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Factors affecting prescriber implementation of medication appropriateness recommendations in hospitalised older adults

Kieran Dalton BPharm MPharm MPSI

A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Pharmacy

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Head of School

Prof. Stephen Byrne

Supervisors

Prof. Stephen Byrne

Prof. Denis O'Mahony

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Declaration

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ACOVE	Assessing Care of Vulnerable Elders
ADE	Adverse drug event
ADR	Adverse drug reaction
AOU	Assessment of Underutilization of Medication
APEASE	Acceptability, Practicability, Effectiveness/cost-effectiveness, Affordability, Safety/side-effects, Equity
ARB	Angiotensin Receptor Blocker
BCT	Behaviour change technique
BCW	Behaviour Change Wheel
BPSD	Behavioural and psychological symptoms of dementia
C	Control
CDS	Clinical decision support
CDSS	Clinical decision support system
CGA	Comprehensive geriatric assessment
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COREQ	Consolidated Criteria for Reporting Qualitative Research
COX-2	Cyclooxygenase-2

CPOE	Computerised provider order entry
DDI	Drug-drug interaction
df	Degrees of freedom
DMARD	Disease-modifying anti-rheumatic drug
ED	Emergency department
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
EPOC	Effective Practice and Organisation of Care
EPR	Electronic prescription record
FEV1	Forced expiratory volume in 1 second
FORTA	Fit fOR The Aged
FYI	For your information
GFR	Glomerular filtration rate
GP	General practitioner
I	Intervention
ICD	International Classification of Diseases
IQR	Interquartile range
IV	Inverse variance
kPa	Kilopascal
MAI	Medication Appropriateness Index
MRC	Medical Research Council
NSAID	Non-steroidal anti-inflammatory drug

NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development
OPERAM	OPtimising ThERapy to prevent Avoidable hospital admissions in the Multi-morbid elderly
pCO_2	Partial pressure of carbon dioxide
PICOS	Participants, interventions, comparisons, outcomes, and study design
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescribing
pO_2	Partial pressure of oxygen
PPI	Proton pump inhibitor
PPO	Potential prescribing omission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	Randomised controlled trial
SaO_2	Oxygen saturation
SENATOR	Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons
SNRI	Serotonin-noradrenaline re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older People's Prescriptions

TCA	Tricyclic antidepressant
TDF	Theoretical Domains Framework
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Publications and Presentations

Peer-reviewed full paper publications

1. **Dalton K**, O'Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. Age Ageing. 2018 Jun 8;47(5):670-8. (Chapter 2)

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2. **Dalton K**, O'Mahony D, Cullinan S, Byrne S. Factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR trial – a qualitative study. (Chapter 3)

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3. **Dalton K**, Curtin D, O'Mahony D, Byrne S. Computer-generated STOPP/START recommendations for hospitalised older adults: evaluation of the relationship between clinical relevance and rate of implementation in the SENATOR trial. (Chapter 4)

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4. **Dalton K**, O'Mahony D, O'Sullivan D, O'Connor MN, Byrne S. Prescriber implementation of STOPP/START recommendations for hospitalised older adults: a comparison of a pharmacist approach and a physician approach. Drugs Aging. 2019 Mar 8;36(3):279-88. (Chapter 5)

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1. **Dalton K**, O'Mahony D, Cullinan S, Byrne S. Factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR trial - a qualitative study. Int J Pharm Pract. 2019; 27(Supplement 2):25-26.
2. **Dalton K**, Curtin D, O'Mahony D, Byrne S. Evaluation of the clinical relevance of computer-generated STOPP/START recommendations for hospitalised older adults. Int J Pharm Pract. 2019; 27(Supplement 2):6.
3. **Dalton K**, O' Mahony D, O'Sullivan D, O'Connor MN, Byrne S. Prescriber acceptance of STOPP/START recommendations for hospitalised older adults: pharmacist versus physician – secondary analysis of data from two randomised controlled trials. Int J Pharm Pract. 2018; 26(Supplement 1):21-22.
4. **Dalton K**, O' Brien G, O'Mahony D, Byrne S. Computerised Medication Analysis Designed to Minimise Inappropriate Prescribing in Older Hospitalised Patients: A Systematic Review. European Geriatric Medicine. 2017; 8(Supplement 1):213-214.
5. **Dalton K**, O'Sullivan D, O'Connor MN, Byrne S, O' Mahony D. Prevention of Adverse Drug Reactions in Hospitalized Older Patients: Physician versus Pharmacist. Innovation in Aging. 2017; 1(Supplement 1):433-434.

Posters and presentations

1. **Dalton K**, O'Mahony D, Cullinan S, Byrne S. Factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR trial - a qualitative study. Health Services Research & Pharmacy Practice Conference, 8th – 9th April 2019, Birmingham, United Kingdom – Oral presentation.
2. **Dalton K**, Curtin D, O'Mahony D, Byrne S. Evaluation of the clinical relevance of computer-generated STOPP/START recommendations for hospitalised older adults. Health Services Research & Pharmacy Practice Conference, 8th – 9th April 2019, Birmingham, United Kingdom – Oral presentation.
3. **Dalton K**, O' Mahony D, O'Sullivan D, O'Connor MN, Byrne S. Prescriber acceptance of STOPP/START recommendations for hospitalised older adults: pharmacist versus physician – secondary analysis of data from two randomised controlled trials. Health Services Research & Pharmacy Practice Conference, 12th – 13th April 2018, Newcastle, United Kingdom – Oral presentation.
4. **Dalton K**, O' Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. European Geriatric Medicine Society Conference, 20th – 22nd September 2017, Nice, France – Oral presentation and Poster presentation.

5. **Dalton K**, O'Sullivan D, O'Connor MN, Byrne S, O' Mahony D. Prevention of Adverse Drug Reactions in Hospitalized Older Patients: Physician versus Pharmacist. International Association of Gerontology and Geriatrics World Congress, 23rd – 27th July 2017, San Francisco, United States of America – Poster presentation.
6. **Dalton K**, O' Mahony D, O'Sullivan D, O'Connor MN, Byrne S. Prescriber acceptance rates of STOPP/START recommendations in hospitalised older adults: physician versus pharmacist. All-Ireland Schools of Pharmacy Conference, 24th – 25th April 2017, Cork, Ireland – Oral presentation.

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Thesis Abstract

Introduction

Despite the well-documented association between potentially inappropriate prescribing (PIP) and adverse outcomes for hospitalised older adults, the prevalence of PIP remains unacceptably high. Recommendations to improve medication appropriateness in hospital often come from sources external to the attending prescribing team, such as pharmacists and computerised system alerts. However, these recommendations to minimise PIP are not always implemented by prescribers, meaning that PIP can continue, thereby increasing the risk of adverse drug reactions (ADRs), rehospitalisation, and higher healthcare costs.

Interventions with sufficiently high rates of adherence to medication appropriateness recommendations among prescribers are more likely to result in significantly improved patient outcomes in comparison to those interventions with lower implementation rates, which often show non-significant effects on key outcomes. Thus, it is imperative that prescribing optimisation interventions achieve sufficiently high prescriber implementation rates for these recommendations to be clinically effective. However, it is not always clear which specific intervention components are essential to high implementation rates of prescribing recommendations.

Therefore, the overarching aim of this thesis was to identify the key factors affecting prescriber implementation of recommendations to improve medication

appropriateness in hospitalised older adults, focusing on the factors affecting implementation of i) computer-generated recommendations and ii) pharmacist recommendations.

Methods

Initially, a systematic review and meta-analysis were undertaken to ascertain the effectiveness of computerised interventions in minimising PIP in hospitalised older adults. Secondly, a semi-structured qualitative interview study was conducted alongside the Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons (SENATOR) trial to determine the key factors affecting prescriber implementation of the SENATOR software-generated recommendations, which aimed to reduce PIP and ADRs in hospitalised older adults. Based on these qualitative findings, an evaluation of the clinical relevance of SENATOR's computer-generated recommendations based on Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria (version 2) was performed. Subsequently, the association between the clinical relevance of the recommendations and their implementation by prescribers was assessed. Thereafter, the prescriber implementation rates of STOPP/START recommendations from a physician approach and a pharmacist approach were compared. Finally, a further semi-structured qualitative interview study was conducted to identify the key factors affecting physician prescriber implementation of pharmacist recommendations aimed at optimising medication appropriateness in hospitalised older adults.

Results

The systematic review and meta-analysis showed that computerised interventions can significantly reduce PIP in hospitalised older adults ($p < 0.05$). Of the nine included studies, five reported prescriber implementation rates for the computer-generated recommendations, ranging from 22.5% – 95%, but none of the included studies comprehensively explored the underlying reasons for non-implementation. The qualitative study conducted alongside the SENATOR trial identified four key factors affecting prescriber implementation of the computer-generated recommendations:

i) Computerised output: the clinical relevance and method of provision for the recommendations.
ii) Acute hospital environment: the timing and location of recommendations in a busy and often pressurised clinical setting.
iii) Prescriber role and identity: the responsibility, experience, and specialty of prescribers, as well as their attitude towards research studies.
iv) Patient-specific details: knowing the patient, patient preferences, and their acutely ill status in hospital.

The study evaluating the clinical relevance of the computer-generated SENATOR recommendations showed that nearly three quarters of the 925 computer-generated STOPP/START recommendations generated were judged to be clinically relevant (73.6%), whilst the remainder were judged to be of '*no clinical relevance*' (21.5%) or of potential '*adverse significance*' if implemented (4.9%). Recommendations judged to be of higher clinical relevance were significantly more

likely to be implemented than those of lower clinical relevance ($p < 0.05$), substantiating the findings from the preceding qualitative study that clinical relevance was a key factor affecting implementation.

In the study comparing the implementation of pharmacist-provided and physician-provided STOPP/START recommendations, prescribers implemented a significantly greater proportion of physician recommendations in comparison to pharmacist recommendations (83.4% versus 37.8%; $p < 0.0001$). The final qualitative interview study found that the key factors affecting prescriber implementation of pharmacists' medication appropriateness recommendations for hospitalised older adults were:

i) Clinical relevance and complexity of the recommendation.

ii) Interprofessional communication.

iii) Prescriber role and identity.

iv) Knowing each other and developing trusting relationships.

v) Hospital environment.

Conclusion

This thesis has made a significant contribution to the understanding of the key factors affecting prescriber implementation of recommendations to improve medication appropriateness in hospitalised older adults. Prescriber non-implementation of these recommendations is not attributable to one easily identifiable cause, and it is likely that a multi-faceted approach will be required in future interventions. The novel studies conducted in this thesis will facilitate the

development of theoretically-informed interventions that result in enhanced prescriber implementation of these recommendations, ultimately with the aims of substantially reducing PIP and improving health outcomes for hospitalised older adults.

Chapter 1: Introduction

1.1 Chapter description

This chapter provides an overview of the literature which informed my research. I begin by discussing the increasingly ageing population and the complexity associated with prescribing in older adults. Secondly, I define what is meant by '*potentially inappropriate prescribing*' (PIP) in this older patient group, its prevalence, and the associated consequences for patients and healthcare systems. Following this, I describe the common types of interventions that have been conducted in hospital settings to reduce PIP in older adults. Thereafter, I focus on prescriber implementation of recommendations to optimise prescribing in older adults, and explain how this behaviour can be targeted in future interventions. Finally, I present the hypothesis underpinning my research and an outline of the overall aims and objectives of this thesis.

1.2 The ageing population

Healthier lifestyles, improving socioeconomic conditions, advances in medicine, and greater access to healthcare have contributed to significant gains in life expectancy over time [1]. Within the 36 member countries of the Organisation for Economic Co-operation and Development (OECD), the average life expectancy at birth is now 80.6 years, ten years higher than it was in 1970 [2]. Rising life expectancy in both sexes and decreasing fertility rates mean that older adults comprise an ever-expanding proportion of the global population. The percentage of people aged ≥ 65 years in OECD countries has grown from 10% in 1970 to 17% in 2015, and is predicted to reach 28% by 2050 [3]. Older adults (≥ 65 years) have much higher rates of medication consumption and health services utilisation than their younger counterparts [4]. Thus, healthcare systems worldwide face significant challenges to meet the needs of this increasingly ageing population.

At present, the growing proportion of older adults is placing a substantial burden on already-strained resources in all areas of healthcare. With an ageing population and associated increased workload, general practitioners (GPs), often find that they have increasingly limited time to thoroughly review older patients' healthcare needs and complex medication regimens [5, 6]. In secondary care, older adults now occupy over half of acute hospital bed days in the United Kingdom (UK) and Republic of Ireland [7, 8]. Discharging these patients from acute care beds is often complicated further by a lack of bed availability in step-down facilities and long-term care facilities, where older adults occupy the majority of beds [9].

However, the challenge facing health services in most developed countries is not simply a matter of increased numbers of older adults. These patients often have multimorbidity, defined by the World Health Organisation (WHO) as the "*coexistence of two or more chronic conditions in the same individual*" [10], which is increasingly more common with advancing age and complicates their healthcare [11, 12]. A systematic review reported that the prevalence of multimorbidity in older adults ranged from 55% to 98% [13]. Thus, although a 65-year-old in the OECD population could today expect to live an additional 19.5 years on average, only 9 of these are likely to be '*healthy years*' [14].

Multimorbidity is associated with increased functional decline, cognitive decline, poorer quality of life, greater morbidity, and mortality [15-18]. Not surprisingly, multimorbidity significantly contributes to increased primary care consultations, hospital visits, hospital admissions, as well as escalating the need for specialised care [11, 19-22]. In fact, healthcare utilisation increases significantly with each additional chronic condition in older adults [11, 23]. Moreover, the presence of multimorbidity increases the requirement for multiple medications concomitantly. Medications are the most common form of healthcare intervention worldwide, but despite their many benefits in reducing the progression of chronic diseases in patients by treating and preventing illness, they are also the most common cause of iatrogenic harm [24]. Polypharmacy, most commonly defined as the concurrent use of five or more regular medications [25], is highly prevalent in multimorbid older adults and is associated with negative health outcomes, mostly arising from adverse drug reactions (ADRs) [26, 27]. Older adults are particularly vulnerable to these

medication-related harms due to physiological changes and altered pharmacokinetics and pharmacodynamics associated with advancing age [28]. Therefore, the safe prescribing of medications in older adults presents unique challenges not encountered when prescribing for younger patient populations [29].

1.3 The complexity of prescribing in older adults

Prescribers commonly find a greater degree of heterogeneity amongst our aged population than in the younger adult population, with a spectrum ranging from those who are fit and healthy to those who are frail and multimorbid [30]. Interindividual variability in health, disease, and pharmacotherapy increases significantly with ageing, which adds to the complexity of prescribing and makes it difficult to predict how older adults will respond to different medications.

1.3.1 Age-related changes in pharmacokinetics and pharmacodynamics

With advancing age, the body undergoes several physiological changes which can affect pharmacokinetics and pharmacodynamics. Age-related alterations in pharmacokinetics mean that older adults often have changes in the absorption, distribution, metabolism, and excretion of drugs – which can affect the onset of action, peak concentration, and duration of effect of medications [28, 31]. Moreover, age-related pharmacodynamic changes result in altered drug sensitivity, and can affect older adults' response to drugs that work at certain receptors or organ systems.

1.3.1.1 Pharmacokinetics

The oral absorption of drugs may be affected by age-related changes in the gastrointestinal tract, including reduced gastric acid secretion, delayed gastric emptying, decreased splanchnic blood flow, as well as prolonged intestinal transit time [32]. However, these changes may more commonly affect the rate of oral drug absorption rather than the extent of absorption [28, 33].

Age-related changes in body composition have a substantial effect on drug distribution. Total body water is reduced by 10% – 15% from age 20 years to age 80 years [34]. Therefore, the volume of distribution for hydrophilic drugs (such as aspirin, lithium, and digoxin) decreases in older adults, leading to higher plasma concentrations, and increasing the risk of toxicity [35]. The decrease in total body water coincides with a reduction in lean body mass, mostly skeletal muscle. This decline in lean body mass contributes to a proportional increase in total body fat. This means that lipophilic drugs have a greater volume of distribution in older adults, and are eliminated more slowly due to their accumulation in adipose tissue. Consequently, lipophilic drugs such as benzodiazepines have prolonged half-lives in older patients, protracting the risk for unwanted side effects, including confusion, drowsiness, and falls. Furthermore, weight loss and frailty may commonly occur in very old individuals, contributing to a decrease in the proportion of body fat. This, in turn, lowers the volume of distribution of lipophilic drugs and results in increased serum drug concentrations [36].

The most clinically significant age-related pharmacokinetic changes involve drug elimination, i.e. primarily through hepatic metabolism and/or renal excretion [37,

38]. In older adults, the liver mass is generally reduced by 20% – 30%, resulting in a decrease in the total number of drug-metabolising enzymes [39]. Thus, hepatic drug metabolism is reduced in advanced age and drug-drug interactions may be more clinically significant. Furthermore, a concomitant reduction in hepatic blood flow by approximately 20% – 50% in older adults means that drugs are presented to the liver at a much slower rate [40, 41]. This is particularly significant for drugs that are extensively extracted from the blood by the liver (e.g. propranolol, morphine, amitriptyline, verapamil); as their metabolism is '*blood-flow limited*', lower doses are often required in older patients [42].

