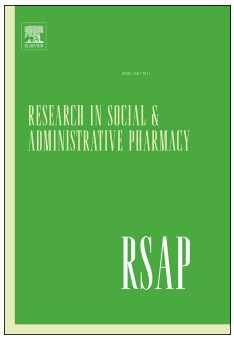

Effectiveness and cost effectiveness of pharmacist input at the ward level: A systematic review and meta-analysis

Dalia M. Dawoud, Maria Smyth, Joanna Ashe, Thomas Strong, David Wonderling, Jennifer Hill, Mihir Varia, Philip Dyer, Julian Bion

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Title:

Effectiveness and cost effectiveness of pharmacist input at the ward level: a systematic review and meta-analysis

Authors:

Dalia M Dawoud[1,2*]

[1] Lecturer, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom.

[2] Associate Professor, Clinical Pharmacy Department, Faculty of Pharmacy, Cairo University, Cairo, Egypt.

Maria Smyth[3]

[3]Senior Research Fellow, National Guideline Centre, Royal College of Physicians, London, United Kingdom

Joanna Ashe[3]

[3]Senior Information Scientist, National Guideline Centre, Royal College of Physicians, London, United Kingdom

Thomas Strong[3]

[3]Technical Adviser, National Institute for Health and Care Excellence, London, United Kingdom

David Wonderling[3]

[3]Head of Health Economics, National Guideline Centre, Royal College of Physicians, London, United Kingdom

Jennifer Hill[3]

[3]Guideline Lead, National Guideline Centre, Royal College of Physicians, London, United Kingdom

Mihir Varia[4]

[4]Community pharmacist, NHS East and North Hertfordshire Clinical Commissioning Group, Hertfordshire, United Kingdom

Philip Dyer[5]

[5]Consultant, Diabetes, Endocrinology and Acute Internal Medicine, Diabetes Centre, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

Julian Bion[6]

[6]Professor, Intensive Care Medicine, University of Birmingham; Honorary Consultant in Intensive Care medicine, Queen Elizabeth Hospital, Birmingham, United Kingdom

*__Corresponding author__:
Dr Dalia Dawoud
Address:

School of Life and Medical Sciences
University of Hertfordshire
Health Research Building, Room 2F412
College Lane, Hatfield, AL10 9AB
United Kingdom

Tel: +44 (0) 1707 285155
Mobile: +44 (0) 7747610292
Email: ddawoud@hotmail.com
ORCID ID: orcid.org/0000-0002-2105-1937

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DD, MC, JA, TS, DW, JH, MV and JB have no interests to declare. PD reports support from Welsh Acute Physician Society Meeting 21st June 2018 https://acutemedwales.org.uk/ during manuscript writing-up.

ABSTRACT

Background

Pharmacists play important role in ensuring timely care delivery at the ward level. The optimal level of pharmacist input, however, is not clearly defined.

Objective

To systematically review the evidence that assessed the outcomes of ward pharmacist input for people admitted with acute or emergent illness.

Methods

The protocol and search strategies were developed with input from clinicians. Medline, EMBASE, Centre for Reviews and Dissemination, The Cochrane Library, NHS Economic Evaluations, Health Technology Assessment and Health Economic Evaluations databases were searched.

Inclusion criteria specified the population as adults and young people (age >16 years) who are admitted to hospital with suspected or confirmed acute or emergent illness. Only randomised controlled trials (RCTs) published in English were eligible for inclusion in the effectiveness review. Economic studies were limited to full economic evaluations and comparative cost analysis. Included studies were quality-assessed. Data were extracted, summarised. and meta-analysed, where appropriate.

Results

Eighteen RCTs and 7 economic studies were included. The RCTs were from USA (n=3), Sweden (n=2), Belgium (n=2), China (n=2), Australia (n=2), Denmark (n=2), Northern Ireland, Norway, Canada, UK and Netherlands. The economic studies were from UK (n=2), Sweden (n=2), Belgium and Netherlands. The results showed that regular pharmacist input was most cost effective. It reduced length-of-stay (mean= -1.74 days [95% CI: -2.76, -0.72], and increased patient and/or carer satisfaction (Relative Risk (RR) =1.49 [1.09, 2.03] at discharge). At £20,000 per quality-adjusted life-year (QALY)-gained cost-effectiveness threshold, it was either cost-saving or cost-effective (Incremental Cost Effectiveness Ratio (ICER) =£632/ QALY-gained). No evidence was found for 7-day pharmacist presence.

Conclusions

Pharmacist inclusion in the ward multidisciplinary team improves patient safety and satisfaction and is cost-effective when regularly provided throughout the ward stay. Research is needed to determine whether the provision of 7-day service is cost-effective.

