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MEDICATION ERROR AT THE PRIMARY SECONDARY CARE INTERFACE: COSTS, CAUSES, CONSEQUENCES

Thesis presented by

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For the degree of

Doctor of Philosophy

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LIST OF PEER REVIEWED PUBLICATIONS

Papers (from thesis):

Walsh EK, Sahm LJ, Bradley C, Dalton K, O'Sullivan K, McCarthy S, Connolly E, Fitzgerald C, Smithson WH, Kerins D, Byrne D, Kearney PM. The PHARMS (Patient Held Active Record of Medication Status) study: a mixed methods feasibility study. British Journal of General Practice 2019 DOI: 10.3399/bjgp19X702413

Walsh EK, Sahm LJ, Kearney PM, Smithson WH, Ngwa C, Kerins D, Dalton K, Connolly E, Byrne D, Carey M, Bradley CP. The PHARMS Feasibility Study (Patient Held Active Record of Medication Status): a research proposal. BMC Research notes 2018 DOI: 10.1186/s13104-017-3118-3

Walsh EK, Hansen CR, Sahm LJ, Kearney PM, Doherty E, Bradley CB. The Economic Impact of Medication Error: A Systematic Review. Pharmacoeipdemiology and Drug Safety 2017 25;(2)3-23 DOI: 10.1002/pds.409

Abstracts (from thesis):

Walsh EK, Hansen CR, Sahm LJ, Kearney PM, Doherty E, Bradley CP. The Economic Impact of Medication Error: A Systematic Review. Pharmacoeipdemiology and Drug Safety 2016 25;(2)3-23 DOI: 10.1002/pds.409

Walsh EK, Sahm LJ, Kearney PM, Smithson H, Byrne D, Kerins D, Ngwa C, Fitzgerald C, McCarthy S, Connolly M, Carey M Bradley C. The Patient Held Active Record of Medication Status (PHARMS) Feasibility Study: Research in progress**.** International Journal of Integrated Care 2017; 17(5): A28. DOI: 10.5334/ijic.3329

Papers (related-directly to thesis):

Kearney A. **Walsh EK,** Kirby A, Halleran C, Byrne D, Haugh A, Sahm LJ. A Budget Impact Analysis of a clinical medication review of patients in an Irish University teaching hospital. Global and Regional Health Technology Assessment Journal 2018 DOI: 10.1177/2284240318807726

Kearney A, Halleran C, **Walsh EK**, Byrne D, Haugh J, Sahm LJ. Medication reviews by a clinical pharmacist in an Irish university teaching hospital. Pharmacy 2017, *5*(4), 60; DOI:10.3390/pharmacy5040060

Hansen CR, **Walsh EK**, Bradley CB, Sahm LJ. Teaching prescribing: just what the doctor ordered? A Thematic Analysis of the Views of Newly Qualified Doctors. Pharmacy 2017 5(2); 32. DOI:10.3390/pharmacy5020032

Michaelsen M, **Walsh EK,** McCague P, Bradley CB, Owens R, Sahm LJ. Prescribing error at hospital discharge: a retrospective review of medication information in an Irish hospital. Irish Journal of Medical Sciences. 2017, 186(3); 795–800 DOI: 10.1007/s11845-017-1556-5

Papers (related-other):

Stott D, Rodoni N, Kearney PM….**Walsh EK** et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism New England Journal of Medicine April 3, 2017 DOI: 10.1056/NEJMoa1603825

O'Riordan D, Aubert C, Kearney PM, Sinnott C… **Walsh EK** et al. Prevalence of potentially inappropriate prescribing among older European adults: a cross-sectional study. BMJ Open 2018 8:e019003. DOI: 10.1136/bmjopen-2017-019003

AWARDS AND IMPACT

The PHARMS (Patient Held Active Record of Medication Status) study: a mixed methods feasibility study

- Hugh McGavock Bursary for best abstract
  PRIMM conference December 2018

- James McCormick Award for best research project
  AUDGPI conference March 2019

- AUDGPI Bursary for best research presentation
  AUDGPI conference March 2019

- Selected for showcasing at the Irish National Council for Clinical Information Officers Forum May 2019
- Highlighted by the editor of the British Journal of General Practice at time of publication April 2019 with provision of a summary to the press

Economic impact of medication error: a systematic review

- Identified by Pharmacoepidemiology and Drug Safety as one of the top 20 most downloaded papers in the 12-month period post publication
- Included as a chapter in a national UK review on the burden of medication error (18)

ABBREVIATIONS

ADE: Adverse Drug Event

BPMH: Best Possible Medication History

CONSORT: Consolidated Standards of Reporting Trials

CPI: Consumer Price Index

CFIR: Consolidated Framework for Implementation Research

DDI: Drug Drug Interaction

EHR: Electronic Health Record

EMA: European Medicines Agency

FEMPI: Financial Emergency Measures in the Public Interest

GP: General Practitioner

GMS: General Medical Services

HIPE: Hospital Inpatient Enquiry

HIQA: Health Information Quality Authority

HSE: Health Services Executive

ICGP: Irish College of General Practitioners

IHI: Individual Health Identifier

IMC: Irish Medical Council

IT: Information Technology

IV PCA: IV Patient Controlled Analgesia

MRC: Medical Research Council

NCC MERP: National Coordinating Council for Medication Error Reporting and Prevention

NCHD: Non consultant hospital doctor

NHS: National Health Service

OECD: Organisation for Economic Co-operation and Development

pADE: Preventable Adverse Drug Event

PHARMS: Patient Held Active of Medication Status

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PRSI: Pay Related Social Insurance

RCGP: Royal College of General Practitioners

SES: Socioeconomic Status

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

WHO: World Health Organization

DECLARATION

I declare that this thesis has not been submitted for another degree either at University College Cork or elsewhere. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of the thesis. The library may lend or copy this thesis on request.

_____ _____

Signed Date

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THESIS ABSTRACT

Background

Medication error is an important patient safety issue worldwide and results in morbidity, mortality and economic burden. The true cost of medication error is unclear from current evidence. Medication error is particularly common at the primary secondary care interface as patients move between hospital and the community. Developing interventions to reduce medication error (and in particular error at this interface in care) is currently an international priority. Existing interventions, such as medication reconciliation, are often resource intensive. Within healthcare systems, where resources are limited, measures to reduce costs and improve process efficiency are required in addition to optimising patient care.

Aim

The overarching aim of this thesis is to examine medication error at the primary secondary care interface in terms of cost, causes and consequences in order to develop a pragmatic intervention to facilitate its reduction.

Structure and methods

The Medical Research Council, UK (MRC) guidance on the development and evaluation of complex interventions in healthcare was employed.

Existing evidence on the cost of medication error was systematically reviewed and synthesised in a narrative synthesis. A cost per error was extracted and expressed in Euro.

A cross-sectional study was conducted. The study examined an existing process of medication reconciliation in terms of factors predicting time burden and associated financial cost. Logistic regression was used to investigate associations between patient characteristics and clinically

significant errors and additional time. Cost for additional time was calculated in terms of hospital pharmacist salary.

The new evidence generated was used, along with the existing evidence base, to develop a novel intervention aiming to reduce the occurrence of medication error at the primary secondary care interface. The intervention, the PHARMS (Patient Held Active Record of Medication Status) device, is a patient held electronic record used to transmit medication information between primary and secondary care.

The intervention was evaluated by a mixed methods feasibility study (non-randomised controlled intervention and a process evaluation of qualitative interviews and non-participant observation). The study was informed by the Consolidated Framework for Implementation Research (CFIR). The occurrence of medication error was compared between groups and factors associated with medication error investigated using negative binomial regression. Thematic analysis of data from semi-structured interviews with key stakeholders was conducted.

Results

Systematic review: 16 studies were included in the systematic review. The review identified that medication error is associated with significant economic impact with an associated cost of up to €111,727.08 per error. In view of the limited parameters used to establish economic impact, it was concluded that the true economic burden of medication error may have been underestimated to date.

Cross-sectional study: 89 patients were included. Having a personal record of medication at admission (OR 3.30, 95% CI: (1.05 to 10.42), p=0.004) was a significant predictor of additional time. No significant associations were found between the occurrence of clinically significant error and additional time (p>0.05). The most common reason for additional time was clarifying issues

pertaining to communication of medication information from primary care. Projected annual five year costs for the mean additional time of 3.75 minutes of the study were €1.8-1.9 million.

Feasibility study: 102 patients were included (Intervention n=41, Control n=63). Total error number was lower in the intervention group Median=1 (0,3 IQR) than the control group Median=8 (4,13.5 IQR) p <0.001, with the clinical significance score in the intervention group Median= 2 (IQR 0,4) also being lower than the control group Median=11 (IQR 5,20) p <0.001. The device was found to be technically implementable using existing IT infrastructure and acceptable to all key stakeholders.

Conclusion

Medication error is a costly problem, the true extent of which may have been underestimated. Issues pertaining to communication of medication information at the primary secondary care interface were identified as contributing to the economic burden associated with medication reconciliation. In addition, it was identified that increasing time for medication reconciliation may not necessarily result cost savings in terms of reducing medication error. The intervention developed as a result of this thesis may have the potential to facilitate more efficient medication reconciliation and reduce medication error at the interface of primary and secondary care. This may result in both clinical and economic benefit.

Limitations

The overall numbers of patients included in the cross-sectional and feasibility studies in this thesis are small. In addition, these studies included only older adult patients in a single geographical location and involved a single hospital.

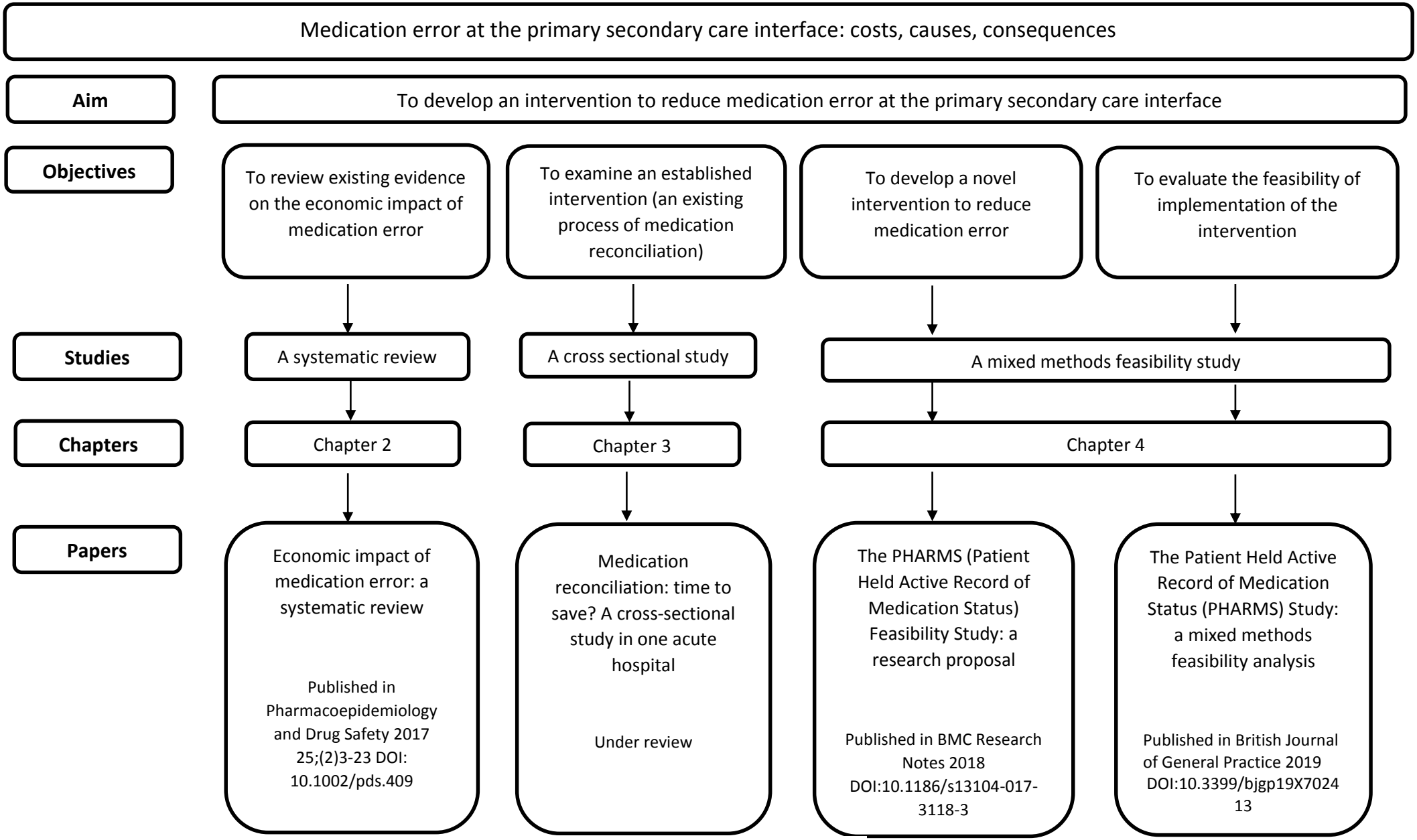


Figure 1 1: Outline diagram of thesis

1. INTRODUCTION

Medication error is the single most preventable cause of patient harm worldwide (1, 2). Medication error frequently occurs as patients transition between primary and secondary care and is particularly common among older adult patients (3-7). The impact of such error at the primary secondary care interface ranges from process inefficiency in primary and secondary care to significant patient morbidity, mortality and economic burden (8). With a growing aging population worldwide, overall healthcare utilisation is increasing (9). The occurrence of medication error at the primary secondary care interface places an additional burden on healthcare systems already struggling to meet current demands. Establishing effective methods to reduce medication error at this interface in care is currently an international priority (2). Within the Irish healthcare system resources are limited (10). Measures to reduce costs and improve process efficiency are required in addition to optimising patient care. Examining medication error at the primary secondary care interface in terms of cost, causes and consequences is essential for the development of pragmatic effective methods to successfully address this important patient safety issue.

In the following review of the literature international evidence is presented initially in each section, followed by Irish evidence where available. In the absence of Irish evidence, international evidence, as it applies to the Irish context, is discussed.

1.1 Medication error

The medication use process involves a number of steps namely; prescribing, transcribing, dispensing, administration and monitoring of medication. Medication error is defined as a mistake occurring at any point during the medication use process (8). Medication may be associated with unavoidable

patient harm in the absence of error when adverse drug events (ADEs) arise due to medication side-effects. Though not all medication errors result in harm, the ADEs associated with medication error are preventable however, and hence the associated harm is avoidable. Reduction of medication error is currently an international priority with the World Health Organisation (WHO) stating their intent to "reduce the level of severe avoidable harm related to medications by 50% over 5 years globally" in 2017 (2). The United States Institute of Medicine's landmark report in 1999 "To Err is Human: Building a safer Health System" first highlighted the association of error in the healthcare system with patient morbidity and mortality and noted medication errors to be a major cause of iatrogenic harm (1). ADEs are reported to account for between 6.5% and 24% of acute hospital admissions with more than half the ADEs, being attributable to medication error (11-15).

The reported prevalence of medication errors among patients in primary and secondary care varies from approximately 6% (16, 17) to 91% (17, 18). Multimorbidity (the presence of two or more chronic conditions) (19) and polypharmacy (the co-prescribing of five or more medications) (20) have been identified as risk factors for medication error. A greater prevalence of medication error has been reported in multimorbid patients and those taking multiple medications (18, 21, 22) (23-27) and this is of particular relevance in relation to the aging populations in Ireland (and worldwide) who are more susceptible to these issues. Medication error has been identified as a major issue in the Irish context (28). A national clinical incident five-year review from 2010 to 2014 in Ireland found that medication errors accounted for 14.7% of the ten most commonly reported incidents and account for approximately 10% of adverse clinical incidents occurring nationally in older adult patients (29). In addition, medication error accounts for up to one quarter of litigation claims against Irish GPs (30).

The consequences of medication error are ADEs, drug-drug interactions, lack of efficacy, suboptimal patient adherence and experience and poor quality of life. In turn, these may have significant health

and economic consequences, including the increased use of health services, preventable medication-related hospital admissions and death (8, 31). The estimated cost of a preventable ADE (pADE) was calculated at USD $4,800 per event in a landmark study conducted by Bates *et al* in 1995 (32), with costs as high as $10,375 per pADE subsequently being reported (33, 34). A review published in 2018 estimates costs of pADEs in the National Health Services (NHS), UK as £98.5 million per year, consuming 181,626 bed-days, causing 712 deaths and contributing to 1,708 deaths. The costs of primary care pADEs are estimated to be £83.7 million; causing 627 deaths and secondary care pADEs to be £14.8 million; causing 85 deaths and contributing to 1,081 deaths (18). There is currently a lack of evidence regarding cost of medication error in the Irish context. The physical and psychological consequences for patients as a result of medication errors, in addition to decreased patient satisfaction and lack of trust in the healthcare system, also contribute to economic burden (35).

Prescribing error is thought to be the most significant form of medication error with over half of medication errors resulting in ADEs occurring at the prescribing stage (31) (36). Inappropriate prescribing refers to the use of a drug where the risk of an adverse event outweighs the clinical benefit, particularly if a safer or more effective alternative therapy is available. Potentially inappropriate prescribing refers to such inappropriate prescribing as identified by standardised tools such as Beer's criteria and STOPP/START (37). The prescribing of potentially inappropriate medications does necessarily represent prescribing error however. The possibility exists of an intentional and informed decision on the part of the prescriber to prescribe a high risk medication.

Estimated prevalence of prescribing error in secondary care ranges from 8% to 31% (38-40). Figures of between 45 and 57% of prescribing errors detected in the hospital setting have been reported as having the potential to cause patient harm (41-43). Multiple perceived causes for prescribing error in the hospital context have been identified and include knowledge deficits among junior doctors, time pressure and poor communication and documentation of medication information (40, 44, 45).

Prescribing error is also prevalent in primary care (46-48). Prescribing error rates of between 1 and 90 per 100 prescriptions issued have been described (48). Up to 72 % of prescribing errors occurring in the primary care setting have been reported as having the potential to cause patient harm (49). Prescribing error occurring in primary care has also been attributed to time pressure and workload. In addition problems with the timeliness, legibility, content, and layout of secondary care correspondence have been cited as contributory factors (47).

Up to 50% of medication errors occur during transitions of care (3, 50) and such errors frequently occur among older adult patients (51, 52). Transitions of care are defined as "the various points where a patient moves to, or returns from, a particular physical location or makes contact with a health care professional for the purposes of receiving health care" and includes transitions between home, hospital, residential care settings and consultations with different health care providers in out-patient facilities (53). The primary secondary interface has been identified as a particular care transition where medication error is likely to occur (54-56) and incorrect medication information at this interface has been noted to be a major source of medication error in the Irish context (29). Reduction of medication error at the transitions of care has been highlighted as a key objective both nationally by the Health Information Quality Authority (HIQA) and internationally by the WHO (8, 57).

Broadly defined as any mistake in the prescribing, dispensing, or administration of a drug, definitions for medication error vary in the literature with no one standard definition being applied universally (58-60). A recent systematic review has highlighted the need for uniform terminology improve communication between key stakeholders namely patients, clinicians, healthcare professionals, researchers, and policy makers to successfully address the problem of medication error (60). In response to the issues surrounding terminology the European Medicines Agency (EMA) produced a guide to promote a common approach to recording, coding, reporting and assessment of medication errors (61). The EMA defines medication error as "an unintended failure in the drug treatment

process that leads to, or has the potential to lead to, harm to the patient", specifying that a failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failures (62). This definition is used throughout the thesis.

Medication errors can be classified in a number of different ways (63). Errors can be classified according to stage of occurrence in the medication use process namely prescribing, transcribing, dispensing administration and monitoring. Another approach classifies errors according to mistakes made in either the planning or action stage of medication use (knowledge or action based errors). A further approach to classification uses the types of error such as wrong dose, route or frequency (8, 18, 63). The classification systems for medication error are not mutually exclusive and no evidence base currently exists for using a single system. The WHO states that classification selection is dependent on purpose and setting (8).

In terms of implications for patient safety and practice establishing the clinical significance or level of harm associated with medication errors is required. Errors may however be captured in advance of reaching the patient or the clinical outcome of the error may be unknown. Hence establishing clinical significance of medication errors may require subjective judgement. The method described by Dean et al is a validated and reliable method using the judgement of healthcare professionals in the absence of knowledge of patient outcomes (64). Systems to classify the clinical significance of medication errors vary in the literature. The EMA classification classifies errors as; (i) potential errors, (ii) intercepted errors, (iii) errors without harm and (iv) errors with harm (61). Nesbit *et al* assign a probability of a harm occurring due to an ADE on a five point scale ranging from; no harm to high (65, 66). The Hartwig Severity assessment scale rates the severity of ADEs on a seven point scale ranging from; no change required to the drug treatment in question, to death (67). The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy of medication errors classifies errors as causing no harm, harm, or death. It further rates errors, causing harm, on a four point scale from; temporary harm requiring intervention, to intervention required

to sustain life (68). Bates *et al* classify medication errors as significant (little or no threat to the patient's life function), serious (associated with a serious level of risk that is not high enough to be life-threatening) or life-threatening (error that if not treated would put the patient at risk of death) (32, 69). This classification system was recently used by Pevnick *et al* to calculate a novel error score for individual patients to quantify clinical significance. Error severity weights of 1^2=1 (significant), 2^2=4 (serious) and 3^2=9 (life-threatening), respectively, are assigned to reflect the relative capacity of each error type to cause patient harm and a summation of scores used to calculate the final score for an individual patient (70). The EMA classification system (61) is used in this thesis (Chapter 2) with the classification system of Pevnick *et al* (70) used to assign clinical significance of medication error (Chapters 3 and 5).

1.2 Primary and secondary care in Ireland

1.2.1 Structure

The Irish healthcare system has been described as a two tier system providing both public and private care. The General Medical Services (GMS) is a public system covering primary and secondary care costs for approximately 46% of patients in Ireland, with 46% of patients currently paying for private health insurance to cover potential costs of secondary care (71).

Primary care for citizens in Ireland has been defined as "first level contact that is fully accessible by self-referral and has a strong emphasis on working with communities and individuals to improve their health and social wellbeing" (72). Primary care services include general practice (GP), community nursing, occupational therapy, pharmacy, physiotherapy, speech and language therapy and social work (72). General practitioners (GPs) are central to the delivery of patient care in the Irish primary care context. The estimated number of GPs currently in practice in Ireland is 3,523 (73).

Most GPs in Ireland are self-employed, though they provide care which is state funded for GMS patients on a contractual basis. Over half of GPs work in group practices of three or more GPs, with 18% of GPs currently operating as sole practitioners (73).

Secondary care in Ireland is comprised of 48 public hospitals funded by the state through the Health Service Executive (HSE) and 21 private hospitals. The HSE is the national body responsible for the delivery of public healthcare in Ireland. Public hospitals are grouped into three categories based on hospital status and level of treatment complexity. Category 1 (the highest level of treatment complexity) is comprised of Health Service Executive (HSE) regional hospitals and teaching hospitals, Category 2 includes HSE county hospitals and non-teaching hospitals, and Category 3 is made up of HSE district hospitals (74). There are 2951 consultants and 6209 non consultant hospital doctors (NCHDs) currently employed within public and private hospitals in Ireland (75).

The GMS is a public system providing medical cards to patients on the basis of means testing, with additional cards being awarded to particular patients with specific medical needs associated with high medical expenditure. A full GMS medical card entitles the holder to access their GP and to receive public hospital care without incurring any costs. In addition, patients with a full medical card receive prescribed medications for the nominal charge of €2.00 for each item that is dispensed, up to a maximum of €20 per month per person or family (76). A GMS GP visit card entitles the holder to visit a GP without charge, and in 2015, non means tested GP visit cards were given to all patients 70 years and over and to all children aged less than six years. The GP is paid an annual fee of €43-270 (dependent on age and gender) per capita by the GMS (77, 78). Ireland is the only EU country in which the health system does not cover the cost of accessing a GP for all patients. Patients not covered by the GMS pay their GP a fee per consultation (circa €50)(71).

All patients in Ireland not covered by the GMS are entitled to subsidised public hospital care. Private health insurance covers inpatient and outpatient hospital care. Private hospitals only provide care

for patients with private health insurance (74) with some private care also being delivered in public hospitals alongside public care (71).

In Ireland, general practice facilitates appropriate access to specialist services and investigations in secondary care, operating as a gatekeeper with in the healthcare system for both public and private patients. GPs in Ireland conduct 20 million consultations per annum delivering services in primary care ranging from antenatal care to chronic disease management (73, 79). The majority of patients attending a GP in Ireland are managed in primary care with a recent Irish study giving a figure of approximately one in ten patients for patients referred to secondary care. This proportion of care provided in primary and secondary care is in line with findings from other healthcare systems internationally (80-82).

1.2.2 Patient population

Data from the 2016 census in Ireland indicates that the population of Ireland is 4.7 million, an increase of 12.2% since 2006. The most significant increase has been in the population aged over 65 years. Each year the population aged over 65 increases by almost 20,000 people, and by almost 3,000 for those aged 85 years and over (83). Irish figures reflect the global context with the population aged 60 years or over worldwide numbering 382 million in 1980, 962 million in 2017 and projected to reach nearly 2.1 billion by 2050 (84). A growing aging population results in increased prevalence of chronic disease. Furthermore, many of this population have multimorbidity. Thus multimorbidity is also increasing worldwide (85-89). Consequently, an increase in healthcare utilisation in both primary and secondary care has been noted internationally (89, 90). This is likewise reflected by the growing demand for healthcare services among the older adult population in Ireland. Increased frequency of general practice consultations has been described (91). In

addition, figures for hospital admissions in 2015, demonstrated that patients aged 65 years and over occupied 53.4% of total hospital inpatient bed days (92).

1.2.3 Political and economic landscape

In 2008, Ireland faced an economic crisis. The Financial Emergency Measures in the Public Interest (FEMPI) Act was brought into effect in 2009. Government payments to GPs were reduced as a result of this Act. GMS payments to GPs were reduced by 8% in 2009, by a further 8-15% in 2010 and by a further 7.5% in 2013 (93). In contrast, during this time, there was a 70% increase in the number of patients eligible for a GMS card due to a reduction in their incomes. Many GPs have struggled with increasing demand in the context of reduced payment. Emigration of Irish GPs has increased since 2009 which has resulted in a current manpower crisis in Irish general practice (77, 79). Ireland currently has 76 GPs per 100,000 population, compared to Canada or Australia, which have over 100 per 100,000 population (79).

International evidence suggests that increasing numbers of GPs is associated with a consistent reduction in all-cause mortality and improved self-reported health (94). Furthermore, increasing spending in primary care can yield up to a six fold return on overall health spending (95, 96). Ireland currently spends the fifth highest amount on health in the world, ranking 7th in the Organisation for Economic Co-operation and Development (OECD) in terms of spending per capita (97). Recent figures show however that just 4.9% of the Irish health budget was allocated to primary care (98). High occupancy rates for acute care beds in Ireland are suggestive of excessive numbers of patients being treated at a secondary care level (99).

The need to move to a primary care centric healthcare system has recently been identified by the Irish government and the HSE (100). The need to improve resourcing of primary care has been

highlighted with an additional half a billion euro a year of funding over 10 years recommended to develop a functioning primary care based healthcare system (77).

1.2.4 The primary secondary care interface

The primary secondary care interface describes the journey of the patient and the communication between health care professionals as the patient moves between primary and secondary care (101) (102). The integration of health services across primary and secondary care poses a challenge for all healthcare systems and the primary secondary care interface has been identified as problematic for healthcare providers and users alike (101, 103). Suboptimal and fragmented patient care has been described with the potential for patient harm (104). Poor co-ordination of care and inadequate transfer of patient information have been highlighted as issues (105-107). Achieving successful communication between clinicians in primary and secondary care is challenging (108, 109).

Lack of integration between primary and secondary care is a current issue in the Irish healthcare system (110). Both GPs and hospital consultants in Ireland have expressed a willingness to provide more seamless patient care but have highlighted the absence of structures to facilitate integrated care at a local level (111, 112). Transmission of accurate patient information in a timely manner between primary and secondary care has been identified as key to facilitating successful integrated care (110). Efforts have been made to improve transmission of patient information at the primary secondary care interface. Guidance has been produced for Irish GPs on referral information being sent to secondary care by the Irish College of General Practitioners (ICGP), with standardised paper based and electronic referral templates now in existence (113). A document outlining a national standard for discharge information was also published in 2013 (114). In practice however, transmission of patient information between general practice and hospital remains an issue (110).

