www.academia.edu/34807407/Cost_of_Developing_a_New_Drug_Tufts_Center_for_the_Study_of_Drug_Development [Accessed 7 May 2018].

Valenzuela, D. and Shrivastava, P. (2005). *Interview as a Method for Qualitative Research. Presentation.* [online] Available at: http://www.public.asu.edu/~kroel/www500/ Interview%20Fri.pdf [Accessed 7 May 2018].

Wagner W. (2013). *Science in the Administrative Process: A Study of Agency Decision making Approaches*. University of Texas School of Law. [online] Available at: https://www.acus.gov/sites/default/files/documents/Science%20in%20Regulation_Final%20Report_2_18_13_0.pdf [Accessed 7 May 2018].

Wahlster, P., Brereton, L., Burns, J. et al. (2016). *Guidance on the integrated assessment of complex health technologies - The INTEGRATE-HTA Model*. 2016. [online] Available at: http://www.integrate-hta.eu/downloads/ [Accessed 7 May 2018].

Walker, S., McAuslane, N., Bujar, M., Connelly, P. and Liberti, L. (2018). *Quality decision-making practices: Their application and impact in the development, review and reimbursement of medicines*. 1st ed. Based on the proceedings of a Workshop convened by the Centre for Innovation in Regulatory Science CIRS), June 15-16 2017, Tysons Corner, Virginia.

Walker, S., McAuslane, N., Liberti, L and Connelly, P. (2012). B*uilding the Benefit Risk*

*Toolbox: Are there enough common elements across the different methodologies to enable a consensus on a scientifically acceptable framework for making benefit-risk decisions?* Based on the proceedings of a Workshop convened by the Centre for Innovation in Regulatory Science CIRS), June 20-21 2012, Washington, DC.

Walker, S., McAuslane, N., Liberti, L., Leong, J. and Salek, S. (2014). A Universal Framework for the Benefit-Risk Assessment of Medicines. *Therapeutic Innovation & Regulatory Science*, 49(1), pp.17-25.

Wang, T., McAuslane, N., Liberti, L., Connelly, P. (2016). CIRS *R&D Briefing 60: Early scientific advice from HTA agencies: How does the effective use of the various kinds of advice support a positive HTA recommendation?* Centre for Innovation in Regulatory Science. [online] Available at: http://www.cirsci.org/wp-content/uploads/2016/10/CIRS-RD-Briefing-60-Early-scientific-advice-from-HTA-agencies_Sept-2016.pdf. [Accessed 7 May 2018].

Wang, T., McAuslane, N., Lipska, L., Liberti, L. (2015*). Building quality in HTA process and decision making: Can key performance measures of good practices in HTA be identified*? Centre for Innovation in Regulatory Science. [online] Available at: http://cirsci.org/sites/default/files/ISPOR_2015.pdf. [Accessed 7 May 2018].

Wertz, F.J. (2011). *Five ways of doing qualitative analysis: phenomenological psychology, grounded theory, discourse analysis, narrative research, and intuitive inquiry*. Guildford Press. US: New York.

Westley, F. R. (1990). Middle managers and strategy: microdynamics of inclusion. *Strateg. Manage. J*. 11, pp.337–351.

Wood, N. L. (2012*). Individual Differences in Decision-Making Styles as Predictors of Good Decision Making*. Master's thesis, Graduate College of Bowling Green State University, Ohio.

World Health Organisation (WHO). (2017). *Clarification with Respect to a Stringent Regulatory Organization as Applicable to the Stringent Regulatory Authority (SRA) Guideline*. [online] Available at: https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf [Accessed 7 May 2018].

World Health Organization (WHO). (2015). *Good Review Practices: Guidelines for National and Regional Regulatory Authorities*. WHO Technical Report Series, No. 992, Annex 9. Geneva: WHO. [online] Available at: http://apps.who.int/medicinedocs/en/d/Js21902en/ [Accessed 7 May 2018].

Yin, R.K. (2003). *Case Study Research: Design and Methods*. 3rd ed. London: SAGE publication.

## Appendix 1: The Quality of Decision-Making Orientation Scheme (QoDoS)

### The Quality of Decision-Making Orientation Scheme (QoDoS) ©

The statements in the questionnaire relate to your views on your personal and your organisation's *decision-making processes for major strategic choices within your organisation.*

Please mark clearly one box for each statement. Assume that Not at all = 0% of time; Sometimes = 25% of time; Frequently = 50% of time; Often = 75% of time; Always = 100% of time. If not sure, please tick the box that you feel is the most appropriate.

No data that will identify an individual or an organisation will be reported, or details made to a third party.