In addition to a decline in hepatic metabolism, ageing is associated with a reduction in the excretory capacity of the kidney [43]. Renal mass decreases by approximately 25% – 30%, with a 1% reduction in renal blood flow annually in adults from age 50 years and over [39]. Furthermore, the glomerular filtration rate (GFR) declines by an estimated 0.75 ml/minute/year on average in patients between the age of 30 and 90 years [44]. However, longitudinal studies have shown that there may be no significant decrease in GFR in approximately one third of older patients; thus, individual patient comorbidities are key factors affecting renal function with advancing age [44, 45].

Reduced renal clearance in older adults results in elevated drug plasma levels and prolongs the drug's half-life, thus increasing the risk of ADRs [46]. For example, age-related reductions in renal function and water volume make older adults more susceptible to toxicity from water-soluble drugs, particularly those with a narrow therapeutic index, such as aminoglycosides, lithium, and digoxin [47-49]. However,

in contrast to hepatic elimination, altered drug levels due to age-related changes in renal function can be more easily predicted by calculating GFR [50]. Accordingly, it would be prudent to monitor GFR with the use of renally excreted drugs in older adults, with dose adjustment where appropriate.

1.3.1.2 Pharmacodynamics

In addition to these pharmacokinetic changes, ageing also has an impact on the body's response to drugs, i.e. pharmacodynamics. At the receptor level, ageing may lead to changes in the number of receptor sites, drug affinity for receptors, or in signal transduction mechanisms. For example, the abundance of dopaminergic receptors in older adults is reduced causing greater blockade with standard doses of metoclopramide at dopamine D_2 receptors when compared with younger adults, and increases the risk for parkinsonian side effects [35]. Older adults generally have increased pharmacodynamic sensitivity to drugs, particularly those that act on the central nervous system. For example, increased sensitivity to benzodiazepines, tricyclic antidepressants (TCAs), and antipsychotics can result in increased sedation and augment the risk of falls. Conversely, older adults may have decreased sensitivity to other drug classes; for example, reduced drug binding affinity at β-adrenergic receptors in older adults may lead to a decrease in the sensitivity and clinical response to β-agonists and β-blockers [51, 52].

At an organ system level, older adults may experience accentuated pharmacodynamic responses due to age-related changes in homeostatic mechanisms [53]. An example of this may be seen with volume-depleting drugs such as diuretics, whereby insufficient responses to hypovolaemia are mainly due

to age-related impairments of cardiovascular reflex function. Therefore, this increased pharmacodynamic sensitivity is not due to an increased drug-receptor effect, but rather an exaggerated reaction to the drug's effect on volume depletion, which may result in orthostatic hypotension and falls in older adults [34]. Furthermore, these patients may be more sensitive to the troublesome anticholinergic effects of some drugs such as dry mouth, constipation, and urinary retention; however, the underlying reason for older adults' increased sensitivity to some ADRs, such as those mentioned, is not always clear [54].

1.3.2 Guidelines

Best practice would advocate prescribers to comply with evidence-based guidelines when initiating or optimising medications for patients. However, despite being the main users of medications, older adults are often underrepresented in guidelines and in the clinical trials on which the guidelines are based [55]. These trials include patients that are usually selected by strict criteria, often comprising narrow subsets of the population which do not represent the typical patient with the condition [56]. In fact, older adults are commonly excluded from these clinical trials, especially those with multimorbidity [57].

This means that existing clinical practice guidelines are largely focused on single diseases, and many do not consider multimorbidity, despite its high prevalence. However, it should be noted that recent guidelines for some chronic conditions, such as heart failure, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, have attempted to incorporate advice on likely comorbidities [58-60], but these guidelines often only consider one comorbid condition at a time [61].

Therefore, indiscriminate application of prescribing guidelines based on data extrapolated from younger populations may not be justified when prescribing for older adults [26, 62]. Consequently, this often results in healthcare professionals prescribing medications for older patients without a clear evidence base or denying them a treatment they may possibly benefit from [63].

1.3.3 Multimorbidity and multiple healthcare providers

Older patients with complex multimorbidity often attend several different healthcare providers working across multiple sites [64]. With multiple clinicians providing care to older patients with numerous chronic diseases, the number of prescribed medications can accumulate dangerously, particularly as many clinicians may be hesitant to discontinue medications started by fellow prescribers [65]. Furthermore, various prescribers treating the same patient may have different treatment priorities, and commonly a holistic approach to older patient care may be lacking, with each prescriber focusing solely on their area of expertise. This increases the possibility for drug-drug interactions as well as drug-disease interactions, whereby beneficial medications for one condition may be harmful for another (e.g. pioglitazone for diabetes mellitus can exacerbate heart failure) [66]. This emphasises that older patients under the care of multiple prescribers are at a heightened risk of both inappropriate prescribing and ADRs, with each additional prescriber's influence on a patient's pharmacotherapy reported to increase the ADR risk by 30% [67, 68].

These negative patient outcomes are frequently due to suboptimal communication between prescribers [69]. This is particularly problematic on transitions of care, but

may also exist between prescribers practising in the same setting [70]. The incomplete transfer of important patient information between prescribers can result in inaccurate patient records, which hinder informed decision-making and predisposes to potentially inappropriate prescribing (PIP). For example, the prescription of duplicate therapies or counter-acting drugs can occur when prescribers are not aware of their peers' therapeutic plans [71].

This lack of information sharing between prescribers adds to the intricacy of prescribing for older patients. The GP is often consigned the responsibility of managing the patient's pharmacotherapy and liaising with the various prescribers involved in the patient's care. However, due to the evolving nature of general practice, older patients may often see more than one GP. This is becoming increasingly more common with a trend towards larger, multi-partner practices [72]. Having multiple prescribers in primary care may impact on continuity of care and prescriber familiarity with individual patient cases [73]. Greater continuity of care is associated with reduced rates of hospitalisation, emergency department (ED) visits, disease complications, as well as lower healthcare costs [74]. Continuity of care and familiarity with individual cases have also been shown to be important in the community pharmacy setting. While most older adults obtain all their prescriptions from one pharmacy, studies have shown that those who use more than one pharmacy are at an increased risk of drug-drug interactions and non-adherence with their medications [75]. However, the issue of multiple healthcare providers is much more problematic in the hospital setting, whereby clinicians with different expertise and varying levels of experience in dealing with multimorbid

older patients are often challenged with complex pharmacotherapy decisions that may be outside of their specialist area for multimorbid older patients that they are not familiar with [76].

1.3.4 Polypharmacy

The presence of multiple prescribers involved in the care of multimorbid older adults has made polypharmacy, and even hyperpolypharmacy (the use of 10 or more regular medications concomitantly), increasingly more prevalent in older adult populations [77-79]. Polypharmacy increases the likelihood of both adverse drug-drug and drug-disease interactions, adding both to the complexity of prescribing and the risk of adverse clinical outcomes in older patients [80].

Despite these potential dangers, polypharmacy is often clinically appropriate when treating older patients with several chronic conditions. Multiple medications are often required in combination to treat, delay the progression of, or ameliorate the symptoms of disease [81], with evidence-based practice guidelines often recommending the use of more than one medication as first-line therapy in some chronic conditions (e.g. heart failure) [58]. Furthermore, the use of appropriate polypharmacy to manage chronic disease can extend patients' life expectancy, improve their quality of life, and prevent complications such as disability and unnecessary hospitalisations [81, 82]. Given the possibility of both positive and negative outcomes in older adults, it is no surprise that polypharmacy has been termed a '*necessary evil*' [82]. Balancing the risks and benefits of using a multitude of medications concomitantly remains a significant challenge for prescribers caring for older patients in all care settings.

In summary, reduced drug elimination, coupled with a typically increased sensitivity to medications, renders older adults more susceptible to ADRs. These patients often require lower doses than younger populations, but it is difficult to predict medication response due to interindividual variability in older adults' drug handling. The paucity of prescribing guidelines for multimorbid older adults with polypharmacy means that increased caution is necessary when initiating medications, along with close monitoring of drug response to ensure both therapeutic efficacy and to prevent PIP and medication-related harm.

1.4 Potentially inappropriate prescribing (PIP) in older adults

1.4.1 Defining PIP

PIP is a term which describes a wide range of suboptimal prescribing practices encompassing, but not limited to, the following:

- Misprescribing, i.e. erroneously prescribing a drug that is needed. This may include prescribing the wrong drug (e.g. because of drug-drug or drug-disease interactions), selecting an inappropriate formulation or route of administration, or the use of drugs lacking cost-effectiveness where equally efficacious cheaper alternatives exist [83-85].
- Overprescribing, i.e. the prescription of medications at a dosage, frequency, or duration in excess of what is clinically needed, or for which no clear clinical indication exists [70, 85].

- Underprescribing, i.e. the prescription of too low a dose to be effective or the failure to prescribe appropriate drug therapy when it may be of benefit to the patient [70, 86].

PIP can often result in the appearance of potentially inappropriate medications (PIMs) in older adults' pharmacotherapy, where the associated risks may outweigh the benefits, and can often predispose patients to an unacceptably increased risk of ADRs [70]. It is widely acknowledged that certain medications should be used with caution or completely avoided in older adults, particularly when there may be an effective safer alternative [4, 87]. Common examples of PIMs in older adults include the following:

- long-term prescription of benzodiazepines or neuroleptics in patients who are at an increased risk of fall [88], or
- metoclopramide in patients with Parkinson's disease [88], or
- anticholinergics in patients with delirium or dementia [88].

However, PIP does not only comprise the prescription of PIMs, but also includes potential prescribing omissions (PPOs), i.e. non-prescription of certain medications that older patients may benefit from [89]. PPOs are often highly prevalent in patients with common conditions such as hypertension, heart failure, atrial fibrillation, and osteoporosis [89, 90]. Whilst some PPOs may be unintentionally overlooked by prescribers due to lack of knowledge around evidence-based secondary preventative therapies (e.g. the absence of a bisphosphonate in a patient with osteoporosis), others may be intentionally and inappropriately withheld due to ageist attitudes or other unjustifiable reasons such as therapeutic nihilism or

ignorance of medication benefit to older people in certain circumstances (e.g. the omission of anticoagulation to prevent a cardio-embolic stroke in a patient with known atrial fibrillation) [91].

Polypharmacy is intimately linked with PIP and is one of the principal risk factors for PIM prescription in older adults [92]. Studies have shown an increased likelihood of PIMs with each additional medication prescribed [67, 93]. Furthermore, polypharmacy can exacerbate the risk of a so-called '*prescribing cascade*' developing, whereby an ADR or side effect of one medication is inadvertently misinterpreted as a new condition, and consequently results in the unnecessary prescription of a new medication to treat it, rather than discontinuation of the causative agent [94]. For example, a patient who develops ankle oedema as a side effect to a calcium channel blocker for hypertension is subsequently prescribed a loop diuretic to manage the oedema, rather than switching to an alternative antihypertensive.

Paradoxically, patients with polypharmacy may also be more susceptible to underprescribing compared to those receiving fewer medications [95]. The negative connotations associated with the term '*polypharmacy*' may be a causative factor for the underutilisation of potentially beneficial, clinically indicated medications [96]. Prescribers may be reluctant to add to patients' drug burden for fear of adverse events; however, underprescribing itself is associated with adverse health outcomes [97]. Therefore, it is crucial for prescribers to focus not just on the number of medications prescribed alone, but to distinguish between appropriate polypharmacy and inappropriate polypharmacy in order to facilitate the

deprescribing of PIMs and the optimal utilisation of appropriate medications through detection of PPOs [25].

1.4.2 Prevalence of PIP

Despite increased awareness about PIP, it remains highly prevalent in older adults globally [98-100]. PIP prevalence can vary between different healthcare settings, but usually rises steadily from primary care through secondary care and further into long-term care settings [89, 92, 101-108]. The median PIP prevalence of community-dwelling older adults across Europe was found to be 22.6% in a systematic review by Tommelein *et al.* [103]. Moreover, a study from six hospitals in six European countries showed an overall PIM prevalence of 51.3% and an overall PPO prevalence of 59.4% in hospitalised older adults [92]. Furthermore, in older people in the long-term care setting, a recent systematic review comprised of mostly European studies reported a median PIM prevalence of 61.1% and a median PPO prevalence of 48.6% [108]. Examples of reported PIM and PPO prevalence from studies conducted in different healthcare settings in Ireland are illustrated in **Table 1.1**.

Table 1.1: Prevalence of potentially inappropriate prescribing (PIP) in older adults (≥ 65 years) across healthcare settings in Ireland

Healthcare setting	Number of patients	PIM prevalence	PPO prevalence
Primary care			
- Ryan *et al.* [101]	1329	21.4%	22.7%
- Moriarty *et al.* [102]	2051	52.7%	38.2%
Hospital			
- Gallagher *et al.* [104]	715	34.5%	-
- Barry *et al.* [89]	600	-	57.9%
- Hamilton *et al.* [105]	600	56.2%	-
Long-term care			
- Ryan *et al.* [106]	313	59.8%	42.2%
- O'Sullivan *et al.* [107]	732	70.8%	-

PIM: Potentially inappropriate medication PPO: Potential prescribing omission

It must be acknowledged that the rates of PIP are dependent on the PIP assessment tool utilised to detect prevalence. More recent versions of these tools may be capable of identifying additional instances of PIP in older adults; therefore, the true prevalence rates may be higher than reported [109].

PIP is usually more prevalent in community-dwelling older adults when they are in the hospital setting compared to when they are being managed in primary care. This hospitalised patient cohort are particularly at risk of PIP as they are often acutely unwell, have a wide range of comorbidities, and are often assessed and medicated by multiple prescribers. Furthermore, these patients are especially

susceptible to PIP at points of care transition [76]. However, admission to hospital may provide an opportunity to review older patients' pharmacotherapy – this is particularly vital when the cause of admission may be medication-related. Laroche *et al.* observed that hospitalisation in an acute geriatric unit resulted in a significant reduction in PIP from admission to discharge [110]. However, the acute hospital environment is not always conducive to pharmacotherapy optimisation [111]. Moreover, older patients can often be exposed to new and possibly unnecessary medications during hospitalisation [67, 76]. Studies have shown that the prevalence of PIP in older adults may be higher or remain unchanged after hospitalisation in comparison to pre-admission, potentially exposing these patients to an increased risk of medication-related harm [112, 113].

1.4.3 Consequences of PIP

The high prevalence of PIP in older adults is a major public health concern worldwide. In 2017, the WHO launched its third Global Patient Safety Challenge: '*Medication Without Harm*', aiming to reduce severe avoidable medication-related harm by 50% within 5 years [114]. PIP in older adults can contribute to a wide range of adverse patient outcomes and increased healthcare utilisation. PIP is associated with increased ED visits and unplanned hospitalisations [104, 115-118], prolonged hospital stays [119, 120], as well as increased morbidity and mortality [121, 122]. Many of these adverse outcomes in older adults are related to ADRs, and studies have shown that PIP is one of the main risk factors for ADRs [105, 123].

As well as effects on morbidity and mortality, ADRs can result in exorbitant healthcare costs. In 2002, a study calculated that approximately 76,800 older

people experience an avoidable hospital admission in the Netherlands each year resulting from preventable ADRs, at an average cost of €2,128 per drug-related admission [124]. In addition, it has been reported that ADRs extend hospitalisation by an additional 2 to 4 days on average [125], with the average cost of an in-hospital ADR estimated at €2,250 [126]. Furthermore, PIP in older adults results in superfluous medication costs. Cahir *et al.* reported the annual cost of PIMs in Ireland to be €45 million, equating to 9% of the total expenditure on pharmaceuticals in those aged ≥ 70 years [127].

Ultimately, PIP results in significant morbidity in older adults and increased healthcare costs, both in terms of greater medication usage and healthcare utilisation requirements to manage negative health consequences. However, certain adverse patient outcomes associated with PIP are potentially preventable. For example, approximately 70% of ADRs may be avoidable, most of which are also predictable [105, 128]. Not all risk factors for ADRs in older adults are amenable to intervention (e.g. age-related changes in pharmacokinetics and pharmacodynamics); however, PIP is one such risk factor that can be identified and targeted by interventions. Therefore, it is not surprising that PIP reduction has been the focus of many hospital-based interventions to prevent ADRs and other medication-related adverse patient outcomes.

1.5 Interventions to reduce PIP in hospitalised older adults

Hospitalisation may provide an opportunity to review the appropriateness of prescribing in a high-risk older adult population. However, without clear evidence of adverse outcomes such as ADRs, it can be difficult to prospectively determine prescribing that is truly inappropriate for older adults [129]. The term '*PIP*' includes the word '*potentially*' to emphasise that some PIP instances may not be truly inappropriate in all patient cases, and any pharmacotherapy review should also consider the individual patient's preferences, goals of care, and life expectancy [130]. This ambiguity can make PIP more difficult to identify in hospitalised older patients, and even more difficult to intervene.

Whilst educational interventions have been a common approach taken to improve prescribing appropriateness in older adults in other healthcare settings [131-142], there are limited studies of this nature in hospitals [143-145]. Henceforth, interventions commonly employed with a more direct approach to minimising PIP in hospitalised older adults, and their associated outcomes, are outlined in the following section.