Up to 20% of an Irish GP's time during a working day is currently spent on paperwork and administrative tasks (115). Contacting hospital staff to clarify issues pertaining to inadequate or inaccurate patient information from secondary care has been identified as a major source of frustration for GPs (77), with issues frequently arising in relation to hospital discharge information (116, 117). Such information is commonly generated by junior doctors (doctors in their first one to two years post qualification) and despite the efforts made to standardise information at this point in care, there is considerable variation at a local level. Omissions and inaccuracies are frequently reported by GPs (116-118). In addition, timeliness of receipt of discharge information is also an issue with information frequently not being received by a patient's GP for a number of days following discharge (116, 118).

Poor availability of up to date and accurate information pertaining to a patient's medication following hospital discharge is of particular concern for GPs (119-121). Pharmacists may only dispense a seven day supply of medications to patients who are medical card holders from a prescription issued by a hospital doctor (122). Hence, these patients frequently attend their GP immediately following discharge to have their medications transcribed onto a GMS prescription. A report published in October 2018, whilst acknowledging the role that GPs play in reviewing and transcribing prescriptions from hospital doctors in terms of identifying errors pertaining to prescribing , also identifies this restriction as a source of inefficiency in general practice (10).

1.2.5 Information Technology (IT) in healthcare

Internationally there has been a move towards the greater use of IT in healthcare and many countries have implemented electronic health records (EHR). In the past 20 years Irish GPs have invested in IT and currently more than 90% of GPs in Ireland use electronic patient record systems (123). Administrative, clinical, and prescribing details are recorded electronically together with

correspondence from other healthcare professionals in primary and secondary care (77). A secure clinical email system (Healthmail) was developed in 2014 for all primary healthcare providers in Ireland. The majority of users are GPs, with use of the system by pharmacists beginning in 2017 (124). Systems for electronic referral (e-referral) from general practice to Irish hospitals are also in place.

IT is less widely used in hospitals in Ireland than in primary care and infrastructure is not yet sufficiently developed to support a full EHR (110, 125). Use of Healthmail and e-referral varies between hospitals (77). In 2004 investment in IT in healthcare and allocation of staff to the health information area was recommended as part of the National Health Information Strategy (126). However, this investment and allocation of staff did not take place until 2015. In addition, though an individual Health Identifier (IHI) has been identified as key to progression in terms of Electronic Health Record (EHR) development and implementation, legislation to facilitate this was not put in place until 2014. An IHI has not yet been issued to patients in Ireland (125). Nonetheless, following publication of the e-health strategy and the appointment of a Chief Information Officer for health, progress has been made recently in the secondary care setting and in November 2016 Cork University Maternity Hospital became Ireland's first hospital to operate a complete EHR system (125).

Despite the fact that routine electronic communication of patient information between primary and secondary care has been identified as crucial to the successful delivery of integrated care in Ireland, notwithstanding recent advances in IT in healthcare, this has yet to be achieved (110). Current practice is the *ad hoc* transfer of discrete components of patient information between hospital and general practice with considerable local variability.

1.3 Medication reconciliation

Medication reconciliation, first described in 2003, was named as one of the five elements of the WHO High 5's project addressing patient safety issues in 2006 (127). It is the term used for the process of identifying and correcting medication errors as patients move between different care stages and settings (128). The goal is to develop an accurate list of all medications a patient is taking that is available at all stages and settings of care, hence effectively communicating changes to medications to both the patient and healthcare providers as the patient transitions through the healthcare system. It is based on the premise that safe use of medication requires knowledge and consideration of all the medications that a patient is taking in order to avoid omissions, duplications, dosing errors and potential adverse drug-drug interactions (DDI) with new drugs being prescribed (128, 129).

The WHO outlines seven guiding principles for medication reconciliation as listed in Table 1.1 (128):

Table 1 1: WHO principles for medication reconciliation

Guiding principles for medication reconciliation
1. An up to date and accurate patient medication list is essential to ensure safe prescribing in any setting.
2. A formal structured process for reconciling medications should be in place across all interfaces of care.
3. Medication reconciliation on admission is the foundation for reconciliation throughout the episode of care.
4. Medication reconciliation is integrated into existing processes for medication management and patient flow.
5. The process of medication reconciliation is one of shared accountability with staff aware of their roles and responsibilities.
6. Patients and families are involved in medication reconciliation.
7. Staff responsible for medication reconciliation are trained to take a medication history and reconcile medicines

The process of medication reconciliation involves a series of steps outlined in Figure 1.2 (130):

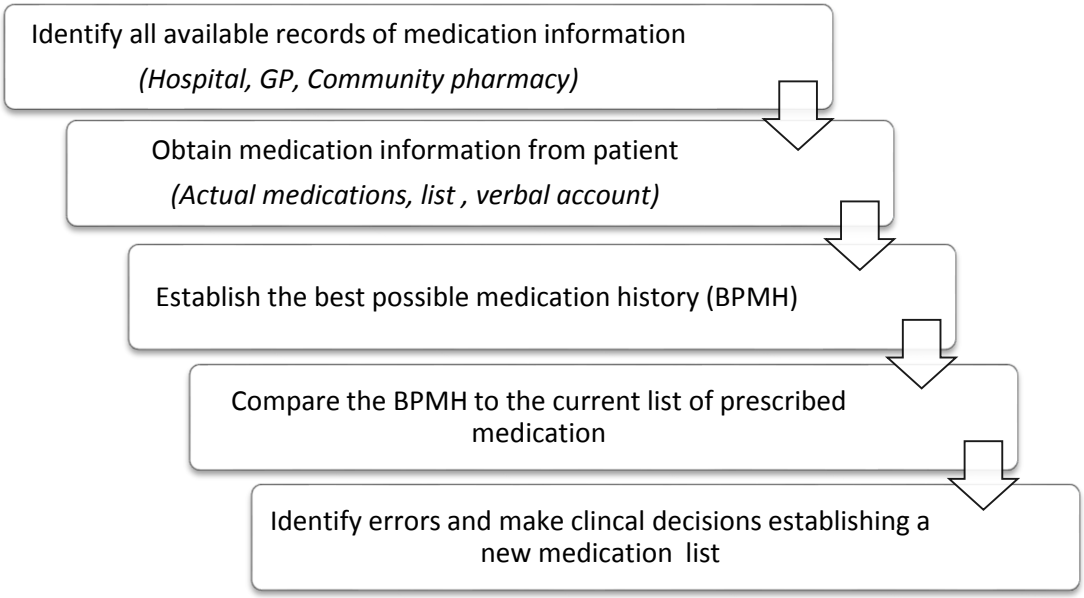


Figure 1 2: Process of medication reconciliation

In establishing the best possible medication history (BPMH) it is recommended that a number of sources of medication information are used (131). Sources of information include records from the hospital, GP and community pharmacy in addition to information held by the patient. The role of the pharmacist in establishing an accurate medication history is well established (132, 133) and ideally a pharmacist should be involved in establishing the BPMH and the comparison of that list with prescribed medication. When a pharmacist is not available it is recommended that the tasks be undertaken by a healthcare professional e.g. physician, nurse or pharmacy technician who has been appropriately trained (128). The process of medication reconciliation outlined in Figure 1.2 is used in Chapter 3 of this thesis.

Guidance suggests that medication reconciliation should be multidisciplinary and that the patient and families/carers should be directly involved in the process resulting in “a conscientious, patient centred, inter-professional process that supports optimal medicines management”. It is also recommended that the process integrates into usual care (128, 134). Different strategies have been

reported for medication reconciliation in the literature. The most common interventions described are pharmacist led. Interventions employing information technology, education, standardised tools and complex multi-faceted approaches have also been described (135-137) . No consensus exists regarding the optimal method however (138) .

A body of evidence exists to support the practice of medication reconciliation. The process has strong face validity; as capturing medication errors of clinical significance has the potential to positively impact not only patient morbidity and mortality, but also healthcare costs by preventing adverse drug events (128, 139). Medication reconciliation is currently widely advocated by professional and accrediting bodies internationally namely; the Joint Commission (USA), the Institute for Healthcare Improvement (USA), the National Institute for Health & Clinical Excellence (UK), the Canadian Patient Safety Institute, the Institute for Safe Medication Practices (Canada) and the Health Information Quality Authority (Ireland) (140-144).

Difficulties with implementing medication reconciliation across healthcare systems have recently been identified however (134, 145, 146). In practice, medication reconciliation interventions may not necessarily integrate seamlessly into usual care. Complexity, which affects workflow, and resource intensity resulting in opportunity cost, have been highlighted as issues (136, 147). Current evidence has failed to demonstrate a significant associated reduction in healthcare costs (136, 147). In terms of healthcare utilisation, a Cochrane review published in 2018 concluded that (based on the pooled results of five randomized controlled trials) medication reconciliation had little or no impact on unplanned prehospitalization with moderate-certainty evidence (RR 0.72, 95% CI 0.44 to 1.18). It was noted that, although the medication reconciliation interventions were similar and all involved clinical pharmacist establishing a BPMH, local variability was an issue.

In practice, medication reconciliation is often implemented only among high-risk patients such as complex polypharmacy patients (128). In the Irish context medication reconciliation is currently implemented on an *ad hoc* basis with implementation frequently restricted to areas such as geriatric

medicine. With medication reconciliation representing a potential solution to the growing issue of medication error however, there is an urgent need to look at how cost-effective, universal implementation can be achieved (136).

1.4 Research aim and objectives

Medication error at the primary-secondary care interface is currently a major patient safety issue. Within the Irish healthcare system resources are limited. Measures to reduce costs and improve process efficiency are required in addition to optimising patient care. Although medication reconciliation facilitates the reduction of medication error, complexity and cost are issues and there is currently is a dearth of novel interventions to facilitate the process. Examining medication error in terms of cost, causes and consequences is essential for the development of an intervention to facilitate its reduction.

Aim:

The aim of this research is to develop an intervention to reduce medication error at the primary secondary care interface

Objectives:

1. To review existing evidence on the economic impact of medication error
2. To examine an established intervention (an existing process of medication reconciliation) at the primary secondary care interface
3. To develop a novel intervention to reduce medication error at the primary secondary care interface
4. To evaluate the feasibility of implementation of the intervention

1.5 Theoretical framework

The process of developing and introducing an intervention in a healthcare context is complex. Many interventions found to be effective in health services research fail to be successfully implemented and hence fail to improve patient care (148). Barriers to implementation may occur at multiple levels: the patient level, the provider level, the organizational level or the policy level (149). To address such issues, the UK Medical Research Council (MRC) recommends a structured methodological approach in developing a complex intervention in the healthcare setting. Systematic development is recommended based on best available evidence and appropriate theory (150) . The steps recommended in development have been followed in this thesis and are outlined in Figure 1.3.Following development, the MRC recommends testing of interventions in a phased approach beginning with a feasibility study and moving on to exploratory and finally definitive evaluation (150).

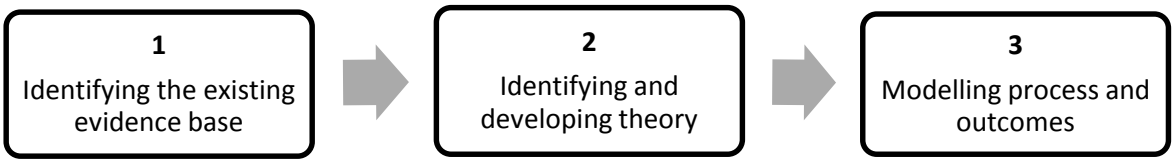


Figure 1 3: **Steps of the development stage of a complex intervention outlined in the MRC methodological approach**

Step 1 Identifying the existing evidence base:

Existing evidence has identified medication error as a source of morbidity, mortality and financial cost. The frequent occurrence of medication error at the primary secondary care interface and the need for novel interventions to assist with medication reconciliation at this care transition have also been described.

In this thesis the existing evidence was supplemented by new evidence firstly in relation to the economic impact associated with medication error (Chapter 2), secondly in relation to deficits in knowledge and records of medication among at risk patients at the primary secondary care interface (Chapter 3) and thirdly in relation to issues in communication of medication information between primary care and secondary care (Chapter 3).

Step 2 Identifying and developing theory:

Successful development and implementation of a novel intervention within the healthcare setting requires a detailed understanding of the context in which it is being introduced and potential barriers to implementation. The development and introduction of intervention at the interface of primary and secondary care involves multiple stakeholders (patients, healthcare professionals and information technology personnel), and two settings of care. To explore the issues surrounding development and implementation, the Consolidated Framework for Implementation Research (CFIR) was used and is described in Chapter 4. The CFIR is a meta-theoretical framework. It combines key elements from published implementation theories and provides a structure to verify what works, where and why across multiple contexts. It consists of five domains. Each domain consists of factors and influences which impact the degree to which an intervention or practice is adopted (151):

- Intervention characteristics
- Outer setting
- Inner setting
- Characteristics of the individuals involved
- Process of Implementation

Step 3 Modelling process and outcomes:

Modelling a complex intervention before a full scale evaluation can provide important information about the design of the intervention and the evaluation. The MRC guidance states that a series of

studies may be required to progressively refine the design before proceeding to full scale evaluation. Chapter 4 outlines planning of intervention evaluation and a preliminary assessment of acceptability and feasibility.

2 ECONOMIC IMPACT OF MEDICATION ERROR: A SYSTEMATIC REVIEW

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2.1 Abstract

Background

Medication error is a significant source of morbidity and mortality among patients. Clinical and cost-effectiveness evidence are required for the implementation of quality of care interventions. Reduction of error-related cost is a key potential benefit of interventions addressing medication error.

Aim

The aim of this review was to describe and quantify the economic burden associated with medication error.

Methods

The review was registered with PROSPERO 05/08/15 (Registration no: CRD42015024202). A search strategy was developed and PubMed, Cochrane, Embase, CINAHL, EconLit, ABI/INFORM and Business Source Complete were searched. Studies published 2004-2016 assessing the economic impact of medication error were included. Cost values were expressed in Euro 2015. A narrative synthesis was performed.

Results

4572 articles were identified from database searching and 16 were included in the review. One study met all applicable quality criteria. 15 studies expressed economic impact in monetary terms. Cost per error per study ranged from €2.58 to €111,727.08. Healthcare costs were used to measure economic impact in 15 of the included studies with one study measuring litigation costs. Four studies included costs incurred in primary care with the remaining 12 measuring hospital costs. Five studies looked at general medication error in a general population with 11 studies reporting the

economic impact of an individual type of medication error or error within a specific patient population.

Conclusion

Considerable variability existed between studies in terms of financial cost, patients, settings and errors included. Many were of poor quality. Assessment of economic impact was conducted predominantly in the hospital setting with little assessment of primary care impact or impact of errors occurring at the primary-secondary care interface. Limited parameters were used to establish economic impact. The economic burden associated with medication error may have been underestimated to date. Future work is required to assess economic impact using parameters inclusive of health care professional time and costs pertaining to primary care, patients and society.

2.2 Introduction

Medication error is a significant source of preventable morbidity and mortality among patients (1). The medication use process involves drug prescription, preparation, dispensing and administration. Definitions of medication error vary in the literature (152) and errors may occur at any point in the medication use process and may involve physicians, pharmacists and nurses in primary, secondary and tertiary care settings. Additionally, patients may not take medications as prescribed, a phenomenon referred to as medication non-adherence (153). Medication error may result in preventable adverse drug events (pADEs) resulting in patient harm and considerable financial cost (1). Not all medication errors result in patient harm but may however be associated with other negative consequences such as inefficiency and inappropriate use of resources, contributing to economic burden (154). Medication safety is a key component in quality of patient care and developing strategies to reduce medication error is currently an international priority (140)

Interventions to reduce medication error may target health-care professionals inclusive of physicians, pharmacists and nurses and additionally may target patient-non adherence. Increasingly interventions to improve quality of care in the health care sector are required to demonstrate effectiveness from both a clinical and cost perspective. When conducting an economic evaluation of a quality improvement intervention the identification, measurement and valuation of both the relevant costs and the relevant benefits is required (155). Due to the complex nature of the medication error process; interventions to reduce medication error are often multifaceted and resource intensive (156, 157). In the case of interventions to reduce medication error, reduction of the cost due to error is a key potential benefit. Hence an accurate estimate of the economic burden associated with medication error is necessary to inform the successful development and implementation of interventions focussing on its reduction.

The aim of this review is to establish the economic impact of errors associated with the prescription, preparation, dispensing and administration of medication. Additionally, the review will identify methods and parameters used when calculating the cost of medication error and also identify the types of medication error that result in economic burden. It will provide evidence for healthcare decision makers regarding the costs associated with medication error and will also highlight areas requiring further study for practitioners and policymakers.

2.3 Methods

Search strategy

The protocol for the systematic review was registered with PROSPERO 05/08/15 (Registration no: CRD42015024202). Searches were conducted of the following databases: PubMed, Cochrane, Embase, CINAHL, EconLit, ABI/INFORM and Business Source Complete in June 2015 for publications dating back to January 2004. The search was updated in April 2016. The search strategy was developed by the primary author in association with a medical librarian. A PubMed Strategy was developed and appropriate Medical Subject Headings (MeSH) terminology was utilised. The following search terms were employed: (Cost OR Cost analysis OR Econ*) combined with (Medication error OR Inappropriate Prescribing OR "Inappropriate Medication" OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* keywords were used for additional databases. (See Appendix 1 for the full search strategy). Search results from multiple databases were transferred to a reference manager- End Note. Title review was conducted by the primary author (EW). Studies that clearly did not meet eligibility criteria were excluded. Abstract review was performed by the primary author and studies that did not meet the inclusion criteria were excluded. Full text review was performed

by EW and secondary author (CH). Where disagreement arose between the primary and secondary authors regarding study inclusion a third author (LS) was involved and a consensus was reached.

Review criteria and data extraction

The review was conducted according to the PRISMA guidelines (158). (See Appendix 1) Studies were required to meet the criteria specified in Table 2.1.

Table 2 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Published peer reviewed full text articles	Non-peer reviewed literature e.g. technical reports, Letters to the editor, newspaper articles Grey literature
Studies published in the English language	
Studies focussing on errors in the prescribing, transcribing, dispensing or administration of medication	Studies focussing on the prescribing of potentially inappropriate medications, non-compliance or non-adherence to medication. Studies focussing on non-preventable adverse drug reactions
Studies focussing on the economic burden associated with medication error	Studies focussing on errors in drug manufacturing Economic evaluations of interventions to reduce error Studies evaluating non-medication related medical error Studies comparing costs of adverse drug reactions of two or more medications

Medication error was defined as "an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient" as per the European Medicines Agency (EMA) Good Practice Guide on recording, coding, reporting and assessment of medication errors (62). Failure in the drug treatment process was defined as human or process mediated failures rather than lack of efficacy of the drug and included errors of omission. Four categories of medication errors were included in the review:

1. Medication errors with harm
2. Medication errors without harm
3. Intercepted medication errors

4. Potential medication errors

The definition does not include adverse drug events and adverse drug reactions that are non-preventable. For studies assessing the economic impact of adverse drug reactions or events, each study was required to specify in the methods section that adverse drug events or reactions were preventable, avoidable or directly due to medication error. If not specified, the study was excluded from the review. Additionally, the prescribing of potentially inappropriate medications and non-compliance/non-adherence to medication were not included in the definition of medication error used in this review. Inappropriate prescribing refers to the use of a drug where the risk of an adverse drug event outweighs the clinical benefit, particularly if a safer or more effective alternative therapy is available (37). Potentially inappropriate prescribing refers to such inappropriate prescribing as identified by standardised tools such as Beer's criteria and STOPP/START (37). Not all potentially inappropriate medications detected in this manner necessarily represent medication error however. The possibility exists of an intentional and informed decision on the part of the prescriber rather than the occurrence of true medication error.

The references of eligible studies and previously published systematic reviews were hand searched to identify any additional studies pertaining to the economic impact of medication error not captured by database searching. Studies which met the inclusion criteria were reviewed and data extracted by the primary and secondary authors (EW and CH) using a data collection form. (See Appendix 1)

Information collected included details of authors, type of medication error, study setting, study population, study sample size, economic method, outcome measures and results.

Quality assessment:

Due to the lack of risk of bias assessment tools or established methodological guidance on how to conduct a critical appraisal of the economic burden of medication error, assessment of study quality was challenging. Due to variability in terms of study design of the included studies standardised tools assessing quality from an epidemiological perspective could not be applied universally to the studies (159). Additionally, other checklists for critical appraisal of economic studies pertained specifically to economic evaluations and could not be applied (160, 161). As cost-of-illness studies aim to assess the economic burden of particular health conditions on the general population a tool used for critical appraisal of cost of illness studies was sought. A number of tools used in previous studies for quality assessment were potentially applicable to the included studies (162-165). The six parameters pertaining to cost-of illness as described by Cooper et al incorporated the key components of the quality assessment tools reviewed (165). Quality assessment was conducted using the parameters described by Cooper et al with the addition of a parameter pertaining specifically to medication error. No study was excluded based on quality assessment. The parameters used are outlined below:

The approach used for quality assessment was applicable to all of the included studies but only assessed quality from economic and error reporting perspectives.

1. Viewpoint/perspective (e.g. patient/health service) of the analysis clearly stated and justified.
2. Study population clearly stated.
3. All relevant medical and/or non-medical costs included and their sources clearly stated.
4. All costs adjusted for differential timing, where appropriate: discounting applied to costs if a study was conducted over > 1 year.
5. Incremental/attributable costs calculated: calculation of difference in costs incurred by the study population and a non-exposed population.
6. Sensitivity analysis performed to address uncertainties or methodological controversy.

An additional seventh parameter was added to assess study quality based on the EMA guidance on the appropriate recording and reporting of medication errors (62):

7. Clear statement if reported costs pertained to an actual or potential error and if the error was associated with harm

Data Synthesis

A narrative synthesis was performed using the approach described by Popay et al (166):

1. Results were tabulated and a preliminary synthesis performed.
2. Data were transformed and a common rubric established so as to express the results in a common numerical value. Costs in all studies were expressed in Euro 2015 values and a cost value per medication error was calculated where data were available.
3. Relationships within and between studies were explored.
4. Robustness of the synthesis was assessed.

Subgroup analysis was stated a priori and was conducted by age (> or < 65 years) and type of medication error.

In order to adjust for the inflation rate over time cost in each of the studies was inflated to 2015 values using the consumer price index (CPI) for medical and non-medical resources for each individual country (167). Each value was then converted to Euro using the exchange rate from November 2015. Where year of currency was absent from the study, the year of publication was used (Appendix 1).

2.4 Results:

Following elimination of duplicates, the search strategy yielded 4572 titles for review. Reasons for exclusion are outlined in Fig 2.1. Disagreement arose regarding inclusion of one study between the primary and secondary authors (EW and CH). The definition of medication error used in this study was "harm resulting from not following the professional standard or poor organisation of care" (168). The meaning of the term "professional standard" was unclear. Prescribing appropriateness indicators could be regarded as a professional standard raising the possibility of potentially inappropriate prescribing rather than true medication error as per the inclusion criteria. The opinion of a third author (LS) was sought and a consensus was reached to include the study.

A summary of the 16 studies which met inclusion criteria is listed in Table 2.2. The studies were conducted in the USA (n=7), Europe (n=5) Asia (n=3) and South America (n=1).

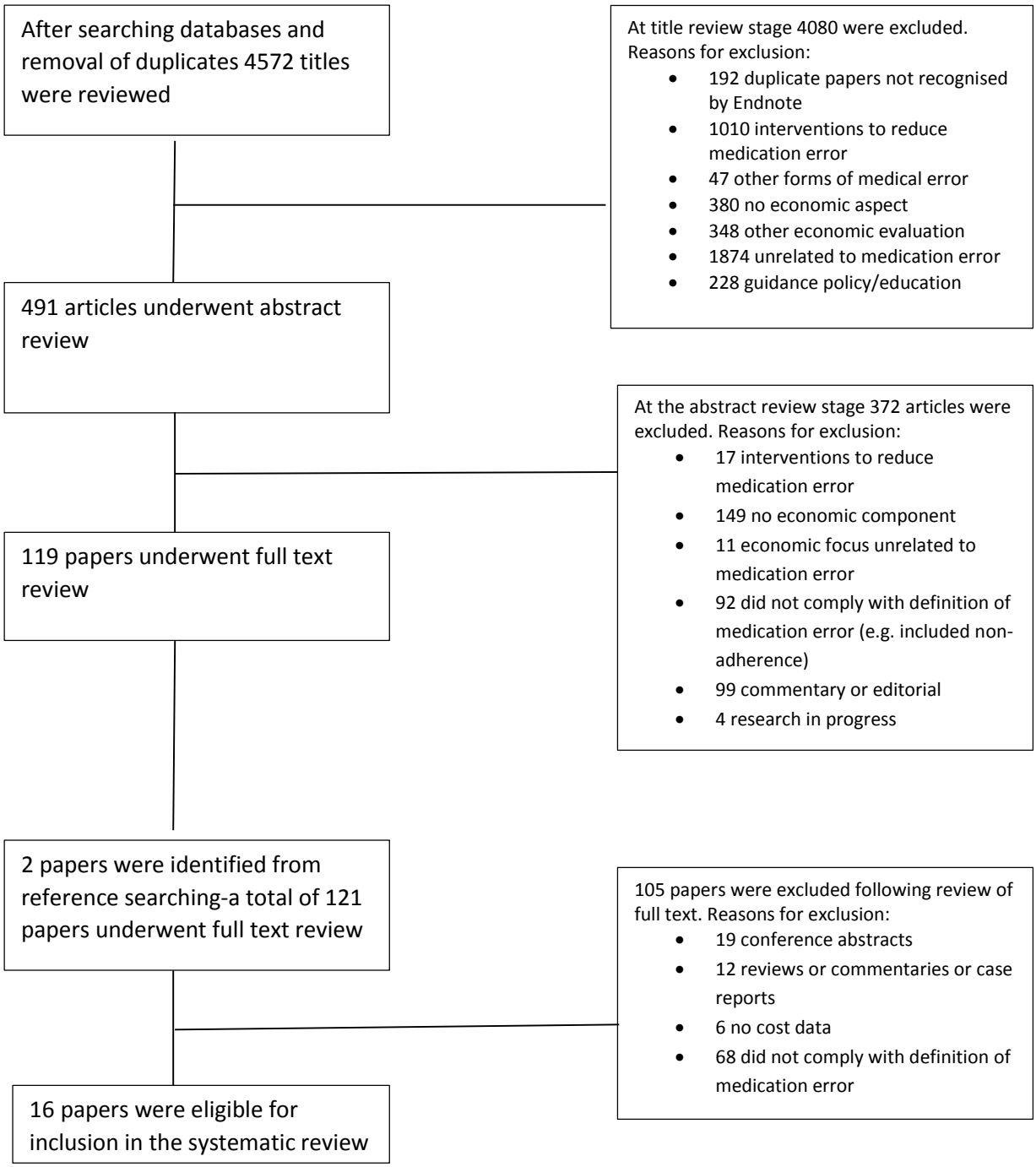


Figure 2 1: Reasons for exclusions of studies

First author Year	Title	Study design Methods used to identify error	Study population Study setting	Sample size patients	Sample size errors	Type of medication error (EMA Classification*)	Economic method	Outcome measure	Results
Studies reporting the economic impact of general medication error									
Choi (169) 2016	Incidence and treatment costs attributable to medication errors in hospitalized patients	Case control: Retrospective review of voluntary error reports completed by physicians, pharmacists and nurses	Hospital in patients (secondary /tertiary care), USA	57,554	470	Error of ordering, transcription, dispensing and administration. Errors with harm and without harm	Measuring of direct costs via recycled prediction and Blinder-Oaxaca methods	Additional hospital treatment costs incurred by patients experiencing a medication error	470 errors costed (with and without harm): Recycled prediction method: €8278.94 Blinder-Oaxaca decomposition method: €7851.87
Samp (170) 2014	Economic evaluation of the impact of medication errors reported by US clinical pharmacists	Cross sectional: Retrospective review of errors observed by clinical pharmacists in practice	Patients in primary/ secondary/ tertiary care, USA	Not stated	779	pADE **(Any preventable event that may cause or lead to inappropriate medication use or patient harm) Errors with harm Errors without harm	Measuring of direct costs, Economic modelling	Costs due to error: -monitoring (costs of monitoring tests) -medication regimen change (pharmacists dispensing fee) -permanent harm to patient (equated to harm resulting from stroke) combined with the probability of the outcome occurring	Cost per error (with and without harm): **1** €85.82 (base case) **2€** 86.58 USD (Monte Carlo simulation)