#### Background questions

Gender: ☐ Male ☐ Female ☐ Other

Job title: _____

How many years of professional experience have you to date? _____

Organisation: ☐ Regulatory Agency ☐ Pharmaceutical Industry ☐ HTA ☐ Academia ☐ Other

#### Part I: Organisational-level influences

| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-Making Approach** | | | | | | |
| 1. My organisation evaluates the impact of the decisions it makes | | | | | | |
| 2. My organisation's decision making is transparent | | | | | | |
| 3. My organisation's decision making is consistent | | | | | | |
| 4. My organisation uses a structured approach in its decision making | | | | | | |
| 5. My organisation's decision making is influenced by external stakeholder's demands | | | | | | |
| 6. My organisation assigns qualitative values to its decision-making criteria | | | | | | |
| 7. My organisation assigns quantitative values to its decision-making criteria | | | | | | |
| 8. My organisation is open to using better alternatives in its decision making | | | | | | |
| 9. My organisation encourages innovative decision making | | | | | | |
| 10. My organisation considers uncertainties in relation to its decision making | | | | | | |
| 11. My organisation provides training in the science of decision making | | | | | | |
| 12. My organisation re-examines its decision making as new information becomes available | | | | | | |
| **B. Decision-making culture** | | | | | | |
| 13. My organisation has suffered a negative outcome due to slow decision making | | | | | | |
| 14. My organisation's culture has resulted in its inability to make a decision | | | | | | |
| 15. My organisation's decision making is influenced by organisational politics | | | | | | |
| 16. My organisation's decision making results in making the same mistake as in the past | | | | | | |
| 17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | | | | | | |
| 18. My organisation underestimates problems which adversely impact its own decisions | | | | | | |
| 19. My organisation continues with projects/products which should be terminated at an earlier stage | | | | | | |
| 20. My organisation's decision making is influenced by similar organisations or competitors | | | | | | |
| 21. My organisation's decision making is influenced by incentives or penalty payments | | | | | | |
| 22. My organisation effectively communicates the decisions it makes | | | | | | |
| 23. My organisation provides clear and unambiguous instructions for decision making | | | | | | |

1 

## Part II: Individual-level influences

| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-making competence** | | | | | | |
| 24. My decision making is knowledge based | | | | | | |
| 25. My decision making is consistent | | | | | | |
| 26. I consider uncertainty and unknowns in my decision-making approach | | | | | | |
| 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | | | | | | |
| 28. I present contingencies or achievable options as part of my decision making | | | | | | |
| 29. My decision making is transparent | | | | | | |
| 30. I understand the context of the decision I am being asked to make | | | | | | |
| 31. I understand the importance of the decisions I make | | | | | | |
| 32. I use a structured approach in my decision making | | | | | | |
| 33. I assign qualitative values to its decision-making criteria | | | | | | |
| 34. I assign quantitative values to its decision-making criteria | | | | | | |
| 35. I receive training in the science of decision making | | | | | | |
| 36. I use intuition or "gut-feeling" in my decision making | | | | | | |
| 37. My professional experience is important when having to make challenging decisions | | | | | | |
| **B. Decision-making style** | | | | | | |
| 38. Emotion is part of my decision making | | | | | | |
| 39. I have experienced "paralysis by analysis" caused by my slow decision making | | | | | | |
| 40. I have experienced a negative outcome by a decision not being made | | | | | | |
| 41. In my decision making, I make the same mistakes as in the past | | | | | | |
| 42. Recent or dramatic events greatly impact my decision making | | | | | | |
| 43. My procrastination has resulted in a negative outcome | | | | | | |
| 44. My decision making could be improved by assigning relative importance to decision criteria | | | | | | |
| 45. I underestimate problems which adversely impact my decision making | | | | | | |
| 46. I continue with projects/products which should be terminated at an early stage | | | | | | |
| 47. I feel that I could make better quality decisions | | | | | | |

## Appendix 2: The Centre for Innovation in Regulatory Science R&D Briefing 61

# Building Quality into Decision-Making Processes in Medicines' Development, Regulatory Review and Health Technology Assessment


Transparency • Predictability • Consistency

**Contents**



**R&D BRIEFING 61**

CIRS Centre for Innovation in Regulatory Science

1

Transparency • Predictability • Consistency

## Background to quality decision making

*"An organisation that seeks to improve its productivity should also routinely measure the quality of its decision making"* (From Thinking Fast and Slow, Kahneman, 2011)

The various decisions made by pharmaceutical companies, regulatory authorities and health technology assessment (HTA) agencies throughout the life cycle of medicines are critical for ensuring that appropriately safe and effective medicines become available in a timely and efficient manner. Despite this, there is a paucity of research into the quality aspect of decision making in medicines' research and development.

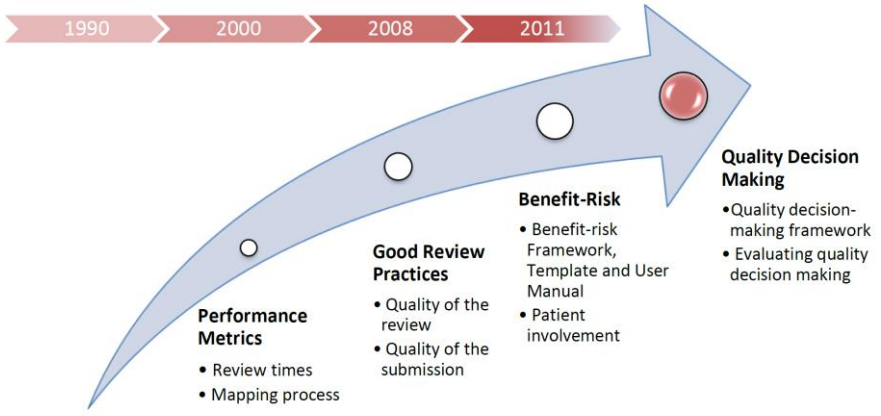
At a Centre for Innovation in Regulatory Science (CIRS) Workshop in 2004, Professor Larry Phillips, a Professor of Decision Analysis at the London School of Economics, discussed the "science of decision making" saying that ". . . In an uncertain world, it is perfectly possible to make a good decision that has poor consequences and, equally, to make a bad decision and come up with a good outcome. On balance, however, the long-running use of good systems for making decisions will generally give better outcomes."