KEY WORDS

Clinical pharmacy, Systematic review, Meta-analysis, Cost effectiveness, acute medicine

INTRODUCTION

Adverse drug events (ADEs) are common in clinical settings, with a reported incidence from 2.3% in paediatric inpatients to 27.4% in adult outpatients.[1 2] In adult inpatients, the reported incidence is 6.5%.[3] These ADEs are direct causes of patient harm, dissatisfaction, prolonged hospital stay and increased costs. Pharmacists are considered the medication experts in the health care team. Their extensive training in and knowledge of pharmacology and therapeutics have placed them in the best position to undertake this role and to advise other health care professionals on matters relating to appropriate prescribing and safe use of medicines.[4]

The pharmacist role in the hospital setting has evolved over the years, moving from a wholly dispensary-based role to a more clinically-focused one based on the ward.[5] In fact, the presence of a ward-based pharmacist has become common practice in the UK.[6] More recently, pharmacists have been granted the authority to prescribe medications in a number of countries including the UK and Canada.[7] This has allowed clinical pharmacists who practise in hospitals to be more directly involved in patient care.

In the UK, medical wards have access to some level of pharmacist input; however, the pharmacist may be responsible for covering several areas concurrently, limiting the level of detail they can bring to medicines management and patient and staff communication.[6] This is particularly important for an ageing population with multiple co-morbidities for whom polypharmacy adds complexity and may indeed be the cause of the acute admission.[8] Additionally, it has been argued that the input of a ward-based pharmacist, particularly at discharge, can improve patient flow by expediting the discharge process and alleviating the pressure that the “exit block”, created by delayed discharge, can have on emergency department performance and the emergency access target achievement.[9]

In 2014, the National Institute for Health and Care Excellence (NICE) was commissioned to develop a guideline to advise the National Health Service (NHS) in England on various aspects of the delivery of emergency and acute medical care services.[10] One of the aspects identified as a priority to be examined in the guideline was the role of ward-based pharmacists with the aim of assessing the impact of their interventions on improving patient and process outcomes in the acute and emergency medical care pathway within NHS hospitals.

Hence, this systematic review was undertaken as part of the guideline development process to assess the outcomes of ward-based pharmacists’ interventions for patients admitted to hospital with a suspected or confirmed acute medical emergency.

METHODS

A systematic literature review was undertaken to synthesise the evidence that assessed the effectiveness and cost-effectiveness of the presence of ward-based pharmacists for patients with a suspected or confirmed acute medical emergency. It was undertaken in accordance with the standard methods for reviewing the clinical and economic evidence specified in the NICE guidelines development manual.[11] No ethics approval was required for this work.

Protocol development

The protocol for reviewing the effectiveness evidence was developed and approved by the guideline development group (GDG), a team of experts consisting of 19 health care professionals including acute care clinicians and a pharmacist in addition to two lay members and a technical team. The protocol specified the inclusion and exclusion criteria (including the population, interventions and comparators, outcomes and study design). These are briefly outlined below (Box 1).

The protocol for reviewing the economic evidence was aligned with this in terms of the population, interventions and comparators. Full economic evaluations (studies comparing costs and health consequences of alternative courses of action which include cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Exclusion criteria for the economic review included the following:

1- Economic studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects.
2- Studies published before 2005, because health services change rapidly and therefore the costs and benefits of treatments soon become out of date.
3- Studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the guideline context and the study limitations (see Quality Assessment below).

The clinical and economic review protocols are presented in Appendix 1 in the Supplementary Material.

Box 1: Population, Intervention, Comparator, Outcomes (PICO) and inclusion/exclusion criteria of the clinical review

Population

The population of interest was defined as adults and young people (16 years and over) admitted to hospital with a suspected or confirmed acute medical emergency (AME).

Interventions and comparators

The intervention was defined as "presence of medical ward-based pharmacists" and the comparator as "No ward-based pharmacists". The intervention was further stratified as either for less than 7 days a week or for 7 days a week.

Outcomes

-Mortality during the study period,
-Avoidable adverse events during the study period,
-Quality of life during the study period,
-Patient and/or carer satisfaction during the study period,
-Length of stay in hospital during the study period,
-Readmissions within 30 days, future admissions to hospital (over 30 days),
-Discharges during the study period,
-Prescribing errors during the study period,
-Missed medications during the study period,
-Medicines reconciliation during the study period,
-Staff satisfaction during the study period.

Inclusion and exclusion criteria

The key population inclusion criterion was:

- Adults (18 years and over) and young people (16-17 years) who seek, or are referred for, emergency NHS care for a suspected or confirmed acute medical emergency.

The key population exclusion criteria were:

- Children
- People with acute obstetric emergencies
- People with acute metal health emergencies, once a diagnosis has been made
- People with acute surgical emergencies, once a diagnosis has been made
- People who have experienced major trauma, complex or non-complex fractures or spinal injury
- People in hospital who are not there for an acute medical emergency (i.e. elective admissions) and do not develop an acute medical emergency during their stay
- People already in hospital with acute deterioration
- People with chronic conditions who are being managed as outpatients but who require an elective admission for treatment form specialists who may be involved in the acute pathway.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

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Information sources and search strategies

Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Searches were restricted to papers published in English and were conducted in Medline, EMBASE, Centre for Reviews and Dissemination (CRD) and The Cochrane Library.

The economic evidence was identified by conducting a search in Medline and EMBASE, using economic filters. Searches were also conducted in the economics-specific databases NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment database (HTA); which were searched via CRD.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking the GDG members to highlight any additional studies. Searches were quality assured by a second information scientist before being run and were updated in December 2016. All search strategies are listed in Appendix 2 of the Supplementary Material.