Table 2 2: Studies included in the systematic review

Hughes (171) 2012	The cost of adverse drug events in community hospitals	Comparative study (Case V total study population comparison): Retrospective review of patient records to identify preventable adverse drug events	Hospital inpatients (secondary/ tertiary care,) The Netherlands	2,100	190	pADE** (an error in the process of ordering, delivering or administering a drug resulting in patient harm) Errors with harm	Measuring of direct costs, opportunity and capital costs	Additional costs incurred by cases: **1** Hospitalisation cost (Operating cost, capital cost) **2** Length of hospital stay Unadjusted Adjusted for age, sex, illness severity, individual hospital	Cost per error (with harm): 1 Increase in average hospitalisation cost €6432.16/€4659.76 (mean/median) 2 Increase in average length of stay unadjusted 4.64/4.0 days (mean/median) adjusted 3.37/2.36 days (mean/median
Hoonhout (168) 2010	Nature, occurrence and consequences of medication-related adverse events during hospitalisation. A retrospective chart review in the Netherlands	Cross sectional: Retrospective review of patient records by a nurse and 2 physician reviewers to identify preventable adverse drug events	Adult inpatients in community hospitals (secondary care), USA	7,889	45	pADE** (harm caused by medication due to not following the professional standard or poor organisation of care) Errors with harm	Measuring of direct costs (potential costs)	Potential clinical costs as decided by an expert panel: **1** Excess length of stay **2** Excess hospitalization costs	Cost per error (with harm): **1** Excess length of stay 6.9 days (95% CI 2.2, 7.8) **2** Excess hospitalisation costs €3456.38 (95% CI €1172.,€6105.14)
Pinilla (172) 2006	Case control analysis of the financial cost of medication errors in hospitalised patients	Case control: Retrospective review of voluntary error reports completed by physicians, nurses and pharmacists	Adult inpatients in private hospital (tertiary care), Spain	172 (86 per arm)	86	Errors of validation, dispensing, administration, inattention, illegibility, labelling, packaging, lack of recording, misinterpretation Errors with harm Errors without harm	Measuring of direct costs	Only errors reaching the patient were costed Additional costs incurred by patients: **1** Hospital costs (cost of stay, drugs, radiology. Healthcare material) **2** Length of stay	63 errors costed (with and without harm): **1** €2184.93/€1510.15(mean/median) greater hospital costs **2** 303days of additional hospitalisation

Studies reporting the economic impact of an individual type of medication error or error within a specific population

Zaidi (173) 2015	Quantifying and reducing inhaler prescription errors in secondary care	Cross sectional: Review of incorrect prescriptions by pharmacists	Hospital inpatients prescribed an inhaler (secondary/ tertiary care), UK	Not stated	61	Prescription error (incorrect device, strength or drug) Intercepted medication errors	Measuring of direct cost	Cost of erroneous medication	Cost per error (intercepted error): €67.93 (mean)
Zahari (174) 2014	Duplication of oxycodone prescriptions at pharmacy department, Hospital University Sains Malaysia (HUSM)	Cross sectional: Retrospective, prescription review	Hospital inpatients Prescribed oxycodone 14-90 years (secondary/ tertiary care), Malaysia	212	103	Prescription error (duplication) EMA Classification unknown	Measuring of direct cost	Cost of medication	Total cost (EMA Classification unknown) €3308.80
Gharekhani (175) 2014	Frequency, types and direct related costs of medication errors in an academic nephrology ward in Iran	Cross sectional: Prospective, detection of medication errors by clinical pharmacists on a nephrology ward	Adult inpatients prescribed 1 or more medications in a hospital nephrology ward (tertiary care), Iran	350	1372	Prescription errors, transcription errors, drug administration errors Intercepted medication errors	Measuring of direct costs	Medication cost	1372 errors costed (intercepted): €7683.20
Al-lela (176) 2012	Estimation of immunization providers' activities cost, medication cost and immunization dose errors	Cross sectional: Retrospective review of immunisation records	Children 0-18months in Public Health Clinic (primary care), Iraq	528	483	Unnecessary (early) and invalid (extra) immunisation dose EMA classification unknown	Measuring of direct costs	**1** Cost of vaccine **2** Cost of service (time and average salary of administrator, physician and nurse)	483 errors costed (EMA classification unknown): 288 Early vaccine doses: Vaccine cost €244.51 Service Cost €497.14 195 Extra doses: Vaccine Cost € 176.52 Service Cost €325.30 Total cost: €1243.47

Lahue (177) 2012	National burden of preventable adverse drug events associated with inpatient injectable mediations: healthcare and professional liability costs	Case control: Retrospective review of medication error reporting system database for preventable adverse drug reactions with classification by 2 independent physicians	Hospital inpatients in receipt of an injectable medication (secondary/ tertiary care), USA	37,513	303	pADE** (an injury occurring as a result of an error in the medication use process) Errors with harm	Measuring of direct costs, modelling	Additional costs incurred by cases: -Inpatient services -Post discharge physician services combined with the probability of a pADE occurring	Cost of errors (with harm): 1 Cost of pADEs per hospital admission: €2879.03 (95% CI €2507.54, €3343.39) 2 Annual additional cost of pADEs in USA: €3.65 billion (95% CI €2.51, €4.73) 3 Average annual inpatient cost of pADEs per hospital: €576,420
Ranchon (178) 2011	Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs	Cross sectional: Prospective, observation of routine practice with errors being detected by pharmacists, pharmacy technicians, physicians, nurses,	Patients receiving anti-neoplastic agents in inpatient and day care units (secondary/ tertiary care), France	341	449	Errors of prescription, preparation, administration Intercepted medication errors	Measuring of direct costs (potential costs)	Potential clinical costs as decided by an expert panel 1 Cost of new potential hospitalisation 2 Cost of potential prolongation of hospitalisation 3 Cost of medication 4 Length of stay	449 errors costed (intercepted errors): 1 Cost new potential hospitalisation €9678.87 2 Cost potential prolongation of hospitalisation €65961.38 3. Medication cost €25842.29 Total 1-3: 101482.54 **4** 216 additional hospital days
Hellinger (179) 2010	The cost and incidence of prescribing errors among privately insured HIV patients	Comparative (exposed V unexposed): Retrospective review of health insurance database to detect prescription of anti-retroviral drugs and interacting drugs	Patients with HIV with private health insurance in primary/ secondary/tertiary care, USA	12,226	644	Drug-drug interaction Unknown EMA classification	Measuring of direct costs	Annual healthcare utilisation cost incurred by those exposed to error: -Inpatient: cost of stay, laboratory, physician fee -Outpatient: all services physician's fees in outpatient & emergency dept	Additional annual cost (EMA classification unknown): €4, 337.52

Cranshaw (180) 2009	Litigation related to drug errors in anaesthesia: an analysis of claims against the NHS in England	Cross sectional: Retrospective review of National Health Service (NHS) litigation authority database of clinical claims made against the NHS from patients alleging harm from drug errors in anaesthesia	Patients alleging harm from drug errors in anaesthesia in hospital (secondary/ tertiary care), UK	1067	62	Drug administration error (wrong drug, dose, order, route or drug omission) Errors with harm	Measuring of direct costs	Cost of clinical claims made against the NHS by patients	62 errors costed (with harm): €6,927078.96
Meissner (181) 2009	The rate and costs attributable to intravenous patient controlled analgesia (IV PCA) errors	Cross sectional: Retrospective review of database of medication errors reported on a voluntary basis by nurses and pharmacists	Hospital inpatients in receipt of IV PCA (secondary/ tertiary care), USA	Not stated	2356	Errors of communication, name confusion, storage, human factors, systems, ignored contraindications, equipment Errors with harm Errors without harm	Measuring of direct and opportunity costs (potential costs)	Potential clinical costs due to error as decided by an expert panel: <u>Direct costs</u>: additional drug therapy, lab tests, radiology, hospital length of stay, medical supplies, labour-nurse, pharmacist, physician <u>Opportunity costs:</u> missed revenue from the hospital that could have been generated should the error not have occurred have occurred	Cost per error (with and without harm): -Overall: €827.99 (mean) -Communication €1312.58 (mean) -Name confusion €101.31 (mean) -Storage: €262.29 (mean) -Human factor €803.76 (mean) -Systems error: €1004.13(mean) -Contraindicated: €657.41 (mean) -Equipment related €1338.47(mean) -Default: €451.41 (mean) 63 errors (with and without harm)

									1 €2184.93/€1510.15 (mean/median) greater hospital costs **2** 303 days of additional hospitalisation
Moura (182) 2009	Drug-drug interactions associated with length of stay and cost of hospitalisation	Comparative study (exposed V unexposed): Retrospective review of hospital pharmacy prescription records for drug interactions	Hospital inpatients > 18 yrs, length of stay>24hours (secondary /tertiary care), Brazil	589	220	Drug-drug interaction EMA Classification unknown	Measuring of direct costs	**1** Additional length of hospital stay patients exposed to drug-drug interaction **2** Association of exposure to drug-drug interaction with high cost of hospitalisation	Economic impact (EMA classification unknown): **1** Increased mean length of stay of 7 days **2** Positive association with high cost of hospitalisation (OR 3.1, 95% CI 2.19-4.42)
Field (183) 2005	The costs associated with adverse drug events among older adults in the ambulatory setting	Case control: Retrospective review of ambulatory medical records for preventable adverse drug events by trained clinical pharmacists and classification by a pharmacist and nehprologist	Elderly patients (65 years and over) enrolled in Medicare in ambulatory care: multispecialty group practice (primary care), USA	2500 (1225 per arm)	323	pADE** (Injury resulting from a drug error) Errors with harm	Measuring of direct costs	Additional health service utilization cost incurred by the case group: -Inpatient stay -Emergency Department visit -Outpatient care -Pharmacy (drug cost)	Cost per error (with harm): €1867.08 (95%CI €244.51, €4779.98)

*European Medicine's Agency (EMA) Classification:

1. Medication errors with harm
2. Medication errors without harm
3. Intercepted medication errors
4. Potential medication errors

**pADE: Preventable Adverse Drug Event

Quality Assessment

Table 3 outlines the parameters used to assess study quality. The viewpoint adopted was explicitly stated in only four of the studies (170, 172, 177, 181) but could be implied by the cost data used in all cases. The study population was provided by all studies, as was a clear description of the costs used in the analysis. Discounting was applicable to four of the included studies but was not conducted in any of the four studies. All other studies estimated costs over a one-year period or less. Less than half (n=7) of the studies measured incremental costs with a sensitivity analysis being conducted in only two of the included studies. Nine of the included studies reported medication errors as per the EMA guidance (62). Only one of the included studies fulfilled all applicable quality criteria (177).

Table 2 3: Assessment of study quality

Study	Viewpoint	Population	Relevant costs	Discounting	Incremental costs	Sensitivity analysis	Costs reported as per EMA* guide
Choi **(169)**	[+]	+	[+]	0	+	0	[+]
Samp **(170)**	+	+	[+]	N/A	0	+	+
Hughes **(171)**	[+]	+	[+]	0	[+]	0	+
Hoonhout **(168)**	[+]	+	[+]	N/A	0	+	+
Pinilla **(172)**	+	+	[+]	N/A	+	0	+
Zaidi **(173)**	[+]	+	0	N/A	0	0	[+]
Zahari **(174)**	[+]	+	0	N/A	0	0	0
Gharekhani **(175)**	[+]	+	[+]	0	0	0	0
Al-lela **(176)**	[+]	+	[+]	N/A	0	0	0
Lahue **(177)**	+	+	[+]	N/A	+	+	+
Ranchon **(178)**	[+]	+	[+]	N/A	0	0	+
Hellinger **(179)**	[+]	+	[+]	N/A	[+]	0	0
Cranshaw **(180)**	[+]	+	[+]	N/A	0	0	+
Meissner **(181)**	+	+	+	0	0	0	+
Moura **(182)**	[+]	+	[+]	N/A	+	0	0
Field **(183)**	[+]	+	[+]	N/A	+	0	+

Notation based on Rothfuss et al (184): +, present; [+], partly fulfilled; 0, absent. N/A, non-applicable

*EMA: European Medicines Agency

Study design and population:

Nine studies were cross-sectional in design (168, 170, 173-176, 178, 180, 181) four of case-control design (169, 172, 177, 183)and three comparative studies of modified case-control design (171, 179, 182)

Studies were conducted primarily among hospital inpatients (n=12) (168, 169, 171-175, 177, 178, 180-182) with four studies including patients in primary care (170, 176, 179, 183) ; two of which assessed economic impact exclusively among primary care patients (176, 183).

The majority of studies (n=15) examined economic impact of error in an adult study population (168-175, 177-183). Of these 15 studies, two examined economic impact in elderly patients (>65 years) (168, 183). Field et al assessed economic impact of medication error solely among elderly patients (183) whereas Hoonhout et al completed a separate assessment of economic impact of medication error in patients <65 years and >65 years respectively (168). A further eight of the included studies examined economic impact within specific patient groups namely: patients experiencing drug errors during anaesthesia (180), hospital inpatients on a nephrology ward (175), patients with HIV (179), hospital inpatients in receipt of an injectable medication (177), hospital inpatients in receipt of intravenous patient controlled analgesia (181), hospital inpatients in receipt of anti-neoplastic agents (178), patients prescribed oxycodone (174) and hospital inpatient prescribed inhaled medication (173). A single study described economic impact in a paediatric population (children 0-18 months)(176).

Methods used to establish economic impact:

Of the included studies 12 measured actual costs pertaining to medication errors to which the study population was exposed (169, 171-177, 179, 180, 182, 183). Three studies measured potential costs

due to medication error as decided by an expert panel (168, 178, 181). Three studies used economic modelling (169, 170, 177). The first of these calculated costs using economic methods inclusive of variables such as age, sex and co-morbidity (169). The second combined the costs of errors detected among the study population with the probability of the error occurring (177) and the third combined the cost of errors detected with the probability of the outcome measure occurring (170).

Parameters used to establish economic impact:

Healthcare costs:

Of the included studies, fifteen calculated healthcare costs associated with medication error (168-179, 181-183). Healthcare costs were comprised of costs associated with hospitalisation, medication, outpatient care and primary care. The parameter used most frequently to establish economic impact of medication error in the included studies was cost of hospitalisation (n=11)(168-172, 177-179, 181-183).

1. *Hospitalisation costs:*

A total of 11 studies measured hospitalisation costs, all demonstrating increased economic burden associated with medication error (168-172, 177-179, 181-183). One of the studies using hospitalisation costs expressed economic impact in terms of increased mean length of stay and a positive association with a high cost of hospitalisation (182). In the 10 other studies that expressed economic impact in monetary terms; five used health insurance databases (170, 177-179, 183) to calculate hospitalisation costs, three used hospital account information (169, 171, 172), one used a combination of information from hospital accounts and health insurance databases (168) and one used a combination of fee schedules and published literature (181). The definition of hospitalisation costs varied between all 11 studies.

Six of the included studies used hospitalisation costs as an isolated measure of economic impact (168, 169, 171, 172, 181, 182). Moura et al assessed economic impact among hospital inpatients in

Brazil exposed to prescribing error. Economic impact was not expressed as a monetary figure but rather by mean length of hospital stay and association with cost of hospitalisation in exposed patients (182). In an American study Choi et al described excess hospital treatment costs for those experiencing a medication error. No breakdown of costs was given and hospital database information was used to calculate costs (169) . In a study conducted among hospital inpatients in the Netherlands Hoonhout et al described excess hospitalisation costs among those experiencing a pADE. Costs pertaining to medical and nursing staff, drugs, equipment, inpatient stay and medical procedures were described. A combination of hospital account information and health insurance (Dutch Healthcare authority) information were used in this study (168). In a Spanish study Pinilla et al calculated additional hospitalisation costs incurred by patients experiencing medication error. Costs were inclusive of inpatient stay, drugs, scans and healthcare material and hospital account information was used to calculate costs (172).

Two of the studies using hospitalisation costs as an isolated measure of economic impact used more in-depth costing (171, 181). Hughes et al calculated additional hospitalisation costs incurred by patients experiencing a pADE. The study was conducted among hospital inpatients in the USA and additional hospital operational and capital costs were calculated using hospital account information. Hospital operating cost was defined as “the fixed and variable costs for operating a hospital for example, labour and maintenance” and capital costs defined as “the infrastructural cost of buildings and equipment” (171). Meissner et al calculated hospitalisation costs among hospital inpatients experiencing medication error relating to intravenous patient controlled analgesia (IV PCA). Costs were inclusive of medication, laboratory tests, radiological imaging, inpatient stay, medical supplies, medical pharmacy and nursing staff. Additionally, Meissner et al included missed hospital revenue or opportunity cost defined as “income that could have been generated should the error not have occurred” when calculating hospitalisation costs. Costs were calculated using fee schedules and published literature (181).

A further five studies used hospitalisation costs in combination with other measures. Field et al assessed the economic impact of pADEs among elderly ambulatory patients in the USA. Hospitalisation costs in this study were inclusive of inpatient stay and emergency department visits. Additionally, medication costs and outpatient costs inclusive of physician fee, diagnostic tests, laboratory tests, home health visits, medical equipment and ambulance fee were calculated using a health insurance (Medicare) database (183). Hellinger et al assessed the economic impact of prescribing error among patients with HIV in the USA. Hospitalisation costs inclusive of inpatient stay, laboratory and physician fee were calculated as were additional outpatient costs inclusive of all services and physician fees in outpatient and emergency departments using health insurance (Marketscan) database information (179). Lahue et al described economic impact associated with pADEs among hospital inpatients in the USA in receipt of an injectable medication. Hospitalisation costs defined as inpatient services were calculated with additional costing of post discharge physician services using health insurance (Medicare) cost (177). Ranchon et al calculated hospitalisation costs inclusive of inpatient stay in addition to medication costs in hospital inpatients in France receiving anti-neoplastic agents who were exposed to medication error. Cost information was obtained from the French health insurance system (178). Samp et al assessed economic impact in patients experiencing a pADE by using 3 parameters: (1) hospitalisation costs represented by inpatient monitoring costs, (2) cost of changes in medication defined as a pharmacists dispensing fee and (3) costs of permanent harm to a patient defined as the cost of a stroke. Cost information was obtained from health insurance database (Medicare) information and from the literature (170).

2. *Medication costs:*

Cost of medication was used as a measure of economic impact in eight of the included studies. All 8studies demonstrated an increase in medication costs due to medication error. Methods to determine the cost of medication varied between studies and in three of the studies it was not explicitly stated how cost of medication error was calculated.

Three studies used medication cost as the sole measure of economic impact (173-175). Gharekhani et al calculated the economic impact of medication error among patients on a nephrology ward in Iran by calculating the cost paid by the patient or the patient's insurance agency for erroneous medications and the equipment required for medication administration such as syringes or infusion sets (175). Zahari et al calculated the cost of medication error due to prescription duplication and defined cost of medication broadly as "current drug price"(174). Zaidi et al calculated the cost of an incorrectly prescribed inhaler using the hospital drug formulary (173).

Medication cost was used to measure economic impact in combination with other parameters in 6 other studies (168, 172, 176, 178, 181, 183). Al-lela et al reported the cost of erroneous childhood vaccines and used medication cost in combination with immunisation service cost. Medication cost was calculated as vaccine cost obtained from the Department of Health (176). Field et al used hospitalisation and medication costs in their analysis. Medication costs were defined as "the average wholesale cost on the day they were dispensed"(183). Hoonhout et al included medication costs as a subgroup of hospitalisation costs. Medication costs were obtained from "Dutch guideline prices" for hospitals (168) . Meissner et al also included medication costs within hospitalisation costs. The method of establishing costs specific to medication is not explicitly stated (181). Pinilla et al also included medication costs within hospitalisation costs. Overall costs were derived from the hospital accounting system but how costs specific to medication were calculated was not specifically stated (172). Ranchon et al used medication cost in combination with hospitalisation cost. Medication cost pertained to cost of anti-neoplastic agents. It was implied but not explicitly stated that medication cost was derived from French public health insurance data (178).

Costs for particular class of medication were provided in three of the included studies namely vaccines, inhaled medications and oxycodone (173, 174, 176). No other study specified the type of medication being costed.

3. *Primary care costs:*

Direct costs specific to primary care were calculated in two studies. Al-lela et al costed the time of primary care physicians, nurses and administrators in providing erroneous childhood immunisations in public health clinics in Iraq. Salary information was obtained from the Department of Health in Iraq (176). The errors identified occurred in primary care and the subsequent cost consequences were costs incurred in primary care. As previously described, Field et al included physician fee, diagnostic tests, lab tests, home health visits, medical equipment and ambulance costs in their analysis of the economic impact of pADEs among ambulatory elderly patients in the USA. It was unclear if the errors identified occurred in primary care or in the hospital setting. Separate primary care costs were not available in this study r as the economic impact reported was a combination of both hospital and primary care costs (183).

4. *Outpatient care costs:*

Direct costs pertaining to outpatient care were calculated in three studies. All three studies used health insurance database information when calculating costs. Field et al included costs pertaining to physician fee, diagnostic tests, laboratory tests and medical equipment (183). Hellinger et al calculated costs pertaining to services and physicians fees in outpatient facilities but did not provide a breakdown of what the services included (179). Lahue et calculated costs pertaining to post discharge physician services but did not specify what the services included (177).

Non-healthcare costs:

One of the included studies calculated costs that were not related to the provision of healthcare but rather to health-professional litigation costs associated with medication error (180).

1. *Litigation costs:*

Litigation costs, defined as the cost of clinical claims made against the National Health Service (NHS) in the UK regarding medication errors during anaesthesia, were used in a single study and were used

as an isolated measure of economic impact. Cost information was obtained from the NHS litigation authority database (180).

Economic impact of medication error:

Thirteen of the included studies expressed economic impact in monetary terms with one study (182) using length of hospital stay as the primary outcome measure. The economic impact of medication error calculated by the different studies varied considerably.

Five of the included studies reported a cost for medication errors associated with harm (168, 171, 177, 180, 182, 183), four studies reported a combined cost for medication errors associated with harm and without harm (169, 170, 172, 181) and three studies reported costs for intercepted medication error (173, 175, 178).

Cost per medication error was extracted from 12 of the included studies: see Table 4. A cost per error for general medication error was available in five of the included studies (168-172). The other seven costs per error pertained to individual types of medication error or medication error within a specific population (173, 175, 176, 178, 180, 181, 183). Mean cost per error per study ranged from €2.58 to €111,727.08. The lowest costs per error were those associated with unnecessary and invalid immunisations in children (176) and the highest costs per error were litigation costs associated with medication errors during anaesthesia (180).

Table 2 4: Reported economic impact and cost per medication error

Study	Reported economic impact	Cost per error (Euro 2015)
General medication error		
Choi **(169)**	Cost of 470 medication errors among hospital inpatients:	17.6/16.7* **Figures from 2 different mathematical models*
Samp **(170)**	Cost per pADE	86.13
Pinilla **(172)**	For 62 medication errors among hospital inpatients: Cost Excess length of stay	2,184.93/1510.15 (mean/median)
Hoonhout **(168)**	Per hospital inpatient with pADE: 1. Excess length of stay 2. Cost per pADE	3456.38
Hughes **(171)**	Per community hospital inpatient with pADE: 1. Excess length of stay 2. Cost per pADE	6,432.16/4,659.76 (mean/median)
Individual type of medication error within a specific population		
Al-lela **(176)**	Cost of 483 erroneous vaccines	2.58
Gharekhani **(175)**	Cost of 1372 medication errors on a nephrology ward	5.6
Zaidi **(173)**	Cost per erroneous inhaler prescription	67.93
Ranchon **(178)**	For 449 errors among patients receiving antineoplastic agents Cost Excess length of stay	226.02
Meissner **(181)**	Cost per medication error among inpatients in receipt of IV patient controlled analgesia	827.99
Field **(183)**	Cost per pADE in ambulatory elderly patients	1, 867.08
Cranshaw **(180)**	Cost of 62 drug errors in anaesthesia	111,727.08

pADE=Preventable adverse drug event

Types of medication error:

Cost information on an individual type of medication error was available in 10 of the included studies. Meissner et al reported individual costs for errors of communication, name confusion, storage, human origin, systems, contraindicated medication, equipment and default respectively (181). Four further studies reported the economic impact of prescribing error (173, 174, 179, 182). Five of the included studies reported economic impact of pADEs (168, 170, 171, 177, 183). None of the studies reported errors of omission.

Subgroup analysis:

Three subgroups were identified and are described in Table 5; firstly, the economic impact of prescribing error, secondly the economic impact of pADEs and thirdly the economic impact of medication error in elderly patients. Four of the included studies reported economic impact of prescribing error (173, 174, 179, 182). Five of the included studies reported economic impact of pADEs (168, 170, 171, 177, 183) . Two of the included studies assessed economic impact of medication error in elderly patients (>65 years) (168, 183). Study population and measures of economic impact varied between studies.

Table 2 5: Subgroups (prescribing error, pADE, medication error in elderly patients)

Error	Study population	Measure of economic impact	Reported economic impact
Prescribing error			
Drug-drug interaction **(179)**	Patients with HIV	Additional annual healthcare utilisation cost	€4274.50
Drug-drug interaction **(182)**	Hospital inpatients	Increased length of hospital stay	7 days
Drug duplicaton **(174)**	Patients prescribed oxycodone	Total cost of medication	€3,244.97
Error of preparation, strength or dose **(173)**	Patients prescribed inhalers	Cost per medication error	€67.93
pADE			
pADE **(171)**	Community hospital inpatients	Additional hospitalisation costs per pADE	€6314.35/4574.41 (mean/median)
pADE **(177)**	Hospital inpatients receiving an injectable medication	Additional hospitalisation or post discharge physician services costs of pADEs: 1. Per hospital admission 2. Annual cost 3. Annual inpatient cost	 1. €2879.03 2. €3.6 billion 3. €567,943.22
pADE **(170)**	Patients in hospital and primary care	Costs of monitoring, medication regimen change, permanent harm to patient per pADE	€84.56 (€85.31 using sensitivity analysis)
pADE >65 years			
pADE **(168)**	Hospital inpatients	Additional hospitalisation costs per pADE 1.Patients <65 years 2.Patients>65 years	 €3277.29 €3440.88
pADE **(183)**	Ambulatory patients >65years	Additional primary and secondary health care utilisation cost per pADE	€2599.96

pADE=Preventable adverse drug event

2.5 Discussion

Studies included in this review assessed the economic impact of medication error in nine different countries over an 11-year period (2004-2015). Considerable variability existed between studies in terms of study design, study population, types of medication error, cost parameters and financial

information sources. Hence meaningful comparison of economic impact between studies was limited. A difference of greater than €100,000 was detected between the lowest and highest costs per individual medication error. Establishing an overall pattern was possible however as all of the included studies found medication error to be a significant economic healthcare burden in their respective settings with all studies reporting increased financial costs or length of hospital stay.

Three of the included studies did report a similar cost outcome of additional healthcare utilisation costs per pADE. The highest cost of €6314.35/4574.41 (mean/median) was reported in a study among inpatients in community hospitals in the USA (171) with lower costs of €3440.88 reported in a Dutch study among elderly hospital inpatients (168) and of €2599.96 in an American study among elderly ambulatory patients (183). The study reporting the highest cost per pADE used additional capital and operating costs in their calculation of hospitalisation cost (171) which may account for the difference in cost and may suggest that studies not including such costs are under estimating the true economic impact of medication error. The reason for lower costs in the American study among ambulatory elderly patients compared to the Dutch study among elderly inpatients may be due to the differing countries and healthcare systems. Additionally, the difference may be due to increased morbidity among hospital inpatients compared to ambulatory patients hence contributing to greater costs. As only hospitalisation costs are reported in the Dutch study however, the difference could also suggest that medication errors among patients in primary care are associated with a lower economic burden than those occurring in a hospital setting.

The review identified that the economic impact of medication error has been predominantly explored in the hospital setting and that hospitalisation costs represent the parameter used most frequently to establish the economic impact of medication error. However, variability was detected in both the definitions of hospitalisation costs and the sources of financial information used between studies. Additionally, it was identified that limited parameters have been used to date to establish economic impact of medication error, with included studies using only four parameters in addition

to hospitalisation costs namely; medication costs, outpatient costs, primary care costs and litigation costs. Although medication costs were reported for half of the studies, methods to establish medication cost were not explicitly stated nor could they be isolated from overall costs reported in three of the included studies. A minority of studies (176, 177, 179, 183) reported outpatient costs and costs occurring in primary care.