In addition, recent CIRS Workshop participants have recommended that the quality of the decision-making processes for these functions be considered separately from the decisions themselves.

*"Delinking the regulatory review process from the process of making decisions should be explored. Although the quality of decision making is of equal importance to the quality of review process and procedure, methods for enhancing and measuring that quality have yet to be outlined."* (Recommendation from CIRS Emerging Markets Workshop December 2011)

*"Explicitly explore quality in decision making separately from the quality of submissions and reviews and develop or identify an instrument to be used to assess the robustness of deliberative processes within HTA agencies"* (Recommendation from CIRS HTA Workshop December 2013)

As a consequence, CIRS initiated a programme that aims to address the research gap in quality decision making in the area of medicines' development, review and HTA assessment. This programme represents a natural evolution of CIRS work in performance metrics, good review practices and benefit-risk assessment. The overall aim is to develop a quality decision framework and evaluate quality decision-making practices in order to identify markers that build quality into decision making throughout medicines' development, regulatory review and reimbursement.

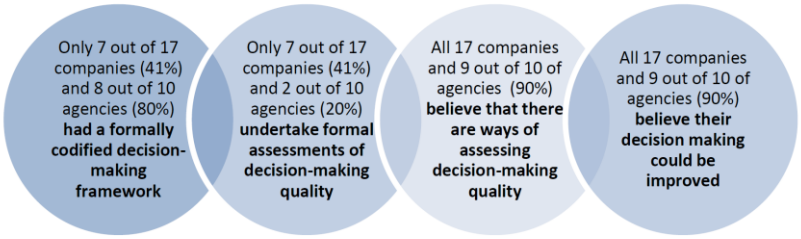


## Background to quality decision making

As part of its programme in quality decision making, *in 2015, CIRS conducted a study among 17 pharmaceutical companies and 10 regulatory agencies* to identify current decision-making practices used by companies' in their decision to submit and by agencies' in their decision to approve a new drug application. It also looked to ascertain how they measure the quality of the decision-making process and the challenges and solutions[1].

**Key results from the questionnaire indicated that:**




Moreover, the majority of company and agency participants identified instances of decision-making biases within their organisation. *Other hurdles by companies and agencies to quality decision quality decision making, as well as suggested solutions are listed below:*

| Company-identified hurdles | Agency-identified hurdles | Suggested solutions |
|---|---|---|
| •Excessive optimism<br>•Poor assessment of uncertainty or strength of evidence<br>•Internal misalignment<br>•Data availability<br>•Time pressure | •Lack of knowledge with regard to decision making<br>•Reluctance to discuss uncertainties or value judgements<br>•Ensuring consistent review or evaluation practices<br>•Data availability<br>•Resource constraints | •Establish or implement a structured decision-making framework<br>•Education on decision making<br>•Multistakeholder inclusion<br>•More formal review of qualty decision making |

The study results demonstrated that the quality of decision making is influenced by the processes and procedures within companies and agencies. Organisations believe their decision making could be improved and the first step to achieve this, which CIRS has already initiated, would be to assess current practices and evaluate the quality of decision making within regulatory and HTA agencies as well as pharmaceutical companies. In addition, CIRS will be conducting a similar questionnaire to the above, but amongst HTA agencies and pharmaceutical companies to explore quality decision making in the area of medicines' reimbursement.

[1] Bujar M, McAuslane N, Salek S, Walker S. Quality of regulatory decision-making practices: issues facing companies and agencies. *Ther Inn Reg Sci.* 2016;DOI: 10.1177/2168479016628573.

## Development of the 10 Quality Decision-Making Practices

In order to investigate and identify the important issues that influence quality decision making, semi-structured interviews were carried out with 29 key opinion leaders from regulatory agencies and pharmaceutical companies[2]. The study participants were invited to discuss and review their perception of decision making within their organisation, its role in drug development and regulatory review, their awareness and use of decision-making techniques and the impact and monitoring of decisions. The analyses resulted in the identification of a number of overarching themes in quality decision making, which are exemplified below with quotations from interviewees.