Study selection

The titles and abstracts of records retrieved were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria (see the review protocols in Appendix 1 of the supplementary materials). For the effectiveness evidence, parallel randomised controlled trials (RCTs) were included. A sample of 10% of the abstract lists was double-sifted by a second reviewer and any discrepancies were rectified.

Data extraction and synthesis

Data were extracted from the included studies into standard evidence tables. Meta-analyses of the efficacy data were conducted using Cochrane Review Manager (RevMan5)[2] software to combine the data given in all studies for each of the outcomes of interest. Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk (RR)) for the binary outcomes, which included: mortality, admission, readmission and adverse events. The absolute risk difference was calculated using GRADEpro software, [12] using the median event rate in the control arm of the pooled results. For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated.

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included: quality of life, length of stay in hospital (LOS), patient and/or carer satisfaction.

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out as per the protocols.

NICE economic evidence profile tables were used to summarise cost and cost-effectiveness estimates from the included studies. These show the incremental costs, incremental effects (for example, quality-adjusted life-years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base-case analysis in the study, as well as information about the assessment of uncertainty in the analysis. When a non-UK study was included, the results were converted into pounds sterling using the appropriate purchasing power parity.[13] Cost effectiveness was assessed based on a cost-effectiveness threshold of £20,000 per QALY gained; in line with the NICE reference case; where ICERs less than the specified threshold indicate cost effectiveness.[11]

Quality assessment

The evidence for outcomes from the included RCTs were evaluated using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) was used to assess the quality of the evidence for each outcome, taking into account individual study quality and the meta-analysis results.[12] Each outcome was first examined for each of the quality elements (see Supplementary material, Appendix 3, Table 3.1 for details). Publication bias was only taken into consideration in the quality assessment if it was apparent.

The methodological quality of the economic evidence and its applicability to the UK context were assessed using the economic evaluation checklist from the NICE guidelines manual, and included in the economic evidence profile (see Appendix 3 in the Supplementary Material for the possible ratings for each dimension and their criteria).[11]

Patient involvement

Two lay members were part of the guideline development group and contributed to the development of the review protocol. The choice of the outcome measures was informed by their views of which outcomes were critical from a patient perspective. The analysis methods and results were regularly presented to and validated by all the group members including the two lay members.

RESULTS

The search for RCTs retrieved 3196 records. Of these, 20 papers reporting on 18 RCTs were included in the review. [14-33] A list of the excluded studies with reasons for exclusion are presented in Appendix 4 in the Supplementary Material. The economic search retrieved 918 records, of which 7 papers reporting on 7 studies were included.[17 21 34-38] The PRISMA flow diagrams of both searches are presented in Appendix 5, Figure 5.1 and Figure 5.2**.**

The studies were split into 3 strata: regular ward-based pharmacist input (where the ward-based pharmacist provided interventions throughout the patient stay on the ward, which included both admission and discharge services), pharmacist input at admission, and pharmacist input at discharge. The interventions and comparators were often not well defined and there was variation across the studies in their composition.

The characteristics of the included RCTs and economic studies are summarised in Tables 1 and 2**,** respectively**.**

Table 1: Characteristics of the included studies- clinical evidence

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
1.Regular ward-based pharmacist input						
Claus 2014[17]	Belgium	Surgical ICU admissions (n=69) within a university hospital. **Inclusion** - over 16 years of age, length of stay greater than 48 hours. **Exclusion** - none stated.	RCT	Pharmacist present on the ward. Duties included making active recommendations and performing patient follow-up.	Pharmacist is present on the ward but recommendations were not passed on to the primary care giver.	In-hospital mortality.
Iowa Continuity of Care Study trial: Farris 2014 (Farley 2014)[19 20]	USA	General medicine, family medicine, cardiology or orthopaedic admissions (n=631) within an academic tertiary care hospital. **Inclusion** - patients with certain disease classifications: hypertension, hyperlipidaemia, heart failure, coronary artery disease, myocardial infarction, stroke, transient ischemic attack, asthma, chronic obstructive pulmonary disease or receiving oral anticoagulation.	RCT	Pharmacy case manager. Duties included medication reconciliation, ward visits and discharge service.	Nurse based medication reconciliation and discharge service.	Preventable adverse drug events in-hospital; post-discharge (90 days) hospital Readmission at 30 days; Admission at 90 days Medication appropriateness index (MAI) at discharge; 30 days; 90 days.
Gillespie 2009[21]	Sweden	Patients (n=400) admitted to the 2 acute internal study wards at a University teaching hospital.	RCT	Pharmacist present on the ward. Duties included taking part in the rounding team,	No pharmacist involvement in the healthcare team at	Overall survival at 12 months, reported as hazard ratio.