1.5.1 Prescribing assessment tools

Prescribing assessment tools are used to identify PIP instances in older adults, and are commonly employed in intervention studies to reduce PIP [146-148]. These approaches employ the use of explicit (rule-based) or implicit (judgment-based) criteria, or a combination of both. In 2013, a systematic review by Kaufmann *et al.* found 46 assessment tools to identify PIP, 28 (61%) of which were explicit, 8 (17%) were implicit, and 10 (22%) used a combined approach. Thirty-six (78%) of these

tools were aimed towards older people, with the remainder not specifying the target age group [149].

1.5.1.1 Explicit criteria

Explicit criteria are clearly defined statements that highlight instances of PIP, typically developed based on published evidence and expert opinions using consensus techniques [70]. These criteria are usually focused on drugs that should be avoided or used with caution in older adults in general or in certain disease states. Whilst they can be applied with little or no judgment, they often do not consider factors such as patient preferences, comorbidities, life expectancy, and quality of life [85].

Explicit criteria have high reliability and reproducibility, and can be readily applied in a structured manner to large cohorts of older patients; therefore, they are commonly deployed in intervention strategies to reduce PIP in hospitalised older adults [83]. A broad spectrum of explicit criterion-based tools has been developed worldwide [87, 88, 150-158]. However, lack of transferability outside the country of origin is a common drawback with many explicit PIM lists [70]. Most significantly, very few of these criteria have been proven to be more effective than standard pharmaceutical care when applied to older patients' prescriptions in randomised controlled trial (RCT) settings [62].

The explicit PIP tools most commonly utilised and cited in the literature are Beers criteria, Screening Tool of Older People's Prescriptions (STOPP) criteria, and Screening Tool to Alert to Right Treatment (START) criteria [87, 88]. Beers criteria, first published in 1991, were originally developed to identify PIM use in nursing

home residents [159]. Updated most recently in 2019, and now on their sixth iteration, Beers criteria currently include 30 criteria highlighting medications or medication classes to avoid in older adults, and 16 criteria specifying over 40 medication or medication classes to use with caution or to avoid in certain diseases or conditions [87]. Like many of the other explicit tools, Beers criteria do not assess for underprescribing. Furthermore, there are no RCTs demonstrating that application of Beers criteria to older patients' prescriptions results in improved clinical outcomes.

The STOPP and START criteria were first published together in 2008 as an explicit screening tool to enable healthcare professionals to appraise older patients' pharmacotherapy in the context of their concurrent diagnoses [160]. The most recent iteration – STOPP/START version 2 – contains 114 criteria, of which 3 are implicit prescribing rules (**Appendix 1**) [88]. STOPP criteria identify PIMs and START criteria identify PPOs, and they have been used in tandem as a successful intervention in RCTs to significantly reduce PIP, medication costs, and ADRs in hospitalised older adults [146, 148]. To date, the only other set of explicit prescribing criteria that have been shown in an RCT setting to improve clinical endpoints are the Fit fOR The Aged (FORTA) criteria [161]. In this RCT, Wehling *et al.* showed that application of FORTA criteria produced significant reductions in overprescribing, underprescribing, ADRs, as well as significant improvements in activities of daily living. The most recent iteration of the FORTA criteria contains 264 medications or medication classes organised into 26 main indication groups, whereby the prescriber is guided to the safest/most effective medications for each

of the common clinical conditions listed, including hypertension, atrial fibrillation, COPD, diabetes mellitus, and dementia [158].

PIP instances identified by explicit criteria-based tools may not always be truly inappropriate. These criteria were developed to complement good clinical judgment, not to replace it. Occasionally, instances of so-called '*PIP*', as defined by explicit criteria, may be clinically justified, e.g. the use of propranolol to treat benign essential tremor, or the use of amitriptyline to treat severe postherpetic neuralgia (propranolol and amitriptyline being identified as drugs to be avoided at all times in Beers criteria). Patient-specific information is often required to identify true instances of PIP. A recent systematic review has shown that trials deploying criteria requiring detailed patient information, such as STOPP/START and FORTA criteria, are more likely to have a positive impact on clinical endpoints than criteria which are primarily drug-oriented, such as Beers criteria [162]. However, time constraints, particularly in the busy acute hospital setting, may be an obstacle to systematically applying an extensive set of criteria to multimorbid older adults with complex polypharmacy. Digitalisation of such criteria for the purpose of automated rapid deployment may be key in facilitating their routine application in clinical practice [88].

1.5.1.2 Implicit criteria

In contrast to the explicit criteria described above, implicit criteria consist of quality indicators of prescribing that are focused on the patient rather than on particular drugs or disease states. The user employs patient-specific information, published evidence, and one's own pharmaceutical knowledge to make judgments about

appropriateness [76]. Whilst there are several implicit tools in the literature to evaluate prescribing in older adults [163], the most commonly used is the Medication Appropriateness Index (MAI) [164]. This tool contains ten criteria which are used to rate the appropriateness of each medication the patient is prescribed, posing questions such as:

- "*Is there an indication for the drug?*"
- "*Is the medication effective for the condition?*"
- "*Is the duration of therapy acceptable?*"

The sum of all the ratings for each criterion produces a measure of the overall appropriateness for that medication. This procedure is then repeated for each medication. However, the MAI does not assess for underprescribing. Instead, the Assessment of Underutilization of Medication (AOU) tool can be used to implicitly identify PPOs [165], and has been used to complement the application of MAI in measuring prescribing appropriateness [146].

Some implicit criteria-based tools have been deployed as an intervention in primary care, long-term care, and community pharmacy settings [166-168]. In the hospital setting, implicit criteria have primarily been employed to assess prescribing appropriateness as an outcome measure rather than as the sole intervention component [163, 169, 170]. However, the Assessing Care of Vulnerable Elders (ACOVE) criteria – which contain a broad set of quality indicators in caring for older adults, of which 24 (6%) are related to medication [171] – have been applied in the form of an intervention checklist to improve the appropriateness of prescribing thromboprophylaxis in hospitalised older adults [172].

The main advantage of implicit criteria-based tools is that they can focus more on the needs of individual patients. They have been shown to have good inter-rater agreement [163, 164], but successful deployment depends on the users' levels of knowledge and experience. However, the most significant limitation in applying implicit criteria is their highly time-consuming nature. Thus, their employment has been primarily within the realm of research, with limited applicability to interventions in routine clinical practice.

1.5.2 Geriatrician-based assessments

Given the complexity of prescribing for older adults, it would seem logical that a pharmacotherapy review by a physician specialised in geriatric medicine would be valuable in improving the appropriateness of prescribing in hospitalised older adults. Patients under the care of geriatricians are less likely to have instances of PIP compared to those without specialist geriatrician care [173]. In the hospital setting, it is common for other specialist physicians to ask for a geriatrician's expert review of older patients' pharmacotherapy, particularly those with complicated medication regimens relating to complex comorbidity and geriatric syndromes. Studies have shown that recommendations provided by physicians specialised in geriatric medicine can significantly decrease PIP in hospitalised older patients, with reductions in PIMs, PPOs, and ADRs [146, 148, 174].

A comprehensive geriatric assessment (CGA) is a geriatrician-based intervention that enables pharmacotherapy optimisation as part of a more global evaluation of older patients' healthcare problems, including assessment of their cognitive and physical functional status, quality of life, and life expectancy [175]. CGA

encompasses a thorough and holistic review of an older patient's healthcare needs by a multidisciplinary team comprising a geriatrician and a number of other healthcare professionals, e.g. nurses, physiotherapists, occupational therapists, nutritionists, and pharmacists [70, 85]. This holistic approach provides an opportunity to utilise the knowledge and expertise of each multidisciplinary team member to make informed decisions in devising comprehensive treatment strategies specifically tailored for individual patients [176].

Several RCTs have proven that CGA in the inpatient hospital setting can be effective in improving prescribing appropriateness [177-179]. Owens *et al.* reported a significant reduction in '*inappropriate medication choices*' after CGA compared to usual care in a single-centre RCT [177]. Similarly, a Norwegian study found a significant decrease in anticholinergic drugs, antipsychotics, and drug-drug interactions in the CGA intervention group compared to usual care [178]. Furthermore, Schmader *et al.* conducted a multi-centre RCT which showed that CGA significantly reduced the prevalence of inpatient PIMs and PPOs compared to usual care; however, there was no significant difference in ADRs between these groups [179]. A recent systematic review and meta-analysis has shown that older adults who receive CGA are more likely to be alive and in their own homes at follow-up than older people who do not receive CGA, but CGA may result in increased costs [180]. Furthermore, no CGA studies to date have shown significant improvements in clinical outcomes directly related to prescribing optimisation in hospitalised older patients (such as reducing ADRs).

Pharmacotherapy review as part of a CGA allows for a multidimensional interdisciplinary approach but may be time-consuming and resource-intensive. With an increasingly ageing population and a limited number of geriatricians, a medication review by a geriatrician as part of a CGA is not a feasible option for all hospitalised older adults, and perhaps is most suitable for those older patients with complex multimorbidity, frailty, or other geriatric syndromes [181].

1.5.3 Pharmacist interventions

With their training and expertise in pharmacotherapy, hospital pharmacists are well positioned to recognise and resolve instances of PIP in older adults, either independently or as part of a multidisciplinary team [169, 182]. Pharmacist initiatives to improve the appropriateness of prescribing in older adults may include practices such as:

i) medication review,
ii) participation in multidisciplinary team meetings and/or ward rounds,
iii) delivery of education sessions, and
iv) provision of patient counselling.

Pharmacist interventions of this nature usually involve a standardised assessment of older patients' prescriptions, followed by provision of recommendations to the prescriber to optimise pharmacotherapy. These recommendations may be in the form of written communication, verbal communication, or through a combination of approaches. Face-to-face discussion with the prescriber, usually a physician, is highlighted in the literature as the preferred method of communication by pharmacists to resolve pharmacotherapy issues [183].

In previous studies, pharmacist interventions have achieved significant improvements in medication appropriateness in hospitalised older adults [169, 184-186]. Furthermore, a number of RCTs have also illustrated that pharmacist interventions can have a significantly positive impact on patient outcomes. Gillespie *et al.* showed that pharmacist interventions in hospitalised patients aged 80 years and older resulted in a 16% reduction in all hospital visits, a 47% reduction in ED visits, and an 80% reduction in drug-related readmissions compared to standard care (i.e. without direct involvement of ward-based pharmacists) [187]. O'Sullivan *et al.* showed that a structured pharmacist review of medication significantly decreased the proportion of older patients experiencing incident ADRs in hospital compared to patients receiving usual hospital pharmaceutical care (13.9% versus 20.7%; $p = 0.02$) [147]. Furthermore, the interventions described in both RCTs were shown to be cost-effective [147, 187]. In fact, most clinical pharmacist interventions have been shown to be cost-effective as implementation costs are generally offset by cost savings associated with the reduction in PIP and ADRs [188-190].

However, not all pharmacists have expertise in geriatric pharmacotherapy. Therefore, intervention delivery and success may depend on the training and experience of the individual pharmacist. The specialisation of hospital pharmacists with further expanded roles may prove beneficial in achieving enhanced patient medication-related outcomes. The advent of pharmacist prescribing in some countries – either as collaborative, supplementary, or independent prescribers – has transformed the manner in which some pharmacists make interventions to improve older patients' pharmacotherapy. For example, pharmacists making

prescription changes as part of a collaborative prescribing initiative in an Irish hospital has been shown to significantly improve medication appropriateness in older adults [191]. A recent systematic review has provided evidence that hospital pharmacists can prescribe to the same standards as doctors [192]. However, there is limited evidence to date to show that pharmacist prescribing interventions improve both medication appropriateness and clinical outcomes in hospitalised older adults.

1.5.4 Computerised interventions

Most computerised interventions aiming to improve prescribing appropriateness include either computer-based alerts or clinical decision support systems (CDSSs), usually embedded within computerised provider order entry (CPOE) systems to facilitate safer electronic prescribing. CDSSs are software applications designed to assist prescribers regarding drug choice, dosage, monitoring, potential interactions, as well as highlighting instances of PIP.

A fundamental component to the success of these computerised interventions is that they are integrated with patients' electronic prescription records (EPRs) or electronic health records (EHRs), which may include an EPR as well as clinical data on the patients' comorbidities and laboratory results. By linking these electronic records to computerised algorithms based on explicit prescribing rules, such as Beers criteria or STOPP/START criteria, detection of PIP and decision support at the point of prescribing can be provided, often in the form of an electronic alert. However, creating computerised algorithms to incorporate the complexity of prescribing for older adults can be profoundly challenging, especially given the

degree and wide range of multimorbidity and polypharmacy that often accompany the age-related changes in pharmacokinetics and pharmacodynamics in older people [193]. If the quality of the computerised algorithms is suboptimal, this can result in the generation of alerts that are of low relevance or the production of too many alerts. This predisposes to the phenomenon of '*alert fatigue*', whereby clinicians may be overloaded with alerts and clinically important information may be ignored, increasing the risk of patient harm [194].

Despite the increasing deployment of these computerised interventions in hospitals in developed countries [195], their routine use in developing countries is often constrained by limited resources, and thus significant investment would be required [196]. However, once implemented, studies have proven that these interventions can be cost-effective by preventing medication errors, adverse drug events (ADEs), and reducing patients' hospital length of stay [197].

Reviews have shown that computerised interventions can be successful in improving prescribing appropriateness for older adults in different healthcare settings [198, 199]. Two controlled studies have shown improved health-related outcomes with significant reductions in ADEs and inpatient falls respectively arising from application of such computerised interventions [200, 201]. However, most of the interventions in the literature are single-centre studies and do not routinely show improvements in patients' health-related outcomes. Two European multi-centre RCTs have recently been completed which deployed the STOPP/START criteria (version 2) in computerised interventions – Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons

(SENATOR) and OPtimising ThERapy to prevent Avoidable hospital admissions in the Multimorbid elderly (OPERAM) [202, 203]. The SENATOR RCT's primary aim was to reduce in-hospital ADRs, and the primary aim of the OPERAM RCT to reduce drug-related rehospitalisations. The results from both RCTs have not been published yet, but future interventions of this kind must demonstrate improved patient outcomes if they are to be utilised routinely in clinical practice.

1.5.5 Multiple component interventions

Given the complexity associated with optimising prescribing for older adults in an acute hospital environment, many research groups have conducted multiple component interventions which incorporate one or more of the elements described in the interventions above. Two studies have shown that a pharmacist medication review in combination with applying STOPP/START criteria or an adjusted STOPP tool have resulted in significant reductions in PIP, ADRs, ED visits without subsequent hospitalisation, as well as a significant improvement in patient quality of life [147, 185]. In addition, collaborative approaches between pharmacists and physicians have been shown to significantly improve the appropriateness of prescribing in hospitalised older patients, with significant reductions in ED visits [182, 187, 204]. Furthermore, some research groups have utilised computerised interventions in combination with other components to reduce PIP in this older patient group. Stevens *et al.* showed that combining a CDSS intervention with education and individual provider feedback can significantly reduce the number of PIMs in older adults in the ED [205]. Similarly, Cossette *et al.* have shown that pharmacist review of alerts from a computerised system in combination with CGA

and education can also significantly decrease PIM use [206]. However, when multiple component interventions are successful in reducing PIP, it is not always clear which elements were effective, thus making replication problematic.

In summary, many of the interventions described throughout this section have shown significant reductions in PIP, but few studies produce significant improvements in clinical outcomes for hospitalised older patients. Even with the success of some initiatives, many of these interventions have been conducted in single centres or in a specific context that may not be transferable to other settings. Furthermore, few studies have demonstrated sustainable reductions in PIP, and therefore PIP prevalence remains unacceptably high. It has been hypothesised that low prescriber implementation rates of recommendations to improve appropriateness of prescribing may be maintaining this high prevalence of PIP, and potentially contributing to avoidable ADRs [147, 187]. Given the clear link between PIP, adverse patient outcomes, and increased healthcare costs, it is surprising that these low rates of prescriber implementation have not been extensively investigated in the literature to date.

1.6 Prescriber implementation of recommendations: a target for behaviour change interventions

1.6.1 Prescriber implementation rates of medication appropriateness recommendations

From the interventions described above, it is clear that many of the recommendations to improve the appropriateness of prescribing in older adults come from sources external to the prescribing team, for example: from geriatricians, pharmacists, and computerised systems (e.g. CDSSs or computerised alerts). Most geriatrician reviews of this nature are requested by other specialist physicians, and therefore their pharmacotherapy recommendations are highly likely to be implemented. However, recommendations from other external sources that have not been specifically requested by the prescribing team are less likely to be followed. The implementation rates of recommendations from pharmacist-based and computerised interventions to improve prescribing appropriateness in hospitalised older adults generally range from 39% – 69% [169, 186, 187, 207-209] and 29.3% – 95% [200, 201, 210, 211] respectively. If these pharmacotherapy recommendations are not implemented, it means that the high prevalence of PIP continues in these older patients, augmenting the risk of ADRs, rehospitalisation, and increased healthcare costs.