The review established that to date primarily healthcare costs have been used to determine the economic impact of medication error (168-179, 181-183), with litigation costs being the only additional cost parameter used (180). Only two of the included studies conducted more in-depth costing of health care related costs through the calculation of hospital operating and capital costs (171)and opportunity cost pertaining to missed hospital revenue (181). Hence the true economic burden of medication error may have been underestimated to date.

Economic impact associated with an individual type of medication error could only be extracted in five of the included studies (173, 174, 179, 181, 182). Although four studies reported the economic impact of prescribing error and hence provided information on the economic impact associated with medication error in a particular health care professional group; namely doctors, the outcome measures varied considerably limiting comparison.

Comparison with previous reviews

No previous systematic review has examined the economic impact specifically pertaining to medication error. Lassetter et al conducted a literature review on quality of care and cost issues pertaining to medical error, drug related problems and medication errors in 2003. Although a substantial economic impact was reported, the authors did not distinguish between the economic impact of drug related problems and medication error in their review (185). Chiatti et al conducted a systematic review on the economic burden of inappropriate prescribing, lack of adherence and compliance and adverse drug events in the elderly. Again although a substantial economic burden

was identified, the authors did not separate preventable adverse drug events that are consistent with medication error from adverse drug events in general (186).

Non-adherence to medication and potentially inappropriate prescribing have been included in other reviews (185, 186) but were excluded from this systematic review. Non-adherence, may represent an intentional decision made by an individual patient rather than the unintentional over or underuse of medication i.e. medication error. Inappropriate prescribing refers to the use of a drug where the risk of an adverse drug event outweighs the clinical benefit, particularly if a safer or more effective alternative therapy is available (37). Potentially inappropriate prescribing refers to such inappropriate prescribing as identified by standardised tools such as Beer's criteria and STOPP/START (37). Not all potentially inappropriate medications detected in this manner necessarily represent medication error however. The possibility exists of an intentional and informed decision on the part of the prescriber rather than the occurrence of true medication error.

Overall completeness and applicability of evidence:

Due to the heterogeneity of the included studies a meta-analysis could not be performed.

Half of the included studies examined the economic impact of medication error within a specific patient group and hence the results may not be generalizable to a general patient population.

Additionally, the majority of studies used a broad definition of medication error and did not stratify individual types of medication error in their cost analysis. Hence the evidence was insufficient to identify the types of medication error most likely to result in economic burden or to identify a particular group of health care professionals responsible for errors likely to result in economic burden.

Errors of omission were absent from the included studies. Hence where medication costs are used to calculate the economic impact of medication error, the true economic burden may be underestimated.

None of the studies looked at economic implications from a patient or societal perspective. Indirect costs were largely absent from studies to date with no studies considering costs such as loss of earnings. Quality of life was not considered in any of the included studies. This is in keeping with the findings of a recent review conducted by Patel et al of approaches used for calculating the cost of medication errors (187). In addition, the costs explored from a primary care perspective were limited and costs pertaining to time of general practitioners and pharmacists were absent. GPs and community pharmacists as accurate providers of patients' medication information, play a key role in reducing medication error (121). A study conducted in the United Kingdom found that a pharmacist involved in dispensing a prescription with errors or missing information spent on average 5.7 minutes per problem with a range from 0.2-48 minutes (188). A similar time burden amongst GPs is likely and would suggest a significant unexplored economic burden.

Quality of the evidence:

As methodology varied between studies and details of how cost information was obtained was lacking in a number of studies, it is not surprising that a lack of consistency was identified between results. An overall absence of high quality studies in this area was highlighted with only one study (177) fulfilling all applicable quality criteria. Additionally, reported costs in 3 studies were based on potential costs as decided by an expert panel (168, 178, 181). The potential for subjectivity exists and evidence from the opinion of expert groups has traditionally been regarded as the lowest level in the hierarchy of levels of evidence (189).

Potential biases in the review process:

The year of publication was used in 4 of the included studies to inflate costs to 2015 values as no year was specified in the studies. This could result in a potential inaccuracy if the cost information was in fact obtained in an earlier year. The review was limited to English language publications and as grey literature was not sought may also be subject to a publication bias. Assessment of study

quality was challenging due to variability in terms of study design of the included studies. The approach used for quality assessment was applicable to all of the included studies but only assessed quality from economic and error reporting perspectives. Standardised tools assessing quality from an epidemiological perspective could not be applied universally to the studies (159). Additionally, other checklists for critical appraisal of economic studies pertained specifically to economic evaluations and could not be applied (160, 161).

Recommendations:

In order to allow meaningful comparison between studies assessing the economic impact of medication error, standardisation in terminology pertaining to medication error is required. Future studies should provide additional information on firstly the types of medication error being costed and secondly the consequences of errors in terms of patient harm. The recent EMA guidance on recording, coding, reporting and assessment of medication errors has the potential to enhance future work in this area (62). Future studies would be strengthened by applying a case-control design so that incremental costs can be calculated. Greater detail is also required from an economic perspective. Clear descriptions of cost sources and explicit cost calculations are required as recommended by Patel et al in their recent review of approaches for calculating the cost of medication errors (187). Additionally, the timeframe during which the costs are calculated should be specified. A greater breadth of costs also needs to be explored in future studies. Direct costs, indirect costs and psychosocial costs should all be included to determine the true economic burden of medication error.

2.6 Conclusion

This systematic review suggests that the true economic impact of medication errors has not been accurately estimated to date. Studies evaluating the economic impact of medication error have been

primarily conducted among hospital inpatients and have focused mainly on the hospitalisation costs associated with medication error. Information on the cost of medication error in primary care or at the primary secondary care interface is limited. Restricted parameters were used to establish cost with limited information on costs such as healthcare professional time. Variability was detected in methodology and many studies were of poor quality. Future work is required firstly to assess the economic impact of individual types of medication error and secondly to assess economic impact in a broader context inclusive of primary care, patients and society.

3 MEDICATION RECONCILIATION: TIME TO SAVE? A CROSS SECTIONAL STUDY FROM ONE ACUTE HOSPITAL

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UNDER REVIEW

3.1 Abstract

Background

Medication errors frequently occur at the primary secondary care interface and are associated with morbidity, mortality and economic burden. Medication reconciliation is an established intervention to reduce such errors. Current evidence supports the practice of medication reconciliation but has not demonstrated a reduction in healthcare costs. Complexity and resource intensity have been highlighted as issues.

Aim

To examine an existing process of medication reconciliation to identify factors associated with additional time for medication reconciliation and determine if this increased duration of medication reconciliation is associated with detecting errors of clinical significance.

Methods

A cross sectional study was conducted in the geriatric medicine ward of an acute hospital. Issues arising during medication reconciliation incurring time burden additional to the usual process were logged and quantified by pharmacists. Regression analyses investigated associations between patient characteristics and clinically significant errors and additional time. Cost for additional time was calculated in terms of hospital pharmacist salary. Projected five year costs for all patients in all hospitals in Ireland were calculated.

Results

89 patients were included in the final analysis. Approximately half of the sample (n=42) required additional time for medication reconciliation. Having a personal record of medication at admission (OR 3.30, 95% CI: (1.05 to 10.42), p=0.004) was a significant predictor of additional time. No significant associations were found between the occurrence of clinically significant error and

additional time ($p>0.05$). The most common reason for additional time was clarifying issues pertaining to illegibility or missing faxed primary care medication information. Projected annual five year costs for the mean additional time of 3.75 minutes of the study were €1.8-1.9 million.

Conclusion

Spending additional time on medication reconciliation is associated with economic burden and may not yield benefit in terms of capturing clinically significant errors. Improving communication of medication information between primary and secondary care and developing improved patient held records of medication may improve efficiency within the medication reconciliation process.

3.2 Introduction:

Medication error is the single most preventable cause of patient harm, with errors being particularly common among older adult patients as they transition between primary and secondary care (1, 4, 6, 190). Adverse drug events (ADEs) associated with medication error result in patient morbidity and mortality (191-193). Significant associated economic burden has been reported (18, 183, 194). With a growing aging population worldwide, the prevalence of medication error among multimorbid patients taking multiple medications is increasing (23, 24). Establishing effective methods to reduce medication error is currently an international priority in healthcare (84, 128, 141, 195).

Medication reconciliation (the term used for identifying and correcting medication errors as patients transition between different stages and settings of care) aims to reduce the occurrence of medication error (196). Widely advocated by professional and accrediting bodies, the goal is to develop an accurate list of a patient's medications to avoid errors such as omissions, duplications, dosing errors or drug interactions (128, 140, 197, 198). Hospital admission has been identified as a point in care where medication error is likely to occur and the frequent occurrence of error in medication history-taking at admission is well documented (127, 128, 199). Such errors have the potential for adverse consequences not only during the inpatient stay, but also at, and following, discharge (190, 200-202). Hence, the gold standard medication reconciliation process should begin within 24 hours of admission. This process involves reviewing and combining available sources of pre admission medication information to form the best possible medication history (BPMH), comparing this to prescribed medications to make a definitive list and communicating the new list to caregivers and the patient (128, 203). The process has strong face validity; as capturing medication errors of clinical significance has the potential to positively impact not only patient morbidity and mortality, but also healthcare costs by preventing adverse drug events (128, 139).

Though efforts have been made at an international level to standardise the process of medication reconciliation, consensus regarding the optimal method has not been reached (138). International guidance recommends a multidisciplinary approach integrated into existing processes for medication management and patient flow (128). Though different strategies have been reported for medication reconciliation (130, 204, 205), the majority of the literature to date has focused on pharmacist led interventions (136, 138). Recently, concerns regarding the feasibility of implementation of medication reconciliation on a universal basis across health care systems have been voiced (147). In practice, medication reconciliation interventions may not necessarily integrate seamlessly into usual care. Complexity, which affects workflow, and resource intensity resulting in opportunity cost, have been highlighted as issues (136, 147).

Despite the body of evidence that exists to support the practice of medication reconciliation (56, 69, 202, 206), current evidence has failed to demonstrate a reduction in healthcare utilisation and costs (136). In practice, medication reconciliation is often implemented only among high-risk patients such as complex polypharmacy patients (128). With medication reconciliation representing a potential solution to the growing issue of medication error however, there is an urgent need to look at how cost-effective, universal implementation can be achieved (136). It is timely, therefore, to reflect on what factors may contribute to the increased use of resources and resulting costs associated with current modalities of medication reconciliation.

Medication reconciliation is a multistage process and is time intensive. Studies show that the time taken to complete the process for an individual patient varies between 20 -92 minutes (70, 197, 198, 207). Currently, there is a paucity of evidence to explain the large variation in time for medication reconciliation with a lack of clarity in the literature regarding what factors may cause an increased time burden within the medication reconciliation process. As time incurred in providing the service has an associated cost, additional time can only be of economic benefit if it is associated with capture of clinically significant errors and hence the prevention of patient harm. It is currently

unclear if increased duration of medication reconciliation is of greater benefit in terms of capturing errors of clinical significance. The dual aims of this study were; (i) to determine factors associated with additional hospital pharmacist time for medication reconciliation and (ii) to determine if this increased duration of medication reconciliation is associated with detecting errors of clinical significance.

3.2 Methods

This cross-sectional study was conducted in the geriatric medicine ward in an urban university teaching hospital situated in the south of Ireland. Medication reconciliation is routinely conducted by hospital pharmacists following the admission of an older adult patient to this ward.

Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals (Date: 27-06-17, Ref: ECM 3 (aaa) 04/07/19).

Though prior studies have examined medication reconciliation processes in terms of time taken, no previous study has reported factors associated with additional time, nor tested for association of additional time with errors of clinical significance. The existing literature could hence only inform study design in a broad sense. To address pragmatic issues in terms of design of this study, an initial meeting was convened with consultant gerontologist (KO'C), clinical pharmacist (CH), academic pharmacist (AF) and lead researcher (EW). EW subsequently met with epidemiologist (PK), academic GP (CB) and economist (AK) to devise a pragmatic study design that could address the research question in a robust manner whilst acknowledging, and operating within, the unavoidable constraints of a busy working hospital environment. It was hence agreed to collect data from a census sample of patients over a 3-month period during the provision of routine care. Data were

collected during the 3-month period June-August 2017. All patients admitted to the ward during the study period were eligible for inclusion.

During the study period four hospital pharmacists completed routine medication reconciliation using the standard process which is outlined in Figure 1. Medication reconciliation is performed within working hours Monday to Friday and is completed (where possible) within 24 hours of a patient's admission. The process outlined in Figure 1 is consistent with the standard steps outlined in international guidance on medication reconciliation (128, 140, 203) and the previously established median time for completing the process is 47.5 minutes, in keeping with the literature (197, 203)(Appendix 1). In conducting medication reconciliation, the hospital medical record of the patient, i.e. the paper chart, is reviewed initially by the pharmacist. A list of medications is requested from the patient's GP, the community pharmacist or the residential care facility by telephone and subsequently received by fax. The patient's own medication (or list of same) is used as an additional source of medication information when available. The BPMH is compiled for each patient and subsequently compared with the inpatient drug chart. Errors are noted and the medical team notified.

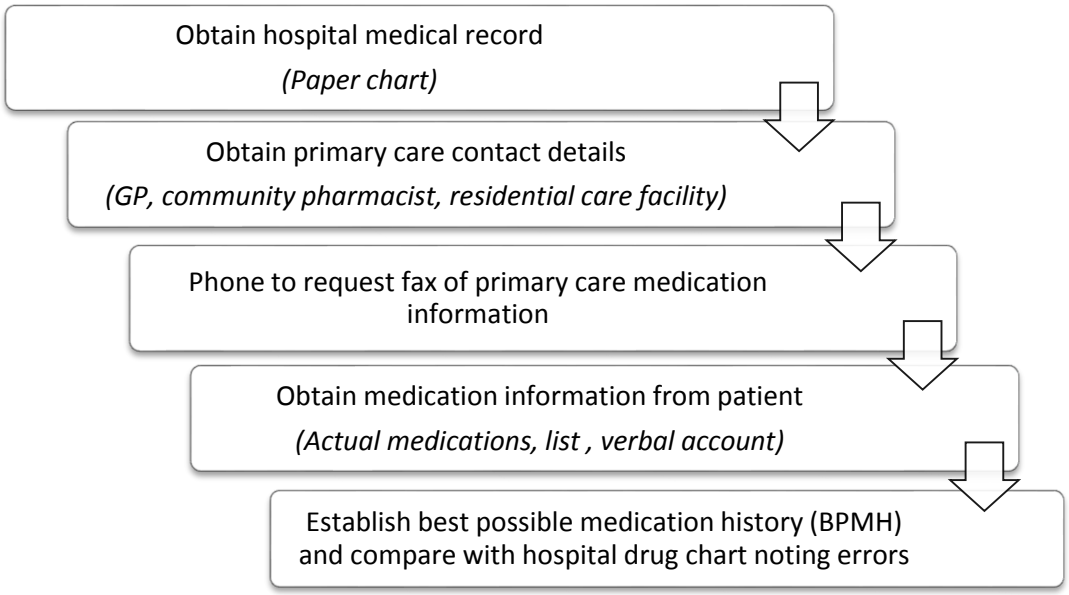


Figure 3 1: **The process for medication reconciliation**

During the three-month study period, pharmacists were asked to log issues arising during medication reconciliation that incurred a time burden additional to the usual process outlined in Figure 1; to describe the nature of the issue arising; and to quantify, in minutes, the additional time spent. In addition, data on the following variables were collected on patients undergoing medication reconciliation during the three-month study period: age, gender, socioeconomic status (SES), number of co-morbidities, functional status, day and time of hospital admission, presence of a patient held written record of medication (list or actual medications), patient's ability to provide accurate verbal account of medication, presence of an accompanying relative or other adult at time of hospital admission and whether referral to hospital was by a GP /other doctor versus self-referral. Medical card status was used as a proxy measure for SES. Functional status was assessed in terms of independence relating to continence, mobility, feeding and dressing as documented in the patient's notes. The patients' ability to provide an accurate verbal account of medication was judged by the pharmacist. Selection of variables was informed by review of the literature and expert opinion of the research team (KO'C, AF, LS, PK, CB, EW). The variables listed represented the most appropriate range of explanatory variables that could be collected during the provision of routine care.

Medication errors identified were recorded. Errors were reviewed independently by a GP and a hospital pharmacist to establish clinical significance. Any disagreements were resolved with the input of another GP. Errors were classified as significant, serious and life-threatening in ascending order of clinical significance in accordance with the approach described by Pevnick *et al* (70). Error severity weights of 1^2=1 (significant), 2^2=4 (serious) and 3^2=9 (life-threatening), respectively, were chosen to reflect the relative capacity of each error type to cause patient harm, if undetected, and an error score was calculated for each patient (70).

Data were anonymized, coded and entered into an Excel (Microsoft Excel; IBM Corp.) spreadsheet on a password protected computer. Statistical analysis was conducted using IBM SPSS version 24

(IBM SPSS Statistics for Windows, Version 24.0. Released 2016. Armonk, NY: IBM Corp.) and Stata Version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). Descriptive statistics were obtained.

Additional time taken was split into two categories as almost half the study sample did not require additional time for medication reconciliation (no: n=42; yes: n=47). Binary logistic regression was used to investigate associations between additional time being required for medication reconciliation (yes/no) and gender, age, functional status, SES, number of co-morbidities, time of hospital admission, written record of medication, number of medications, knowledge of medication, being accompanied at admission and being referred by a GP/other doctor. Univariable and multivariable binary logistic regression analyses estimated unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for additional time taken. As the sample size was relatively small from a statistical perspective and the sample size requirement for binary logistic regression is high (208), bivariate screening (univariable analyses) was used to decide which independent variables to include in the multivariable model (209). Independent variables with $p<0.10$ in the univariable analyses were included in the multivariable regression model.

To investigate factors associated with number of medication errors and error score, regression models for count data were used. Several regression models were compared to determine the model that best fit the data. The models compared were: (1) Poisson; (2) Negative Binomial; (3) zero-inflated Poisson and (4) zero-inflated Negative Binomial. The Poisson regression model assumes a Poisson distribution where the variance equals the mean while the Negative Binomial model allows the variance to be greater than the mean by including an over-dispersion parameter (alpha). The zero-inflated models allow for an excess number of zeros (with respect to a Poisson or Negative Binomial distribution). The likelihood ratio test was used to determine if the Negative Binomial model was a better fit than the Poisson model. A zero-inflated model was compared with its corresponding non-inflated model (e.g. zero-inflated negative binomial vs negative binomial) using

the Vuong test (210). Robust standard errors were used as recommended by Cameron and Trivedi (211). Zero inflated negative binomial regression analyses estimated incidence rate ratios (IRRs) and their corresponding 95% CI for numbers of medication errors and error scores.

Statistical significance was determined using a p value of <0.05

The cost of additional time taken for medication reconciliation was calculated from a hospital perspective. This was based on the hourly cost of employing a hospital pharmacist (grade 7) using the Health Service Executive (HSE) salary scales (212). Pay related social insurance (PRSI), pension contributions and hospital overheads were included in the cost, in line with Health Information Quality Authority (HIQA) guidelines (213) (Appendix 2). Annual total figures for the population and hospital inpatients in Ireland were obtained from the census of the Irish population (214) and the Hospital Inpatient Enquiry (HIPE) database respectively (215) . Projected population rates were calculated (216) (Appendix 2). Predicted population and inpatient discharge figures for the five year period 2017-2020 were calculated (217) (Appendix 2). The projected cost over this five-year period was estimated based on the cost of additional time established during the study. The cost of additional time per patient was used as a baseline and annual total cost subsequently calculated using the predicted inpatient figures for the five-year period.

3.3 Results

A total of 97 patients were admitted during the three-month study period. Eight patients did not undergo medication reconciliation; two patients were not taking any medications at admission, one patient was in receipt of end of life care and five patients had medication reconciliation previously performed at another location in the hospital. The final analysis included 89 patients.

Patient characteristics are described in Table 3.1. The mean age of the patients within the sample was 82 years. The majority were female (63%, n=55) and medical card holders (78%, n=69). All patients had additional co-morbidities and the mean number of medications taken at admission was 8. A minority had knowledge of their medication (15%, n=12) or held a personal record of their medication (27%, n=23). The majority were not fully independent in activities of daily living (80%, n=71). Approximately half of patients were admitted during normal working hours (44%, n=39), were accompanied when admitted to hospital (53%, n=47) and were referred to hospital by a doctor (56%, n=49).

Table 3 1: **Patient characteristics**

Demographic		
Age, mean (min, max) Years		82 (60,98)
Female gender, n (%)		55(63)
Medical card holder, n (%)		69 (78)
Morbidity		
Number of co-morbidities, n (%)	1-3	18 (21)
	4	21 (24)
	5+	49 (55)
Independent in ADL, n (%)		18 (20)
Medication		
Medications on admission, mean (SD)		8 (5)
Patients with a written record of medication at admission, n (%)		23 (27)
Patients able to provide accurate verbal account of medication at admission, n (%)		12 (15)
Admission		
Admitted between the hours of 9am-5pm Monday to Friday, n (%)		39 (44)
Accompanied at time of admission, n (%)		47 (53)
Referred to hospital by a doctor, n (%)		49 (56)

Medication errors were detected in 46% of patients (n=41). A total of 94 errors were identified. 56 errors were classified as significant and 38 as serious. No life threatening errors were detected. The categories of error are shown in Table 3.2. The most common type of error was omission of pre-admission or regular medications

Table 3 2: **Categories of medication error (n=94)**

	n (%)
Omission	58 (61.7)
Dose	13 (13.8)
Frequency/timing of administration	13 (13.8)
Duplication	3 (3.2)
Commission	2 (2.1)
Brand/Preparation	4 (4.3)

Additional time to reconcile medications was required in 47% of patients (n=42). Additional time spent per patient in resolving issues varied between 1 and 30 minutes. The mean additional time spent reconciling medications per patient was 3.75 minutes (SD 5). 32% of patients (n=36) required additional time of between 1-5 minutes and 15% (n=17) required additional time of between 5-30 minutes.

The reasons for additional time are outlined in Table 3.3. For 93% of patients (n=39) the time was spent on telephone calls to resolve issues arising during the medication reconciliation process. Resolution required between 1 and 2 calls per patient. The total number of calls made was 63. Calls were made to the GP, community pharmacist, nursing home or relative of the patient and the reasons for these calls are outlined in Table 3. The most common reason for additional telephone calls (n=20) was to clarify issues pertaining to illegibility or missing information on faxed lists of medication information. For the remaining 7% of patients requiring additional time (n=3) the time was spent on consultation with the patient or a pharmacy colleague and chart review.

Table 3 3: Reasons for additional time

Telephone calls (n=63)
Clarification of discrepancies between GP and Pharmacy medication information (n=17): GP dose errors (n=3) GP omission errors (n=6) Additional incorrect medications present on GP records (n=2) Medication absent in GP record as only prescribed in hospital (n=1) Community pharmacy omission errors (n=3) Additional incorrect medications present on community pharmacy records (n=2)
Clarification of whether the prescribed items were currently being dispensed i.e. whether the patient had collected a prescription for these items (n=10)
Clarification of whether medications were being taken by the patient as prescribed (n=13)
Clarification of issues pertaining to illegibility or information missing from fax (n=20)
Re-request sending of fax (n=2)
Consultation (n=2)
Discussion with another pharmacy colleague regarding an individual medication (n=1)
Discussion with patient regarding dosing (n=1)
Chart review (n=1)
Checking through drug charts and discharge prescriptions from previous admissions (n=1)

The results of the univariable and multivariable logistic regression analyses are outlined in Table 3.4. In the multivariable analysis, after controlling for the other variables in the model, having a written record of medication remained a significant predictor of additional time (p=0.04). The odds of requiring additional time were 3.3 times higher for those who had a personal record of medication compared to those without a record (OR 3.30, 95% CI: (1.05 to 10.42)). No significant associations

were found between the occurrence of significant or serious errors and additional time (p=0.05 for both).

Table 3 4: **Association of predictors and additional time***

	Univariable			Multivariable		
Predictors of additional time	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Gender						
Female (ref)	-					
Male	0.76	(0.32 to 1.80)	0.53	-	-	-
Age	0.99	(0.93 to 1.05)	0.81	-	-	-
Medical card						
No (ref)	-					
Yes	0.67	(0.25 to 1.82)	0.43	-	-	-
No. of co morbidities	1.04	(0.84 to 1.28)	0.74	-	-	-
No. of medications at admission	1.10	(1.00 to 1.21)	0.06	1.04	(0.93 to 1.17)	0.50
Functional status						
Not independent (ref)	-					
Independent	0.66	(0.23 to 1.86)	0.43	-	-	-
Accompanied						
No (ref)	-					
Yes	2.60	(1.10 to 6.11)	0.03	2.48	(0.95 to 6.47)	0.06
Source of admission						
Self-referral (ref)	-					
Doctor referral	0.55	(0.24 to 1.30)	0.17	-	-	-
Time of admission						
Out of hours (ref)	-					
Mon-Fri 9am-5pm	0.62	(0.27 to 1.44)	0.27	-	-	-
Knowledge of medication						
No (ref)	-					
Yes	0.40	(0.11 to 1.44)	0.16	-	-	-
Written record						
No (ref)	-					
Yes	2.86	(1.03 to 7.91)	0.04	3.3	(1.05 to 10.42)	0.04
Significant errors						
No (ref)						
Yes	2.56	(1.00 to 6.54)	0.05	2.01	(0.69 to 5.89)	0.20
Serious errors						
No (ref)						
Yes	2.71	(1.03 7.16)	0.04	2.17	(0.72 to 6.57)	0.17

*from binary logistic regression analyses

The results of the zero inflated negative binomial regression analyses are shown in Table 3.5. The only patient characteristic that significantly affected both the error number and clinical significance score was the number of medications taken by a patient on admission. For every extra medication that a patient had on admission, error count increased by 16% (IRR 1.16, 95% CI: (1.09 to 1.23), $p<0.001$) and the clinical significance score increased by 14% (IRR 1.14, 95% CI: (1.02 to 1.28), $p=0.02$). Patients referred to hospital by a doctor had a 62% reduction in error number compared to those who self-referred (IRR 0.38, 95% CI: (0.19 to 0.77), $p=0.008$).

Table 3 5: Association of predictors and medication error*

	Error number			Error score		
Predictors of medication error	IRR	95% CI	p value	IRR	95% CI	p value
Gender						
Female (ref)	-					
Male	0.69	(0.24 to 1.95)	0.48	0.99	(0.03 to 3.33)	0.99
Age	0.98	(0.93 to 1.02)	0.40	0.96	(0.89 to 1.04)	0.33
Medical card						
No (ref)	-					
Yes	0.78	(0.32 to 1.87)	0.58	0.97	(0.5 to 1.87)	0.92
No of co morbidities	1.11	(0.92 to 1.35)	0.29	1.10	(0.86 to 1.4)	0.46
No of medications at admission	1.15	(1.09 to 1.23)	<0.001	1.14	(1.02 to 1.28)	0.02
Functional status						
Not independent (ref)						
Independent	0.93	(0.40 to 2.13)	0.86	0.75	(0.32 to 1.76)	0.51
Accompanied						
No (ref)	-					
Yes	0.87	(0.39 to 1.95)	0.73	0.66	(0.38 to 1.17)	0.16
Source of admission						
Self- referral (ref)	-					
Doctor referral	0.38	(0.19 to 0.77)	0.008	0.45	(0.18 to 1.16)	0.10
Time of admission						
Out of hours (ref)	-					
9am-5pm	1.15	(0.69 to 1.92)	0.58	1.48	(0.81 to 2.72)	0.20
Knowledge of medication						
No (ref)	-					
Yes	0.73	(0.28 to 1.85)	0.50	0.89	(0.33 to 2.39)	0.82
Written record						
No (ref)	-					
Yes	0.74	(0.29 to 1.88)	0.53	0.50	(0.16 to 1.53)	0.23

*from zero-inflated negative binomial regression analyses

The hourly salary cost of pharmacist time was estimated at €44.93 (Appendix 2). The mean additional time for medication reconciliation was 3.75 minutes per patient with an associated pharmacist salary cost of €2.86 per patient. If an additional 5 minutes was considered, the cost per patient increased to €3.82. The cost of the maximum duration of 30 minutes of additional time

detected during the study was €22.92 per patient. The projected costs of additional time for medication reconciliation for the five-year period 2017-2021 are outlined in Table 3.6.