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		Inclusion - 80 years of age. **Exclusion** - previously been admitted to the study wards during the study period or had scheduled admissions.		documenting medication history, and discharge counselling.	the ward level.	Admission at 12 months
Kucukarslan 2003 [23]	USA	All patients (n=165) admitted to 1 of the 2 internal medicine study wards within a tertiary care hospital. **Inclusion** - admitted to the internal medicine service and remained in the same patient care unit until discharge. **Exclusion** – none given.	Quasi-RCT	Pharmacist present on the ward. Duties included taking part in the rounding team, documenting medication history, and discharge counselling.	Standard care from 1 pharmacist (implication in paper that this is not ward-based).	Avoidable adverse drug events until discharge. Length of stay in-hospital (reported as mean difference). Re-admission (unclear follow-up time, reported as percentage reduction).
Shen 2011 [29]	China	n=354 inpatients in 2 respiratory wards diagnosed with respiratory tract infections. **Exclusion**: transferred from other medical departments; transferred to other medical departments for further treatment; already received antibiotics before admission; did	RCT	Clinical pharmacist part of the treating team – communicated any potentially inappropriate antibiotic use (indication, choice, dosage, dosing schedule, duration, conversion) with the	Standard treatment strategies performed by the physicians and nurses without pharmacist involvement.	Length of stay.

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		not receive antibiotics during hospitalisation.		physician to discuss and make recommendations.		
Scullin 2007[28]	Northern Ireland	Admitted patients (n=762) to the 4 medical study wards within 3 general hospitals. **Inclusion**: taking at least 4 regular medication, were taking a high risk drug(s), were taking antidepressants and were 65 years old or older, had a hospital admission within the last 6 months, prescribed antibiotics on day 1 of admission. **Exclusion** - scheduled admissions and patients admitted from private nursing homes.	RCT	Pharmacist present on the ward. Duties included admission services, in-patient monitoring, and discharge services	Traditional clinical pharmacy services (no further details given).	Admission at 12 months. Mortality at 12 months. Length of stay.
Spinewine 2007[30]	Belgium	All eligible patients (n=186) admitted to the Geriatric Evaluation and Management (GEM) unit within a university teaching hospital. GEM unit accepted patients over 70 years of age.	RCT	Pharmacist present on the ward. Duties included taking part in the rounding team, documenting medication history, and discharge counselling.	Usual care (no details of any clinical pharmacist involvement).	Rate of death at 1 year follow-up. Satisfaction with information received. Admission at 12 months. Medical appropriateness index.
Zhao 2015 &	China	n=90 patients admitted to the	RCT	Interventions by	Conventional	Avoidable adverse

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
Zhao 2015B[32][33]		cardiology ward in a hospital. **Inclusion**: diagnosis of CHD by physician, accepted ≥4 kinds of drugs, ≥18 years, primary high school education, able to complete the study, available for telephone follow up. **Exclusion**: pregnant/lactating women, patients enrolled in other studies, severe co-morbidities, family history of psychosis, and barriers to communication.		clinical pharmacists including individual drug regimens, attending daily medical rounds, advice to physicians, education of medical staff, patient education on lifestyle changes, psychological interventions such as stress reduction, medication counselling at discharge, monthly follow up telephone calls post-discharge.	medical treatment without pharmacist participation.	events (adverse drug reactions). Patient and/or carer satisfaction.
2. Ward-based pharmacist input at admission						
Aag 2014[14]	Norway	Consecutively admitted patients (n=201) to the Cardiology study ward at a University hospital. **Inclusion** - aged 18 and over. **Exclusion** - terminal illness, isolated due to an infectious disease, unable to communicate in either Norwegian or English.	RCT	Pharmacist medication reconciliation.	Nurse medication reconciliation.	Medication discrepancies identified at admission. Prescribing physician agreement to act upon medication discrepancies identified

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
Khalil 2016 [22]	Australia	n=110 adult medical patients admitted to the acute assessment and admission (AAA) unit via the ED during pharmacy operating hours (8.30am – 5pm). **Exclusion**: not admitted to the AAA ward within 24 hours; no medications prior to admission; not a general medical patient.	RCT	Pharmacist-initiated medication reconciliation – pharmacist obtained a 'best possible medication history' from the patient and/or other sources, undertook admission medication reconciliation, reviewed current medications and the need for new medications in relation to the admission diagnosis, developed a medication management plan with the referring senior medical officer and charted on the electronic medication administration record	Usual care – medication orders charted by medical staff.	Prescribing errors.
Lind 2016 [24]	Denmark	n=448 patients arriving at the acute admission unit on weekdays 9am-4.15pm.	RCT	Clinical pharmacist intervention - obtaining medication history (using a	Standard care – on arrival, patients triaged by a nurse, then seen by a	Length of stay on the acute admission unit (defined as interval in minutes between

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		Inclusion: ≥18 years, taking ≥4 drugs daily (including over-the-counter, herbals and supplements). **Exclusion**: terminal or intoxicated; assigned to triage level 1; referred to acute outpatient clinic; unable to give informed consent; interviewed by physician prior to giving informed consent; unexpected overnight stay.		minimum of 2 sources, 1 of which was an interview with the patient and/or relatives where possible), entering prescriptions into the electronic medication module (EMM), medication reconciliation, reviewing overall medication treatment and writing a note in the electronic medical record.	physician who was responsible for obtaining medication history, reconciling and assessing medication treatment and entering prescriptions in the EMM.	arrival and discharge or transfer to a hospital ward).
Lisby 2010[25]	Denmark	Consecutively admitted patients (n=100) to acute internal medicine study ward within 1 regional hospital. **Inclusion** - patients were 70 years or older.	RCT	Pharmacist admission review.	Senior physician admission review.	Self-experienced quality of health at 3 months. Length of stay in hospital. Admission rate at 3 months. Mortality.
Nester 2002[26]	USA	Consecutively admitted patients (n=100) to a tertiary care	Quasi-RCT	Pharmacist medication reconciliation.	Nurse medication reconciliation.	Medication discrepancies