**Theme 1**

*"There is a difference between the* ***organisational decision-making process and that of the individual.*** *We have a good understanding of how a committee makes a decision, but we do not necessarily understand how individuals on that committee have made their own decision"* Regulatory agency

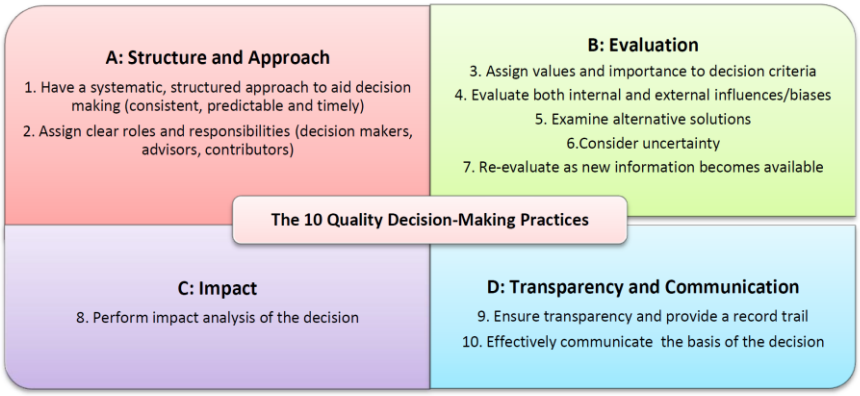
**Theme 2**

*"Transparency, the justification for decisions, and* ***understanding why a decision has been made need to be documented****, it is good practice"* Regulatory agency

**Theme 3**

*"****It is important that we are trained in decision making.*** *We also need an understanding and practical application of the tools which can assist our decision making"* Pharmaceutical company

A major outcome of this study has also been the identification of the *10 Quality Decision-Making Practices (QDMPs)* that underpin a quality process and that were considered as relevant by both pharmaceutical companies and regulatory agencies. This set of holistic practices can be mapped against the key frameworks used during medicines' development, particularly in the area of benefit-risk assessment as well as the science of decision making. The 10 QDMPs are organized into four areas, namely, 'Structure and Approach', 'Evaluation', 'Impact' and 'Transparency and Communication'




[2] Donelan R, Walker S, Salek S. Factors influencing quality decision-making: regulatory and pharmaceutical industry perspectives. *Pharmacoepidemiol Drug Saf.* 2015;24: 319-328.

## Development of the 10 Quality Decision-Making Practices

**As a result of the discussion from CIRS Workshops in June 2015 and February 2016[3], the following Guidance Notes were produced to describe the 10 QDMPs in more detail.**

**QDMP 1. Have a systematic, structured approach to aid decision making (consistent, predictable and timely)**

- *Establish the decision context, objectives and assumptions made.*
- *Employ frameworks, guidelines and tools for structuring the decision-making process.*
- *Such an approach should ensure that the process is systematic, which in turn would enable better consistency compared with similar past decisions, as well as predictability and timeliness.*

**QDMP 2. Assign clear roles and responsibilities (decision makers, advisors, information providers)**

- *The roles and responsibilities should be clearly defined in terms of individuals who provide information (including external input), compared with those who advise on the decision or make the final decision.*
- *The roles and responsibilities of each stakeholder (regulatory authorities, HTA agencies and companies) should be transparent and well communicated, which should help manage expectations.*

**QDMP 3. Assign values and relative importance to decision criteria**

- *The relevant criteria for the decision must be determined to ensure that these are in line with the decision context and overall objective. The criteria should be weighted, for example, by ranking or rating their relative importance.*

**QDMP 4. Evaluate both internal and external influences/biases**

- *Stakeholders need to be aware of personal considerations, subjective influences and biases, acknowledge them and minimise where possible. Potential biases that need to be considered[4]:*
  - *Action-oriented bias: excessive optimism, overconfidence in own judgement and gut-feeling*
  - *Interest-oriented bias: inappropriate attachments and misaligned incentives*
  - *Pattern recognition: generalising based on recent events and seeking out information that supports a favoured decision, which could lead to perpetuating previous mistakes*
  - *Stability bias: preference for status quo and tendency for inertia in the presence of uncertainty*

**QDMP 5. Examine alternative solutions**

- *Decision makers should actively explore possible options during the decision-making process.*
- *The alternatives need to be assessed, for example using a SWOT analysis, against the relevant decision criteria in order to determine the best outcome.*

**QDMP 6. Consider uncertainty**

- *The extent and limitations of available information need to be judged for each decision criterion in relation to the alternative options.*
- *Stakeholders must be explicit regarding acceptability of benefits and harms and how this affects their approach.*

**QDMP 7. Re-evaluate as new information becomes available**

- *This should be actively carried out at all stages during the lifecycle of medicines' development.*
- *This may be a safeguard against plunging in or procrastination and/or perpetuating previous mistakes as well as identifying cultural/organisational/hierarchical influences (e.g. individual vs. organisational, group successes and group failures).*

**QDMP 8. Perform impact analysis of the decision**

- *The impact of the decision needs to be considered on both internal and external stakeholders.*
- *The analysis must relate to present situation, but also to the future and should take into account elements of quality/validity of data, political/financial/competitor influences and procedures for similar decisions.*

**QDMP 9. Ensure transparency and provide a record trail**

- *It must be clear how the decision was made and details must be consistently documented in a manner that can be easily followed or audited by appropriate stakeholders.*

**QDMP 10. Effectively communicate the basis of the decision**

- *The basis of the decision needs to be appropriately communicated to the relevant stakeholders, both internally and externally.*