Pharmacist interventions with higher prescriber implementation rates for medication appropriateness recommendations [186, 187] are more likely to result in significantly improved patient outcomes in comparison to those with lower

implementation rates, which often show non-significant patient outcomes [207, 208]. However, O'Sullivan *et al.* showed that a structured pharmacist intervention in 361 patients with only 38.5% of medication appropriateness recommendations implemented can still result in a clinically significant 6.8% absolute risk reduction in patients with ADRs compared with standard pharmaceutical care (p = 0.02) [147, 169]. Moreover, as the authors suggested, an enhanced implementation rate may have generated a further reduction in ADRs.

A narrative review on computerised interventions in various healthcare settings has suggested that computer-generated recommendations can be successful in improving prescribing appropriateness in older adults, but there is limited evidence showing how their implementation affects important patient outcomes such as hospital length of stay, rehospitalisation, and mortality [198]. Nevertheless, studies have shown significant reductions in both in-hospital falls and ADEs with relatively low implementation rates of 31% and 29% respectively [200, 201]. Further research is clearly required to assess the effectiveness, implementation rates, and patient outcomes specifically associated with computer-generated recommendations to improve the appropriateness of prescribing in hospitalised older adults.

In studies with pharmacist and computer-generated recommendations, the reported implementation rate is merely a quantitative measure of the intervention's success. Many of these studies do not provide sufficient information on how the recommendations were communicated, how the intervention integrated into practice, or any specific barriers encountered. Therefore, it is important that quantitative and qualitative research be used in tandem to inform

the design of future intervention strategies targeting medication appropriateness in older adults.

1.6.2 Identifying behavioural components affecting implementation

Interventions based on medication appropriateness recommendations with high implementation rates are more likely to translate into improved clinical outcomes for hospitalised older patients compared to interventions with low implementation rates. Therefore, it would seem logical that future interventions should aim to attain high uptake rates for these recommendations. However, it is not always clear for researchers which specific intervention components contribute to achieving high implementation rates. Robust qualitative research is required to ascertain the key factors affecting prescriber behaviours concerning implementation of these recommendations. By identifying the pertinent barriers and facilitators, future interventions can be targeted towards changing practice to increase the implementation of recommendations.

1.6.2.1 Behaviour change in healthcare interventions

The UK Medical Research Council (MRC) framework advocates the incorporation of a theoretical basis into the development of complex interventions [212]. However, previous systematic reviews of interventions designed to change professional practice have shown that limited numbers of studies report using theory to inform intervention design [213, 214], even though the evidence from the literature demonstrates that theory-based behaviour change interventions are more effective than those without a theoretical base [215]. There are many different health psychology theories that could be utilised to inform and develop interventions

[216]. While the use of a single theory may be justified, it is preferable to utilise a more comprehensive approach to increase the likelihood of identifying all relevant factors underpinning a specific behaviour [217]. The Theoretical Domains Framework (TDF) is one such validated tool that has been synthesised using 33 behaviour change theories [217]. The TDF, now on its second iteration, is comprised of 14 domains based on 84 theoretical constructs related to behaviour change (**Appendix 2**). This integrative framework makes behaviour change theory more accessible to healthcare researchers, particularly those without a background in health psychology [218]. As a result, the TDF has been widely used by healthcare researchers to explain practice implementation problems and to inform interventions [219-223].

Whilst the TDF can be applied to quantitative data (e.g. from questionnaires), it is most commonly employed in qualitative studies (e.g. using interviews or focus groups). Even though no formal guidelines have been established on how to apply the TDF to qualitative interview studies, formulating topic guides based on the TDF is a well-established approach to ensure that intervention development is theory-based [224]. This allows exploration of interviewees' perceptions on how each domain may affect the target behaviour, which provides greater clarification on the TDF-related barriers and facilitators that could be targeted by an intervention [225]. Thereafter, the transcripts are usually coded into the theoretical domains, with the most relevant domains or overarching themes representing the factors that predominantly influence the target behaviour [224]. The TDF is commonly employed with the Behaviour Change Wheel (BCW) (**Appendix 3**) to inform the

design of future interventions [226]. Having identified the relevant theoretical domains, these can then be mapped to the BCW to identify intervention functions as well as several behaviour change techniques (BCTs) that may be appropriate in addressing the target behaviour [226, 227].

1.6.2.2 Informing the development of interventions with enhanced prescriber implementation rates

In developing behaviour change interventions to optimise prescribing, one must be clear on the behaviour(s) being targeted. Hence, it is important now to distinguish between the behaviours of '*prescriber acceptance*' and '*prescriber implementation*' of medication appropriateness recommendations. Whilst many prescribers may agree with these recommendations and accept that action may be required, issues such as forgetting (due to distraction in the busy clinical setting) or patient preference can be problematic and prevent their implementation. The term '*prescriber implementation*' demonstrates that the recommendation has been actively executed, and studies have shown large discrepancies between rates of prescriber acceptance and prescriber implementation of medication recommendations [228, 229]. Therefore, TDF-related qualitative studies in this research area should specifically explore the barriers and facilitators to successful implementation of medication recommendations provided to prescribers, and not just their acceptance of them.

The TDF has been used previously to explore the influences on prescriber behaviour regarding appropriate prescribing for older adults in different healthcare settings, with the subsequent identification of possible intervention types that may be

suitable in future studies using the BCW [111, 230, 231]. Going beyond this, the TDF and BCW have been exploited successfully to develop interventions to improve prescribing. Cadogan *et al.* have shown that an intervention developed using the TDF to improve appropriate polypharmacy for older people in primary care is feasible and acceptable to stakeholders [232]. Furthermore, Elouafkaoui *et al.* have shown that a TDF-informed intervention can be successful in significantly improving antibiotic prescribing practices of dentists [233]. Therefore, it would seem reasonable to expect that the TDF could also be employed in a similar fashion i) to explore the behavioural determinants underpinning prescriber implementation of medication appropriateness recommendations for older adults in the hospital setting, and ii) to use these findings to inform the development of future interventions to improve prescribing.

To date, the TDF has not been used to specifically assess factors affecting prescriber implementation of medication appropriateness recommendations from sources such as pharmacists and computer systems in the hospital setting. Therefore, these represent significant gaps in our knowledge and evidence base. By identifying the key barriers and facilitators to implementation of medication appropriateness recommendations from robust qualitative research methods, interventions can be tailored to address issues affecting prescriber implementation, and ultimately to improve medication appropriateness in hospitalised older adults.

1.7 Summary

PIP in older adults remains a significant healthcare problem worldwide. Despite the myriad of interventions that have been evaluated, there is still no widely accepted optimal strategy for reducing PIP in older hospitalised patients. Many interventions in hospital settings consist of recommendations from sources external to the prescribing team. However, these recommendations to improve the appropriateness of older patients' pharmacotherapy are not always implemented by hospital prescribers, despite the abundant quantity of evidence highlighting the adverse outcomes that PIP may cause in this patient population.

Rather than maintaining a continued focus on conducting further interventions that may not be evidence-based, a clear gap in the evidence base must be addressed first, i.e. the key underlying factors affecting prescriber implementation of these medication appropriateness recommendations in the hospital setting. In addressing this knowledge gap, future theoretically-informed interventions can be designed that tackle the issue of non-implementation, thus improving medication appropriateness and patient outcomes.

1.8 Hypothesis, aims, and objectives

1.8.1 Hypothesis

The basis of this research is the knowledge that prescriber non-implementation of prescribing recommendations to improve medication appropriateness results in PIP continuation in older adults, thereby increasing the risk for adverse clinical outcomes. Robust research is required to investigate the reasons behind non-implementation of prescribing recommendations in order to inform the design of future interventions to effectively minimise PIP in hospitalised older adults.

1.8.2 Thesis aim and objectives

The overarching aim of this thesis is to identify the key factors affecting prescriber implementation of medication appropriateness recommendations in hospitalised older adults, focusing on the factors affecting implementation of i) computer-generated recommendations and ii) pharmacist recommendations.

Firstly, two definitive objectives were formed *ab initio* to achieve the aim of identifying the factors affecting prescriber implementation of these computer-generated recommendations:

1. To systematically review the literature in order to establish the effectiveness of computerised interventions designed to improve medication appropriateness in hospitalised older adults, the implementation rate of the computer-generated recommendations, and their associated clinical outcomes (Chapter 2).

2. To determine the key factors affecting prescriber implementation of computer-generated recommendations in the multi-centre SENATOR RCT using semi-structured interviews with physician prescribers and trial researchers (Chapter 3).

Thereafter, based on the findings from Chapter 3, a third objective was defined in order to achieve this aim:

3. To systematically evaluate the clinical relevance of the computer-generated recommendations in the SENATOR trial and to determine if the relevance of recommendations was associated with their rate of implementation (Chapter 4).

Furthermore, two specific objectives were defined in order to achieve the aim of identifying the key factors affecting prescriber implementation of pharmacist recommendations to improve the appropriateness of prescribing in hospitalised older adults:

1. To compare the prescriber implementation rates of STOPP/START recommendations between a pharmacist approach and a physician approach in the same hospital, and to identify components within the intervention approaches that may have affected the implementation rates (Chapter 5).
2. To explore the key factors affecting prescriber implementation of pharmacist recommendations in the hospital setting using semi-structured interviews with physician prescribers and pharmacists (Chapter 6).

1.8.3 Thesis outline

Each of the five objectives outlined above are associated with a specific study chapter (Chapters 2 – 6), which are then followed by an overarching discussion chapter (Chapter 7). **Figure 1.1** illustrates how the individual studies undertaken as part of this doctoral research address the thesis aims and objectives and, when combined, these chapters provide a comprehensive investigation into the key factors affecting prescriber implementation of medication appropriateness recommendations in hospitalised older adults.

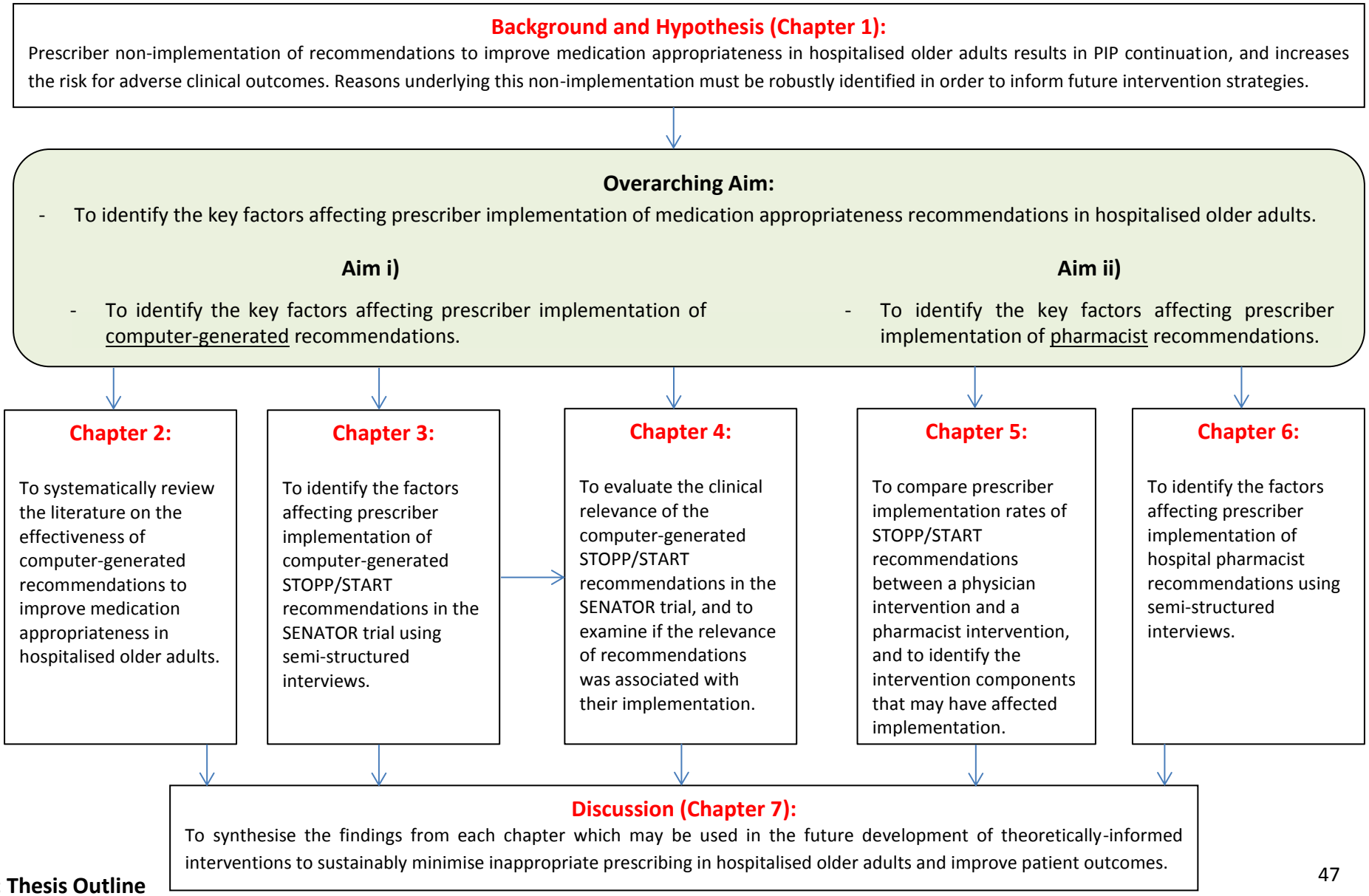


Figure 1.1: Thesis Outline

Chapter 2: Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis

2.1 Chapter description

In Chapter 1, I explained how hospitalised older adults are particularly vulnerable to PIP, and how computerised interventions may be effective in identifying PIP in this patient group. In this chapter, I conduct a systematic review and meta-analysis to examine the effectiveness of computerised interventions in minimising PIP in hospitalised older adults, with a secondary focus on the implementation rates of these computer-generated recommendations. An addendum is provided at the end of this chapter with a discussion of up-to-date search results.

The work of this chapter has been published as: *Dalton K, O'Brien G, O'Mahony D, Byrne S. Computerised interventions designed to reduce potentially inappropriate prescribing in hospitalised older adults: a systematic review and meta-analysis. Age Ageing. 2018 Jun 8;47(5):670-8.*

2.2 Abstract

2.2.1 Introduction

Computerised interventions have been suggested as an effective strategy to reduce PIP for hospitalised older adults. This systematic review and meta-analysis examined the evidence for efficacy of computerised interventions designed to reduce PIP in this patient group.

2.2.2 Methods

An electronic literature search was conducted using eight databases up to October 2017. Included studies were controlled trials of computerised interventions aiming to reduce PIP in hospitalised older adults (≥ 65 years). Risk of bias was assessed using Cochrane's Effective Practice and Organisation of Care (EPOC) criteria.

2.2.3 Results

Of 653 records identified, eight studies were included - two randomised controlled trials, two interrupted time series analysis studies, and four before-after studies. Included studies were mostly at a low risk of bias. Overall, seven studies showed either a statistically significant reduction in the proportion of patients prescribed a PIM (absolute risk reduction 1.3% – 30.1%), or in PIMs ordered (absolute risk reduction 2% – 5.9%). It was only possible to include three studies in the meta-analysis for one of the primary outcomes – which demonstrated that intervention patients were less likely to be prescribed a PIM (odds ratio 0.6; 95% confidence interval [CI] 0.38, 0.93). No computerised intervention targeting PPOs was

identified. There is insufficient evidence thus far to suggest that these interventions can routinely improve patient-related outcomes.

2.2.4 Conclusion

This systematic review concludes that computerised interventions are capable of statistically significantly reducing PIMs in hospitalised older adults. Future interventions should strive to target both PIMs and PPOs, ideally demonstrating both cost-effectiveness data and clinically significant improvements in patient-related outcomes.

2.3 Introduction

Prescribing medications for older adults is a challenging process due to age-related alterations in pharmacokinetics and pharmacodynamics, often coupled with multimorbidity and polypharmacy [13, 28, 77]. In the hospital setting, older patients are commonly exposed to new medications under the care of multiple prescribers in the management of acute illness; this increases the risk for drug-drug interactions, drug-disease interactions, PIP, and ADRs [76].

Computerised interventions have been suggested as an effective strategy to support healthcare professionals' decision-making and improve medication appropriateness for hospitalised older adults [85]. However, given the complexity associated with prescribing in this patient group, distinct challenges arise in designing software algorithms to generate patient-specific recommendations by factoring in all pertinent patient information [193], e.g. which may include a wide range of comorbidities, medications, and laboratory parameters.

In hospital settings, electronic prescribing and CPOE systems have been shown to reduce prescribing errors and aid in the prevention of ADEs [234, 235]. However, no review has yet summarised the evidence regarding the impact of computerised interventions in hospital to reduce PIP specifically in older adults. Therefore, the primary aim of this study was to collect all currently available evidence of prospective controlled studies that have utilised computerised interventions capable of independently identifying PIP and which aimed to improve the appropriateness of prescribing in hospitalised older adults (≥ 65 years). Second, it

aimed to quantify the effect that these computerised interventions could have on reducing PIP in hospitalised older adults by conducting a parallel meta-analysis.

2.4 Methods

This systematic review and meta-analysis were reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [236], and the PRISMA checklist is provided in **Appendix 4**. The inclusion criteria, exclusion criteria, and methods for the analysis were established in advance and documented in a protocol, which was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the identification number CRD42017059795.