Table 3 6: Projected costs for Ireland 2017-2021

	2017	**2018**	**2019**	**2020**	**2021**
Projected population	4,775,850	4,827,736	4,880,185	4,933,205	4,986,800
Projected total inpatient discharges	643,008	651,932	660,980	670,153	679,454
Projected cost					
3.75 minutes	€1,805,698	€1,830,759	€1,856,167	€1,881,928	€1,908,047
5 minutes	€2,407,528.86	€2,440,942.14	€2,474,819.15	€2,509,166.33	€2,543,990.20
30 minutes	€14,445,173.16	€14,645,652.83	€14,848,914.90	€15,054,997.97	€15,263,941.19

The estimated annual cost for 2017-21 period for the mean additional time of 3.75 minutes is projected to be between €1.8-1.9m for all patients in all acute public hospitals in Ireland. If an additional 5 minutes was spent completing medication reconciliation the projected cost rises to between €2.5m and €2.6m for all acute hospitals. If the time spent per patient increased to 30 minutes there would be an increase to between €14.7m and €15.6m for the period 2017-2021.

3.4 Discussion

Summary

This study examined a routine medication reconciliation process currently in place in an Irish hospital. This study found that approximately half of the patients undergoing medication reconciliation required additional time which varied between 1 and 30 minutes per patient, with a

mean additional time of almost four minutes per patient. The projected five year cost of the mean additional time if applied to all patients and all acute hospitals in Ireland is between €1.8-1.9 million. If the maximum additional time of 30 minutes per patient detected in this study is spent, the projected five year cost rises to between €14.7-15.6 million. This study found however, that additional time spent conducting medication reconciliation was not associated with clinically significant medication errors, suggesting that spending extra time is currently not preventing clinically significant patient harm and associated costs and hence may be an inefficient use of resources.

Additional time in the vast majority of cases was spent on calls to the GP, community pharmacists, nursing home or relative of the patient. The most common reason for these telephone calls was to clarify issues pertaining to illegibility or missing information on faxed lists of medication information. Having a patient held written record of medication (either a written list or actual medications) was significantly associated with additional time for medication reconciliation suggesting that such records may not be accurate or useful in their current form.

Similar to other healthcare systems, though universal provision is advocated at a national level in Ireland, medication reconciliation is currently provided on an *ad hoc* basis. It is frequently limited to high risk patients such as the complex older adult patient population of this study and uncertainty currently exists as to how universal implementation can be achieved. If issues pertaining to the transmission and recording of medication information identified in this study could be addressed, there may be potential for time and cost savings thus enhancing process efficiency and facilitating widespread implementation of medication reconciliation.

Comparison with literature

This study adds to the body of evidence supporting the practice of medication reconciliation as a method to reduce medication error and improve patient safety (218). Just under half of the patients in this study had medication errors detected. This is comparable to the findings of other studies of medication reconciliation among older adult patients at hospital admission which report error in 40% or more of patients (190, 219-221), with omission of a patient's regular medications being the most common type of error detected (7, 55, 206, 221).

This study found that as the number of pre admission medications increased, the number and clinical significance of errors also increased, further adding to the evidence base supporting the practice of medication reconciliation among a polypharmacy population. Polypharmacy is a risk factor for adverse drug reactions and events (23, 24) and its association with medication error captured during medication reconciliation has previously been described (190, 206, 222).

The use of multiple sources of medication information in forming the BPMH is a necessary step in medication reconciliation (128). In keeping with previous studies, the pharmacists in the study used hospital, patient and primary care (GP and community pharmacist) medication information to establish the BPMH. Difficulties associated with communication of patient information between primary and secondary care are well established (101, 223, 224). Though general practitioners (GPs), community pharmacists and residential care facilities are all sources of accurate medication information, it has been established that such information may not be readily available at the time of hospital admission (69, 131, 225).The most common reason for additional time being required for medication reconciliation in this study was clarification of issues pertaining to illegibility/missing information on faxed lists of pre-admission medication information or the re-requesting of information from GPs and pharmacists. Evidence supports use of the electronic health record (EHR) in medication reconciliation to provide pre-admission medication information when forming the

BPMH (137, 138, 190, 226). However, implementation of the EHR has not been straightforward internationally. Use of a complete patient EHR in the hospital setting is not yet routine and telephone, fax and letters frequently remain routine as methods of information transfer at the primary secondary care interface (227, 228).

Fewer than one in five (15%) of patients were able to provide an accurate verbal account of the medications they were taking. Lack of knowledge among patients regarding prescribed medications is well documented with figures varying between 4 and 42% of patients having accurate knowledge of their medications in the literature (229, 230). In particular, older adult patients taking multiple medications may lack knowledge of prescribed medication (231-233). In addition, acute illness and underlying conditions may impede the capacity of the patient to communicate clearly at time of hospital admission. Prior research has suggested that medication reconciliation could be facilitated by patients bringing their own medications during care transitions (234). However, this was not supported by our study. We found that increased time for medication reconciliation was in fact associated with patients having their own medications or a written record of same at time of admission suggesting that such information may not be accurate or useful in its current form.

Reduction in healthcare costs due to medication reconciliation in terms of cost avoidance through ADE prevention has been described (33, 139). Although patient harm was prevented through the identification of 94 errors of clinical significance in the study, almost half of the patients required additional time to reconcile their medications and greater additional time was not associated with capturing errors of greater clinical significance. As additional time is associated with an economic burden, this may offer an explanation as to why evidence in a recent Cochrane review failed to demonstrate a reduction in healthcare utilisation and costs associated with medication reconciliation (136). This study suggests that cost savings may be made by improving process efficiency and reducing time for service provision.

Strengths and limitations

To our knowledge, this is the first study identifying factors associated with an increased time burden during the medication reconciliation process and examining the association of time with the clinical significance of medication errors identified. The study was conducted among older adult patients admitted to hospital undergoing routine medication reconciliation. No exclusion criteria were applied and a standard process of medication reconciliation which adhered to international guidelines was used, suggesting that the results may be applicable to a general population and other healthcare systems. Conducting the study during the provision of routine care resulted in some limitations however. Four pharmacists were involved which may have affected homogeneity of data collection. In addition, as pharmacists were required to log issues incurring a time burden additional to the usual medication reconciliation process, there was an unavoidable subjective element to data collection. The small scale of the study is a significant limitation as the study was limited to a single ward in a single centre. However, our findings in terms of error rates and risk factors for occurrence of errors are similar to those reported in other studies, suggesting that findings in terms of additional time may also be generalizable. A further larger scale study is required however.

3.5 Conclusion

Medication reconciliation is undoubtedly of benefit to both patients and healthcare providers. The primary secondary care interface, as patients transition between the community and hospital, is a point in care that is error prone. A medication omitted, added or prescribed incorrectly has the potential to cause, at a minimum, patient discomfort, or confusion for GPs, pharmacists, nurses and hospital doctors. The question is now, therefore, not whether we should implement medication reconciliation across healthcare systems, but rather how we can enhance process efficiency for cost-

effective and sustainable implementation. This study suggests that spending additional time on medication reconciliation may not necessarily yield benefit in terms of capturing clinically significant errors. In addition, this study suggests that savings of circa €1.9 to €15 million over 5 years could be generated by avoiding an extra time burden of between 3.75 and 30 minutes in terms of hospital pharmacist time when conducting medication reconciliation. Most additional time was spent by pharmacists in obtaining and clarifying pre-admission medication, with illegible or incomplete medication information from GPs and community pharmacists frequently being an issue. Developing accessible and accurate medication information at time of hospital admission should be a priority across healthcare systems. Employing electronic methods of medication information transfer between primary and secondary care may be of benefit. The findings of the study also suggest that additional time is required to reconcile the medications of patients who hold a personal record of their medication, which may indicate that current records held by patients are not accurate or useful. As the one constant in transitional care, developing improved patient held records of medication may improve efficiency within the medication reconciliation process.

4. THE PHARMS (PATIENT HELD ACTIVE RECORD OF MEDICATION STATUS) STUDY: A MIXED METHODS FEASIBILITY STUDY

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4.1 Abstract

Background

Medication errors frequently occur as patients transition between hospital and the community at time of hospital discharge and may result in patient harm. Novel methods are required to address this issue.

Aim

To assess the feasibility of introducing an electronic patient held medication record at the primary secondary care interface at time of hospital discharge.

Methods

A mixed methods study (non-randomised controlled intervention and a process evaluation of qualitative interviews and non-participant observation) among patients >60 years in an urban hospital and general practices in Cork, Ireland. Number and clinical significance of errors was compared between discharge prescriptions of intervention and control groups. Semi structured interviews were conducted with patients, junior doctors, GPs and IT professionals, in addition to direct observation of the implementation process.

Results

102 patients were included in the final analysis (Intervention n=41, Control n=63). Total error number was lower in the intervention group Median=1 (0,3 IQR) than the control group Median=8 (4,13.5 IQR) $p < 0.001$, with the clinical significance score in the intervention group Median= 2 (IQR 0,4) also being lower than the control group Median=11 (IQR 5,20) $p < 0.001$. The device was found to be technically implementable using existing IT infrastructure and acceptable to all key stakeholders.

Conclusion

The results suggest that using a patient held electronic medication record within existing systems in general practice and hospital is feasible, acceptable to both patients and doctors and may reduce medication error.

4.2 Introduction

Background

Existing evidence suggests that errors frequently occur at the primary-secondary care interface, when patients move between the hospital and the community at time of admission to and discharge from hospital. One in five patients experiences an adverse event within three weeks of hospital discharge (104). Medication error is a major potentially preventable source of these adverse events (104, 235). Uncertainty surrounding what medications have been added, stopped or altered in hospital, is a common issue for general practitioners (GPs) and has the potential to lead to medication error (116, 236-238). Communication of discharge medication information to GPs is often not timely resulting in an absence of up to date information when issuing a prescription (105, 106). The accuracy of medication information received is an additional concern due to the frequent occurrence of prescribing error in the hospital setting (38, 120, 239).

Medication reconciliation, the formal process for identifying and correcting unintentional medication discrepancies during transitional care, is widely advocated (141, 195, 240). The goal is to provide the patient and healthcare professionals with an up to date and accurate list of medications that is available in all settings and stages of care (134). Consensus has not been reached regarding the optimal method of generating and documenting accurate medication information during transitional care however (241), and the availability of such a list largely remains elusive in day to day practice.

In a consensus statement on medication reconciliation Greenwald *et al* stated: "A personal health record that is integrated and easily transferable between sites of care is needed to facilitate successful medication reconciliation"(134). In recent years significant developments pertaining to eHealth, "the use of information and communication technologies for health," have taken place (242). Electronic patient health record systems are now used by more than 90% of GPs in Ireland and

the UK (243, 244). Successful integration and transfer of electronic patient information between sites at a local, national and international level remains a challenge however (244-248). Complete and universal electronic integration of patient information within and between primary and secondary care settings has yet to be achieved.

The patient represents the one constant in the transitional care process and patient held records may improve continuity of care and enhance patient empowerment (249). Evidence suggests improved quality, completeness and timeliness of delivery of electronic discharge information with a subsequent reduction in medication error (250-252). Hence, an electronic patient held medication record may provide a solution to current issues arising at hospital discharge. GPs have a central role in overall patient care and have been identified as accurate providers of patient medication information(121). Giving the patient's GP overall responsibility for adjusting and updating an electronic patient held medication record could potentially reduce errors arising from the involvement of multiple doctors in different stages and settings of care (22, 253).

Intervention development:

The UK MRC recommends a structured methodological approach in developing a complex intervention in a healthcare setting (Figure) Systematic development is recommended based on best available evidence and appropriate theory.

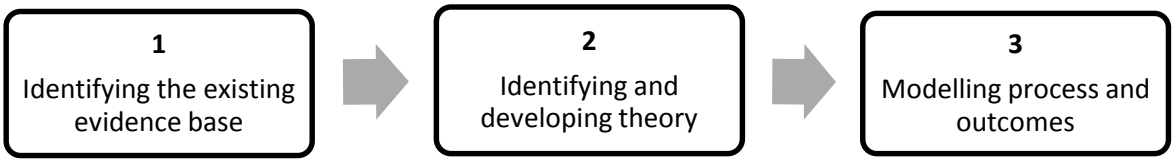


Figure 4 1 Steps of the development stage of a complex intervention outlined in the MRC methodological approach

Step 1 is to review existing evidence (150). Existing evidence has identified both the need for novel interventions to assist with medication reconciliation and the potential of an electronic patient held medication record to provide a solution (134, 138, 254). In accordance with same; an electronic patient held medication record was developed. The development of such a novel electronic intervention compatible with diverse and constantly evolving electronic healthcare systems presented challenges however. Implementation of eHealth to date has not been straightforward (246, 255). Use of paper records within our current healthcare systems may well be outdated, but the attributes of simplicity and universal applicability remain relevant. To this end, we sought to use a simple and universally employed Universal Serial Bus (USB) technology when developing the novel patient held electronic patient held medication record (256).

A secure password protected device was developed through collaboration between the Department of General Practice University College Cork (UCC), GP software provider Si-Key Ltd, INSIGHT Centre for Data Analytics UCC, The Health Information Systems Research Centre UCC, the Tyndall Institute and the Technology Transfer Office, UCC.



Figure 4 2: **Image of electronic patient held medication record**

The device developed (Figure4.1) operates through the USB port of any computer following the installation of appropriate software. The device, though operating via USB technology, differs from a traditional USB memory devices which have previously been used to store patient information (257).

No information is stored on the device. The device functions in essence like a key, facilitating transfer of medication information to and from the GP record. The device is initially activated and linked to the patient's electronic record in the GP surgery. The device, once activated, has four functions when inserted into the USB port of a computer where appropriate software has been installed:

i. To extract the patient's pre-admission medication information from their GP file: this appears as a list on the computer screen.
ii. To generate the patient's discharge prescription. Medications are selected from a drop down menu and the prescription can subsequently be printed.
iii. To provide free text boxes where alterations to the patient's pre-admission medication made during the inpatient stay can be noted while generating the discharge prescription.
iv. To transmit the discharge prescription and associated explanations of alterations in medication electronically to the patient's electronic record in general practice. The discharge information appears as a separate document in the patient's file in general practice. This information can then be reviewed and approved by the patient's GP and used to adjust the master medication list.

Medication information viewed via the device is the patient's medication list as it appears in their electronic record in general practice. Hence this device is an active record of medication. The master list is held and can only be adjusted by the patient's GP thereby giving a single healthcare professional control of the medication record. The device is compatible with the four accredited GP software systems in Ireland: Socrates, Complete GP, Health One, Helix Practice Manager and can be used in any computer once appropriate software has been installed.

Step 2 of the development stage of a complex intervention outlined in the MRC methodological approach is to identify and develop theory (150). Due to previously documented difficulties encountered in applying research to practice in the healthcare context, exploring the issues surrounding development and implementation of this novel intervention prior to a definitive evaluation is essential. Hence, the Consolidated Framework for Implementation Research (CFIR) was used in this study. The CFIR is a meta-theoretical framework. It combines key elements from published implementation theories and provides a structure to verify what works, where and why across multiple contexts. It consists of five domains. Each domain consists of factors and influences which impact the degree to which an intervention or practice is adopted (151).

1. Intervention characteristics
2. Outer setting
3. Inner setting
4. Characteristics of the individuals involved
5. Process of Implementation

Aim

Successful development and implementation of a novel intervention within the healthcare setting requires a detailed understanding of the context in which it is being introduced and the potential barriers to implementation. The overall aim of this study was to assess the feasibility of introducing an electronic patient held medication record at the primary secondary care interface at time of hospital discharge, firstly by examining the performance of the device, and secondly by determining the acceptability of the initiative to key stakeholders (patients, doctors, information technology (IT) personnel) and identifying the barriers and facilitators to the process of its implementation.

4.3 Methods

Study design

A mixed methods study, comprising a non-randomised controlled intervention and a process evaluation comprising qualitative interviews and non-participant observation was conducted. Realist evaluation, informed by the approach used by Rycroft-Malone *et al* (258), was conducted by combining an experimental study design with exploratory research in order to identify issues pertaining to implementation. Realist evaluation is underpinned by a realist philosophy of science which is situated between the extremes of positivism and relativism. Realist evaluation aims to answer the question "What works for whom in what circumstances and in what respects, and how?" (259, 260). The aim of combining a controlled intervention with qualitative interviews and non-participant observation was to answer this question, thus evaluating feasibility in a thorough and pragmatic manner.

Ethical approval

Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals (Date: 28-10-15, Ref: ECM 4 (e) 01/09/15 & ECM (yyy) 03-11-15).

Study setting

The study was conducted in the five general medical and surgical wards of an urban 350 bed hospital and general practices in Cork, Ireland between January and July 2016. Following analysis of referral patterns over a two-month period four urban GP practices were selected for the intervention group on the basis of having high rates of referral to the secondary care facility.

Sample size

A sample size of 65 patients per arm was calculated. Previous work in the same clinical setting indicated a rate of 1.1 medication errors per prescription from a total of 1600 prescriptions written

with in a similar timescale to that envisaged in the feasibility study (120). A sample size of 65 from a population of 1,600 prescriptions would be capable of providing estimates of the difference in medication error rates of 10% with a confidence of 90% (261).

Preparation and training

Information regarding the study was disseminated to all clinical staff of the participating hospital via email in advance of commencing the study. The lead researcher (EW) presented at teaching sessions for medical, nursing and allied healthcare professional staff. Additionally, EW provided two dedicated training sessions regarding use of the device to the junior doctors of the secondary care facility and an education session to each of the four participating general practices.

Software was installed on one computer in each of the four participating general practices and on one computer on each of the five general hospital wards to enable the integration of the patient held medication record into the existing primary and secondary care IT systems.

Patient recruitment

Following admission to hospital potentially eligible community dwelling older adult patients (≥ 60 years) prescribed three or more medications were identified from a patient admission list generated on a daily basis. Patients who were resident in long-term care facilities, unable to provide written informed consent or in receipt of end of life care were excluded. Written informed consent was obtained from patients.

Patients from the four GP practices were assigned to the intervention group and issued with an electronic patient held medication record. The patients in the intervention group were asked to retain the device during their inpatient stay. Intervention patients were identified by a sticker in their medical notes, nursing notes and drug chart. A note was also entered by EW into their medical and nursing notes. The device was used at time of discharge by a junior doctor when generating the discharge

prescription. Eligible patients from GP practices, other than the four intervention practices, were assigned to the control group and received usual care in the form of a handwritten discharge prescription.

Data on pre admission and hospital discharge medication information, patient age, length of stay, medication number on admission and functional status were collected for all patients. Functional status was assessed in terms of independence relating to continence, mobility, feeding and dressing as documented in the patient's hospital medical record. Medical card status (means-tested national public health insurance system entitling the holder to free access to healthcare) was used as a proxy measure for socioeconomic status (SES). Data was collected by three members of the research team (EW, EMcC, MC) from the patient's hospital medical record. A pragmatic approach was adopted in terms of selection of variables. The selection was informed by review of the literature and expert opinion of the research team (PK, CB, LS, EW). The variables listed represent the broadest range of explanatory variables that could readily be collected from patient information available in the clinical setting.

Ethical issues

Written informed consent was obtained from all participants. In view of the inclusion of potentially vulnerable older adult patients in the study, ability to provide informed consent and to be interviewed as part of the study was assessed on a case by case basis, liaising with medical/nursing staff and family members where appropriate.

To limit any possible loss of confidential information, security was a priority in device development and the device is protected to the highest level. Additionally, patient information accessed via the device has been limited to medication information.

Outcomes

Outcomes of interest reflect the CFIR domains. The outcomes aim to inform a future definitive evaluation. Study measures were mapped to the CFIR domains by the research team (EW, LS, PK, CB).

Table 4 1: **CFIR domains and relevant study measures**

CFIR domains	How the domain aligns with the implementation of the electronic patient held medication record	Relevant study measures
Intervention characteristics	Relative advantage of device over usual practice Use of device (design and complexity)	Perceptions of hospital healthcare professional, GPs and patients regarding use of the device (qualitative interviews) Non-participant observation
Outer setting	Importance as perceived by wider secondary and primary care stakeholders Promotion of use of the device from clinical and administrative directors/leaders within the participating hospital and general practices	Perceptions of hospital healthcare professionals, GPs and patients regarding potential of the device (qualitative interviews) Occurrence of medication error (quantitative analysis of medication information) Non-participant observation
Inner setting	Readiness for change, quality of communication and teamwork within the participating hospital and general practices	Perceptions of hospital healthcare professionals, GPs and IT staff (qualitative interviews) Non-participant observation
Individual characteristics	Knowledge, beliefs and motivation of individuals involved in the study	Perceptions of hospital healthcare professionals, patients and GPs (qualitative interviews)
Implementation process	Establishing a plan for evaluation on a larger scale Methods to engage relevant individuals	Perceptions of hospital healthcare professionals, patients, GPs and IT staff (qualitative interviews) Non-participant observation

Clinical outcomes

Discharge prescriptions of intervention and control patients were examined for errors and patients' doctors informed if errors posing clinical risk were detected. Errors pertained to:

Patient demographic and legal requirements (262)

- Name and address
- Date
- Age or date of birth
- Prescribers signature
- Irish Medical Council (IMC) registration number for the prescribing physician

Therapeutics

- Legibility/accuracy of spelling
- Presence of strength/dose/frequency
- Quantity
- Presence of drug-drug interactions as per Stockley's Drug Interactions (15)
- Omission of a pre-admission medication (235)

Errors were reviewed independently by a GP (EW) and by a clinical pharmacist (LS) and classified as significant, serious or life-threatening. Any discrepancies were resolved with the input of another GP (CB). Error severity weights of 1^2=1 (significant), 2^2=4 (serious) and 3^2=9 (life-threatening), respectively, were assigned to reflect the relative potential of each error type to cause patient harm and an error score was calculated for each patient (70).

Data were anonymised, coded and entered into a Microsoft Excel (2010) spreadsheet on a password protected computer. Statistical analysis was conducted using IBM SPSS version 24. Differences in baseline characteristics between groups were tested using chi-squared test (for the categorical variables of gender, socioeconomic status, and functional status), t test (for the normally distributed continuous variable of age) and Mann Whitney U test (for the continuous variables of length of stay and medications on admission with a distribution deviating from normality). Total error numbers and error scores (continuous variables with a distribution deviating from normality) were compared

between groups using Mann Whitney U test. Occurrence of individual types of error (categorical variable yes/no) between groups was compared using Fisher's exact text (expected cell count < 5). To investigate factors associated with number of medication errors and error score, regression models for count data were used. Regression models were compared to determine the model that best fit the data. The models compared were: Poisson and Negative Binomial. The Poisson regression model assumes a Poisson distribution where the variance equals the mean while the Negative Binomial model allows the variance to be greater than the mean by including an over-dispersion parameter (alpha). The likelihood ratio test was used to determine if the Negative Binomial model was a better fit than the Poisson model. Negative binomial regression models were used to analyse the association of group, gender, functional status, SES, age and length of stay with error numbers and error scores respectively. Statistical significance was determined using a p-value of <0.05.

Process evaluation

Qualitative interviews

Semi structured interviews were conducted with a census sample of the healthcare professionals involved in the study (junior doctors, GPs and IT professionals). Suitability of patients for interview was checked with the patient's GP prior to contacting the patient and all intervention patients who were available to participate were contacted. The topic guides for the interviews were developed by EW based on review of the literature and also based on practical considerations pertaining specifically to the PHARMS device. Opinion of the research team (LS, CB, PK, SmcC and CF) was sought and the guides revised accordingly. Interviews were recorded, transcribed and coded. Data were analysed iteratively using thematic analysis (263). It was intended at the outset of the study to map interview findings to the CFIR. Dual independent coding of the first three transcripts of interviews with GPs, junior doctors and patients (n=9) was conducted by two members of the research team (EW and LS). Transcripts were read and initial codes were generated, discussed at a

research meeting and a coding system agreed. It was concluded by EW and LS that the planned deductive approach to analysis based on the CFIR might not adequately represent the interview findings. The expert opinion of CB was sought and it was decided to adopt a more inductive approach to analysis. There were pragmatic constraints to adopting a fully inductive approach however as specific information pertaining to the technology needed to be gathered in each interview and reported in the results. The agreed approach to analysis therefore a blend. All subsequent interviews were analysed by EW adhering to the principles of constant comparison (264) and overseen by LS and CB. Though the prompts used during the interviews evolved, with prompts being changed and refined during the course of the interviews, the same topic guides were used throughout. Dual independent coding of all interviews with IT professionals (n=2) was conducted by EW and SMcC. Codes were discussed and a coding system agreed. NVivo Software Version 11 was used for data management. Topic guides are included in Appendix 2.

Non-participant observation

Direct observation of the implementation process was conducted (265) by EW and observations recorded as field notes. Participants' behaviours, interactions and actions were observed. Direct observation was used to measure uptake, fidelity and adherence. Uptake was measured by the number of patients approached who were willing to participate in the study. Fidelity was measured by successful transmissions of medication information in the intervention group. Adherence was measured by the number of devices in the intervention group that were used at discharge.

4.4 Results

Patient selection is outlined in Figure 5.1. Characteristics of the intervention and control groups (Table 1) were broadly similar with the exception of age.

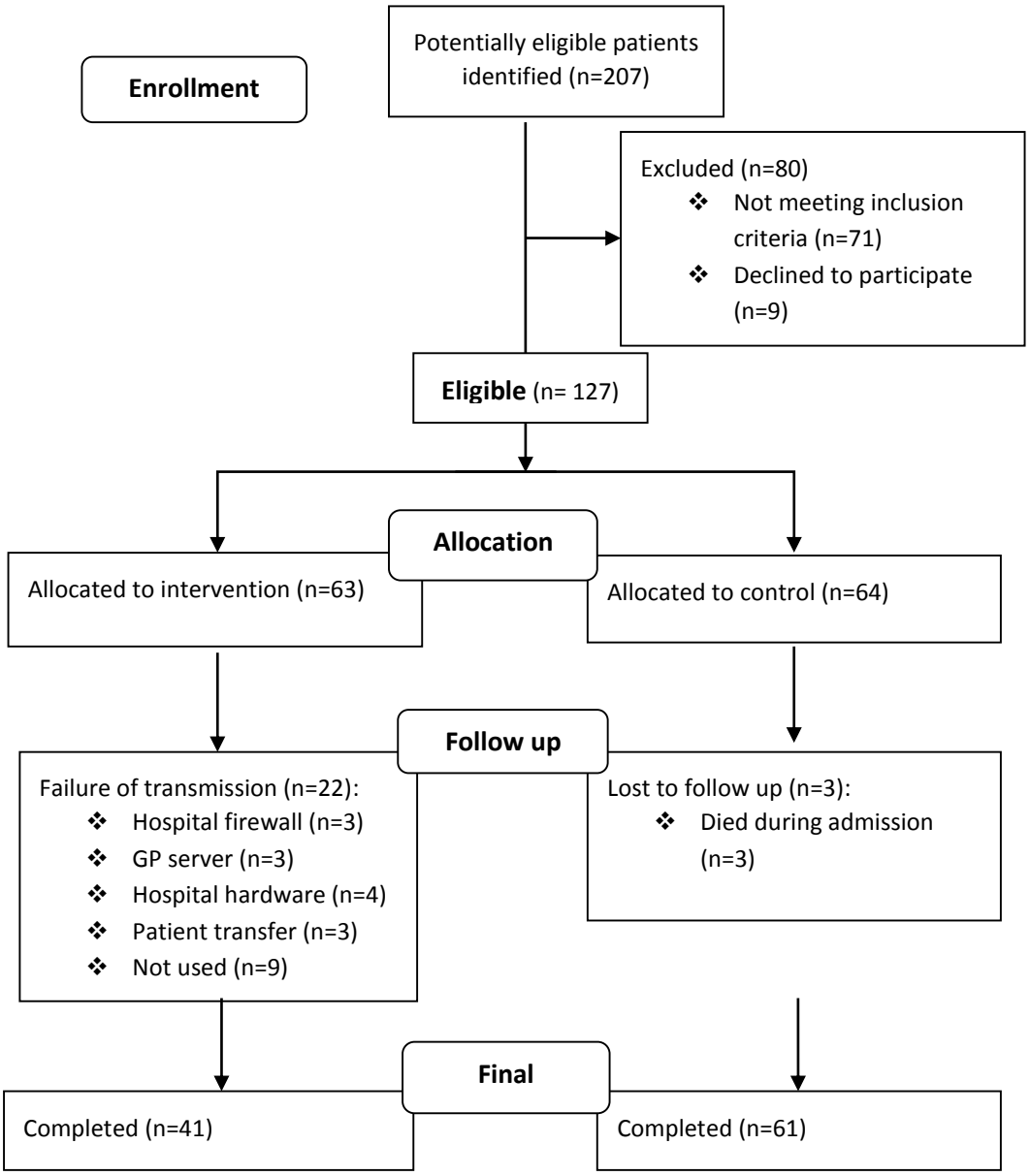


Figure 4 3: **Flow diagram of patient selection**

Table 4 2: **Characteristics of study patients**

	Intervention (n=41)	Control (n=61)	p Value
Gender, male, n (%)	22 (54)	38 (62)	0.51
Age, mean (SD)	72.6 (6.2)	77.4 (7.3)	0.01
Has medical card, n (%)	34 (83)	43 (71)	0.23
Meds on admission, median (Q_1,Q_3)	10 (8,15)	10 (7,13)	0.25
Independent mobility, n (%)	24 (59)	29 (48)	0.38
Independent dressing, n (%)	31 (76)	41 (67)	0.49
Continent, n (%)	31 (78)	56 (91)	0.09
Independent feeding, n (%)	38 (93)	51 (84)	0.30
Length of stay, median (Q_1,Q_3)	6 (3,10)	6 (5,13)	0.21

Prescribing error:

The total error number and clinical significance scores of errors were lower in the intervention group and there were differences across a range of errors between groups with a complete absence of error pertaining to patient information, date, legibility, quantity and prescriber information among the intervention group (Table 5.2).