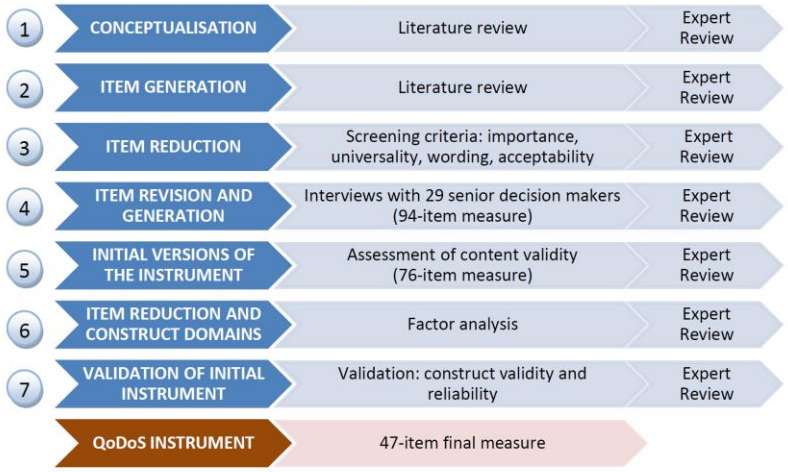
[3] The Centre for Innovation in Regulatory Science. *Publications*. Available at: http://www.cirsci.org/past-workshops-and-publications/

[4] Lovallo D, Sibony O. *The case of behavioral strategy.* McKinsey Quarterly. Available at: http://www.mckinsey.com/insights/ strategy/ the_case_for_behavioral_strategy.

## Development of the Quality of Decision-Making Orientations Scheme

**Recognising the importance of quality of decision making as well as the paucity of information and available instruments, CIRS in collaboration with Cardiff University, initiated a study to develop and validate an instrument for evaluating quality of decision making[5].** This collaboration is now being continued with the University of Hertfordshire. The instrument, named the Quality of Decision-Making Orientation Scheme (QoDoS) was developed and validated using a standardised approach and qualitative as well as quantitative techniques. A flowchart representing the stages in the development of the QoDoS is shown below.




The QoDoS items were generated from 29 face-to-face semi-structured interviews with key opinion leaders from the pharmaceutical industry (n=10), contract research organisations (n=10) and regulatory agencies (n=9). The thematic analysis yielded a 94-item initial version of the QoDoS with a five-point Likert frequency scale response option.

Content validity was established using an expert panel to confirm that the emphasis and the focus of the QoDoS is fit-for-purpose. The experts rated the language clarity, completeness, relevance and scaling of each item on a four-point scale (Strongly agree, agree, disagree and strongly disagree) and the agreement among the panel members was high with an intra-class correlation coefficient value of 0.89 (95% confidence interval = 0.056, 0.99).

Factor analysis was performed on the resulting 76-item instrument and produced a *47-item measure (QoDoS)* organised into four sections namely, organisational decision-making approaches, organisational decision-making culture, individual decision making competencies and individual decision-making style.

The 47-item QoDoS showed high internal consistency (n = 120, Cronbach's alpha = 0.89), high reproducibility (n = 20, intra-class correlation = 0.77) and a mean completion time of 10 minutes. This suggests that the QoDoS is a practical instrument possessing strong psychometric properties of validity and reliability. Moreover, the QoDoS items can be mapped according to the 10 Quality Decision Making-Practices (page 4) and consequently, the degree of incorporation of these 10 QDMPs into agency and company processes can be evaluated. The full instrument is shown on pages 7 and 8.

[5] Donelan R, Walker S, Salek S. The development and validation of a generic instrument, QoDoS, for assessing the quality of decision making. *Frontiers Pharmaceutical Medicine and Outcome Research*. 2016; 7: 180.

Transparency • Predictability • Consistency

## The QoDoS instrument for evaluating quality decision making

### The Quality of Decision-Making Orientation Scheme (QoDoS) ©

The statements in the questionnaire relate to your views on your personal and your organisation's *decision-making processes for major strategic choices within your organisation.*

Please mark clearly one box for each statement. Assume that Not at all = 0% of time; Sometimes = 25% of time; Frequently = 50% of time; Often = 75% of time; Always = 100% of time. If not sure, please tick the box that you feel is the most appropriate.

No data that will identify an individual or an organisation will be reported, or details made to a third party.