A comprehensive electronic search of the literature was conducted using the following eight databases from inception up to and including October 2017: PubMed, EMBASE, Medline (via Ovid), Web of Science, CINAHL, Cochrane Central Register of Controlled Trials, PsycInfo and ClinicalTrials.gov. The search strategy was developed in PubMed using a combination of key words and Medical Subject Headings (as shown in **Appendix 5**). For each of the remaining databases, the search strategy was modified to suit their specific search capabilities if necessary. Additionally, the hand search involved scrutinising the bibliographies of i) any review papers that looked at computerised interventions in reducing PIP in older adults across different healthcare settings and ii) all papers that were included at the full text review stage to ensure no other relevant studies were missed.

2.4.1 Eligibility criteria

Studies were eligible if they described a controlled intervention in which an objective was to reduce PIP in hospitalised older adults (≥ 65 years) using computer-generated recommendations. The primary outcomes of interest for this review were: reductions in PIP or patients with PIP. The secondary outcomes of interest were patient outcomes and implementation rates of recommendations. As determined *a priori*, studies involving a multifaceted intervention would be included only if the effect of the computerised intervention on reducing PIP could be clearly determined. No date or language restrictions were applied.

2.4.2 Study selection

For the first stage of study selection, one reviewer screened titles to eliminate papers that were clearly not relevant to the research question. Secondly, two reviewers independently screened titles and abstracts to identify potentially pertinent full texts. The last stage involved papers being read in full and their suitability for inclusion was determined independently by two reviewers. Two authors were contacted to supply any additional information required to decide on inclusion of the full texts [237, 238]. Consensus on inclusion was reached by discussion between reviewers, with arbitration by a senior supervisor if necessary.

2.4.3 Data extraction

Data extraction was performed by one reviewer and verified by another. A data extraction form was piloted on two papers and adjusted thereafter where necessary. All authors of the included papers were contacted to provide supplementary information where required.

2.4.4 Risk of bias assessments

Two review authors independently assessed risk of bias for the included studies according to Cochrane's Effective Practice and Organisation of Care (EPOC) risk of bias criteria [239]. Consensus on the assessments was reached by discussion, with advice from a senior supervisor if required. This tool was used to determine if any of the included studies were at a high risk of bias which may impact the findings from the narrative summary or meta-analysis.

2.4.5 Data Synthesis

Quantitative analysis was conducted if at least two studies had a common comparable primary outcome measure, and if pooling their results was deemed appropriate. Study heterogeneity was assessed qualitatively by reviewing the differences in the interventions and study design, whereas statistical heterogeneity was assessed using the I^2 statistic. Review Manager 5.3 software was employed to determine the pooled estimate of effect and 95% confidence intervals (CIs), with $p < 0.05$ considered statistically significant. When it was not possible to combine primary outcome data due to the variability in results reporting across studies, or simply due to lack of data available, a narrative summary was provided.

2.5 Results

2.5.1 Search results

A total of 653 studies were identified after duplicates were removed. After the exclusion of records based on their titles and abstracts, 20 full texts were assessed

for eligibility. Eight papers were suitable for inclusion in the systematic review. A PRISMA flow diagram describes the flow of studies in the review [236] and details the reasons for exclusion of full texts reviewed (**Figure 2.1**).

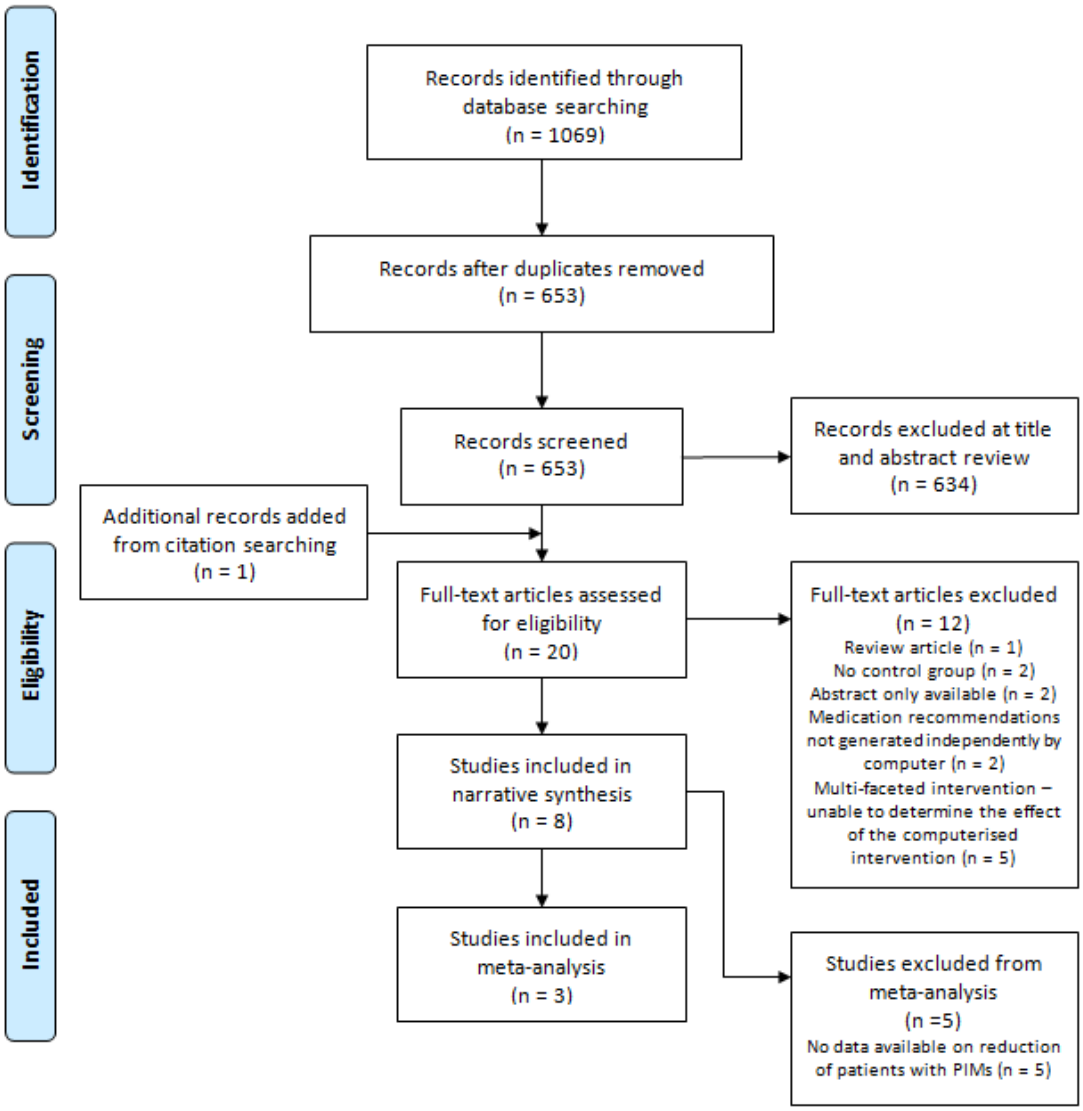


Figure 2.1: PRISMA flow diagram of search strategy results

2.5.2 Characteristics of included studies

The included studies' characteristics and outcomes are provided in **Table 2.1**. A more detailed summary of each intervention is provided in **Appendix 6**. In four of

the studies, the intervention utilised clinical decision support within a CPOE system [200, 201, 210, 240]. In three other studies, the intervention consisted of alerts or reminders embedded into a CPOE system [211, 241, 242]. The remaining study involved the use of INTERcheck® software, a '*computerised prescription support system*' which aimed to reduce PIMs, potentially severe drug-drug interactions, and anticholinergic burden [238]. The medications on admission were reviewed using the computerised tool and changed according to the INTERcheck® indication. This was the only included intervention not conducted at the point of PIM prescribing. In total, there were 18,507 control patients and 24,535 intervention patients across 6 of the studies [201, 210, 211, 238, 240, 241]. One study did not report the total number of patients – primary author contacted: data no longer available [242]. The remaining study reported patient visits only [200].

Six of the eight included studies utilised computerised alerts or reminders incorporated into a CPOE system, which appeared in various forms to notify healthcare professionals of PIP instances at the time a PIM was ordered [200, 210, 211, 240-242]. While some alerts simply provided information to the healthcare professional to guide prescribing [200, 242], others provided recommendations that required acceptance or rejection at the time of medication ordering [240]. Five of the six studies that utilised alerts or reminders suggested an alternative to PIM use [200, 210, 211, 240, 242]. The study by Lester *et al.* was the exception to this; they stated that the suggested alternative may also be inappropriate for certain older patients, thus forcing the prescriber to think for themselves regarding treatment options and the health status of individual patients [241].

Table 2.1: Characteristics of included studies

Author	Country	Setting	Study Design	Aim of study	Intervention	Number of patients	Reduction in % of patients with PIMs	Reduction in % of PIMs	% Implementation rate of recommendations
Agostini *et al.* [211]	USA	Adult inpatient service in a teaching hospital.	Before-after study	To develop a feasible, inexpensive, point-of-care computerised reminder to improve sedative-hypnotic prescribing in hospitalised older people.	Computerised reminder in a CPOE system aiming to minimise use of diphenhydramine and diazepam, and directing physicians to either a non-pharmacological sleep protocol or to an alternative medication, such as trazodone or lorazepam.	C: 12,356 I: 12,153 Total: 24,509	Prescribing of diphenhydramine and diazepam decreased from 18% in pre-intervention patients to 15% post-intervention[*].	Not stated.	95% - 95% of patients were successfully directed to a nonpharmacological sleep protocol, or to a safer sedative-hypnotic drug.
Boustani *et al.* [240]	USA	Medical ward at a university-affiliated, public hospital.	Randomised controlled trial	To evaluate the efficacy of a CDSS to improve the quality of care for patients with cognitive impairment.	If a physician ordered any one of 18 inappropriate anticholinergic medications in a CPOE system, a CDSS interruptive alert recommended to discontinue the medicine, dose modification, or suggested an alternative.	C: 225 I: 199 Total: 424	Not stated.	More anticholinergic orders were discontinued in the intervention arm (48.9%) versus the control arm (31.2%)[†].	Not applicable.
Ghibelli *et al.* [238]	Italy	Acute geriatric ward in an academic urban hospital.	Before-after study	To evaluate the applicability of INTERcheck® as a means of reviewing older patients' medicines. To evaluate the effectiveness of INTERcheck® in reducing PIMs, potentially severe DDIs, and anticholinergic burden.	The physician utilised a computerised prescription support system (INTERcheck®) to identify PIMs and potential drug-drug interactions, as well as aiming to reduce anticholinergic load and adjust doses in patients with renal impairment.	C: 74 I: 60 Total: 134	Between admission and discharge, the intervention resulted in a reduction in patients with PIMs (41.7% versus 11.6%)[*].	Between admission and discharge, the intervention resulted in a reduction in the prevalence of PIMs out of total medicines (7.6% versus 1.7%)[*].	Not applicable.

Table 2.1: (continued) Characteristics of included studies

Author	Country	Setting	Study Design	Aim of study	Intervention	Number of patients	Reduction in % of patients with PIMs	Reduction in % of PIMs	% Implementation rate of recommendations
Griffey *et al.* [201]	USA	Urban academic tertiary care emergency department.	Interrupted time series	To evaluate the impact of a CDS tool on physician ordering behaviour and ADEs.	When one of the study medications was ordered in a CPOE system for patients ≥ 65 years, a clinical decision support tool modified one or more of the following parameters: medication selection, default dosage, or default frequency. The physician could then choose to accept or override the recommendation. The tool was alternated 'OFF' and 'ON' in consecutive blocks during the study period.	C: 668 I: 739 Total: 1,407	Not stated.	During intervention periods, 69% of initial orders were not consistent with recommendations (potentially inappropriate) versus 77% during control periods[*].	- Of initial medicine orders: 31% were consistent with computerised recommendations for medication dosage/frequency. - 7.5% of suggestions for alternatives were accepted (4/53).
Lester *et al.* [241]	USA	University-affiliated hospital.	Before-after study	To evaluate the impact of "*geriatric alerts*" in the CPOE on ordering patterns of diphenhydramine, metoclopramide, and antipsychotics.	Informational alerts popped up when a PIM was ordered in the CPOE system. The physician was required to acknowledge the alert, before deciding on whether to cancel their order or continue prescribing the medication.	C: 3,259 I: 9,591 Total: 12,850	Pre-alert versus post-alert: patients prescribed diphenhydramine (26.9% versus 20%)[*] and metoclopramide (16.7% versus 12.5%)[*]. There was no decrease in patients prescribed antipsychotics (8.8% versus 9.2%)[†].	Not stated.	Not applicable.
Mattison *et al.* [242]	USA	Urban teaching hospital.	Before-after study	To determine whether a CPOE drug warning system can decrease orders for PIMs in hospitalised older patients.	The CPOE system alerted prescribers when a PIM was ordered by providing a medication-specific warning that advised alternative medication or dose reduction.	Not stated.	The authors state "*a decline in the number of patients exposed to a subset of potentially problematic medications*". Specific figures are not reported, but the authors do state a reduction in the number of PIMs ordered per patient per day (0.07 versus 0.054)[*].	The mean rate of non-recommended medicines (PIMs) ordered decreased from 11.56 to 9.94 orders per day post-intervention[*].	Not applicable.

Table 2.1: (continued) Characteristics of included studies

Author	Country	Setting	Study Design	Aim of study	Intervention	Number of patients	Reduction in % of patients with PIMs	Reduction in % of PIMs	% Implementation rate of recommendations
Peterson *et al.* [200]	USA	Medical, surgical, neurology, and gynaecology services in a tertiary care hospital.	Interrupted time series	To encourage more conservative initial dosing and better psychotropic drug selection among hospitalised older patients.	A decision support tool altered the default dose and frequency for psychotropic medications for patients ≥ 65 years, and suggested an alternative medication when prescribers ordered one of 12 psychotropic medications known to be poorly tolerated in older patients. The support tool was activated for 2 of 4 six-week study periods in an off-on-off-on pattern.	C: 2,515 patient visits I: 2,647 patient visits Total: 5,162	Not stated.	The intervention reduced the prescription of non-recommended drugs (10.8% versus 7.6% of total orders)*.	29.3% - 29.3% of prescriptions for psychotropics agreed with system recommendations.
Terrell *et al.* [210]	USA	Emergency department in a university-affiliated urban public hospital.	Randomised controlled trial	To evaluate the effectiveness of CDS in reducing PIP in older adults	Nine high-use and high impact PIMs, selected by an expert panel consisting of two doctors of pharmacy, two physician information technology experts, three geriatricians, and three emergency physicians.	C: 1,925 I: 1,793 Total: 3,718	There were significantly fewer patients prescribed PIMs by the intervention physicians compared with the control physicians (2.6% versus 3.9%)*.	Lower proportion of inappropriate medications in the intervention group (3.4% versus 5.4%)*.	43% - Decision support was provided 114 times to physicians, who accepted 49 (43%) of the recommendations.

USA: United States of America, CPOE: Computerised physician order entry, C: Control, I: Intervention, CDSS: Computerised decision support system, PIM: Potentially inappropriate medication,

DDI: Drug-drug interaction, CDS: Clinical decision support, PIP: Potentially inappropriate prescribing * Statistically significant difference, † No statistically significant difference.

2.5.3 Results of the risk of bias assessments

The results of the risk of bias assessments are shown in **Table 2.2**. All of the included studies were found to be at a low risk of bias overall, with one exception where the risk of bias was deemed unclear [242]. Both RCTs recognise that they may have been at risk of contamination [210, 240]. However, the potential for contamination in these studies, if present, would tend to bias against finding an effect of the intervention.

According to Cochrane's EPOC criteria [239], the before-after studies must be deemed '*high risk*' with regard to the two selection bias domains. Three of the four before-after studies did not provide enough information to confirm that the baseline characteristics and outcome measurements were similar [211, 241, 242], and thus the risk of bias was deemed '*unclear*'.

Table 2.2: Risk of bias assessments

Author (RCTs* and before-after studies)	Selection Bias					Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Risk of Bias
	Random sequence generation	Allocation concealment	Baseline outcome measurements similar	Baseline characteristics similar	Free of contamination	Outcome assessment	Incomplete data outcomes addressed			
Agostini *et al*. [211]	-	-	?	?	+	+	+	+	+	+
Boustani *et al*. [240]*	+	+	?	+	-	+	+	+	+	+
Ghibelli *et al*. [238]	-	-	+	+	+	+	+	+	+	+
Lester *et al*. [241]	-	-	?	+	+	+	+	+	+	+
Mattison *et al*. [242]	-	-	?	?	+	+	+	+	+	?
Terrell *et al*. [210]*	+	?	?	+	?	+	+	+	+	+

Author (Intermittent time series analysis studies)	Was the intervention independent of other changes?	Was the shape of the intervention effect pre-specified?	Was the intervention unlikely to affect data collection?	Was the knowledge of the allocated interventions adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Was the study free from selective reporting?	Other risks of bias	Overall risk of bias
Griffey *et al*. [201]	+	+	+	+	+	+	+	+
Peterson *et al*. [200]	+	+	+	+	+	+	+	+

Judgments are categorised as 'Low Risk' of bias (+), 'High Risk' of bias (-) or 'Unclear Risk' of bias (?) * RCTs: Randomised controlled trials

2.5.4 Reduction in patients with PIMs

2.5.4.1 Quantitative analysis

Three of the eight studies had data available on the exact number of patients that were prescribed PIMs as an outcome, and so were amenable to quantitative analysis [210, 211, 238]. In these three studies, there were a total of 29,791 patients/patient visits (14,860 and 14,931 in the intervention and control arms respectively). Given the heterogeneous types of intervention and considerable statistical heterogeneity between the study results (I^2 = 82%; p = 0.004), a random-effects model was performed to provide a pooled estimate of effect. The meta-analysis found that patients in the intervention group were less likely to be prescribed PIMs post-intervention (odds ratio 0.6; 95% CI: 0.38, 0.93) (**Figure 2.2**). These three studies were found to be at a low risk of bias, so one can be reasonably confident in the results of this meta-analysis.