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		referral centre. **Inclusion** - over 18, responsive and able to speak English. **Exclusion** - intensive care, ambulatory surgical and labour-and-delivery units.				identified at admission.
Tong 2016[31]	Australia	n=881 patients admitted to the general medical unit (GMU) and emergency short stay unit (ESSU) during pharmacist working hours (7am-9pm). **Exclusion**: medication chart written by a doctor before pharmacist review; admitted to ESSU and not reviewed by a pharmacist.	RCT	Early medication review and charting on admission involving a partnership between a pharmacist and a medical officer – pharmacist took medical history, VTE risk assessment and discussed medical and medication problems with admitting medical officer to agree a medication management plan.	Standard medication charting by medical officers of relevant teams, with subsequent medication reconciliation performed by pharmacist within 24 hours of admission.	Prescribing errors.
3. Ward-based pharmacist input at discharge						
Al-Rashed 2002 [15]	UK	n=83 patients admitted to 2 care of the elderly wards.	RCT	Pre-discharge counselling (24 hours before discharge) by	Normal hospital discharge policy – all patients, their GPs,	Readmission.

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		Inclusion: >65 years, prescribed 4 or more regular items, were to be discharged to their own home and had an abbreviated mental score >7/10, English as a first language, and routine clinical pharmacist assessment that they could have problems with their medicines after discharge.		the clinical pharmacist attached to that ward.	district nurses and carers received a copy of the patient's medication and information discharge summary sheet (MIDS) and patients received a medicine reminder card. Nurse went through (MIDS) with patients.	
Bladh 2011[16]	Sweden	Patients (n=345) admitted on weekdays to the 2 internal medicine study wards at a university hospital. **Inclusion** - capable of assessing their HRQL and giving written informed consent. **Exclusion** - poor Swedish language, planned discharge before intervention can be performed, transferred during their stay to other hospitals or wards not belonging to the Department of Medicine.	RCT	Pharmacist discharge review	Usual care, which was received from the same group of physicians and nurses. No other details given.	EQ-5D summarised index at 6 months follow-up.
Eggink 2010[18]	Netherlands	Patients (n=89) to be discharged (no criteria given) in the	RCT	Pharmacist discharge	Nurse discharge	Prescription errors identified during first

Study	Country	Population	Study design	Intervention	Comparator	Outcomes
		Cardiology study ward within a teaching hospital. **Inclusion** - patients have prescribed 5 or more medicines (from any class) at discharge. **Exclusion** - none stated.		review.	review.	outpatient follow-up.
Nickerson 2005 [27]	Canada	n=253 patients admitted to 2 family practice units. **Inclusion**: not discharged to another hospital, prescribed at least 1 medication at discharge, provided consent, agreement from community pharmacy, no previous study enrolment. **Exclusion**: unable to answer study questions, unavailable for follow-up.	RCT	Seamless care pharmacist at discharge including medication reconciliation, review of drug regime as part of comprehensive pharmaceutical care work-up, identification of problems and communication to community pharmacy, hospital staff and family physician, medication discharge counselling and a medication compliance chart	Standard care at discharge - discharge counselling and manual transcription of discharge notes from medical chart by nurse.	Prescriber errors-unresolved drug therapy inconsistencies and omissions.

Abbreviations: CHD: chronic heart disease; EQ-5D: EuroQol 5 Dimensions questionnaire; GP: general practitioner; RCT: randomised controlled trial,

1 **Table 2: Characteristics of the included studies- economic evidence**

Study	Country	Population	Study design	Follow-up/time horizon	Intervention 1	Intervention 2
1. Regular ward-based pharmacist input						
Claus 2014.[17]	Belgium	Critically ill patients (>16 years of age and with minimum length of ICU stay of 2 days) and in a 22-bed, surgical ICU at Ghent University Hospital, Belgium.	Within RCT analysis of individual patient level data Cost-effectiveness analysis	Length of ICU stay	No clinical pharmacist direct involvement in patient care	A clinical pharmacist is directly involved in patient care
Ghatnekar 2013 [35]	Sweden	Elderly hospital inpatients at Skane University Hospital in Lund, Sweden	Decision tree model Cost-utility analysis	3 months	Standard care (not defined)	Multidisciplinary team including clinical pharmacist undertakes systematic medication review and reconciliation from admission to discharge (the Lund Integrated Medicines Management [LIMM])
Gillespie 2009[21]	Sweden	Elderly inpatients (80 years or older) admitted to 2 acute internal medicine wards at a University Hospital of Uppsala,	Within-RCT analysis Cost-effectiveness analysis	12 months	No pharmacist involvement in the healthcare team at the ward level.	Pharmacist present on the ward.