### Background questions

Gender: ☐ Male ☐ Female ☐ Other

Job title: _____

How many years of professional experience have you to date? _____

Organisation: ☐ Regulatory Agency ☐ Pharmaceutical Industry ☐ HTA ☐ Academia ☐ Other

### Part I: Organisational-level influences

| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-Making Approach** | | | | | | |
| 1. My organisation evaluates the impact of the decisions it makes | | | | | | |
| 2. My organisation's decision making is transparent | | | | | | |
| 3. My organisation's decision making is consistent | | | | | | |
| 4. My organisation uses a structured approach in its decision making | | | | | | |
| 5. My organisation's decision making is influenced by external stakeholder's demands | | | | | | |
| 6. My organisation assigns qualitative values to its decision-making criteria | | | | | | |
| 7. My organisation assigns quantitative values to its decision-making criteria | | | | | | |
| 8. My organisation is open to using better alternatives in its decision making | | | | | | |
| 9. My organisation encourages innovative decision making | | | | | | |
| 10. My organisation considers uncertainties in relation to its decision making | | | | | | |
| 11. My organisation provides training in the science of decision making | | | | | | |
| 12. My organisation re-examines its decision making as new information becomes available | | | | | | |
| **B. Decision-making culture** | | | | | | |
| 13. My organisation has suffered a negative outcome due to slow decision making | | | | | | |
| 14. My organisation's culture has resulted in its inability to make a decision | | | | | | |
| 15. My organisation's decision making is influenced by organisational politics | | | | | | |
| 16. My organisation's decision making results in making the same mistake as in the past | | | | | | |
| 17. My organisation's decision making is influenced by the vested interest of individuals (e.g. conflict of interest) | | | | | | |
| 18. My organisation underestimates problems which adversely impact its own decisions | | | | | | |
| 19. My organisation continues with projects/products which should be terminated at an earlier stage | | | | | | |
| 20. My organisation's decision making is influenced by similar organisations or competitors | | | | | | |
| 21. My organisation's decision making is influenced by incentives or penalty payments | | | | | | |
| 22. My organisation effectively communicates the decisions it makes | | | | | | |
| 23. My organisation provides clear and unambiguous instructions for decision making | | | | | | |

**The QoDoS instrument for evaluating quality decision making**

## Part II: Individual-level influences

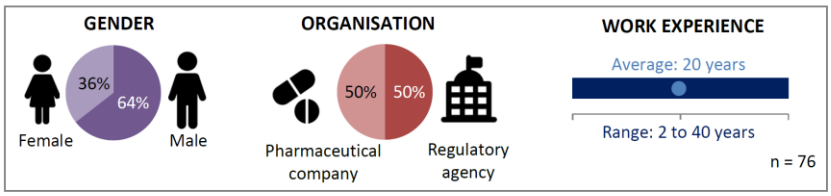
| | Not at all | Sometimes | Frequently | Often | Always | Not applicable |
|---|---|---|---|---|---|---|
| **A. Decision-making competence** | | | | | | |
| 24. My decision making is knowledge based | | | | | | |
| 25. My decision making is consistent | | | | | | |
| 26. I consider uncertainty and unknowns in my decision-making approach | | | | | | |
| 27. I generate a Strengths-Weaknesses-Opportunities-Threats (SWOT) analysis in my decision making | | | | | | |
| 28. I present contingencies or achievable options as part of my decision making | | | | | | |
| 29. My decision making is transparent | | | | | | |
| 30. I understand the context of the decision I am being asked to make | | | | | | |
| 31. I understand the importance of the decisions I make | | | | | | |
| 32. I use a structured approach in my decision making | | | | | | |
| 33. I assign qualitative values to its decision-making criteria | | | | | | |
| 34. I assign quantitative values to its decision-making criteria | | | | | | |
| 35. I receive training in the science of decision making | | | | | | |
| 36. I use intuition or "gut-feeling" in my decision making | | | | | | |
| 37. My professional experience is important when having to make challenging decisions | | | | | | |
| **B. Decision-making style** | | | | | | |
| 38. Emotion is part of my decision making | | | | | | |
| 39. I have experienced "paralysis by analysis" caused by my slow decision making | | | | | | |
| 40. I have experienced a negative outcome by a decision not being made | | | | | | |
| 41. In my decision making, I make the same mistakes as in the past | | | | | | |
| 42. Recent or dramatic events greatly impact my decision making | | | | | | |
| 43. My procrastination has resulted in a negative outcome | | | | | | |
| 44. My decision making could be improved by assigning relative importance to decision criteria | | | | | | |
| 45. I underestimate problems which adversely impact my decision making | | | | | | |
| 46. I continue with projects/products which should be terminated at an early stage | | | | | | |
| 47. I feel that I could make better quality decisions | | | | | | |

***Confidentiality***

If an organisation was to use this survey, it should be noted that all information collected from individual agencies and companies will be kept strictly confidential. No data that will identify an individual agency or company will be reported, or detail made to a third party. External reports or presentation of the data will include only anonymous figures and any appropriate analytical interpretation. Agency or company data will only be provided to the relevant organisations concerned.

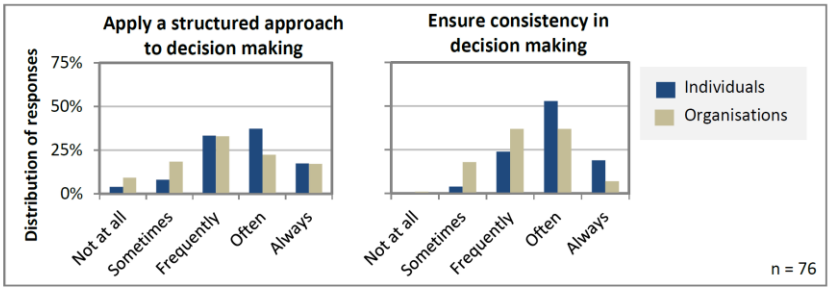
## Practical application of the QoDoS instrument