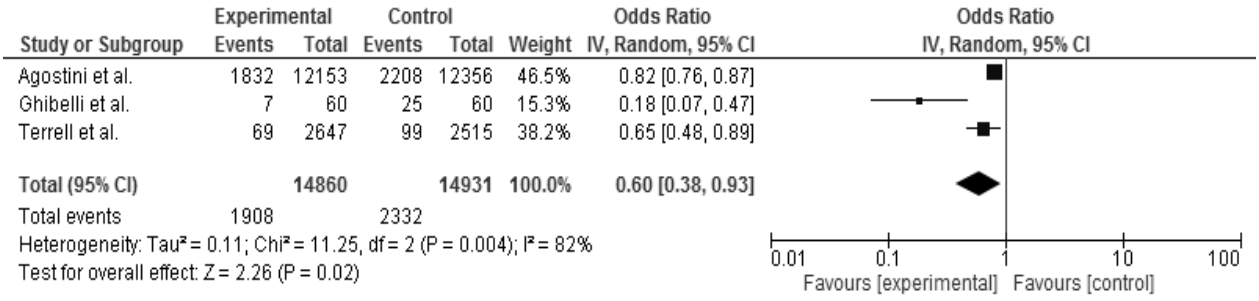


Figure 2.2: Forest plot for the odds ratio for the reduction in the proportion of patients prescribed PIMs post-intervention

2.5.4.2 Narrative summary

Four of the included studies reported results on the effect the intervention had on the proportion of patients prescribed PIMs, all of which showed a statistically significant reduction ($p < 0.05$) for this outcome [210, 211, 238, 241]. Where it was possible to calculate, there was an absolute risk reduction of 1.3% – 30.1% [210, 211, 238], and a relative risk reduction of 16.7% – 72.2% [210, 211, 238, 241] in patients prescribed PIMs across the studies.

2.5.5 Reduction in PIMs prescribed

Due to the variability in which the results were reported, a meta-analysis could not be performed for this primary outcome. Where it was possible to calculate, there was an absolute risk reduction of 2% – 5.9% [200, 210, 238], and a relative risk reduction of 14% – 77.6% [200, 210, 238, 242] in PIMs prescribed across the studies. Overall, six studies showed a reduction in the number of PIMs prescribed when comparing the intervention and control groups, with five studies demonstrating statistically significant reductions ($p < 0.01$) [200, 240, 242]. The only exception to this was the study by Boustani *et al*., whereby the intervention group still had a greater discontinuation rate in anticholinergic drug orders versus the control group, but the difference was not statistically significant (48.9% versus 31.2%; $p = 0.11$) [240]. As previously mentioned, contamination may have been an issue in this study which may have reduced the difference found between the groups. Given the overall low risk of bias in these studies, one can be reasonably confident in the results provided.

2.5.6 Implementation rates of computer-generated recommendations

Four of the included studies have data on implementation rates or levels of agreement with the computer's recommendations (**Table 2.3**) [200, 201, 210, 211].

Table 2.3: Implementation rates of computer-generated recommendations

Author	Intervention type	Medications involved	% Implementation Rates or Agreement with Recommendations (intervention arm)	
			Rate	Details
Agostini *et al.* [211]	Computerised reminder	Diazepam and diphenhydramine	95%	95% of patients were successfully directed to a non-pharmacological sleep protocol, or to a safer sedative-hypnotic drug.
Terrell *et al.* [210]	Computerised decision support	Nine high-use and high impact PIMs	43%	Decision support was provided 114 times to intervention physicians, who accepted 49 (43%) of the recommendations.
Griffey *et al.* [201]	Computerised decision support	Benzodiazepines, NSAIDs, opiates, sedative-hypnotics	31%; 7.5%	Of initial medicine orders: 403/1283 (31%) were consistent with the computerised recommendations for medication dosage/frequency. 7.5% of suggestions for alternatives were accepted (4/53).
Peterson *et al.* [200]	Computerised decision support	Seventy-two medications chosen by expert panel	29.3%	29.3% of prescriptions for psychotropics were in agreement with system recommendations.

PIM: Potentially inappropriate medication; NSAID: Non-steroidal anti-inflammatory drug.

2.5.7 Reasons for not implementing recommendations

Three studies identified reasons why prescribers did not accept or may have overridden the computerised recommendations [201, 210, 242]. A patient having previously tolerated a PIM was the most common reason for non-implementation of recommendations in two of the studies [201, 210], while it remained the second

most common in the remaining study after the reason that the prescriber felt that the regimen was clinically indicated [242]. This perhaps suggests a degree of inertia with regard to addressing PIP in the acute hospital setting.

Some of the other reasons given in these three studies included:

i) On the advice of a consultant, the medicine is not to be changed [201].

ii) No good substitute exists for the medication [210].

iii) The patient insists on the medication [210].

iv) Interaction noted, regimen clinically indicated, will closely monitor [242].

v) Warning noted, will use smaller dose and monitor for side effects [242].

2.5.8 Clinical outcomes

Three of the included studies assessed clinical outcomes [200, 201, 240]. Griffey *et al.* demonstrated a statistically significant reduction in ADEs (3.4% versus 7.1%; $p = 0.02$) [201] and Peterson *et al.* showed a statistically significant reduction in inpatient falls (0.28 versus 0.64 falls per 100 patient-days; $p = 0.001$) [200]. However, there was no statistically significant difference in the remaining fifteen clinical outcomes identified, such as hospital length of stay, readmission rates, or mortality rates (**Table 2.4**).

Table 2.4: Studies which assessed clinical outcomes

Author	Description of Clinical Outcomes
Boustani *et al*. [240]	All clinical outcomes with no statistically significant difference (0/9) No statistically significant effects on health outcomes including: • the mean days of hospital stay (intervention: 7.7 days versus usual care: 6.8, *p* = 0.12), • 30-day mortality rate (intervention: 6% versus usual care: 5.8%, *p* = 0.69), • home discharge (intervention: 43.2% versus usual care: 36.9%, *p* = 0.13), • 30-day readmission rates (intervention: 18.6% versus usual care: 16.4%, *p* = 0.53), • hospital-acquired complications (intervention: 47.2% versus usual care: 44.9%, *p* = 0.94). The hospital-acquired complications included: • incidence of delirium (intervention: 33.7% versus usual care: 31.1%, *p* = 0.78), • the presence of ICD-9 codes of pressure ulcer at discharge (intervention: 12.1% versus usual care: 11.1%, *p* = 0.77), • the presence of ICD-9 code for fall or injury at discharge (intervention: 4.5% versus usual care: 4.9%, *p* = 0.88), • orders for physical restraints or patients observed to be physically restrained (intervention: 11.1% versus usual care: 7.6%, *p* = 0.54).
Griffey *et al*. [201]	One clinical outcome with statistically significant difference* (1/5) No significant differences were observed in: admission rate, reversal drug administration, number of 10-fold orders, or emergency department length of stay. *ADEs: There were 39 ADEs identified, distributed as 8/237 patients (3%; 95% CI: 1% – 6%) during ON periods and 31/436 patients (7%; 95% CI 5% – 9%) during OFF periods (*p* = 0.02).
Peterson *et al*. [200]	One clinical outcome with statistically significant difference† (1/3) No difference between control and intervention for length of stay or altered mental status. †The rate of falls continued to be significantly less (0.28 versus 0.64 falls per 100 patient-days; *p* = 0.001)

ICD: International Classification of Diseases; ADE: Adverse drug event; CI: Confidence interval.

2.6 Discussion

This systematic review and meta-analysis showed that computerised interventions can reduce PIP in hospitalised older adults. Although seven of the eight included studies showed a statistically significant reduction in PIMs ordered or the proportion of patients prescribed PIMs, it is important to note that all of these were single-centre studies. Furthermore, all the included studies in this review were conducted in the United States of America (USA), except for one study conducted in Italy [238], and therefore this may impact on the generalisability of the review findings for other countries.

The implementation rates of the computer-generated recommendations varied highly across the studies that measured this outcome (**Table 2.3**). These findings suggest that interventions that target a smaller number of PIP instances may have greater recommendation implementation rates than those targeting a wider range of PIP instances. One reason for this may be that prescribers could become overwhelmed by the complexity of information provided in broader interventions [243]. It is interesting to note that Agostini *et al.* achieved a 95% success rate in switching to a safer alternative to a PIM, whereas only 4/53 (7.5%) recommendations for alternatives were accepted in Griffey *et al*. [201, 211]. Thus, providing a recommendation for an alternative does not necessarily mean that prescribers will accept this and discontinue the PIM in question. Further qualitative research is required to identify factors affecting implementation of computer-generated recommendations of this kind.

Autonomy is very important when encountering computerised interventions such as these; prescribers should be capable of bypassing recommendations where clinically appropriate [211]. While overrides are often justified, they can be associated with serious adverse events (or even death) if clinically significant information is unintentionally ignored [244]. A common reason for overrides may be due to '*alert fatigue*', whereby prescribers may pay less attention if they are encountering repeated or inappropriate alerts, or are being inundated by a large quantity of alerts [241, 244]. Customisation of alerts for individual institutions may improve their specificity, and potentially reduce the occurrence of this phenomenon [245].

The results of this systematic review are in keeping with that of previous reviews, which have shown that computerised interventions may be effective in improving the appropriateness of prescribing in older adults. One review assessed the use of electronic prescribing and other forms of technology in reducing PIP and polypharmacy in older adults [198], and an older review evaluated computer decision support to improve medication prescribing in older adults [199]; however, both studies broadly looked at interventions across different healthcare settings. This is the first systematic review to focus specifically on computerised interventions which aimed to reduce PIP for older adults in the hospital setting.

It should be noted that only two of the included studies in this review were RCTs, which are considered the most robust way of identifying if a cause-effect relationship exists between an intervention and outcome [246]. The studies included in the meta-analysis were at a low risk of bias; however, the pooled

estimate of effects may have been biased as incomplete reporting in some papers meant that these were the only studies which allowed comparison of one of the primary outcomes (data retrieval bias) [247]. Even though the other studies that assessed this outcome showed a statistically significant reduction in the proportion of patients prescribed PIMs, the pooled estimate may not accurately represent the true effect that these computerised interventions can have on reducing PIP in hospitalised older adults, especially when you consider that the meta-analysis contained studies that were not RCTs. Despite these limitations, this review is valuable for healthcare professionals as it shows that computerised interventions can be implemented in hospital settings to reduce instances of PIP for older patients.

This systematic review aimed to identify computerised interventions targeting PIMs and PPOs. However, the included studies in this review only targeted PIMs, and did not identify medication underuse, i.e. PPOs which older patients may benefit from. Despite the comprehensive search strategy, it is still possible that all relevant papers may not have been identified. A systematic review by Meid *et al*. recommended that future interventions targeting PIP should utilise explicit criteria, such as START, alone or in combination with implicit reasoning, to screen for medication underuse in older people [248]. Thus, if possible, computerised interventions should strive to target PPOs and not just PIMs.

With the increasing prevalence of electronic prescribing and CPOE worldwide, it should be noted that implementing these systems does not always result in positive patient outcomes [249]. Hospital managers and other key stakeholders will have to

devise strategies to allow for successful integration with clinical workflows and with other technologies already in place. All but one of the interventions in this review were conducted at the point of prescribing, which may be a key feature for designing future studies. The advantage of this is that prescribers are prompted in real time to address medication appropriateness issues to reduce the risk of ADE at the earliest possible point.

Hospital managers will also have important roles in assigning funding to these computerised systems. It has been demonstrated that the extra costs associated with the implementation of CPOE with a CDSS are acceptable in the prevention of medication errors and preventable ADEs [250]. Further research should aim to identify how best to integrate these new computerised systems into routine clinical practice, and to explore the factors affecting implementation of computer-generated recommendations.

2.7 Conclusion

Overall, these findings demonstrate that computerised interventions can be effective in significantly reducing PIMs in hospitalised older adults. Larger scale multi-centre RCTs, at national and international levels, are required to further demonstrate the benefit of these interventions across different institutions, ideally showing both cost-effectiveness data and clinically significant improvements in patient outcomes.

2.8 Addendum

2.8.1 Updated search methods

An updated search of the eight electronic databases was conducted in August 2019 to search for all potentially relevant articles published since October 2017, the date of the latest search prior to publication of the systematic review and meta-analysis [251]. Once duplicates were removed, records were excluded based on screening their titles and abstracts. Thereafter, potentially relevant articles were read in full to decide on their inclusion. Authors were contacted to provide any additional information that was necessary to decide on their eligibility for inclusion and/or to provide relevant data based on this review's outcome measures [252-255].

2.8.2 Analysis methods

Quantitative analysis was conducted on the additional studies from the updated search if they had a common comparable primary outcome measure with at least one other study, and if combining their results was considered appropriate. Review Manager 5.3 software was utilised to determine the pooled estimate of effect and 95% confidence intervals (CIs), with $p < 0.05$ considered statistically significant. Where it was not possible or not appropriate to pool primary outcome data, a narrative synthesis was provided. Risk of bias in the additional studies was assessed using Cochrane's EPOC criteria [239].

2.8.3 Updated search results

A total of 234 records were screened after the removal of duplicates, of which 214 records were excluded based on their titles and abstracts. Where available, the full

texts of the remaining records were assessed for inclusion. This resulted in one article meeting the eligibility criteria, which was included in the updated systematic review, as shown in **Figure 2.3**.

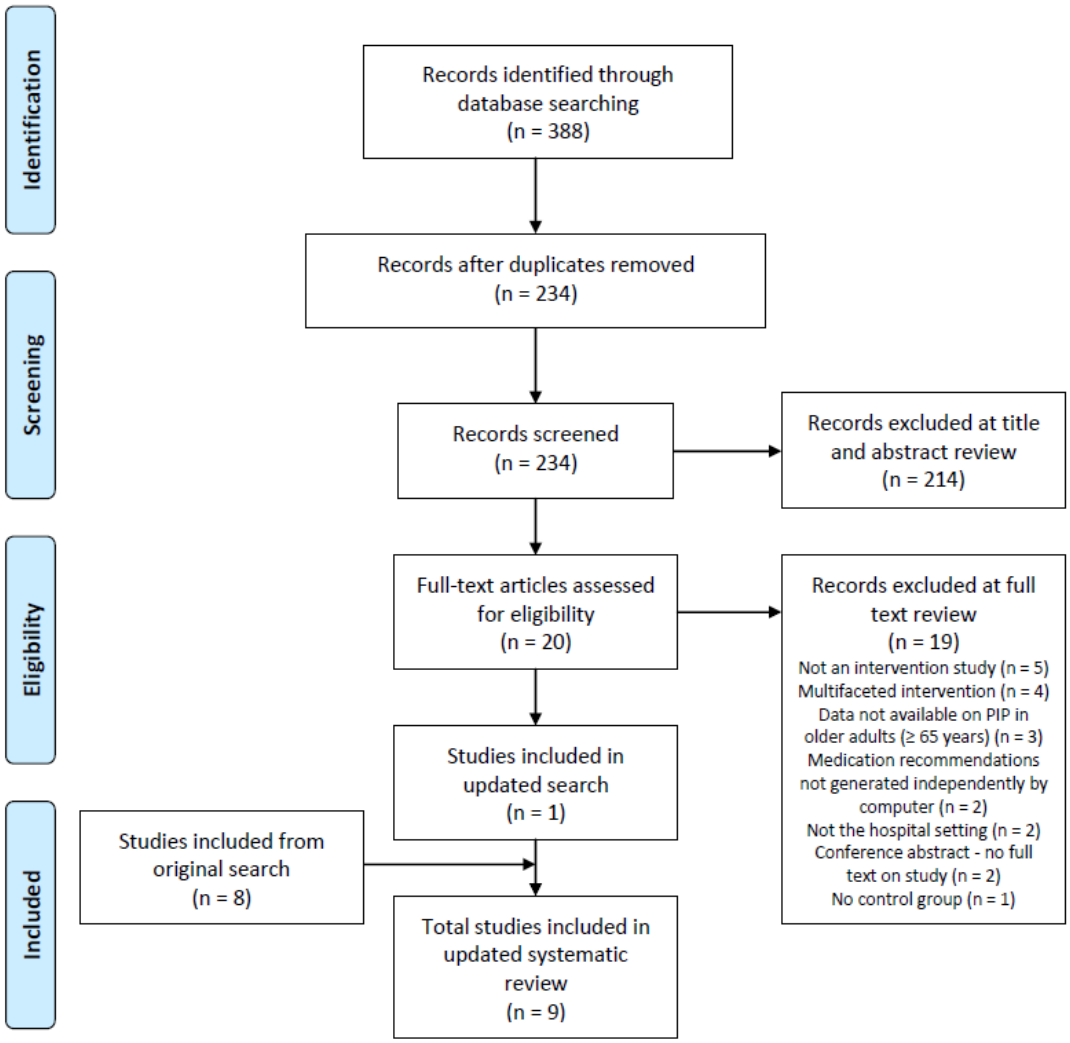


Figure 2.3: PRISMA flow diagram of updated search strategy results

2.8.4 Updated narrative synthesis and meta-analysis

The article from Kim *et al.* was the only one deemed eligible for inclusion after the updated literature search [255]. The aim of this additional study was to identify the effect of the introduction of a CPOE template that altered the default dose listed for

opioids, benzodiazepines, and non-steroidal anti-inflammatory drugs (NSAIDs) for all older adults (aged ≥ 65 years) in the emergency departments of two university-affiliated hospitals in the USA [255]. The primary outcome measure in this study was the difference in frequency of the medications of interest with the recommended starting dose in older adults between two 4-month time periods: from May – August 2015 and May – August 2016, before and after the implementation of a modified CPOE template, which was introduced in both hospitals in September 2015. Pre-intervention, 2561 doses were administered to 1002 patients, of which 1863 were not in line with the recommended dose (72.7%). Post-intervention, 2700 doses were administered to 944 patients, whereby physician prescribers implemented 22.5% of default starting dose recommendations, meaning that 1823 doses that were not in line with the recommended dose (67.5%). The absolute risk reduction and relative risk reduction in non-recommended doses were 5.2% and 7.2% respectively. This reduction in PIP was found to be statistically significant (67.5% versus 72.7%; $p < 0.001$). However, it should be noted that a statistically significant difference was reported in one of the hospital sites (a 9% improvement in recommended dosing) but not in the other. Kim *et al.* did not investigate the effect of the intervention on patient outcomes, and this additional study was judged to have a low risk of bias overall.