Study	Country	Population	Study design	Follow-up/time horizon	Intervention 1	Intervention 2
		Sweden.				
Karnon 2008 [36]	UK	inpatients at 400 beds acute hospital (average hospital size) with around 14 wards	Decision tree model Cost-utility analysis	5 years	No ward-based pharmacist (a pharmacist covers 2 wards of about 30 patients over a morning to provide basic level of pharmaceutical care and in the afternoons they have departmental commitments)	Ward-based senior pharmacist (grade 7/8a) attends rounds with residents, nurses, attending staff each morning; is present in the ward for consultation and assistance to nursing staff during the rest of the morning and is available on call as necessary during the rest of the day.
Klopotowska 2010[37]	Netherlands	Patients in an adult surgical and medical 28-bed ICU of an academic medical centre	Before and after comparative interventional study Cost-consequences analysis	Length of ICU stay.	Standard pharmacy services provided by the hospital pharmacy department.	Two experienced hospital pharmacists present on the ICU daily and attending multidisciplinary patient review meeting.
2. Ward-based pharmacist input at admission						
Fertleman 2005[34]	UK	Medical patients admitted within the preceding 24 hours to a general medical ward	Before-and-after observational study Comparative cost	3 days	Ward-based pharmacist provide pharmaceutical care for 1-2 hours at some	Senior pharmacist present on post-admission (post-take) ward rounds (PTWR)

Study	Country	Population	Study design	Follow-up/time horizon	Intervention 1	Intervention 2
		at a district general hospital (Northwick Park hospital in north-west London)	analysis		time during the day (usual care)	in addition to the usual care
3. Ward-based pharmacist input at discharge						
Wallerstedt 2012[38]	Sweden	Elderly inpatients on 2 internal medicine wards at Sahlgrenska University Hospital, Sweden.	Within-RCT analysis (linked trial: Bladh 2011) Cost-utility analysis	6 months	Usual care, which was received from the same group of physicians and nurses.	Clinical pharmacists delivering a composite intervention consisting of medication review including feedback to physicians on prescribing, drug treatment discussion with the patient at discharge, medication report including summary of drug treatment changes to be sent to the GP

Abbreviations: GP: general practitioner; ICU: intensive care unit; RCT: randomised controlled trial

Regular ward-based pharmacist input

Eight RCTs (n= 2,303) evaluated the outcomes of the presence of a ward-based pharmacist providing regular input.[17 19-21 23 28-30 32 33] In these studies, the pharmacist in the intervention arm was involved in all stages of the patient journey from admissions to monitoring, follow-up and discharge. The evidence suggested reduced mortality (RR= 0.92 (95% CI: 0.72 to 1.16), 3 studies, very low quality), reduced preventable ADEs in hospital (RR= 0.74 (95% CI: 0.06 to 8.57), 2 studies, very low quality) and at 90 days follow up (RR= 0.77 (95% CI: 0.29 to 2.05), 1 study, very low quality), reduced LOS (-1.74 days (95% CI: -2.76 to -0.72), 2 studies, moderate quality), reduced prescribing errors at discharge (- 0.02 (95% CI: -0.12 to 1.08), 2 studies, low quality) and increased patient and/or carer satisfaction at discharge (RR= 1.49 (95% CI: 1.09 to 2.03) and at one month follow-up (RR= 1.79 (95% CI: 1.38 to 2.32), 1 study, low quality). It also reduced hospital admission (RR= 0.93 (95% CI: 0.83 to 1.04), 4 studies, moderate quality) and readmission (RR= 0.92 (95% CI: 0.62 to 1.37), 1 study, very low quality). However, there were increased prescribing errors (measured by medication appropriateness index) at 30 days (2.1 higher (95% CI: 0.45 to 3.75 higher), 1 study, moderate quality) and adverse drug events at 3 to 6 months post discharge (RR= 1.47 (0.26 to 8.33), 1 study, very low quality). The results are summarised in the clinical evidence profile in Table 5.3 and the Forest plots presented in Appendices 5 and 6 of the Supplementary Materials, respectively.

Five economic evaluations were included in this stratum.[17 21 35-37] These were conducted in Belgium (n=3), Netherland (n=1) and the UK (n=1). Three studies reported that the ward-based pharmacist input was dominant (more effective and less costly) compared to usual care. One cost-utility analysis (CUA) showed that the ward-based pharmacist intervention was cost-effective with an ICER of £632 per QALY-gained. One study showed that regular ward-based pharmacist input was less effective and less costly, with no clear conclusion regarding cost effectiveness given the absence of a cost-effectiveness threshold for the reported outcomes. All five studies were assessed as partially applicable with potentially serious limitations. The results are summarised in Table 5.4, Appendix 5 and the quality assessment rationale in Appendix 7 in the Supplementary Material.