One of the objectives of the CIRS programme is to utilise the QoDoS to assess the quality of decision-making process and evaluate the level of incorporation of the 10 Quality Decision-Making Practices within companies, regulatory and HTA agencies. In order to demonstrate the practicality and applicability of the QoDoS for evaluating quality decision making, a study was initiated with 76 participants from 12 regulatory agencies and 23 international pharmaceutical companies, who were asked to complete the tool[6]. The demographics were as follows:




**Study results: Organisational and individual decision making**

The QoDoS enables an evaluation of decision making across both individuals and the perspective of individuals on the organisation as eleven of the QoDoS items are analogous for the organisational and individual parts of the instrument. The results for two common QoDoS items, 'Apply a structured approach' and 'Ensure consistency in decision making' indicate that both were incorporated more at the individual level rather than organisational level of decision making.




Although in practice the two scores should be similar as people make up an institution, individuals tend to score themselves more highly and be more critical of an organisation. While this could be a potential sign of bias, areas of disparity between the two could also indicate areas for improvement for the individuals, which should translate into better practices within the organisation.

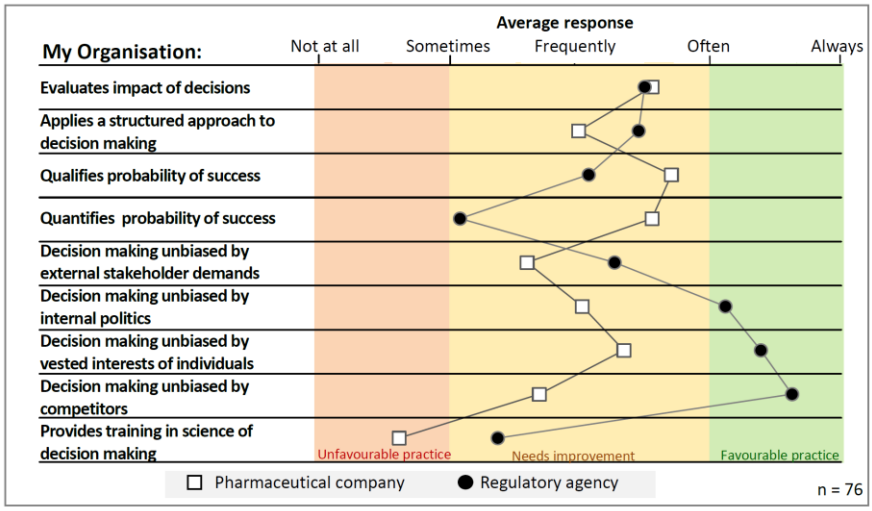
**Study results: Pharmaceutical company and regulatory agency organisational decision making**

An assessment of regulatory agency and pharmaceutical company organisational-level responses identified differences between the two stakeholders. Both considered evaluating the impact of the decisions as important, with agencies using a structured, systematic approach to decision making more frequently than companies. Conversely, there was a general tendency for biases due to politics, competitors or incentives to have more impact on company decision making compared with agencies.

[6] Bujar M, Donelan R, McAuslane N, Salek S, Walker S. Assessing quality of decision making in medicines' development and the regulatory review: Identifying biases and best practices. *Ther Inn Reg Sci*. 2016; doi:10.1177/2168479016662681

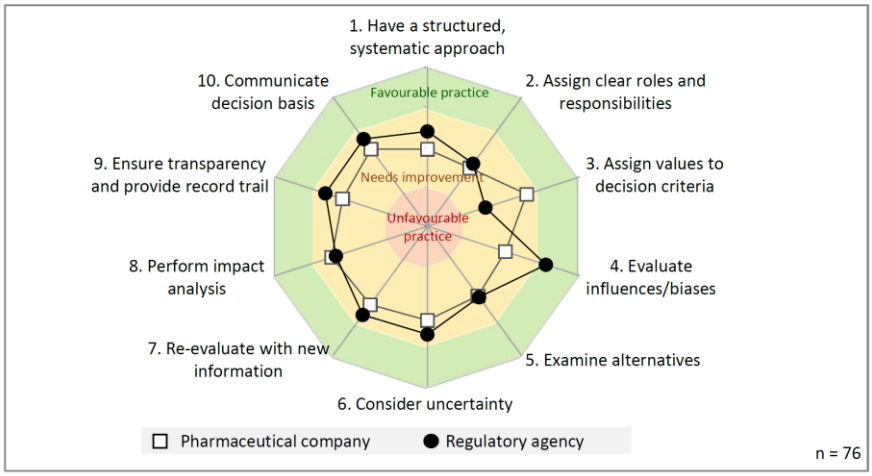
## Practical application of the QoDoS instrument

Whilst it was recognised that the science of decision making is important, training in this area was rarely provided. All responders from agencies and 92% from companies felt that they could improve the quality of their decision making. Nine selected organisational-level QoDoS items are shown below:




**Evaluating the 10 Quality Decision-Making Practices**

Finally, the organisational level agency and company responses were mapped against the 10 QDMPs, demonstrating key differences between company and agency practices and confirming the need for improvement and training in decision making for both stakeholders.