Table 4 3: **Types of errors on discharge prescriptions**

	Intervention (n=41)		Control (n=61)		p Value
	median (IQR)		**median (IQR)**		
Total error number	1 (0 to 3)		8 (4 to 13.5)		<0.001
Clinical significance score	2 (0 to 4)		11 (5 to 20)		<0.001
	n	**(%)**	**n**	**(%)**	
Type of error					
Patient information	0	(0)	2	(3.3)	0.514
Date	0	(0)	5	(8.2)	0.08
Legibility/spelling	0	(0)	5	(8.2)	0.08
Quantity/duration	0	(0)	22	(36.1)	<0.001
Prescriber information	0	(0)	18	(29.5)	<0.001
Drug interaction	16	(39)	26	(42.6)	0.838
Frequency	3	(7.3)	2	(3.3)	1.0
Dose	4	(9.8)	7	(11.5)	1.0
Medication omission	17	(41.5)	46	(75.4)	0.001

Predictors of error number and error score:

The results of the univariable and multivariable analyses are shown in Table 5.3. In the multivariable analysis, after controlling for the other variables in the model, statistically significant lower rates of error numbers and error scores remained in the intervention group. Number of medications on admission was the only other statistically significant predictor of prescribing error number and error score. For an increase of one in preadmission medication number, error count and the clinical significance score both increased by 9%.

Table 4 4: **Association of predictors and number of errors and error score**

	Univariable			**Multivariable**		
ERROR NUMBER Predictors	**Incidence rate ratio (IRR)**	**95% CI**	**p Value**	**Incidence rate ratio (IRR)**	**95% CI**	**p Value**
Group						
Intervention (ref)	-					
Control	3.94	2.44 to 6.36	<0.001	4.88	3.35 to 7.13	<0.001
Gender						
Female (ref)	-					
Male	1.19	0.80 to 1.78	0.39	1.20	0.79 to 1.82	0.39
Age	1.02	1.00 to 1.05	0.083	0.99	0.97 to 1.02	0.63
Medical card status						
Yes (ref)	-					
No	0.96	0.64 to 1.45	0.85	0.92	0.64 to 1.31	0.63
Number medications on admission	1.06	1.02 to 1.10	0.003	1.09	1.05 to 1.14	<0.001
Functional status						
Not independent (ref)	-					
Independent	0.84	0.57 to 1.23	0.38	1.08	0.77 to 1.53	0.65
Length of stay	1.02	1.00 to 1.03	0.10	1.00	0.98 to 1.02	0.94
	Univariable			**Multivariable**		
ERROR SCORE Predictors	**Incidence rate ratio (IRR)**	**95% CI**	**p Value**	**Incidence rate ratio (IRR)**	**95% CI**	**p Value**
Group						
Intervention (ref)	-					
Control	4.30	2.55 to 7.25	<0.001	5.71	3.66 to 8.91	<0.001
Gender						
Female (ref)						
Male	1.44	0.90 to 2.29	0.13	1.36	0.86 to 2.17	0.19
Age	1.02	0.99 to 1.05	0.31	0.99	0.96 to 1.01	0.31
Medical card status						
Yes (ref)	-					
No	0.77	0.49 to 1.21	0.26	0.74	0.49 to 1.12	0.15
Number medications on admission	1.05	1.00 to 1.10	0.07	1.09	1.04 to 1.14	<0.001
Functional status						
Not independent (ref)	-					
Independent	0.98	0.63 to 1.54	0.94	1.16	0.75 to 1.77	0.51
Length of stay	1.00	0.99 to 1.02	0.69	0.99	0.98 to 1.01	0.32

Qualitative interviews evaluating feasibility and acceptability:

Interviews were conducted with a census sample of GPs (n=8), junior doctors (n=13) and IT professionals (n=2). Interviews were conducted with 12 intervention patients (Declined n=2, died n=6, unable to contact n=4, current health issue as determined by GP n=17)

Characteristics of interview participants are shown in Table 5.4

Table 4 5: Characteristics of participants in qualitative interviews (n=35)

	Participants (n)
	GPs (n=8)
Gender	
Male	5
Female	3
Type of practice	
Single handed	1
Group	7
Length qualified	
10-20years	3
20-30 years	4
>30 years	1
	Junior doctors(n=13)
Gender	
Male	6
Female	7
Age	
20-30 years	10
>30 years	3
Length qualified	
1 year	11
2 years	2
	IT professionals(n=2)
Gender	
Male	2
Female	0
Length qualified	
10-20 years	1
>20 years	1
	Patients(n=12)
Gender	
Male	5
Female	7
Age	
60-70 years	7
>70 years	5
Socioeconomic status	
Private health insurance	1
Medical card	11

Interviews identified three main themes: clinical impact, intervention characteristics and integration with usual care. Main themes, sub themes and codes are outlined in Table 5.5. The main themes and the most significant subthemes are discussed.

Table 4 6: Themes, sub-themes and codes describing stakeholder views

Main theme	Sub-themes	Codes
Clinical impact	Communication	Current communication barriers at primary secondary care interface Discharge information accessibility for GPs Patient empowerment Clarity in transitional care
	Error reduction	Occurrence of error in current system Quality of discharge medication information Role of PHARMS device in error reduction
	Future use of PHARMS	Use at admission Use at discharge Use in community pharmacy Use during travel
Intervention characteristics	Physical attributes	Shape and structure of PHARMS device
	Technology	USB Mechanism of operation
	Modification	Integration of information in GP software system Mandatory completion of fields in hospital system Use of hospital formulary Improving patient knowledge
Integration with usual care	Workload	Process efficiency Time constraints
	Deviation from usual practice	Uncertainty regarding PHARMS device operation Infrequent use of PHARMS device Role of nursing staff in facilitating use of PHARMS device
	IT	Hospital hardware issues Mixed electronic and paper hospital record system Security Installation issues in hospital

Clinical impact:

The theme of clinical impact describes the views of interviewees around the potential of the PHARMS device to alter current patient care at the primary secondary care interface.

GPs, patients and junior doctors all described the occurrence of, and difficulties with, medication error and poor communication of medication information within the existing system.

*"**Junior doctor1:** We forever have people coming in who are missing things for a week until someone discovers they're missing whatever"*

*"**GP 1:** And in some cases then you have to follow up with the hospital and following up with the hospital is incredibly time-consuming. Like, really incredibly time-consuming and frustrating and annoying. I mean, I can't be strong enough on how, what a waste of time it is."*

*"**Patient 1:** I remember like one day coming out and the nurse had to ring the doctor to query something because the inhaler they had given me shouldn't be given with the medications I was on"*

Each stakeholder group embraced the device as a potential method of reducing error and improving communication.

*"**GP 7:** It takes some of the inconsistency out of the traditional methods of finding out about patients' change of medication when they've been in hospital. If everyone was doing it we'd have, I suppose, solid prescriptions - we'd know what patients were really on coming out of hospital"*

*"**Junior doctor 4:** ….one person I used it for was one who was in and out like a yo-yo, and in that instance it provided continuity between the people….so I thought it was very valid and useful."*

*"**Patient 3:** Well it's very handy so your GP would have it and [you,] when you go to hospital all your information is on it, it's brilliant".*

GPs found the electronic medication information of benefit at time of discharge.

*"**GP 1:** It was useful because it was instant and because I knew that's changed and it's changed for a reason".*

However, the quality of information received was noted to be variable by GPs and to be dependent on the junior doctor generating the discharge medication information.

*"**GP 2:** I can remember having two different reactions that it very much depended on who had filled in the [information] from the hospital side. One [junior doctor] had made notes about what was stopped and what doses had increased which was really helpful. And the other one was just a prescription"*

The junior doctors felt overall that although the device was useful for GPs and patients at discharge, it was not particularly useful for them when generating discharge information. They felt that it was not their role to reconcile medications at this point in care and that it would be more relevant at admission.

*"**Junior doctor 5:** But it probably would be much [more] helpful if you were doing an admission as a lot of the time, I find, that patients will come in and they won't have the list of medications with them and you end up having to ring the GP anyway. So I think that's when it would become more helpful – at admission rather than discharge"*

Intervention characteristics:

The theme of intervention characteristics refers to the physical structure and technology of the PHARMS device as described by the interviewees.

Patients found the key shaped device acceptable. A minority expressed a preference for an alternative shape to resemble a bank card. The majority expressed difficulty with use of technology and rejected alternative options such as an app.

*"**Patient 2:** It's the likes of us that wouldn't really be tech savvy it would be the ideal thing"*

*"**Patient 1:** They tried to talk me into getting one of the touchphones but I'm sure I have toes for fingers because any time I tried to use it I couldn't"*

Though enthusiastic about having the device to provide information to healthcare professionals, most patients did not want personal access to their medication information.

*"**Patient 2:** I'd leave them [doctors] do what they are doing. I just take my tablets and leave them [doctors] look after it".*

*"**Patient 4:** Now, because I tell you what, you know when a doctor's in front of you lose concentration and you can't remember the names….with the key[device] it would be better"*

USB technology and operation of the device was acceptable to healthcare and IT professionals alike and regarded as a feasible option within the constraints of the current system.

*"**IT 1**: it did actually work …. it could work in hospitals in Ireland…. technology in a public hospital may be behind the other technologies out there. When it comes to a great solution, for example, wireless technology the problem is that technology is not available or accessible"*

Integration with usual care:

The theme of integration with usual care refers to the interviewee's experience of how the PHARMS device performed within the current healthcare system.

Though enhancing process efficiency for GPs, junior doctors found that using the device was an additional work load.

*"**GP 7:** On our end it was probably less work than dealing with traditional prescriptions. So yeah, we're very happy"*

*"**Junior doctor 9:** it's the duplication, the filling out of the discharge summary, and then you're filling out a prescription and you're trying to find a computer."*

Infrequent use significantly impacted acceptability for junior doctors and GPs highlighted full integration and widespread use as key for sustainability.

*"**Junior doctor 11**: I'm sure it would be fine if it were the primary method for every single patient we might – that's the thing that we do. But when you're writing prescriptions all day, you just forget about it".*

*"**GP 7:** It would be no good for just a small portion of one hospital to use it. If it's the whole system then great, otherwise it's just another system that's different. If it's just a small portion of people using it then it's not going to be any good"*

Uncertainty regarding the mechanism of device operation was an issue for GPs, patients and junior doctors alike:

*"**GP 2:** The difficulty was I was feeling vague about it [the device]. So I couldn't really put her [patient] absolutely straight and say 'no, that's not how it's working, that's for the next time your back' and so we [patient and Ps in practice] all agreed that we didn't know how it worked."*

Issues regarding integration were regarded as minor from an IT perspective and confidence in safety and the security of USB technology was expressed

*"**IT 2:** We didn't really have any major technical problems, I would call them glitches and challenges"*

*"**IT 1**: So really if the correct protection is in place, using USB technology is safe"*

Non-participant observation:

A number of issues pertaining to feasibility were identified through non-participant observation.

Uptake:

Patients embraced the concept of the device and were keen to participate in the study with only 9 of the 136 patients approached declining to participate.

All junior doctors were willing to participate with a small number of junior doctors (n=2) becoming "champions" assisting and educating their peers regarding device use.

Fidelity and adherence:

Of the 63 devices issued to patients, 41 were used successfully.

Difficulty in communication between the product developer and hospital IT staff resulted in early stage installation and implementation issues with device failure due to unresolved hospital firewall and GP server issues (n=6).

Basic hospital hardware issues negatively impacted successful device use:

- Failure of use occurred due to simple printer malfunction (n=4).
- Limited availability of computers on hospital wards resulted in junior doctors opting to issue a handwritten prescription rather than using the device (n=2)

A number of devices were not used at discharge (n=10). Three patients transferred to another hospital. Observed additional explanatory factors were:

- Patients did not alert junior doctors to having the device
- Retaining the device was problematic during the inpatient stay due to lack of a dedicated storage location.
- Nursing staff were key to successful use through alerting junior doctors to the presence of devices.

4.5 Discussion

Summary of findings

Introduction of a novel patient held electronic medication record at hospital discharge was shown to be feasible, being both technically implementable and acceptable to key stakeholders. The device was successfully integrated into existing electronic systems in primary and secondary care and medication information successfully transferred between sites. GPs and patients felt it provided a potential solution to current issues of poor communication of medication information and the occurrence of medication error at the primary secondary care interface. Not all devices were used however, with lack of availability of hospital computers and printer malfunction negatively impacting use and junior doctors reporting a perceived greater usefulness at time of hospital admission. The ad hoc nature of device use in the study led to issues of uncertainty and duplication of work. GPs and junior doctors alike advocated more widespread use. Patient education and involvement of nursing staff were also identified as facilitators to future implementation. Regarding device efficacy, lower total error number and clinical significance scores among intervention patients suggested potential to reduce the occurrence of medication error.

Strengths and Limitations

To our knowledge, this is the first study examining the introduction of a patient held medication record using USB technology at the interface of primary and secondary care at time of hospital discharge. This study provides a detailed evaluation of the introduction of this novel electronic method to facilitate medication reconciliation in primary and secondary care from a quantitative and qualitative perspective. The study was conducted among community dwelling older adult patients without significant exclusions, using basic technology and existing basic IT infrastructure, suggesting that the results may be applicable to a general population and other healthcare systems. The small

scale of the study is a limitation however. An additional limitation is the non-randomised study design. However, in terms of baseline characteristics, the groups were reasonably comparable. While the control group had a chronological median age 5 years older than the intervention group, there was no apparent difference in biological age in terms of numbers of medications or functional status. In addition, the multivariable regression model controlled for age as a variable and the difference in error score and count remained between intervention and control groups Younger age did not appear to enhance patients' ability to use the technology based on the difficulties reported by the intervention patients during interviews. Use of specific GP practices may have been a source of selection bias and a further larger scale randomised study is warranted. Although the Hawthorne effect (266) may in part explain the reduction in prescribing error noted among intervention patients, quality of discharge information generated was reported by GPs as varying between junior doctors suggesting this was not universally the case. The control group received handwritten discharge prescriptions. Thus, the impact on error reduction could be less if compared to discharge prescriptions in an existing electronic system. A final limitation that all interviews were conducted by the principal investigator EW, a GP, potentially introducing a social desirability bias among interviewees. However, negative opinions and experiences pertaining to the intervention were actively sought and were reported by all stakeholder groups.

Comparison with existing literature

The study identified the occurrence of prescribing error at the interface of primary and secondary care at time of hospital discharge, a finding frequently reported in the literature (5, 56, 120, 267). Prescribing error among junior doctors is an important patient safety issue (38, 239). Our study highlighted, that lack of an accurate medication list at admission, in addition to a perceived lack of responsibility for medication review at hospital discharge among junior doctors, may be important contributory factors.

Use of the device varied between junior doctors. Prior research has shown the rate at which an individual will adopt a new technology is variable, with the relative advantage of the technology over current practice being the strongest predictor of the rate of adoption (268). Quality of discharge information generated varied between junior doctors. Nine devices issued to patients were not used at time of discharge. Lack of perceived relevance at hospital discharge identified during interviews, may offer an explanation. Conversely, junior doctors promoting use of the device to their peers was noted to be an important facilitator.

Deviation from routine practice was noted to be an issue for both GPs and junior doctors and negatively impacted device usefulness. In line with the findings from our study, a systematic review examining healthcare professionals' perceptions of implementation of electronic systems for medication prescription/use found that such systems positively impact patient safety, but that hardware problems and changes to routine work practice were significant barriers (269).

Previous studies have highlighted that patients perceive difficulties with information transfer at the primary-secondary care interface (270, 271). A perception that their own lack of knowledge and difficulty in communicating with clinicians may contribute to the situation has been described(101). Patients in this study universally embraced the device as a method of improving communication at this interface in care. The patients in the study felt empowered by carrying the device but in general did not want personal access to their medication information and expressed difficulties in using technology. This supports previous research where patients, though lacking familiarity with technology, perceived it to positively impact safety, trusted their healthcare providers and expressed a willingness to embrace novel interventions (272, 273).

Prescribing error has been identified as particularly problematic among older adult patients taking multiple medications (4, 6) and this is confirmed by our study with increasing numbers of admission

medications among study patients predicting error occurrence. Employing electronic methods to generate and transfer discharge medication information has previously been shown to be of benefit in this population (274) and our study demonstrated a statistically significant reduction in both total error number and the occurrence of clinically significant errors among intervention patients. This device however not only facilitates the electronic generation and transfer of discharge medication in information, but has the additional potential to promote medication reconciliation at the point of generating the discharge prescription by providing the prescriber with a list of a patient's pre-admission medications as documented in their GP record. This active electronic record of a patient's pre-admission medication may also have the potential to promote medication reconciliation at the point of hospital admission.

Implications for research/practice

Medication error at hospital discharge is an important issue for GPs, patients, hospital doctors and pharmacists alike. Establishing effective methods of reducing medication error as patients move between hospital and the community is currently an international priority (141, 242). Prior research highlights firstly the importance of integration and communication of medication information between primary and secondary care (237, 275, 276), secondly the need for multidisciplinary and patient involvement (101, 275) and thirdly the benefit associated with electronic systems (250, 251). In technology terms a "minimum viable product" is a basic product solving a core problem (277). Perhaps with regard to medication error during transitional care, it is time to return to basics to meet the immediate clinical need. International implementation of eHealth strategies has not been straightforward and a universal shared care record does not yet exist across healthcare systems. This study demonstrates that this device can be used successfully within existing systems without significant additional IT investment and hence may be complementary to ongoing shared care record development. Though more advanced technologies than USB exist, such technologies may not be

applicable to all healthcare systems, nor (as this study highlighted) acceptable to an older adult population. This feasibility study suggests that the patient held electronic medication record may provide a viable solution to the current issue of medication error at the interface of primary and secondary care. This study has demonstrated that using a USB device is technically and clinically feasible and acceptable and impacts positively on medication reconciliation at the point of hospital discharge. Findings from the study suggest that a larger scale evaluation of the device, including deployment at the point of hospital admission, is now warranted.

5.DISCUSSION

5.1 Summary of findings

Medication error is associated with morbidity, mortality and economic burden and is of particular concern at the primary secondary care interface as patients move between hospital and the community (1, 3, 8). Developing interventions to reduce medication error at this interface in care is an international priority (2). The overarching aim of this research was to explore the cost, causes and consequences of medication error at the primary secondary care interface in order to develop an intervention focused on its reduction. The MRC framework for the development of complex interventions provided a systematic, evidence based approach for intervention development (150). Research evidence on the cost of medication error was systematically reviewed and synthesised. An existing intervention to reduce medication error was examined. Findings from these studies were used to inform the development of a pragmatic novel intervention; namely a patient held electronic medication record. A detailed theoretically informed evaluation of the feasibility of introduction of the intervention at the primary secondary care interface was performed. The overall conclusion is that the intervention developed has the potential to reduce the occurrence of medication error and its associated morbidity, mortality and economic burden, not only in Ireland, but across healthcare systems worldwide.

Establishing an accurate estimate of the cost associated with medication error was the first step in the process of intervention development. When conducting an economic evaluation of a quality improvement intervention in healthcare the identification, measurement and valuation of both the relevant costs and the relevant benefits is required (155). In the case of interventions developed to reduce medication error, reduction of the economic cost associated with the error is a major potential benefit. A narrative synthesis of the existing literature on the economic impact of medication error

identified a lack of information on the cost of medication error in primary care or at the primary-secondary care interface. In addition, limited parameters were used to establish economic impact. Healthcare cost incurred in relation to hospitalisation was the main, and often the only, parameter used in the included studies. It has previously been established that medication error is associated with economic burden (18, 33). Chapter 2 finds that, although considerable financial cost has been documented with estimates of cost per error as high as €111,727.08 (180), the true economic impact of medication error could in fact be greater should additional cost parameters (such as costs pertaining to primary care, patients and society) be considered.

Medication reconciliation is an existing process employed to reduce medication error at the primary secondary care interface. To gain a better understanding of the process in terms of reducing medication error, an existing medication reconciliation process in one institution was examined (Chapter 3). Medication reconciliation is widely advocated by professional and accrediting bodies. Concerns however, have been expressed recently regarding the resource intensity of medication reconciliation and whether it is cost effective in the absence of definitive evidence of the expected reduction in healthcare costs (136, 147). Chapter 3 sought to identify factors associated with an increased time (and hence economic) burden for medication reconciliation and to determine whether there was an association between increased time and detecting errors of clinical significance. Issues pertaining to communication of medication information at the primary secondary care interface were noted to contribute to a time burden and an association between records of medication held by patients and increased time was also described. No association was found between spending additional time and capturing errors of clinical significance. This novel finding suggests that time intensive medication reconciliation may not be generating cost savings in terms of reducing medication error. Further work to establish the potential cost of errors captured is required however. Furthermore, additional time for medication reconciliation may even be contributing to economic burden within the healthcare system due to cost incurred in terms of

healthcare professional time. These findings highlight the need to enhance process efficiency for cost-effective and sustainable implementation of medication reconciliation, whereby the time invested yields the greatest amount of clinical benefit or the process is so time efficient it could be implemented universally. Process efficiency could potentially be enhanced by addressing the issues identified in relation to records of medication held by patients and communication of medication information at the primary secondary care interface.

An intervention, a patient held electronic medication record (the PHARMS device), was developed (Chapter 4) as a novel method of communicating medication information between primary and secondary care aiming to reduce medication error and the associated economic impact. Introducing the PHARMS device at the primary secondary care interface was shown to be technically implementable and acceptable to key stakeholders (namely patients, GPs, IT professionals and junior doctors) (Chapter 4). The device (using basic USB technology) was successfully integrated into existing electronic systems in primary and secondary care and medication information was successfully transferred between sites. Initial technical issues pertaining to the hospital firewall, GP server and hospital hardware were resolved during the course of the study. Lower total error number and clinical significance scores among intervention patients compared to control patients suggests potential to reduce the occurrence of medication error and hence its associated economic burden. The PHARMS device may provide a viable solution to the current issue of medication error at the interface of primary and secondary care.

5.2 Where findings fit in the literature

While there is evidence of the effectiveness of interventions to improve the suboptimal use of medicines, the evidence of cost-effectiveness is significantly more limited (278, 279). A recent

evidence synthesis did not find medication reconciliation to be a cost effective intervention (136). Chapter 2 finds that all costs associated with medication error may not yet have been considered. An underestimation of the true cost of medication error could therefore account for the lack of cost-effectiveness evidence of interventions focused on its reduction. Chapter 3 supports existing literature finding medication reconciliation to be time and resource intensive (147). In terms of increasing time spent on medication reconciliation, an associated economic burden in terms of cost of healthcare professional time was described but cost savings in terms of capturing errors of clinical significance were not identified. This may offer a further explanation as to why medication reconciliation has not been found to be cost-effective in the literature to date.

A systematic review established that most medication errors stem from a lack of effective communication between health care providers during transitions of care (280) and improving communication has been identified as a key strategy in improving overall transitional care (281). Poor communication of medication information between primary and secondary care at hospital admission was identified as an issue in Chapter 3. In addition, when interviewed during the feasibility study, GPs, patients and junior doctors all described experiencing difficulty with communication of medication information between primary and secondary care, not only at hospital admission but also at discharge (Chapter 4). Both hospital admission and discharge have been identified in the literature as transitions in care where medication errors are likely to occur. Some studies suggest hospital admission as the most critical point for occurrence of error, with others suggesting hospital discharge but no consensus exists (279) (107). This thesis finds the occurrence of medication error to be a continuum across the primary secondary care interface, including the transitions of both hospital admission and discharge, and highlights the need to provide accurate medication information to the next healthcare provider in the chain (Chapters 3 and 4). A key finding from the feasibility study was the improved communication of medication information associated with use of the PHARMS device at hospital discharge.

The patient has been identified as having an important role at the primary secondary care interface. It has been suggested that to successfully address the issues at the primary secondary care interface, health care providers need to view the system from the patients' perspective (282) and that patients need to be involved in the transmission of medication information between the different levels of care (279). This work also identifies and supports the role of the patient as a constant within transitional care (Chapter 4).

Benefit has previously been associated with patient held healthcare records and it is now over 10 years since a review outlining the potential of electronic personal health records to improve patient care was published (283). Implementation of such records has not materialised across healthcare systems however. Poor integration with existing electronic systems and non-user friendly design have been identified as issues (284, 285). Acceptability of electronic personal health records to patients has been highlighted as key to successful use (286). In addition, it has been identified that to be actually useful, such a record needs to be dynamic rather than being a static container for data (284). The PHARMS device was found to be an acceptable, active, record of medication that has the ability to successfully integrate into existing systems and hence has the potential to succeed where other personal electronic records have failed. Acceptability to healthcare professionals is also required for universal adoption. Although the PHARMS device was universally useful and acceptable to GPs, junior doctors expressed concerns in relation to lack of time, workload and lack of perceived relevance. Such issues have previously been identified as barriers in research pertaining to EHR implementation (287-289). The lessons learned from EHR implementation in terms of need for full involvement of clinical staff, leadership and training (290) were also found to apply to the PHARMS device (Chapter 4).

5.3 Implications for research

A commentary on the landmark "To Err is Human" report stated: *"If medication errors were a single disease we would be investing more heavily. Research funding for cancer is in the billions, yet the proportion of people who suffer from medication errors is far greater than those with cancer*"(291).

Further research in the area of medication error is warranted and, in particular, research is required to explore the economic impact of medication error. Accurate information on the cost of medication error is required for cost benefit analysis of all interventions facilitating its reduction. Studies examining the economic impact of medication error were found to be of poor quality and to evaluate economic impact using limited parameters. There is a need for future robust, high quality costing studies looking at a broader spectrum of costs associated with medication error inclusive of primary care, patient and societal costs.

In Chapter 3, although patient harm was prevented through the identification of errors of clinical significance in almost half of the study sample, inefficiency and resource intensity associated with medication reconciliation were also identified. The PHARMS device has the potential to facilitate medication reconciliation by providing access to a list of a patient's pre-admission medications as documented in their GP record. Use of the PHARMS device during medication reconciliation at hospital admission has the potential to positively impact process efficiency. A process which is more time (and hence cost) efficient may enable widespread and sustainable implementation of medication reconciliation. Further evaluation is warranted in this context.

Reason's model for error outlines two approaches: the person and the system (292). This thesis finds that both the person and the system should also be considered in implementation of an intervention

to reduce error. Difficulties with intermittent use of the PHARMS device and the need for widespread implementation were identified by GPs and junior doctors during the feasibility study. A reluctance to use the device was also reported by junior doctors. Working with clinicians sceptical of technology was shown to be of benefit in promoting adoption of the EHR (287, 290). In addition, recent evidence suggests successful implementation of electronic tools to support medication reconciliation requires stakeholder involvement in terms of design and implementation features (293, 294). Further evaluation of the PHARMS device requires engagement; not only of doctors, but also of pharmacists as this key stakeholder group was absent from the initial assessment of feasibility.

5.4 Implications for practice

The WHO has identified a number of strategies to reduce medication error during the transitions of care. These strategies include; improved quality and timeliness of discharge information, establishing effective medication reconciliation practices, increasing the involvement of primary care physicians, improving the effectiveness and timeliness of clinical handovers between clinicians and educating and supporting patients, families and carers (102, 295). The PHARMS intervention provides a potential method of reducing medication error during the transitions of care with multiple benefits across these key areas. Due to its use of basic universally applicable USB technology, the PHARMS device has the potential to positively impact international clinical practice.