Ward-based pharmacist input at admission

Six RCTs (n=401) evaluated the role of pharmacists at admission for improving outcomes.[14 22 24-26 31] The pharmacists in the intervention arms in these studies were mainly involved at the admission stage of the patient journey, for example participating in post-take ward rounds, medicines reconciliation and taking medication history. The evidence suggested that pharmacist input at admission may provide benefit in improving

identification of medication discrepancies during medicines' reconciliation at admission (+0.36 (95% CI: 0.07 to 0.65), 2 studies, low quality), reducing medication errors within 24 hours of admission (RR= 0.05 (95% CI: 0.03 to 0.08), 1 study, moderate quality) and increasing physician agreement to act upon medication discrepancies identified (RR= 1.35 (95% CI: 1.13 to 1.63), 1 study, very low quality). However, there was no difference for quality of life (EQ-5D visual analogue scale (VAS): + 6.2 (95% CI: -5.7 to 18.1 higher), 1 study, low quality), LOS (+1.3 hours (-108.96 to 111.56), 1 study, moderate quality), or number of future hospital admissions (- 0.1 admissions per patient (95% CI: -0.38 to 0.18), 1 study, low quality) and a possible increase in mortality at 3 months (RR= 1.57 (95% CI: 0.55 to 4.46), 1 study, very low quality). The results are summarised in the clinical evidence profile in Table 5.3 in Appendix 5 and the Forest plots presented in Appendix 6 of the Supplementary Materials.

One comparative cost analysis (CCA) conducted in the UK showed that pharmacist input at admission was cost saving compared to usual care (mean saving of £142 per patient).[34] The analysis was assessed as partially applicable with potentially serious limitations. The results are summarised in Table 5.4, Appendix 5 and the quality assessment rationale in Appendix 7 in the Supplementary Material.

Ward-based pharmacist input at discharge

Four RCTs (n=770) evaluated provision of ward-based pharmacists' input at discharge.[15 16 18 27] The pharmacists in the intervention arm in these studies were involved only at the discharge stage, for example preparing patients' medications and providing counselling before discharge. The evidence suggested a benefit in terms of reduced prescription errors (RR 0.57 (95% CI: 0.37 to 0.88), 1 study, low quality), reduced readmissions up to 22 days post discharge (RR 0.36 (95% CI: 0.14 to 0.91), 1 study, very low quality) and drug therapy inconsistencies and omissions at discharge (RR 0.06 (95% CI: 0.01 to 0.44), 1 study, moderate quality). There was no evidence of effect on quality of life (EQ-5D VAS: 2.8 (95% CI: -1.83 to 7.43), EQ-5D index: 0.05 higher (95% CI: -0.05 to 0.15), 1 study, very low to low quality). The results are summarised in the clinical evidence profile in Appendix 5, Table 5.3, and the Forest plots presented in Appendix 6 of the Supplementary Materials.

One CUA, conducted in Sweden, showed that the ward-based pharmacist input at discharge was not cost effective, with an ICER of £327,378 per adjusted QALY gained.[38] The analysis was assessed as partially applicable with minor limitations. The results are summarised in Appendix 5, Table 5.4 and the quality assessment rationale in Appendix 7 of the Supplementary Materials.

DISCUSSION

Medication prescribing is the most common healthcare intervention for a patient, and is normally the main course of treatment for the vast majority. The hospital pharmacist is central to ensuring the quality and safety of this process. Pharmacist input can be crucial at all stages of the patient journey with different interventions at each stage. Hence, we stratified the evidence by whether the pharmacist input occurred throughout the patient stay or was only at admission or discharge. The reviewed evidence for all three strata demonstrated some benefits for ward-based hospital pharmacist input, although there was variation in the intensity of the interventions and composition of the comparators. The evidence was of very low to moderate quality due to risk of bias, imprecision and inconsistency for regular ward-based pharmacist input and ward-based pharmacist input at discharge. The evidence reviewed for ward-based pharmacist input at admission was of very low to moderate quality due to risk of bias, imprecision and outcome indirectness as the outcome 'agreement with prescriber' was used as a surrogate outcome for staff satisfaction and was considered an indirect outcome.

The health economic evidence was assessed to be partially applicable (with only 2 studies from the UK and 3 reporting QALYs, which is the outcome measure preferred by NICE). However, it is acknowledged that quality of life is an outcome that may not be sensitive to pharmacist interventions. Hence, studies reporting other outcomes were also considered by the committee when making the recommendations.

The evidence was also considered to have potentially serious limitations with none of the studies being based on a review of the evidence base and the cost components included being variable. No clinical or economic evidence was found relating to 7-day provision of ward-based pharmacist input.

Studies assessing the clinical and economic outcomes of the ward-based, clinical pharmacist role have been accumulating over the years. These studies have generally focused on the effect of pharmacist interventions on medication errors, medicines reconciliation and savings achieved from reduced medication waste and more appropriate prescribing. A number of reviews have assessed this evidence in an attempt to draw conclusions regarding impact on patient outcomes.[39 40] In line with our findings, these reviews have generally shown positive outcomes including reduced prescribing errors, reduced LOS, reduced admission, and improved patient satisfaction and physician agreement to act upon medication discrepancies identified. However, overall, the evidence was relatively weak. The evidence was based mainly on studies with small sample sizes, which contributed to the high risk of bias in the study outcomes and imprecision around the effect estimates.