No data was available on the reduction of the proportion of patients with PIMs from the Kim *et al.* article. Therefore, the study results were not amenable for inclusion in the previously published meta-analysis. However, the nature of the intervention and results reporting in Kim *et al.* were very similar to that of one of

the original eight included studies (the one conducted by Griffey *et al.*) [201], which meant it was possible to pool these results together for a new meta-analysis (**Figure 2.4**). This meta-analysis found that non-recommended doses were less likely to be prescribed in the intervention group (odds ratio 0.72; 95% CI: 0.61, 0.86).

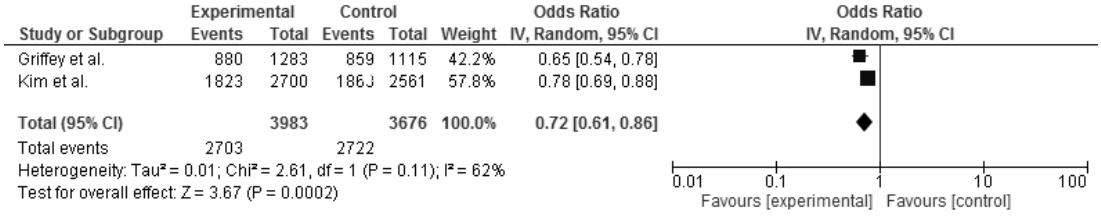


Figure 2.4: Forest plot for the odds ratio for the reduction in the proportion of non-recommended doses prescribed post-intervention

2.8.5 Discussion

The study from Kim *et al.* showed a significant reduction in the number of non-recommended doses of high-risk medications in hospitalised older adults. These findings are line with the studies from the initial search, whereby seven of the eight interventions were found to significantly reduce PIP in this patient group. The 5.2% absolute risk reduction in non-recommended doses (i.e. PIMs prescribed) post-intervention is at the higher end of the range found in the original systematic review (2% – 5.9%), but the 7.2% relative risk reduction for this outcome is below the range from the original included studies (14% – 77.6%) [251]. In the Kim *et al.* study, prescribers implemented 22.5% of default starting dose recommendations from the computer, which was below the range of 29.3% – 95% found in the original articles, and no reasons were provided for prescribers' non-implementation of recommendations.

With the addition of the Kim *et al.* paper after the updated search, eight of the nine included studies were conducted in the USA, which impacts on the generalisability of the findings to hospital settings in other countries. In addition, the transferability of the findings could also be questioned given that a statistically significant reduction in PIP was found in only one of the two hospital settings in the Kim *et al.* study, despite having the '*same*' computerised intervention. As with the majority of the original included articles, Kim *et al.* did not investigate the effect of the intervention on patient outcomes. Given that this updated systematic review has shown that computerised interventions significantly reduce PIP in hospitalised older adults, it is imperative that future studies focus on demonstrating significant improvements in patient outcomes, and not just on reducing PIP.

Due to time constraints, this update to the previously published systematic review was conducted solely by the primary researcher. Hence, it is possible that relevant studies were unintentionally omitted. Therefore, I recommend that an updated systematic review and meta-analysis be conducted by multiple researchers prior to dissemination of the findings.

Chapter 3: Factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR trial – a qualitative study

3.1 Chapter description

In Chapter 2, the systematic review and meta-analysis found that computerised interventions can be significantly effective in reducing PIP in hospitalised older adults. However, the prescriber implementation rates of computer-generated recommendations were found to vary widely in the included studies which reported this measure, and the reasons for non-implementation had not been comprehensively explored across the studies. In this chapter, I conduct a qualitative interview study alongside the SENATOR trial to identify the key factors affecting prescriber implementation of SENATOR's computer-generated medication appropriateness recommendations, which were targeted at reducing PIP and ADRs in hospitalised older adults.

The work of this chapter has been accepted in Drugs & Aging, subject to revisions.

3.2 Abstract

3.2.1 Introduction

The SENATOR trial intervention included the provision of computer-generated medication recommendations to physician prescribers caring for hospitalised older adults (≥ 65 years), with the aim of reducing in-hospital adverse drug reactions. Interim data analysis during the trial revealed that the prescriber implementation rates of the computer-generated STOPP/START recommendations were lower than expected across all six trial sites. The aim of this qualitative study was to identify the key factors affecting prescriber implementation of the medication recommendations in the SENATOR trial.

3.2.2 Methods

Semi-structured interviews were conducted with trial researchers and physician prescribers who were provided with SENATOR recommendations. Content analysis was used to identify the key themes that influenced prescriber implementation of SENATOR recommendations.

3.2.3 Results

Interviews were conducted with ten trial researchers and fourteen physician prescribers across the six trial sites between November 2017 and May 2018. Content analysis identified four key factors affecting implementation of the recommendations.

i) Computerised output: the software could not evaluate the entire clinical context of patients and thus frequently produced recommendations of low clinical relevance.

ii) Acute hospital environment: participants felt that there was often a disconnect between the time prescribers were reviewing the patient and the point at which the recommendations were provided.

iii) Prescriber role and identity: implementation was facilitated by the recommendations reaching a '*decision-maker*'. However, prescriber inertia was highly pervasive, with a particular reluctance among those in specialised roles to prescribe outside their own specialty.

iv) Patient-specific details: interviewees declared that implementation was affected by the patient's acute clinical status, prescribers' familiarity with the individual patient and, to a lesser extent, the patient's own preferences.

3.2.4 Conclusion

This study has demonstrated that the clinical relevance of the SENATOR prescribing recommendations was a significant factor affecting their implementation. Whilst software refinement will be necessary to improve the quality of recommendations, future interventions will need to be multifaceted to overcome the complex prescriber specialty culture within the acute hospital environment.

3.3 Introduction

It was demonstrated in Chapter 2 that computerised interventions can significantly reduce PIP in hospitalised older adults, but with limited benefits proven for patient outcomes [251]. The SENATOR project included a multi-centre RCT whereby the intervention involved the provision of computer-generated pharmacological and non-pharmacological recommendations to attending physician prescribers providing care to older adults in the hospital setting, with the trial's primary aim being to reduce in-hospital ADRs in this patient cohort [202]. The pharmacological recommendations were based on version 2 of the STOPP/START criteria [88], as well as drug-drug and drug-disease interactions identified by approved electronic databases.

An RCT by O'Connor *et al*. had previously demonstrated that relatively high prescriber implementation rates of STOPP and START recommendations were associated with a clinically significant reduction in the proportion of older patients experiencing in-hospital ADRs when comparing the intervention and control groups (21% versus 11.7%) [148]. However, interim data analysis from the SENATOR trial after 12 months of patient recruitment showed that the prescriber implementation rates of the STOPP and START recommendations were lower than expected across all six trial sites. A qualitative study alongside the SENATOR RCT was not planned from the outset, but it was deemed of utmost importance to investigate the possible reasons for the observed low implementation rates as this may impact on the primary outcome of the trial (i.e. hospital-acquired ADRs). Qualitative studies conducted in conjunction with RCTs have been shown to be important in the

evaluation of complex interventions, and are especially important in multi-centre trials, where the '*same*' intervention may be delivered in different ways [256, 257].

Thus, the aim of this qualitative study was to identify the factors affecting prescriber implementation of the computer-generated STOPP/START recommendations in the SENATOR trial intervention, with a view to informing the design of future studies aiming to optimise pharmacotherapy in hospitalised older adults.

3.4 Methods

3.4.1 Context and study setting

This qualitative study was undertaken in conjunction with a larger European research project: the SENATOR study, which included an RCT that was conducted in six large acute teaching hospitals in six European countries (**Table 3.1**). Briefly, as part of the SENATOR intervention, computer-generated pharmacological and non-pharmacological recommendations were provided to physicians caring for the intervention patient group, with the primary aim of reducing in-hospital ADRs. All patients randomised were multimorbid older adults (≥ 65 years) with an expected length of hospital stay > 48 hours. Primary researchers working with the trial were involved with patient recruitment, data collection, data entry into the SENATOR software engine, patient randomisation, and contacting the attending team of physicians (via telephone or face to face, a written note in the patient's clinical record, and email) to inform them that the patient was randomised to the trial

intervention arm, and that computer-generated recommendations were available to be reviewed in the patient's clinical record (either paper-based or electronic record depending on the hospital site). For more information about the RCT, the trial methods have been published in detail elsewhere [202].

Table 3.1: Acute hospital sites where the SENATOR randomised controlled trial was conducted

Number	Hospital
1	Cork University Hospital, Cork, Republic of Ireland.
2	Aberdeen Royal Infirmary, Aberdeen, United Kingdom.
3	Landspitali University Hospital, Reykjavik, Iceland.
4	Ghent University Hospital, Ghent, Belgium.
5	Hospital Universitario Ramón y Cajal, Madrid, Spain.
6	Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Ancona, Italy.

3.4.2 Study design and recruitment

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Republic of Ireland (**Appendix 7**). The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to guide reporting in this study (**Appendix 8**) [258]. Semi-structured interviews were conducted with primary researchers working with the trial and prescribers (medical or surgical) who were provided with the SENATOR recommendations. Semi-structured interviews were chosen as the preferred method of data collection

as they tend to elicit more in-depth descriptions of participants' experiences and perspectives [259].

Interview participants were eligible to be recruited from any of the six hospitals involved with the SENATOR trial (**Table 3.1**). The authors planned to interview i) two medical prescribers per site, ii) one surgical prescriber per site, and iii) two primary researchers per site where possible (as some sites only had one primary researcher still working with the trial). The primary researchers involved with the SENATOR trial were recruited using purposive sampling as there were limited numbers of primary researchers at each site. Snowball sampling was used to recruit prescribers, whereby the SENATOR primary researchers and their colleagues referred the interviewer to prescribers in their site who would participate in the study. Participants were contacted via email and provided with an information sheet and consent form in their native language in advance of the interview.

3.4.3 Data collection

Two separate topic guides comprising a similar line of questioning were formulated for both prescribers and primary researchers, and these were based on a review of the literature, the TDF [217], and the research group's practical knowledge of the RCT (**Appendix 9**). Careful consideration was given to the language used, knowing that English would not be the first language for all participants. The topic guide for interviewing prescribers was piloted with a prescriber who had received SENATOR recommendations in the lead trial site, and this interview was included in data analysis. The topic guide for interviewing primary researchers was piloted with a primary researcher working with a similar RCT in the OPERAM project [203], who

was very familiar with the SENATOR trial procedures. The topic guides were iteratively refined during the study to ensure that emerging themes were explored in subsequent interviews.

All semi-structured interviews were conducted in English by the principal investigator of this study (KD), who was a primary researcher with the SENATOR trial at the time of the interviews. All but one of the interviews were conducted in person. One interview was conducted face to face via Skype® as the primary researcher was not available at the time the interviewer visited the trial site. The interviewer had established a rapport with some of the primary researchers prior to the qualitative study during trial meetings and teleconferences, but no relationship between the interviewer and prescriber participants was established prior to study commencement.

The interviews were conducted in a private area at the participant's workplace from November 2017 to May 2018. Participants were briefed about the study and reassured that all interviews would be anonymised. All interviewees provided written informed consent for participation, and had the opportunity to withdraw from the interview at any time. Interviewees were provided with a sample of a SENATOR report in their native language during the interview as a reminder of the report design and the types of recommendations provided (sample report shown in **Appendix 10**). Field notes were recorded after each interview, and were used to refine topic guides and inform data analysis. Interviews were audio-recorded and transcribed verbatim. Data analysis coincided with data collection, and sampling continued until no new themes emerged. An additional three interviews were

conducted without any new themes appearing to confirm that data saturation had been reached [260].

3.4.4 Data analysis

All transcripts were entered into NVivo® Version 11 to facilitate analysis. The data were analysed in four phases. Phase 1 was a familiarisation phase, which involved reading and re-reading of the transcripts. Phase 2 involved conventional content analysis [261], which comprised open coding to inductively create initial, non-hierarchical codes. These initial codes were subsequently categorised to generate the evolving themes and subthemes. In Phase 3, directed content analysis was employed whereby the transcripts were deductively coded using the TDF to identify the domains present [261]. To ensure validity of the findings, a second researcher (SC) independently identified themes and TDF domains from a sample of ten interview transcripts, with the predominant domains identified through consensus discussion between two researchers (KD and SC). Three factors were considered when identifying predominant domains: i) the frequency of the beliefs in each domain, ii) the presence of conflicting beliefs, and iii) the perceived strengths of the beliefs impacting implementation, as per Patey *et al*. [262]. Lastly, the evolving themes (from Phase 2) and predominant TDF domains (identified in Phase 3) were reviewed further in order to refine the main themes which reflected the key factors affecting implementation of the SENATOR recommendations.

3.5 Results

A total of 24 interviews were conducted (with 12 medical prescribers, 2 surgical prescribers, and 10 primary researchers) across all six SENATOR RCT sites. The average interview length was 24 minutes (range 18-64 minutes). Demographic details of the interviewees are shown in **Table 3.2**.

Table 3.2: Characteristics of interview participants

	Number
Participant type	
Medical Prescriber	12
Surgical Prescriber	2
Primary Researcher	10
Gender	
Male	13
Female	11
Years of post-qualification experience	
< 5 years	6
≥ 5 to < 10 years	6
≥ 10 to < 15 years	3
≥ 15 to < 20 years	4
≥ 20 years	5

3.5.1 Main themes

Four main themes emerged as the key factors affecting prescriber implementation of the STOPP/START recommendations in the SENATOR RCT, namely the computerised output, the acute hospital environment, prescriber role and identity, and patient-specific details. Subthemes are displayed under each of these to help explain the findings, with additional quotations to support these themes in **Appendix 11**.

Theme 1 – Computerised Output

Aid to prescribing, but cannot be trusted blindly

Overall, participants expressed positivity toward the concept of the intervention, and would welcome computerised interventions like SENATOR to be an aid to prescribing in multimorbid older adults. However, most participants acknowledged that the computerised recommendations could not be trusted without careful consideration – the software could not take into account the entire clinical context of the patient, and therefore produced recommendations that were not always specific to each individual patient.

> *"I would not trust them blindly. I have gotten bad and good recommendations, and that's just because the computer programme can't know the whole story".* [Medical Prescriber 3]

Recommendations of low relevance contributing to prescriber fatigue

The general consensus from interviewees was that the software generated a high proportion of recommendations that were of low clinical relevance or inappropriate for the given patient, and that this was one of the main factors why the recommendations were not implemented. When prescribers initially saw reports that contained recommendations that were of low relevance, this would have resulted in their devaluation of the perceived benefits of future reports, contributing to decreased engagement with the SENATOR reports and non-implementation of the recommendations.

> *"I think when people have seen these reports and they've seen recommendations that are inappropriate or irrelevant, I think that can sort of change their perception of the study and of these SENATOR reports, and it can sort of devalue them as well. So, I think maybe…when they see a report the next time that they pay less attention, that they have less trust in it".* [Primary Researcher 7]

Provision of the recommendations

The majority of interviewees liked the design of the report. However, many pointed out that whilst the colours on the report would have grabbed the attention of prescribers, the overall length of the report and the large amount of writing would have been off-putting to readers.