A national clinical incidents report published in 2017 highlighted the prevalence of medication error across the Irish Healthcare system. The need for an EHR which would work seamlessly between the hospital and the community was emphasised. The report stated: “While awaiting the national roll out of an Electronic Health Care Record, the linking of IT systems between hospital and the

community and GP from a medication viewpoint would be useful"(29) . The same report cited the need for "empowerment of the patient/carers/family to become active participant(s) in the multidisciplinary team, particularly at the transitions of care which are the times of high risk". The PHARMS device has the potential to meet the immediate need identified as currently existing within the Irish healthcare system.

It has been identified that care transitions may provide an opportunity in terms of appropriate medication use and adherence (52). The practice of medication reconciliation harnesses this opportunity but resource intensity is currently a barrier to universal implementation. Guidance provided by HIQA on medication safety in Irish hospitals produced in 2018 states the need to "develop a national approach to advance medication reconciliation to include defining responsibility for medication reconciliation and using electronic solutions to reduce time spent by clinical staff on medication reconciliation"(143). The PHARMS device may have a role in assisting with pharmacist led medication reconciliation in terms of enhancing process efficiency for widespread and sustainable implementation.

Having identified that medication error occurs across a continuum of the primary secondary care interface, in order to successfully address this issue we should also view primary and secondary care as a continuum with a single multidisciplinary healthcare team. The healthcare team should include the patient in addition to healthcare professionals from both primary and secondary care. As the patient is the one constant in transitional care and the GP as has a central role in overall patient care, the PHARMS device has the potential to harness the strengths of individual team members. The device also has the potential to improve clinical handover between members of such a multidisciplinary team in both the community and hospital.

5.5 Implications for policy

At a policy level the need to move towards a primary care centric health care system has recently been highlighted nationally and internationally (2, 100). The Irish Department of Health Slaintecare report published in 2017 has called for significant investment in primary care (2, 100). It has previously been suggested however that, as outlined in Figure 6.1 , the most evolved form of healthcare is patient driven and patient centric (247). The innovative use of technology has been identified as having the potential to improve efficiency and safety within the Irish healthcare system (296). Patient held technology has the potential to create patients who can be active partners within the healthcare system, and (in line with the New Haven Recommendations) be involved at the micro-level of direct service provision, rather than being merely passive recipients of healthcare (297). In terms of medication safety the WHO has highlighted that, in addition to medication reconciliation at points of transition, the patient medication record in primary care is of particular importance, especially when patients seek treatment from multiple health care providers (53). The patient also has a role in contributing to medication safety (298).The PHARMS device is currently patient held but does have additional potential to provide the patient with future electronic access to their medication information. Finding from this research suggest that, in terms of medication management, a patient held technology using medication information originating in primary care in the form of the PHARMS device may facilitate care that is both primary care and patient centric.

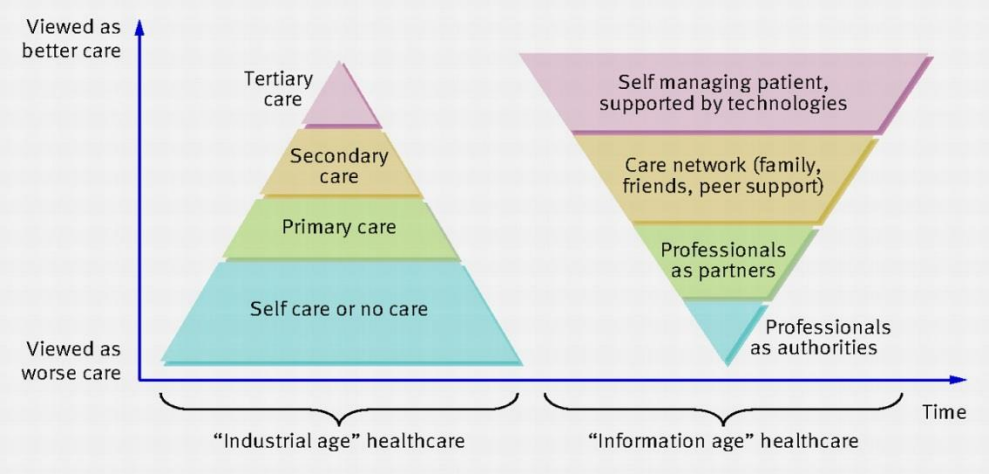


Figure 5 1: Policy vision of health care (284).

The need for cost savings and increased efficiency across healthcare systems is widely recognised. This thesis suggests a number of areas for potential cost savings in healthcare. Firstly, the findings of the systematic review suggest that reduction of medication error would result in significant cost savings (Chapter 2) and that medication error may be reduced by the novel intervention developed (Chapter 4). Secondly, reducing the time spent by healthcare professionals on inefficient processes relating to clarification of medication information in secondary care was shown to have the potential for substantial cost savings (Chapter 3). A recent report produced by the Department of Health in Ireland outlines the need for improved efficiency in general practice and identified transcribing prescriptions and issues pertaining to prescribing as a particular source of inefficiency (10). It is likely that savings could also be made in terms of cost of GP's time, in line with the findings of Chapter 3, by improving process efficiency in relation to communication of medication information at the primary secondary care interface. Finally, a reduction in healthcare costs has previously been associated with patient empowerment (284) and the PHARMS device may promote such empowerment as previously described .

Financial incentives have been key to both successful implementation of strategies to reduce medication error (299) and to implementation of EHR systems internationally (290) (283). The Money Follows the Patient (MFTP) funding model introduced in Ireland in 2014 aims to support patient centred care and to "create incentives that encourage treatment at the lowest level of complexity that is safe, timely, efficient, and is delivered as close to home as possible" (111) Utilizing the aforementioned cost savings to generate financial incentives to promote implementation of this novel intervention would therefore be in line with current policy.

Based on evidence supporting the usefulness of a clearly laid out summary of research findings for policy makers (300), a policy brief was prepared based on the findings of this thesis and presented at a meeting with the HSE IT manager for primary care in Ireland (Appendix 3).

5.6 Strengths and limitations

The strengths and limitations of the individual studies are outlined in Chapters 2 to 4 respectively.

Strengths

The major strength of this thesis was the use of MRC guidance to develop a novel intervention in a robust and structured manner, drawing on existing evidence, establishing new evidence and utilising appropriate theory. A further strength was involvement of a multidisciplinary team who provided diverse skills and views during the course of this research. The input of both a practicing clinician and a commercial provider of GP software throughout intervention development helped maintain a pragmatic focus thus potentially avoiding difficulties previously highlighted in the literature relating to implementing findings from research into clinical practice (301). Employing qualitative and

quantitative methodology was a further strength with the end product of this thesis being evaluated in a robust and detailed manner. An additional strength is conducting the cross-sectional and feasibility studies of this thesis among a general population of older adult patients without significant exclusions. This, in addition to the study findings being supported by existing literature in terms of occurrence of medication error, may suggest that the novel findings of the thesis are applicable to a general older adult population.

Limitations

The overall numbers of patients included in the cross-sectional and feasibility studies of the thesis are small. A further limitation is that the studies included older adult patients in a single geographical location and involved a single hospital. Further research is required involving greater patient numbers, more diverse geographical locations and multiple clinical sites. An additional limitation of this work is that initial assessment of feasibility of the intervention did not involve pharmacists. As pharmacists are key stakeholders in terms of medication error and medication reconciliation, future work involving this group is required. A final limitation is that my background as a clinician in general practice may have influenced my interpretation of findings throughout the thesis. I sought however to involve those in other disciplines including public health, pharmacy, economics and IT at all points during this work to assist in developing a broad and balanced interpretation of results.

5.7 Conclusion

Medication error is an important patient safety issue and developing interventions focused on its reduction is currently an international priority. An accurate estimate of associated economic burden is required to inform the successful development and implementation of such interventions. This thesis suggests that the true cost of medication error may not, so far, have been accurately estimated. Medication reconciliation, as an established intervention to reduce medication error,

lacks evidence in terms of cost effectiveness. This may result, in part, from a time burden incurred due to inefficiencies relating to lack of available and accessible medication information at the primary secondary care interface, but also potentially from the true cost of medication error being underestimated. The novel patient held electronic medication record developed and evaluated during the course of this thesis addresses an important cause of medication error; poor communication of medication information at the primary secondary care interface. As a consequence, it has the potential to both reduce medication error at the primary secondary care interface and to improve process efficiency of medication reconciliation with implications for significant cost savings in healthcare.

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PRESENTATIONS

Oral Presentations

Title of Presentation	Conference Title and Venue	Date
Medication error at the primary-secondary care interface: causes ,costs and prevention	Medication Optimisation in Multimorbidity, UCC	18/09/14
Prescribing error at the interface of primary and secondary care	AUDGPI, Queens University, Belfast	06/03/15
The PHARMS feasibility study	Mercy University Hospital, Cork ➢ Grand rounds ➢ Intern Teaching ➢ Clinical Nurse Manager Meeting	06/01/16
The Economic Impact of Medication Error: A Systematic Review **(3 minute oral presentation associated with poster)**	PRIMM, The Health Foundation, London	29/01/16
The Economic Impact of Medication Error: A Systematic Review	SPHERE Conference, Royal College of Surgeons Ireland, Dublin	29/02/16
The Use of Novel Technology at the Interface of Primary and Secondary Care	iHealth Seminar, University College Cork	06/03/16
The use of novel technology at the interface of primary and secondary care: the Patient Held Active Record of Medication Status (PHARMS) Study (Research in progress)	International Conference of Integrated Care, University College Dublin	08/05/17

The PHARMS (Patient Held Active Record of Medication Status) Feasibility Study	EGPRN Conference, University of Lille, Lille, France	13/05/18
Additional time and cost of medication reconciliation at hospital admission	Grand rounds, Mercy University Hospital, Cork	11/10/18
The PHARMS (Patient Held Active Record of Medication Status) Feasibility Study	PRIMM, The Health Foundation, London	11/12/18
The PHARMS (Patient Held Active Record of Medication Status) Feasibility Study	AUDGPI, RCSI, Dublin	01/03/19

Poster Presentations

Title of Presentation	**Conference Title and Venue**	**Date**
The Economic Impact of Medication Error: A Systematic Review	PRIMM, The Health Foundation, London	29/01/16
The Patient Held Active Record of Medication Status (PHARMS) feasibility study	New Horizons in Medical Research, University College Cork	08/12/16

COURSES COMPLETED AS PART OF PhD

Course	Location	Date	Credits
Good Clinical Practice (GCP) certification	University College Cork	September 2014	N/A
Qualitative interview analysis	University of Oxford	October 2014	N/A
Health economic evaluation	University College Cork	January 2015	N/A
PG 7016 Systematic review module	University College Cork	April 2015	5
N Vivo software training	University of London	October 2016	N/A
ST 6013 Statistics module	University College Cork	June 2017	10

APPENDIX 1: Supplementary material for Chapter 2

An update to the systematic review

A further search of all databases included in the original search was conducted in November 2018. PubMed, Cochrane, Embase, CINAHL, EconLit, ABI/INFORM and Business Source Complete were searched to identify papers published between April 2016 and November 2018. The same search strategy used in the original systematic review (as outlined in this appendix) was utilised. Search results from the multiple databases were transferred to a reference manager (End Note).

Results:

The search yielded 1007 titles for review. Reasons for exclusion are outlined in Figure A1.1.

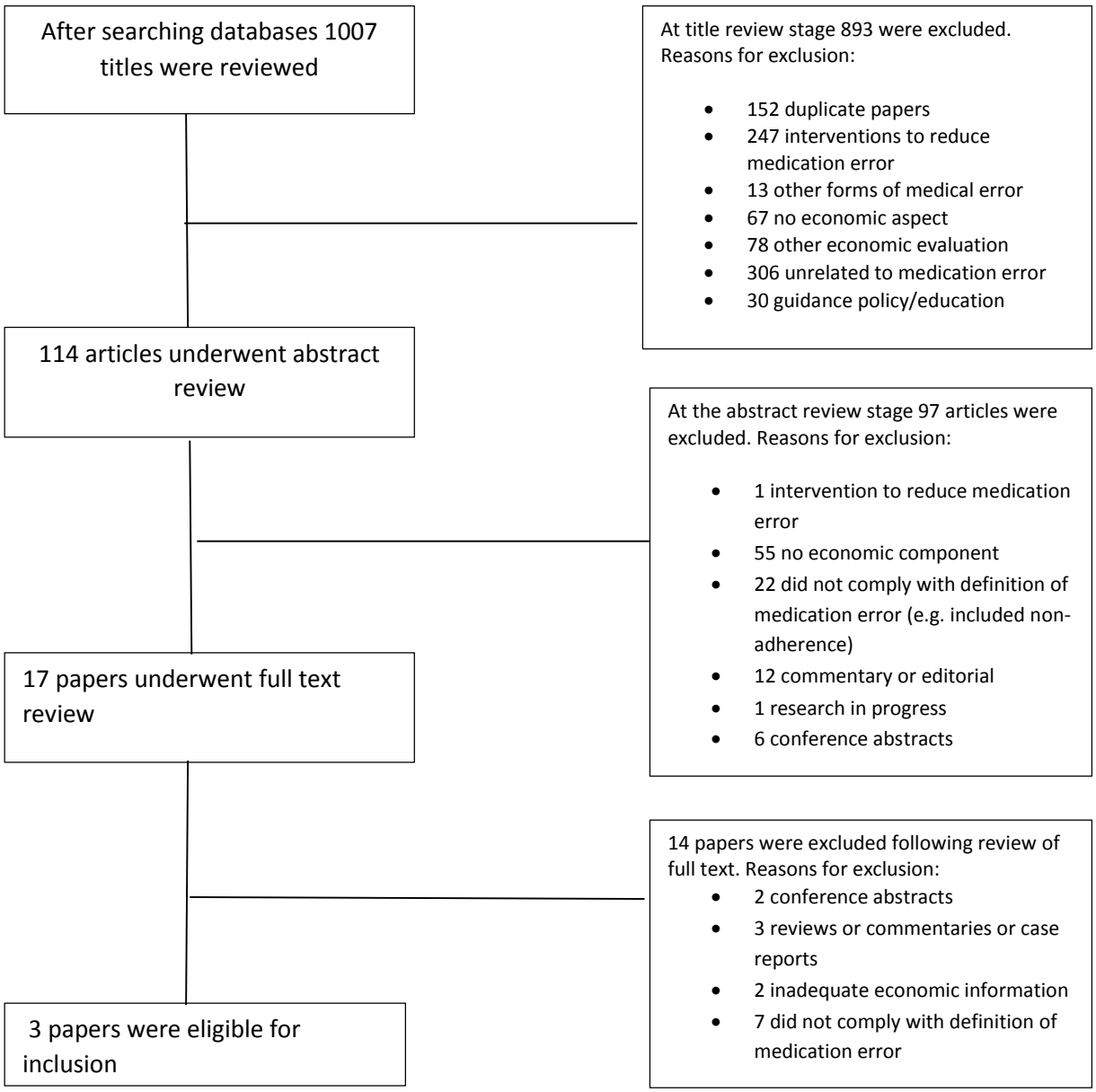


Figure A 1 1: Reason for exclusion of studies

A summary of the studies which met inclusion criteria is listed in Table A1.1. The studies were conducted in the USA (n=1), Europe (n=1) and Canada (n=1).

Table A 1 1 Summary of studies meeting inclusion criteria

First author Year	Title	Study design Methods used to identify medication errors	Study population Study setting	Sample size patients	Sample size errors	Type of medication error EMA Classification*	Economic method	Outcome measure	Results
McCarthy (302) **2017**	Medication errors resulting in harm: Using chargemaster data to determine association with cost of hospitalization and length of stay	Case control: Retrospective review of voluntary error report data using diagnosis codes	Hospital in patients (secondary /tertiary care), USA	3,521	242	Medication error that may have contributed to or resulted in temporary harm to the patient and required intervention Errors with harm	Measuring of direct costs	In case and control groups: 1.Length of stay 2.Cost of hospitalisation	Economic impact of errors potentially associated with harm 1.Median LOS: Case 5.0 (5.0-11.0) Control 5.0 (4.0-7.0) 2.Median Cost Hospitalization: Case $19,444 (13,481-40,580) Control $17, 173 (12,500-27,125) (Additional information on 5 subgroups; antineoplastics, corticosteroids, opiates, Patients >65yrs, <65 years)
Amelung (303) **2017**	Association of preventable adverse drug events with inpatients' length of stay-A propensity matched cohort study	Case control (using propensity score): Retrospective review of medical records	Hospital in patients (secondary /tertiary care), Germany	4,462	220	pADE** as defined by predetermined list of ICD-10 codes Errors with harm	Measuring of direct costs	Excess length of stay	Economic impact of errors associated with harm: Additional LOS incurred by cases: Increased LOS of 1.88 days
Tchouaket (304) **2017**	The economic burden of nurse-sensitive adverse events in 22 medical-surgical units: retrospective and matching analysis	Case control (using propensity score): Retrospective review of medical records	Hospital in patients (secondary /tertiary care), Canada	4,699	29	pADE** Errors with harm	Measuring of direct costs (costs established from literature review)	Hopsitalization costs (as established from literature review)	Economic impact of errors associated with harm: Additional costs incurred by cases: Mean $49.382.4 Median $42,356.0

*European Medicine's Agency (EMA) Classification:

- Medication errors with harm
- Medication errors without harm
- Intercepted medication errors
- Potential medication errors

**pADE: Preventable Adverse Drug Event

Table A1.2 outlines the parameters used to assess study quality. The viewpoint was explicitly stated in one study (304) but could be implied by the cost data used in the other studies. The study population was described (though in varying detail) in all studies and a clear description of the costs used in the analysis was provided in all studies. Discounting was not applied to one study, was not applicable to another and was correctly applied in the third. All three studies measured incremental costs and reported costs as per the EMA guide. One study fulfilled all applicable quality criteria.

Table A1 2: Assessment of study quality

Study	Viewpoint	Population	Relevant costs	Discounting	Incremental costs	Sensitivity analysis	Costs reported as per EMA* guide
McCarthy (302)	[+]	+	[+]	0	+	0	+
Amelung (281)	[+]	[+]	[+]	N/A	+	0	+
Tchouaket (304)	+	+	[+]	+	+	+	+

Notation based on Rothfuss et al (184): +, present; [+], partly fulfilled; 0, absent. N/A, non-applicable

*EMA: European Medicines Agency

All three studies applied a case control design and were conducted among a general population of adult hospital inpatients.

Methods and parameters used to establish economic impact

The three studies measured direct costs pertaining to medication errors to which the study population was exposed. Indirect costs were not measured.

The three studies calculated costs associated with hospitalisation and all demonstrated an increased economic burden associated with medication error.

Two studies expressed economic impact in monetary terms (302, 304) with one study expressing economic impact in terms of increased length of hospital stay (303). One study expressed economic impact in both monetary terms and in terms of increased length of hospital stay (302).

Of the studies expressing economic impact in monetary terms one used information from the hospital accounts system (302) and one used costs taken from a review of the literature (304).

McCarthy et al state using "total hospitalisation cost" information for each patient (302). Tchouaket et al define hospitalisation costs as "hospital related treatment costs due to the prolongation of hopsitalisation by the event" (304). No breakdown of overall hospitalisation cost is giving in any of the included studies.

Economic impact of medication error

Two of the studies provided information on the economic impact of pADEs. McCarthy et al provided an overall estimate of cost of medication errors with the potential to cause harm in case and control groups, in addition to providing information on cost of medication error for five subgroups namely; antineoplastic medication, corticosteroid medication, opiate medication, Patients >65yrs, and patients <65 years.

Discussion:

All studies reported increased financial costs or length of hospital stay associated with medication error and confirm that medication error is associated with a significant economic burden. All studies were conducted among hospital inpatients, and cost of hospitalisation was the only parameter used to establish economic impact. Limited detail was provided from an economic perspective and costs from a primary care, patient and societal perspective were absent.

The findings of the updated search support the original findings of the systematic review and there were no new findings.

Search strategy

Pubmed

(Cost OR Cost analysis OR Econ*)

AND

(Medication error OR Inappropriate Prescribing OR" Inappropriate Medication" OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* OR Medication omission*)

Limit: 01/01/2004 to present, English

CINAHL

(Cost OR Cost analysis OR Econ*) title and abstract

AND

(Medication error OR Inappropriate Prescribing OR" Inappropriate Medication" OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* OR Medication omission*)

Limit: 01/01/2004 to present, English

Econlit

(Cost OR Cost analysis OR Econ*)

AND

(Medication error OR Inappropriate Prescribing OR" Inappropriate Medication" OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* OR Medication omission*)

Limit: 01/01/2004 to present, English

Business Source Complete

(Cost OR Cost analysis OR Econ*)

AND

(Medication error OR Inappropriate Prescribing OR “Inappropriate Medication” OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* OR Medication omission*)

Limit: 01/01/2004 to present, peer reviewed journals, English

Embase

('Cost'/exp OR Cost OR Costs OR ('Cost'/exp OR Cost AND ('Analysis'/exp OR Analysis)) OR Econ*) title and abstract

AND

'Medication'/exp OR Medication AND ('Error'/exp OR Error) OR (Inappropriate AND Prescribing) OR 'Inappropriate Medication' OR (Preventable AND Adverse AND ('drug'/exp OR drug) AND event*) OR (Preventable AND Adverse AND ('drug'/exp OR drug) AND Reaction*) OR (Prescribing AND Error*) OR (Transcription AND Error*) OR ('Medication'/exp OR Medication AND Discrep*) OR (Medication AND Omission*) title and abstract

Limit: 01/01/2004 to present, Human, English

ABI/INFORM

(Cost OR Cost analysis OR Econ*) title and abstract

AND

(Medication error OR Inappropriate Prescribing OR" Inappropriate Medication" OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR Transcription Error* OR Medication Discrep* OR Medication omission*) title and abstract

Limit: 01/01/2004 to present, peer reviewed scholarly journals, English

Cochrane

Medication error

AND

(Cost OR Econ*)

Limit: 01/01/2004 to present

Data Extraction Form:

Table A1 3: Data extraction form

Author:
Year and country:
Title:
Study setting:
Study type:
Study population:
Study sample size
Type of medication error:
Economic method:
Outcome measure:
Results:

PRISMA statement:

Table A1 4: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	40
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	41,42
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	43
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	44
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	44
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	45,46
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	44
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	44
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	45,46

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	46
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	46
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	47,48
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	48
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	48

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	48
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	48
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	50
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	51-56
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	57
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	51-56
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	58-65
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	57
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	67
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	67-69
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	71
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	72,73
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Inflating retrospective costs using the Consumer Price Index (CPI):

1. **CPI:** www.tradingeconomics.com

   Formula: Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Health Information and Quality Authority.www.hiqa.ie/publications/guidelines

   (Latest CPI/Earlier CPIx100) -100=percentage price increase

   Currency conversion: www.x-rates.com Nov 2015

2. **Percentage price increase for each study:**

- **Al-lela** Iraq 2012-2015: (149.7/141x100): **6.17%**
- **Choi** USA 2013-2015: (237.6/232x100): **2.41%**
- **Cranshaw** UK 2009-2015: 128.2/110: **16.5%**
- **Field** USA 2000-2015: 237.6/170: **39.7%** (published 2005 but costs 2000)
- **Gharekhani** Iran 2011-2015: 224.4/90: **149.3%** (published 2014 but costs 2011)
- **Hellinger** USA 2010-2015: 237.6/217: **9.49%**
- **Hoonhout** The Netherlands 2004-2015: 117.18/97.5: **20.18%** (published 2010 but costs stated as 2004)
- **Hughes** USA 2006-2015: 237.6/198: **20%** (published 2012, costs 2006)
- **Lahue** USA 2013-2015: 237.6/232: **2.41%** (published 2012, costs 2013)
- **Meissner** USA 2006-2015: 237.6/198: **20%** (published 2009, costs 2006)
- **Moura:** No monetary cost
- **Pinilla:** Spain 2001-2015: 102.5/77: **33.12%** (published 2006, costs 2001)

- **Ranchon:** France 2008-2015 127.8/117: **9.23%** (published 2011, costs 2008)
- **Samp:** USA 2012-2015 237.6/230: **3.3%** (published 2014, costs 2012)
- **Zahari:** Malaysia 2011-2015 113.9/97: **17.4%**
- **Zaidi:** UK 2013-2015 100/97: **3.09%**

Prospero registration:

Review registered with PROSPERO 05/08/15

Registration no: CRD42015024202

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

The economic burden associated with medication error: a systematic review

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

01/06/2015

4 Anticipated completion date

Give the date by which the review is expected to be completed.

30/11/2015

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Elaine Walsh

7 Named contact email

Enter the electronic mail address of the named contact.
elaine.walsh@ucc.ie

8 Named contact address

Enter the full postal address for the named contact.
G58, Western Gateway Building, University College Cork, Western Rd, Cork

9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.
+353863839492

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
University College Cork
Website address:
www.ucc.ie

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Elaine	Walsh	Department of General Practice, University College Cork
Professor	Colin	Bradley	Department of General Practice, University College Cork
Professor	Patricia	Kearney	Department of Epidemiology and Public Health, University College Cork
Dr	Laura	Sahm	School of Pharmacy, University College Cork
Ms	Christina	Rae Hansen	School of Pharmacy, University College Cork
Mr	James	Gallagher	School of Pharmacy, University College Cork

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
None: systematic review being conducted as part of PhD

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
To quantify the economic burden associated with medication error
To identify parameters used to cost medication error

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
PubMed, EMBASE, CINAHL, Cochrane, Econlit, Business Source Complete, ABI/INFORM

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Medication error

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Patients in primary, secondary and tertiary care without restrictions with regard to age, gender or ethnicity

20 Intervention(s), exposure(s)

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
The exposure to be reviewed is medication error defined as any preventable event that may cause or lead to inappropriate medication use or patient harm Inclusion criteria: 1 Errors pertaining to the prescribing of medication: Therapeutic and legal errors (e.g. incorrect medication, errors of dose/route/frequency, failure to comply with legal requirements of prescribing.) Omissions/discrepancies in the prescribing of medication. Transcription error 2 Errors pertaining to the dispensing of medication 3 Errors pertaining to the administration of medication Exclusion criteria: Prescribing of potentially inappropriate medications Non-compliance or non-adherence to medication. Non-preventable adverse drug reactions

21 Comparator(s)/control

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Not applicable

22 Types of study to be included initially

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Studies evaluating the economic impact of medication error as defined in Section 20 without restrictions pertaining to study design Inclusion criteria: Studies in primary, secondary and tertiary care evaluating the economic implications of medication error. Exclusion criteria: Economic evaluations of interventions to reduce medication error. Studies evaluating non-medication related error e.g. device implantation Studies comparing the costs of the adverse drug reactions of two or more medications.

23 Context

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Studies in primary, secondary and tertiary care including ambulatory and inpatient settings.

24 Primary outcome(s)

Give the most important outcomes.
1. To quantify the cost associated with medication error 2. To identify what costs are associated with medication error and where they are incurred (e.g primary care, hospital, workplace) 3. To review methods used when costing medication error.
Give information on timing and effect measures, as appropriate.
Direct and indirect costs will be identified. Monetary and other cost measures (e.g. length of hospital stay) will be identified.

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
None

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Titles of studies identified from the database search will be reviewed by the primary researcher. Subsequent abstract review will be conducted independently by the primary researcher and another member of the review team to identify studies that potentially fulfil the inclusion criteria. Full text articles of the potentially eligible studies will be obtained and the articles will be reviewed by the 2 researchers. In the event of disagreement over the eligibility of the particular studies the articles will be reviewed by a third reviewer. Data will be extracted from the studies using a prepared data extraction form. Extracted information will include: study setting, study population, patient demographic information. study methodology, type of prescribing error, cost data (direct/indirect, monetary/other), information for assessment of the risk of bias

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

In view of the anticipated heterogeneity of the studies to be included each study will be assessed regarding quality and risk of bias on an individual basis. Appropriate assessment tools will be used as per the Cochrane Bias Methods Group recommendations.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

A narrative synthesis of the studies included will be provided based on the type of medication error, setting of the study, population studied and economic burden identified. It is anticipated that there will be limited scope for meta analysis due to an expected wide variety of prescribing errors and cost outcome measures. However if studies are identified with similar exposure (medication error) and outcome (cost) measures the results will be pooled. The results will be assessed for heterogeneity and a random effects meta analysis conducted if sufficiently homogenous.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

If the necessary data are available subgroup analysis will be conducted by age (65 yrs) and type of medication error (e.g. prescribing error)

Review general information

30 Type of review

Select the type of review from the drop down list.