## The potential impact of evaluating decision making with the QoDoS

**The applicability of the QoDoS for evaluating decision making**

The findings of the study with pharmaceutical companies and regulatory agencies demonstrate that the QoDoS has the ability to identify differences in decision making between individuals and their organisation as well as differences between companies and agencies.

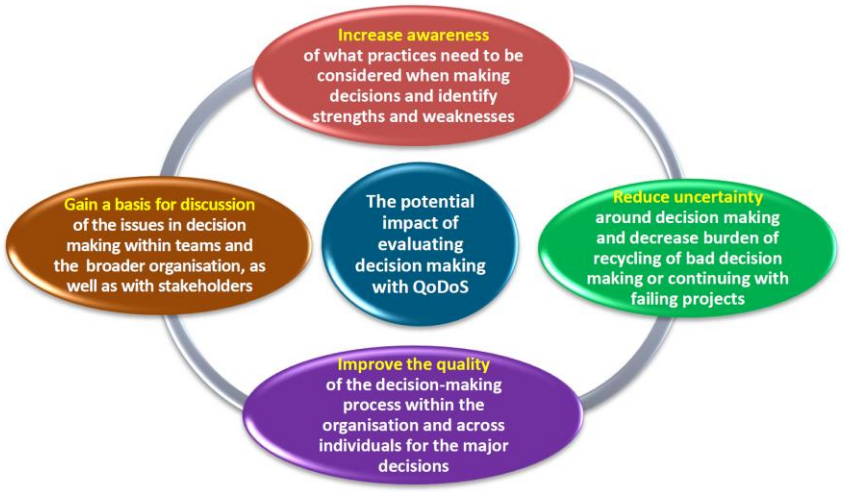
**The potential impact for evaluating quality decision making with the QoDoS in association with the 10 Quality Decision Making Practices**

**Individual knowledge:** Simply completing the instrument can increase an individual's awareness of the issues in decision making, different biases and influences that need to be considered when making decisions, as well as best practices that should be incorporated into an organisation's decision-making framework.

**Internal Monitoring:** The QoDoS can be used by organisations to internally monitor and visualise decision making within and across different teams and divisions to identify strengths and weaknesses. This should facilitate raising sensitive issues by individuals relating to decision making, help with relationship building and ultimately increase trust within the organisation. The QoDoS could also provide the ability to measure change over time in order to determine the impact of training and other improvement initiatives in order to ultimately improve effectiveness across teams, increase productivity in R&D decision making, reduce uncertainty and result in more consistent outcomes for organisations.

**External Benchmarking:** The QoDoS can be utilised to externally benchmark an organisation's decision-making practices and performance compared with other organisations. This in turn could provide a basis for discussion of the issues in the quality of the decision-making processes, thereby encouraging a level of trust and partnership and helping to identify areas for improvement and collaboration. Ultimately, the QoDoS should enable organisations to build quality, transparency and consistency into the critical decisions that are undertaken during the lifecycle of medicines.

**Routine assessments with the QoDoS may offer a number of benefits to organisations and individuals.**



## Conclusions

**In 2015, CIRS initiated a programme in Quality Decision Making with the following aims and activities:**

| ACTIVITIES | AIMS |
|---|---|
| *Surveys and other research projects*<br>*QoDoS studies*<br>*International Workshops* | • Evaluate the current decision-frameworks and understand the characteristics of different decision-making processes<br>• Assess the quality of decision-making processes and practices that need to be considered when making a decision, as well as influences and biases that may impact the process<br>• Develop the principles of a quality decision framework and identify markers and practices that build quality into decision making |

Medicines' Development → Regulatory Review → Health Technology Assessment

An enhanced understanding of how to identify and apply quality decision-making practices may facilitate decision-making approaches and subsequently will enable improved practices for both the individual and the organisation. Ultimately, this will enable improved transparency, predictability and consistency in critical decisions in medicines' development, review and health technology assessment.



**Prepared by**
Magda Bujar, Senior Research Analyst, CIRS, mbujar@cirsci.org
Neil McAuslane, Director, CIRS, nmcauslane@cirsci.org
Sam Salek, Professor, University of Hertfordshire, m.s.salek@herts.ac.uk
Stuart Walker, Professor, University of Cardiff; Founder, CIRS, swalker@cirsci.org

**About CIRS**

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics, formerly the IP & Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science.

CIRS achieves its mission of advancing regulatory and HTA policies and processes by means of the aligned activities of its Health Technology Assessment and Global Development programmes – activities that include international Workshops, Insight Seminars, research projects, publications and presentations and the identification of and advocacy for best international practices. Through these activities, CIRS regularly interacts with international pharmaceutical companies, regulatory agencies and HTA and coverage bodies to address the overlapping themes of metrics, to manage uncertainty and improve predictability; quality of process, to improve the development of development, regulatory and health technology assessment processes and ultimately the quality of decision making and alignment, promoting convergence within and across organisations and stakeholders.

Website: www.cirsci.org

***If your organisation would be interested in participating in a QoDoS study, please contact one of the authors listed above.***