The mechanism by which pharmacists might improve patient outcomes would most likely be through minimising prescribing errors, by ensuring appropriate prescribing and also by deprescribing/discontinuation of drugs. Pharmacist education and input is also likely to improve patient and/or carer satisfaction.[41] Evidence was found for these outcomes, though not in all strata and with some inconsistencies. For example, some evidence showed increased prescribing errors at 30 days post discharge, measured by research (rather than intervention) pharmacists according to the medication appropriateness index and adverse drug events at 3 to 6 months post discharge. These findings, though unexpected, suggest that the experience of the pharmacist and their integration in the ward team are likely important factors in achieving positive outcomes, because the pharmacists in the study reporting this findings were junior pharmacists and new to the ward team. The impact on quality of life was also modest, which is likely to be due to the acute nature of illness and the short follow-up periods.

Prescription and administration errors are amongst the most commonly identified adverse events during a patient's stay in hospital.[42] Pharmacists, as part of the multidisciplinary team, can reduce these errors and ensure that the patient gets the correct treatment, as well as discontinuing drugs which are no longer required in both the short and long term. The pharmacist has an important educational role which has the potential to improve patients' adherence after discharge. These activities allow doctors to focus on other key patient care priorities.

It is also acknowledged with the aging population that there is an increasing number of patients with multi-morbidities who are exposed to poly-pharmacy.[8] In this situation the pharmacist can play a vital role in advising the medical team regarding drugs and how to prescribe treatment optimally. Involving the pharmacist at hospital discharge may have reduced the need for junior doctors to explain prescribing regimens, and the need for the patient to visit their general practitioner following discharge for drug review. This would improve patient and/or carer satisfaction and have a potential cost benefit.

Pharmacists are also gradually acquiring independent prescribing rights.[43 44] This allows them to correct prescribing errors or make changes directly without the need for doctor involvement. Streamlining the prescribing of medications to take home at the end of hospital stay could also facilitate earlier discharge and allow junior doctors to focus on other tasks produced from the ward rounds.[45] Assessment of the cost effectiveness of prescribing pharmacists in hospital should include these considerations.

The cost effectiveness of the ward-based pharmacist role has been assessed in a number of published economic evaluations. However, unlike the evidence for clinical effectiveness, the generalisability of the findings of these

evaluations from one health care system to another might be limited due to the different funding arrangements and the perspectives used in the analysis.[46-48]

The economic evidence in our review was in favour of the provision of ward-based pharmacist input but the interventions, and therefore results, varied from one country to another. Clinical pharmacists in the reviewed UK studies were generally experienced (band 7/8) and have specialist knowledge in the medications they managed. They also were completely integrated in their clinical teams.[36] This may not be the same profile in the non-UK studies. Additionally, the standard care/control arm in the included economic studies was not always clearly defined and was variable in terms of the level of pharmacist input. Some studies included a specified level of clinical pharmacist input in the control group which was enhanced in the intervention group (for example, by attendance at ward rounds) while others described the introduction of a completely new service. These differences might explain the differences in the findings of these studies, which has also been highlighted by other reviews of this evidence.[47]

With the exception of the UK economic modelling study,[36] all economic studies had a follow-up of 12 months or less and hence would not have assessed the long term impact of the ward-based pharmacist intervention. Additionally, the majority of the studies assessed a limited number of cost categories; focusing on medication costs, pharmacist time and less on other staff time (e.g. freeing up or release of junior doctor time) and patient-related downstream costs.

There was evidence that pharmacist input throughout the hospital stay would achieve saving in terms of medications costs, which was the most frequently assessed cost category in the included studies. One study found the pharmacist cost was completely offset by medication cost savings.[21] The evidence was less clear in terms of impact on other staff time and on long-term patient outcomes, which were not always assessed in the included studies. Where this impact was quantified, the results showed potential for cost saving. Avoiding medication errors that have severe consequences is also an important positive outcome in terms of avoiding litigation costs.[36] Overall, the economic evidence suggested that the regular input by ward-based pharmacists is cost-effective. Pharmacist input only at discharge was not cost effective, but the evidence for this was limited to one Swedish study.[38]

This systematic review demonstrates the potential benefits for patient safety of including ward-based pharmacists in the multidisciplinary team in hospital. Our focus on higher-quality studies permits robust conclusions. However, sample sizes tended to be small, there was some heterogeneity between the interventions

studied, and we did not formally assess publication bias. Nevertheless, our findings are consistent with earlier reviews and have strong face-validity, allowing the guideline committee to recommend the routine inclusion of ward-based pharmacists in the multidisciplinary team managing acutely ill hospitalised patients.[49]

CONCLUSION

Evaluations of the ward-based pharmacist input have largely found it to be both effective and cost effective, particularly when provided throughout the different stages of the patient journey by experienced pharmacists who are integrated in the ward team. The effectiveness evidence, however, was generally of low quality. The economic evidence had potentially serious limitations. The interventions and comparators were often not well defined and there was variation across the studies in their composition.

Nevertheless, the collective body of the available evidence suggests that recommending regular ward-based pharmacist input and inclusion in the multidisciplinary team would offer additional value to the provision of care for those admitted for a suspected or confirmed medical emergency. However, further research is needed to determine the optimal level of involvement of ward-based pharmacists and to assess whether the provision of a 7-day service is cost-effective.

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175 statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of
176 the data analysis.

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