Other

Economic, Harm

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Ireland

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available

Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to a leading journal in this field.

Do you intend to publish the review on completion?

Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

medication error
cost
economic

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.

Ongoing

39 Any additional information

Provide any further information the review team consider relevant to the registration of the review.

The findings of this review will be used to inform further research to be conducted as part of the PhD of the primary researcher

Information on impact of systematic review publication

Web view



Congratulations — your article was one of our top downloaded articles in recent publication history!

Dear Elaine Walsh,

We are pleased to announce that your article **Economic impact of medication error: a systematic review**, published in *Pharmacoepidemiology and Drug Safety*, was one of the journal's top 20 most downloaded recent papers!*

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Your contributions are vital to growing the profile of *Pharmacoepidemiology and Drug Safety*.

Thank you for sharing in our journal's success,
The Editors of *Pharmacoepidemiology and Drug Safety*

** Comparative exercise based on measuring downloads within the first 12 months of online publication, for articles published between July 2016 and June 2018*

APPENDIX 2: Supplementary material for Chapter 3

Clinical Significance of errors: instructions for raters

Definition: this is the degree of patient harm that could be caused by the error.

Significant: an error that can cause patient symptoms that, while harmful to the patient, poses little or no threat to the patient's life function.

Serious: an error than can cause signs/ symptoms that are associated with a serious level of risk that is not high enough to be life-threatening. In addition, a potential ADE is serious if it can cause persistent alteration of daily function.

Life-threatening: an error that can cause signs/symptoms that if not treated would put the patient at risk of death.

Examples of Severity Categories

LIFE THREATENING

Incorrect dose of anti-rejection medication is prescribed in patient with kidney transplant.

Omission of amiodarone at discharge when given for prevention of ventricular tachycardia.

Patient with a prior penicillin anaphylaxis reaction and ordered penicillin at admission.

Incorrect paracetamol dose prescribed at discharge with a total daily dose >15g.

Omission of warfarin at admission in patient with St. Jude's mitral valve replacement.

SERIOUS

Patients' correct dose is 2 mg diazepam, doctor prescribes 10 mg on admission.

Patient with exacerbation of congestive cardiac failure discharged on 1/4 preadmission dose of frusemide.

Omission of beta-blocker at discharge in patient with coronary artery disease.

Concurrent paracetamol prescriptions at discharge with a total daily dose >10g but ≤15g.

Warfarin 5 mg QD prescribed at discharge instead of 3 mg QD (prescribed for atrial fibrillation).

Indomethacin for gout prescribed at discharge to patient concurrently taking Ibuprofen.

Omission of lactulose BD in patient with history of hepatic encephalopathy.

SIGNIFICANT

Omission of diazepam PRN for insomnia at discharge.

Change from laxative bisocodyl PRN to bisocodyl BD

Omission of lisinopril in patient without coronary artery disease, heart failure or valve disease.

Two concurrent paracetamol prescriptions with a total daily dose >4 grams but ≤10 grams.

Omission of tramadol PRN for tension headache.

Additional Examples

Errors that may lead to hypotension or over-treatment of hypertension are considered to be serious.

Errors that may lead to under-treatment of hypertension, angina, or ischemia are considered to be significant.

Errors that may lead to significant over-anticoagulation or under-coagulation are considered to be serious.

Errors that lead to under-treatment of asthma are considered to be significant.

Errors that lead to under-treatment with antibiotics:

- If IV antibiotics were originally prescribed, consider the errors to be serious.
- If oral antibiotics were originally prescribed, consider the errors to be significant.

Errors that lead to over-treatment with antibiotics:

- If either IV or oral antibiotics were prescribed, consider the errors to be significant, unless the antibiotic is directly toxic to end organs in a highly dose-sensitive fashion (e.g., gentamicin), in which case, the severity will be higher (usually serious).

Time and motion study

Table A2 1: Time for medication reconciliation

	Value	Median	Goal
1	76	59.5	50
2	76	59.5	50
3	71	59.5	50
4	59.5	59.5	50
5	59.5	59.5	50
6	55	59.5	50
7	55	59.5	50
8	50	59.5	50
9	50	59.5	50
10	55	59.5	50
11	60	59.5	50
12	34	59.5	50
13	50	47.5	50
14	35	47.5	50
15	25	47.5	50
16	50	47.5	50
17	45	47.5	50
18	31	47.5	50
19	56	47.5	50
20	50	47.5	50
21	50	47.5	50
22	40	47.5	50
23	35	47.5	50
24	30	47.5	50
25	50	47.5	50
26	45	47.5	50
27	50	47.5	50
28	40	47.5	50
29	58	47.5	50
30	78	47.5	50

In 2016 the hospital pharmacists conducted an audit of their medication reconciliation process. An initial time and motion study and established a median time of 59.5 minutes. Following implementation of quality improvement measures to the process a repeat time and motion study and established a median time of 47.5 minutes.

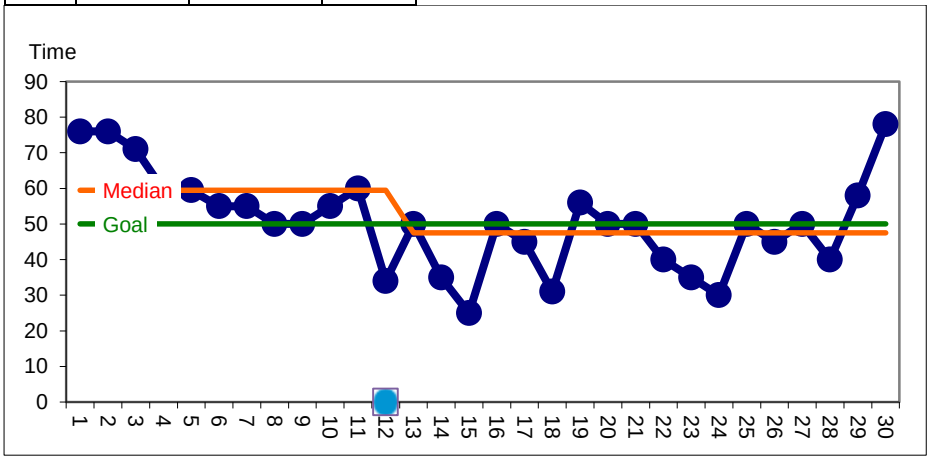


Figure A2 1: Time for medication reconciliation

Cost of pharmacist time

Table A2 2: Pharmacist salary

Annual salary scale of basic grade pharmacist (point 7 of 2017 scale)		€47,595
Employers PRSI +10.75% (Direct Salary Cost)	€5116	
Input Pension Cost +4% (Total Salary Cost)	€1904	
Overheads +25% (Total Staff Cost)	€11899	
Total Cost		€66,514
Hourly rate (based on that have 9 BH and 27 days annual leave i.e.52 -7.2 weeks = 44.8 weeks)		€44.93

Calculating population growth rate and projected population figures

Formula for calculating population growth rate:

$$r = \left(\left(\frac{P2}{P1}\right)^{\frac{1}{t}} - 1\right) * 100$$

- t: Number of years of census period
- P2: Population at the end of the census period
- P1: Population at the start of the census period
- r: Growth annual rate (in %)

Formula for calculating projected population figures:

$$Pt = P0 * \left(1 + \frac{r}{100}\right)^{t}$$

- t: Number of years
- P0: Population at the start
- r: Growth annual rate (in %),
- Pt: Population after t years

STROBE Statement

Table A 2 3: STROBE checklist

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	74
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	75,76
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	77,78
Objectives	3	State specific objectives, including any prespecified hypotheses	79
Methods			
Study design	4	Present key elements of study design early in the paper	79
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	79,80
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	79,80
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	81
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	81
Bias	9	Describe any efforts to address potential sources of bias	81
Study size	10	Explain how the study size was arrived at	79
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	82
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	82,83
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	83
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	82,83

		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	83,84
		(b) Give reasons for non-participation at each stage	83
		(c) Consider use of a flow diagram	N/A
79Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	84
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	84-90
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	87-90
		(*b*) Report category boundaries when continuous variables were categorized	87-90
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	90,91
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	94
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	94,95
Generalisability	21	Discuss the generalisability (external validity) of the study results	94,95
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

Data collection sheet

Study ID	Source Admission	Time admission	Age	Gender	SES	Medication number	Comorbidity number	Continence	Mobility	Feeding

Dressing	Knowledge of medications	Written record of medications

Study ID	Drug with error	Dose	Frequency	Description of error	Total error number	Significant error number	Serious error number	Life-threatening error number	Error score

Study ID	Nature of issue requiring additional time	Time spent resolving issue (mins)	Phonecalls to resolve issue (number)

APPENDIX 3: Supplementary material for Chapter 4

Consent forms

Patient consent form for participation in research study

Section A:

Patient Name:_____

Title of study: PHARMS Study

Doctor Directing Research: Dr Elaine Walsh Phone: 0863839492

You are being asked to participate in a research study. The doctors at University College Cork study medicines and disease and attempt to develop improved methods of managing patients. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate.

Section B

I. **NATURE AND DURATION OF PROCEDURE(S):**

We have looked at prescriptions that patients receive when leaving hospital and we have found mistakes on the prescriptions. These mistakes have the potential to harm you as a patient and to

create difficulty for your GP and pharmacist. We are conducting this study to get more information regarding the causes and consequences of these mistakes. We will collect medication information from your GP, pharmacy and hospital records and look for mistakes. We think that a list of the medication that your GP normally prescribes for you when you are at home would help the hospital doctor when they are writing your discharge prescription. We have developed an electronic device that can access your medication information from your record with your GP. Your GP can use it and the doctor in the hospital can use it. Some patients in the study will be given one of these devices. If you are given a device we will ask you to hold on to the device when you are in hospital and to bring it to any future hospital visits. Only your GP can make changes to the list of your medication that can be seen when using this device. The hospital doctor can add notes about your medication that your GP will see. The study aims to check if using this device can reduce mistakes on prescriptions leaving hospital and secondly to see if doctors and patients find it useful. If you are given a device we will contact you after you go home to conduct and interview regarding your experience with it. Data collected is subject to the Data Collection Act

II. **POTENTIAL RISKS AND BENEFITS:**

The main potential risk for you in this study is that your medication information is being accessed and that other people could have access to it. We have taken every precaution when collecting information and developing the device to make sure the information is secure and to protect the information from being accessed by unauthorized people.

The main benefit for you is that mistakes involving your medication will be picked up and rectified by your hospital doctors or GP. If you are issued with a device you will have an up to date and accurate medication record that is available to any doctor that you might see. It can be used on any computer so if you were for example to travel abroad you could bring it with you. If we can show that using this device reduces mistakes on prescriptions and that patients and doctors find it useful we may be able to improve patient safety nationally and internationally.

III. **POSSIBLE ALTERNATIVES:**

Participation in this study is voluntary and you may choose not to participate.

Section C

AGREEMENT TO CONSENT

The research project and procedures associated with it have been fully explained to me and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning any and all aspects of the project and the procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at the Cork Teaching Hospitals. I have received a copy of this consent form for my records.

I understand that if I have any questions concerning this research, I can contact the doctor(s) listed above. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork.

After reading the entire consent form, if you have no further questions about giving consent, please sign where indicated.

Signature of doctor:_____

Signature of subject:_____

Date: _____ Time:_____AM PM (Circle)

IT professional consent form for participation in research study

Section A:

Name:_____

Title of study: PHARMS Study

Doctor Directing Research: Dr Elaine Walsh Phone: 0863839492

You are being invited to take part in a research study which is being conducted at the University College Cork and the Mercy University Hospital.

Before you decide whether or not you wish to participate you should read the information provided below. You should clearly understand the risks and benefits of participating in this study. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgment.

You are not obliged to take part in this study. You have the right to withdraw your participation at any time (before, during and after the study) for whatever reason without having to justify your decision and without negative impact.

Section B

I NATURE AND DURATION OF PROCEDURE(S):

Why is this study being conducted?

Medication errors frequently occur during transitional care as patients move between different stages and settings of care. Hospital discharge has been identified as a time where medication error is likely to occur with negative consequences for the patient, GP and community pharmacist. Providing junior doctors with a list of medication taken by a patient pre hospital admission may help to reduce error when they generating discharge medication information. Transferring medication information between primary and secondary care is challenging. As a potential solution to the

problem a patient held electronic medication record has been developed within UCC and is now ready to be tested in the clinical setting. This device resembles a key and utilizes the USB port of a computer-see image.



What will your participation involve?.

You are being asked to participate in an interview which will explore your experience of using the device.

Confidentiality

The interview will be treated in a confidential manner and your participation is anonymous. The interview will be audio recorded so that it can be transcribed afterwards. Your name will not be recorded on any information which is collected about you. Instead you will be provided with a unique code. The only person with access to the code will be the investigator. The study results and anonymized excerpts from your interview may be presented at scientific conferences and/or published in an academic journal. The audio recording will be erased once the interview has been transcribed. Transcripts will be stored for 5 years; after which they will be destroyed in line with Data Protection legislation.

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II. POTENTIAL RISKS AND BENEFITS:

What are the possible benefits of participating?

The use of an electronic patient held medication record may potentially firstly reduce the occurrence of patient harm and secondly reduce work load. The information that you can provide from an IT perspective will clarify any technological issues arising from the introduction of this device

Are there any risks of participation?

It is hoped that no significant negative impact will arise from the study. You will have the option to withdraw your participation at any time should you wish.

Section C

AGREEMENT TO CONSENT

The research project and procedures associated with it have been fully explained to me. I have had the opportunity to ask questions concerning any and all aspects of the project and the procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at the Cork Teaching Hospitals. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the doctor(s) listed

above. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork.

After reading the entire consent form, if you have no further questions about giving consent, please sign where indicated.

Signature of doctor:_____

Signature of subject:_____

Date: _____ Time:_____AM PM (Circle)

GP Consent form for participation in research study

Study title: PHARMS (Patient Held Active Record of Medication Status) Study

You are being invited to take part in a research study which is being conducted at the University College Cork and the Mercy University Hospital.

Before you decide whether or not you wish to participate you should read the information provided below. You should clearly understand the risks and benefits of participating in this study. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgment.

You are not obliged to take part in this study. You have the right to withdraw your participation at any time (before, during and after the study) for whatever reason without having to justify your decision and without negative impact.

Why is this study being conducted?

Medication errors frequently occur during transitional care as patients move between different stages and settings of care. Hospital discharge has been identified as a time where medication error is likely to occur with negative consequences for the patient, GP and community pharmacist. Providing junior doctors with a list of medication taken by a patient pre hospital admission may help to reduce error when they generating discharge medication information. The GP has been identified as an accurate provider of such medication information. Transferring medication information between primary and secondary care is challenging. As a potential solution to the problem a patient held electronic medication record has been developed within UCC and is now ready to be tested in the clinical setting. This device resembles a key and utilizes the USB port of a computer-see image. The master medication list may only be modified by you the patient's GP but changes to the patient's medication may be added to the record in the hospital setting.



What will your participation involve?

Eligible patients will be issued with a device during their inpatient stay in the Mercy University Hospital. You will be required to link the device to the patient's record when it is brought to the practice by the investigator. The intern will then be able to view the medication list of your patient as it appears in your record when they are generating the discharge prescription. The intern will note any adjustments made to the patient's medication during the hospital stay. These adjustments will be communicated to you via a note which will appear in the patient's file. Changes to the patient's medication list can only be made by you.

You will also be required to participate in an interview which will explore your experience of using the device.

Confidentiality

The interview will be treated in a confidential manner and your participation is anonymous. The interview will be audio recorded so that it can be transcribed afterwards. Your name will not be recorded on any information which is collected about you. Instead you will be provided with a unique code. The only person with access to the code will be the investigator. The study results and anonymized excerpts from your interview may be presented at scientific conferences and/or published in an academic journal. The audio recording will be erased once the interview has been transcribed. Transcripts will be stored for 5 years; after which they will be destroyed in line with Data Protection legislation.

What are the possible benefits of participating?

You may find that having an up to date record of a patient's medication immediately following discharge is helpful in their management. Errors and omissions on hospital discharge prescriptions result in considerable work load in general practice and using an electronic patient held medication record may potentially firstly reduce the occurrence of patient harm and secondly reduce general practitioner work load.

Are there any risks of participation?

It is hoped that no significant negative impact will arise from the study. There is the potential that using this device may add to your work load. The investigator will ensure that linking the device to the patient's record takes place at a time that is convenient for you. Additionally, due to the small numbers of patients that are involved and the involvement of 3 general practices it is hoped that work load will not be an issue. If difficulties arise the investigator is available to be contacted.

Further information

A copy of the interview transcript and study results can be made available to you.

If you need any further information, do not hesitate to contact the investigator Dr Elaine Walsh, Department of General Practice UCC, elaine.walsh@ucc.ie

Thank you for taking the time to read this information sheet. If you agree to take part in the study, please sign the consent form

I _____ declare that information regarding this study had been given to me and I understand the purpose, methods, risks and benefits of participating in this study.

I am aware that participation is voluntary and that I can withdraw my participation at any time without negative impact.

I give permission for my responses in the interview to be audio-recorded. I understand that my anonymity will be guaranteed.

I understand that anonymized extracts from my interview may be quoted in a publication arising from this study.

I agree that I have received a copy of this Consent Form and a copy of the Information Letter.

I hereby give my informed consent to participate in the research study.

_____	_____
Participant Signature	Date
_____	_____
Signature of investigator	Date

Would you like a copy of the Interview Transcript? YES ☐ NO ☐

Do you want a copy of the findings after the study is completed? YES ☐ NO ☐

Junior doctor consent form for participation in research study

Study title: PHARMS (Patient Held Active Record of Medication Status) Study

You are being invited to take part in a research study which is being conducted at the University College Cork.

Before you decide whether or not you wish to participate you should read the information provided below. You should clearly understand the risks and benefits of participating in this study. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgment.

You are not obliged to take part in this study and if you decide not to participate this will have no effect on your training or evaluation.

You have the right to withdraw your participation at any time (before, during and after the study) for whatever reason without having to justify your decision and without negative impact.

Why is this study being conducted?

Medication errors frequently occur during transitional care as patients move between different stages and settings of care. Hospital discharge has been identified as a time where medication error is likely to occur. Having a patient's pre-admission medication list available at time of hospital discharge may help in reducing error when generating discharge medication information. Additionally, evidence suggests that an electronic record may improve prescribing at time of discharge. A patient held electronic medication record has been developed within UCC and is now ready to be tested in the clinical setting. This device utilizes the USB port of a computer-see attached image. The master medication list may only be modified by the patient's GP but changes to the patient's medication may be added to the record in the hospital setting.

What will your participation involve?

You will be required to use the patient held medication record when writing the discharge prescription of study participants. You will be required to access the electronic medication record on the computer on the ward and to enter any adjustments, additions or cessations of medication that occurred during the hospital stay.

You will also be required to participate in an interview which will explore your experience of using the device.

Confidentiality

The interview will be treated in a confidential manner and your participation is anonymous. The interview will be audio recorded so that it can be transcribed afterwards. Your name will not be recorded on any information which is collected about you. Instead you will be provided with a unique code. The only person with access to the code will be the investigator. The study results and anonymized excerpts from your interview may be presented at scientific conferences and/or published in an academic journal. The audio recording will be erased once the interview has been transcribed. Transcripts will be stored for 5 years; after which they will be destroyed in line with Data protection legislation.

What are the possible benefits of participating?

You may find that having an up to date record of a patient's pre-admission medication list is helpful when generating their discharge prescription. From a societal perspective there is the potential that using an electronic patient held medication record may reduce the occurrence of patient harm via amelioration of the discharge prescribing process with the net result of reducing morbidity, mortality and economic burden.

Are there any risks of participation?

We do not think that participation in this study will have any negative effect on you. However, if

utilization of the device or the interview regarding same causes you difficulty or concern your intern tutor or the investigator may be contacted.

Further information

A copy of the interview transcript and study results can be made available to you.

If you need any further information, do not hesitate to contact the investigator Dr Elaine Walsh, Department of General Practice UCC, elaine.walsh@ucc.ie

Thank you for taking the time to read this information sheet. If you agree to take part in the study, please sign the consent form

I _____ declare that information regarding this study had been given to me and I understand the purpose, methods, risks and benefits of participating in this study.

I am aware that participation is voluntary and that I can withdraw my participation at any time without negative impact.

I give permission for my responses in the interview to be audio-recorded. I understand that my anonymity will be guaranteed.

I understand that anonymized extracts from my interview may be quoted in a publication arising from this study.

I agree that I have received a copy of this Consent Form and a copy of the Information Letter.

I hereby give my informed consent to participate in the research study.

_____ _____

Participant Signature Date

_____ _____

Signature of investigator Date

Would you like a copy of the Interview Transcript? YES ☐ NO ☐

Do you want a copy of the findings after the study is completed? YES ☐ NO ☐

Topic guides for interviews

Topic guide for semi-structured interviews with junior doctors:

1. Experience of using the device
2. Usefulness of the device
3. Difficulties encountered with the device
4. Recommendations for modification of the device
5. Communication with primary care

Topic guide for semi-structured interviews with IT professionals:

1. Experience of use of the device
2. Experience of integration of the device into the existing IT system
3. Difficulties encountered with the device
4. Recommendations for modification of the device

Topic guide for semi-structured interviews with GPs:

1. Experience of using the device
2. Usefulness of the device
3. Difficulties encountered with the device
4. Recommendations for modification of the device
5. Communication with secondary care

Topic guide for semi-structured interviews with patients:

1. Experience of using the device
2. Usefulness of the device
3. Difficulties encountered with the device
4. Acceptability of the device and technology
5. Recommendations for modification of the device

Clinical Significance of errors: instructions for raters

Definition: this is the degree of patient harm that could be caused by the error.

Significant: an error that can cause patient symptoms that, while harmful to the patient, poses little or no threat to the patient's life function.

Serious: an error than can cause signs/ symptoms that are associated with a serious level of risk that is not high enough to be life-threatening. In addition, a potential ADE is serious if it can cause persistent alteration of daily function.

Life-threatening: an error that can cause signs/symptoms that if not treated would put the patient at risk of death.

Examples of Severity Categories

LIFE THREATENING

Incorrect dose of anti-rejection medication is prescribed in patient with kidney transplant.

Omission of amiodarone at discharge when given for prevention of ventricular tachycardia.

Patient with a prior penicillin anaphylaxis reaction and ordered penicillin at admission.

Incorrect paracetamol dose prescribed at discharge with a total daily dose >15g.

Omission of warfarin at admission in patient with mitral valve replacement.

SERIOUS

Patients' correct dose is 2 mg diazepam; doctor prescribes 10 mg on admission.

Patient with exacerbation of congestive cardiac failure discharged on 1/4 preadmission dose of frusemide.

Omission of beta-blocker at discharge in patient with coronary artery disease.

Concurrent paracetamol prescriptions at discharge with a total daily dose >10g but ≤15g.

Warfarin 5 mg QD prescribed at discharge instead of 3 mg QD (prescribed for atrial fibrillation).

Indomethacin for gout prescribed at discharge to patient concurrently taking Ibuprofen.

Omission of lactulose BD in patient with history of hepatic encephalopathy.

SIGNIFICANT

Omission of diazepam PRN for insomnia at discharge.

Change from laxative bisocodyl PRN to bisocodyl BD

Omission of lisinopril in patient without coronary artery disease, heart failure or valve disease.

Two concurrent paracetamol prescriptions with a total daily dose >4 grams but ≤10 grams.

Omission of tramadol PRN for tension headache.

Additional Examples

Errors that may lead to hypotension or over-treatment of hypertension are considered to be serious.

Errors that may lead to under-treatment of hypertension, angina, or ischemia are considered to be significant.

Errors that may lead to significant over-anticoagulation or under-coagulation are considered to be serious.

Errors that lead to under-treatment of asthma are considered to be significant.

Errors that lead to under-treatment with antibiotics:

- If IV antibiotics were originally prescribed, consider the errors to be serious.
- If oral antibiotics were originally prescribed, consider the errors to be significant.

Errors that lead to over-treatment with antibiotics:

- If either IV or oral antibiotics were prescribed, consider the errors to be significant, unless the antibiotic is directly toxic to end organs in a highly dose-sensitive fashion (e.g., gentamicin), in which case, the severity will be higher (usually serious).

CONSORT 2010 checklist: i**nformation to include when reporting a pilot or feasibility trial**

Table A3 1: CONSORT checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	96
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	97,98
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	99-103
	2b	Specific objectives or research questions for pilot trial	103
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	1104,105
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	105
	4b	Settings and locations where the data were collected	105
	4c	How participants were identified and consented	105
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	105

Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	106
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	104,105
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	107-110
Results			
Participant flow (a diagram is	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	111

strongly recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	111
Recruitment	14a	Dates defining the periods of recruitment and follow-up	104
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	112
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	112
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	114
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	112-124
Harms	19	All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	125,126
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	128
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	126-128
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	128,129
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	N/A

Protocol	24	Where the pilot trial protocol can be accessed, if available	223
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14
	26	Ethical approval or approval by research review committee, confirmed with reference number	79

Data collection form

Study ID	Age	Gender	SES	Length of stay	Medication number at admission	Continence	Mobility	Feeding	Dressing

Study ID	Medication	Dose	Frequency	GP	Pharmacy	Drug chart	Discharge prescription	Error description	Error number	Error score

Policy brief



PHARMS: **P**atient **H**eld **A**ctive **R**ecord of **M**edication **S**tatus **Policy Brief**

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Executive summary

Medication error as patients move between hospital and the community is an important patient safety issue. Poor communication of medication information between primary and secondary care is currently an issue within the Irish healthcare system. The PHARMS device is a patient held electronic medication record which uses basic USB technology. The device has been shown to be acceptable to patients, doctors and IT professionals. It can successfully integrate into existing electronic systems in both primary and secondary care without the need for significant investment. It has been shown to reduce medication error at time of hospital discharge.

Introduction

Though in excess of 90% of Irish GPs operate electronic healthcare records (EHR), a mix of paper and electronic records are currently used in Irish hospitals. Communication of patient information between primary and secondary care is problematic. Poor communication of medication information is a major source of medication error resulting in patient morbidity, mortality and economic burden.

Methods

A patient held medication record was developed using USB technology and a thorough initial evaluation was conducted using quantitative and qualitative methods.

Findings

GPs, patients and junior doctors all described the occurrence of, and difficulties with, medication error and poor communication of medication information within the existing system.

We forever have people coming in who are missing things for a week until someone discovers they're missing whatever"

Junior doctor

And in some cases then you have to follow up with the hospital and following up with the hospital is incredibly time-consuming. Like, really incredibly time-consuming and frustrating and annoying. I mean, I can't be strong enough on how, what a waste of time it is.

GP

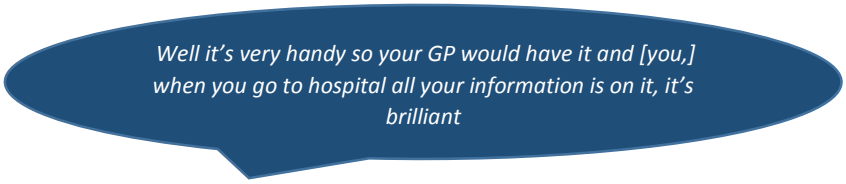
I remember like one day coming out and the nurse had to ring the doctor to query something because the inhaler they had given me shouldn't be given with the medications I was on

Patient

Medication information was successfully transferred between primary and secondary care via the PHARMS device. Compatibility was demonstrated with the four accredited GP software systems in Ireland: Socrates, CompleteGP, Health One, Helix Practice Manager. Successful integration was demonstrated within a basic existing IT hospital system.

Statistically significant lower rates of clinically significant medication errors were found among patient who were issued with a PHARMS device.

The device was acceptable to patients, GPs and hospital doctors.



Patient

Recommendations

- In technology terms a "minimum viable product" is a basic product solving a core problem. With regard to medication error as patients move between hospital and the community, the PHARMS device could be a solution to a core problem.
- Implementation the EHR in Ireland has not been straightforward and a universal shared care record does not yet exist. The PHARMS device can be used successfully within existing GP and hospital systems without significant additional IT investment and therefore may be complementary to ongoing shared care record development.
- Though more advanced technologies than USB exist, such technologies may not be applicable to the Irish healthcare system

PORTABLE DOCUMENT FORMAT (PDF) OF PUBLISHED PAPERS

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