"It's a little bit lengthy maybe because it takes a couple of minutes to read through this and…it's colourful but it's rather dull…in continuous text" [Medical Prescriber 12]

Many prescribers appreciated the face-to-face delivery of the report from the primary researcher as it allowed for discussion on the rationale behind the recommendations, and facilitated their review. However, some primary researchers felt that the status of the person communicating the presence of the recommendations was a factor affecting their implementation.

"I think because I'm not a doctor, it's sometimes difficult to discuss it with them because yeah you can always see you're not on the same level…" [Primary Researcher 1]

Theme 2 – Acute Hospital Environment

Right setting for the intervention?

Participants questioned whether the acute hospital environment was the best setting to conduct this intervention. Some highlighted that making changes in the hospital setting allows for prescribers to monitor patients afterwards. However, many pointed out that the recommendations were focused on the patient's chronic disease management, whereas the prescribers were primarily focused on the acute issues. Interviewees suggested that it may be more suitable to implement the recommendations when patients were in a non-acute setting.

"I think an outpatient setting or a GP setting is a more appropriate place to change a patient's long-term medications - that really you should be making changes when somebody is well". [Primary Researcher 7]

Timing of the intervention and location of the recommendations

Participants strongly felt that the timing of the intervention was a key factor affecting implementation; the recommendations were usually not provided at the time the patients' medications were being reviewed by the prescriber.

"…there was a disconnect between when I saw the report and when I saw the patient, which made it hard maybe to implement any changes that may have seemed reasonable". [Medical Prescriber 1]

The location of the report may also have been an important factor. Interviewees stated that prescribers simply may not have seen the recommendations and could easily go unnoticed in the medical notes or in an email inbox.

"*Well it could be because people didn't look at it…if the information doesn't get to them, they probably don't accept anything*…" [Medical Prescriber 10]

Many suggested that provision of the recommendations at the point of prescribing or integration of the recommendations with an electronic prescription record would increase their visibility and potentially increase their implementation rate.

Unfamiliar intervention in a busy environment

An additional issue identified was that many prescribers did not become familiar with the intervention as it was not ubiquitous for all older patients within the

hospital sites, which may have resulted in reduced engagement with the intervention. However, even when prescribers may have intended on reviewing or implementing the recommendations, they may not have found the time or simply forgot about the intervention due to several other work commitments.

> *"But I think I don't use it enough to immediately be able to read it through quickly which…when you're working under pressure and time constraints in a hospital - if something isn't easy and intuitive to read quickly in less than 30 seconds, you don't have time, you just move on".* [Medical Prescriber 8]

Theme 3 – Prescriber role and identity

Responsibility

Participants acknowledged that prescribers must take ownership of the medications prescribed for patients under their care in hospital. Whilst most prescribers were happy to review the SENATOR recommendations, some attending prescribers showed a reluctance to act on the recommendations in the hospital environment or to take sole responsibility for older patients' pharmacotherapy.

> *"…whose role it is to actually do it? At the moment, I'd say it's nobody's role. Nobody really takes it upon themselves, I would say, to actively review patients' medication like this".* [Primary Researcher 2]

Prescriber specialty and fear of encroachment

It was clear from the interviews that prescribers were much less comfortable in acting on recommendations that were outside their field of specialist knowledge. Interviewees stated that surgical prescribers were much less likely to implement the SENATOR recommendations than medical prescribers, as surgeons were concerned primarily on the acute surgical issue, with less focus given to the patient's chronic medications. Prescribers expressed reluctance in making changes that might encroach on other prescribers' decisions (e.g. the patient's GP or other hospital specialists).

> *"…for me personally, it's mainly if someone else started the medication, and they're going to follow up in that clinic, I'm much less likely to stop something that maybe is, that feels out of my specialty and is being followed up by another specialist…"* [Medical Prescriber 6]

Prescriber outlook toward research studies

It was highlighted that some prescribers who were more open-minded towards research studies were more likely to engage with the intervention and act on the recommendations, whilst others may have appeared less interested and were less likely to implement the recommendations.

> *"…there are clearly two groups – the doctors who are very enthusiastic and the doctors who think 'ugh just another study'…"* [Primary Researcher 6]

Prescriber experience and the need for a '*decision-maker*'

Interviewees recognised that junior prescribers may be more reluctant to change patients' medications than their more experienced colleagues. However, several participants felt that many junior prescribers have the knowledge and skills required to implement these recommendations, but lack the authority to adjust patients' medications without consulting a more senior colleague.

> *"When we discuss the recommendation with the junior doctors, they listen to our discussion, but they are not in a position to change the medication. They have to discuss with the senior person, either registrar or consultant".* [Primary Researcher 9]

Participants indicated that whilst prescriber experience may be influential, it was more important that the recommendations were reviewed by a '*decision-maker*' in the prescribing team, whereby participants most commonly considered the decision-maker to be a more senior prescriber.

> *"I think it's helpful, or more helpful, to speak with the senior doctor, who is a decision-maker. I think the senior person on a medical team would be more likely to implement changes".* [Primary Researcher 7]

Theme 4 – Patient-specific details

Acute status of the patient

Many interviewees recognised that the intervention patients were acutely unwell, and that prescribers were more likely to make prescription changes when patients were more stable. If, however, the recommendations were related to the reason for admission, then this would increase the likelihood that recommendations would be implemented. Prescribers stated that if the patient was not having any problems with certain medications, then it was unlikely that they would make any changes to these prescriptions.

> *"…so people, say, are on lots of stable medications come in with something completely different, I don't really feel that my role then is to meddle, muddy the waters. When people have come in with something that might be related to their medication, I think then yeah that's fine".* [Medical Prescriber 6]

Knowing the patient

Whilst some prescribers emphasised that they were happy to review the SENATOR recommendations as they knew about the patients under their care, interviewees also described that hospital prescribers were often reluctant to act on the recommendations as they did not know enough about these complex multimorbid patients (who were only recently admitted to hospital), or their pharmacotherapy.

> *"I don't know whether that's appropriate or not because I don't know what the decision was to put them on it in the first place".* [Surgical Prescriber 2]

Patient preference

Some interviewees stated that the patient's preference was a factor in whether the recommendations were implemented, and that patients would be resistant to deprescribing of certain medications:

> *"Of course, also patients' will. Like it always suggested to stop the sleep medication but most of the people we try to stop the sleeping medication, they will shoot you".* [Medical Prescriber 4]

3.5.2 Predominant TDF domains

Six domains were found to be predominant in influencing prescriber implementation of the SENATOR recommendations (**Table 3.3**), and these were pervasive in the four main themes depicted. Some of the supporting quotations may illustrate more than one TDF domain due to overlap between the constructs.

Table 3.3: Behavioural determinants affecting implementation of the SENATOR recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Environmental Context and Resources	Right setting?	*"It's the right place to do it, absolutely. Here we are starting a lot of new drugs. Here we have the possibility to monitor the response and the side effects".* [Medical Prescriber 12] *"If you're trying to do it in hospital, I think you're gonna get a lot of the problems we encountered where people don't have time to read through the reports".* [Primary Researcher 2]
	Timing of intervention	*"…if it was present right at the time where they're dealing with the patient, where they're focused on the patient, I think that could absolutely have improved uptake of the recommendations".* [Primary Researcher 7]
	Report location	*"If instead having it inside the history, it was…it appeared with the programme, with the prescription programme, because you have to use it - there's no other way, and probably they would pay more attention".* [Medical Prescriber 10]
Social/ Professional Role and Identity	Professional boundaries	*"It looks like instead of holistic treatment of the patient, each consultant is treating their part".* [Primary Researcher 9] *"They don't feel it's their place. They feel it's a GP's job so they don't want to get involved or they're not confident enough to get involved".* [Primary Researcher 4]
	Responsibility	*"Well I think it's my responsibility to do so as a doctor and I'm the one who has to decide which medicines I give to someone".* [Medical Prescriber 10]

Table 3.3 (continued): Behavioural determinants affecting implementation of the SENATOR recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Memory, Attention and Decision Processes	Cognitive overload	*"…if we could filter out the irrelevant or inappropriate recommendations, I think that the whole value of the report would go upwards very significantly. Because undoubtedly there is a fatigue as well when you get lots and lots of recommendations".* [Primary Researcher 7]
	Need for a '*decision-maker*'	*"I think it's probably more important that it's targeted at the actual decision maker".* [Surgical Prescriber 2]
	Memory	*"…it's all about reminders. I think people are well-intentioned, I think they just forget".* [Medical Prescriber 11]
Goals	Focus on other work commitments	*"…they were rushed, they were busy doing something else, and the recommendations that I would have highlighted to them would not have been seen as a priority, it would have been something that they would have come back to at a later stage".* [Primary Researcher 7]
	Priority is managing the acute issues of the patient	*"…when the patients are admitted in secondary care in hospital, the clinical team only deals with the acute problem. They are not interested in looking into the other medications…"* [Primary Researcher 9]
Intentions	Stability of intentions	*"I'm not gonna start interfering with somebody's medications unless there's a glaring danger in them or I see something that's absolutely contraindicated…"* [Surgical Prescriber 2]
	Intrinsic motivation	*"I think it depends on the person itself if they are open-minded for studies".* [Primary Researcher 1]

Table 3.3 (continued): Behavioural determinants affecting implementation of the SENATOR recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Knowledge	Prescriber knowledge	*"They have conditions that are out of my range of knowledge, and their treatment often…their treatment of one condition might collide with another condition that I'm not an expert in".* [Medical Prescriber 12]
	Knowing the patient	*"…they didn't have a complete picture of the patient when I discussed the recommendation. So, I'm thinking that also is one of the reasons why they don't adapt the change".* [Primary Researcher 9]

TDF: Theoretical Domains Framework GP: General practitioner

3.5.2 Suggestions for future interventions

Some suggestions made by interviewees for future interventions included:

- Having a pilot phase prior to full intervention rollout.
- Integrating the recommendations with electronic prescribing.
- Providing an informed rationale on how each recommendation was generated.
- Adjusting the algorithms to avoid unnecessary recommendations being produced.
- Streamlining the number of recommendations to focus on the most relevant PIP issues only.

3.6 Discussion

This study has generated a deeper understanding of the key factors that affected prescriber implementation of the computer-generated medication recommendations in the SENATOR RCT. Significantly, many of the SENATOR software-generated recommendations were considered of no clinical relevance or inappropriate for the individual patient during the acute care setting, and thus were unlikely to be implemented. The SENATOR intervention targeted a wide range of PIP instances on the basis of STOPP/START criteria version 2. Previous researchers have encountered difficulties computerising these criteria [263], which were not designed specifically to be put into computerised algorithms, and this may be a reason for the difficulty with routinely providing recommendations of high clinical relevance tailored for each patient. Pilot testing the SENATOR software intervention might have identified opportunities for software modification early on in order to reduce the number of irrelevant recommendations produced, as well as to overcome some of the issues identified with delivery of the recommendations to prescribers. Pilot testing did not take place in the SENATOR trial because of time constraints within the project that arose because of unforeseen difficulties with completion of the software construction and challenges with interfacing the software with the electronic case report form. By the time these issues were resolved, there was no time left within the project timeline in which pilot testing of SENATOR software-generated prescribing advice reports could be accommodated given the practical imperative to complete the substantive clinical trial.

The high proportion of irrelevant SENATOR recommendations may have overwhelmed prescribers and thereby incurred user fatigue with the intervention, such that clinically important recommendations may also have been ignored [264]. A recent systematic review indicated that computerised interventions which target fewer PIP instances in hospitalised older adults may have greater recommendation implementation rates than those targeting a wider range of PIP issues [251]. Future interventions of this kind may need to consider producing a smaller number of recommendations that are of high clinical relevance, which are tailored to the specific needs of individual patients in order to increase prescriber implementation rates and reduce PIP.

The acute hospital environment is well-known for being conducive to inappropriate prescribing [265, 266]. The timing of the SENATOR intervention seemed to be inconvenient for some hospital prescribers, who often had several other competing tasks as part of their busy workload. During the trial, prescribers were commonly informed of the recommendations being present in the patients' medical records at a time when they were not reviewing the patient. Whilst prescribers may have intended to examine the SENATOR recommendations, time constraints coupled with their workload may have distracted some prescribers from the intervention. Prescriber implementation rates may be improved if the recommendations are provided simultaneously with the act of prescribing [70]. Although enhancing the environment in which prescribers work is not a simple undertaking, the incorporation of this type of medication optimisation intervention with hospital electronic prescribing systems may aid integration into prescribers' workflow and

facilitate review of the prescribing recommendations [267, 268]. Equally, it may be useful to evaluate if there is increased implementation of these recommendations in other care settings, where patients are more stable, and to further assess if there is a greater impact on patient outcomes.

Whilst computerised interventions are often assumed to provide solutions to minimising inappropriate prescribing, this study corroborates previous findings which show that simply providing computer-generated recommendations does not guarantee their uptake [269, 270]. In the present study, even when the computerised output was accurate, and the clinically relevant SENATOR recommendations were reviewed by prescribers, they were still not always implemented. These findings have highlighted the importance of targeting interventions like this at the decision-makers on the prescribing team as one way to increase the likelihood of recommendation uptake [271]. Prescriber inertia was notably pervasive in the interviews, and was previously found to be the predominant reason for non-implementation of computer-generated guideline-based recommendations in a primary care study [272]. This inertia may be due to fear of negative consequences of changing therapy [273], with a particular reluctance to make prescribing changes outside of one's own specialty [274]. More education and training on geriatric pharmacotherapy is therefore required at both undergraduate and postgraduate levels to reduce this prescriber inertia and to make all prescribers more confident in routinely optimising older adults' pharmacotherapy [111].

Participants recognised that patients' own beliefs also influenced the implementation of the SENATOR recommendations, particularly as some patients preferred to continue taking certain medicines that may be considered '*potentially inappropriate*'. More patient education may be required as previous trials have shown that it can be a significant facilitator in discontinuing PIMs in older adults [275, 276]. Moreover, being highly familiar with the patient's clinical details was considered an important promoter in prescribers acting on the SENATOR recommendations. Hospital prescribers stated that they often know much less about the patients, their comorbidities, or their established pharmacotherapy compared to the GP or other hospital specialists [277, 278]. However, there is evidence that GPs frequently do not receive information on the specific indications of hospital-initiated medications [279], emphasising the need for better information exchange, particularly at care transitions points, to facilitate informed prescriber decisions for older adults in all care settings.

It has already been established above that the person who receives the prescribing recommendations is a significant factor affecting implementation (e.g. based on their level of seniority). However, the person who delivers the prescribing recommendations may also be a factor. A recent study has demonstrated that the type of healthcare professional providing STOPP/START recommendations and the approach taken by that person may substantially influence prescriber implementation rates [280]. Hierarchical differences were implicit in the comments from primary researchers in this study, as they suggested that physician prescribers may have appeared less interested in reviewing the recommendations if they were

not provided by a fellow physician. Future interventions must consider the importance of the particular healthcare professional that provides these types of recommendations, and to balance this against other factors such as cost.

Ultimately, the SENATOR trial demonstrated a negative result for its primary outcome, i.e. no significant difference in the proportion of patients experiencing a non-trivial in-hospital ADR between the intervention and control groups, probably attributable to a low implementation rate of the computer-generated STOPP/START recommendations [281]. When complex interventions produce negative results, as in the SENATOR trial, one may reasonably question if the intervention is inherently ineffective, whether it was improperly employed, or applied in an unsuitable clinical context [282]. Qualitative studies are increasingly advocated in such circumstances as they can draw upon the experiences of those involved with the trial to enable a better understanding of the quantitative results [283]. Although this qualitative study was not used to adjust the SENATOR intervention, it should help inform the design of future interventions of a similar kind. Coordinators of future RCTs with complex interventions should strongly consider the inclusion of parallel qualitative study components, with integration of these findings along with the main trial results.

3.6.1 Strengths and limitations

A robust theoretical framework was used to structure the topic guides, with inductive and deductive approaches both used in data analysis. It has been shown that TDF-based interviews elicit additional themes from participants that would not otherwise be reported compared to studies without a theoretical basis [284, 285].

The relevance of these findings is reinforced by the sampling of participants from six hospitals across Europe. The emergence of common themes from a wide spread of geographical locations enhances the transferability of the findings. Furthermore, all interviews were conducted by the same researcher across all sites, allowing for consistency in both data collection and analysis.

However, a limitation to this study is that the number of eligible interviewees from each site was limited to those who were proficient in English. As it was not the first language of some interviewees, this may have impeded their potential to fully express their exact views. Additionally, the responsibility of selecting prescribers to participate in this study was largely assigned to members of the SENATOR research teams at each site. This delegation of duties, coupled with busy work schedules, may be the main reasons for the small sample size of surgical prescribers interviewed.

Finally, one interview was conducted face to face via Skype®; however, this was not perceived to be an issue as the interviewer had previously built a rapport with this primary researcher in person at a trial meeting. Skype® has been shown to be a viable research medium to conduct semi-structured interviews, and could be considered for future qualitative studies alongside multi-centre RCTs where geographical proximity may be an issue in conducting interviews in person [286, 287].

3.7 Conclusion

This study clearly demonstrates the value of qualitative evaluation methods in assessing the delivery of complex interventions within RCTs. The findings highlight the difficulties associated with optimising prescribing in hospitalised older adults, and that a multifaceted approach will be required to tackle these issues. The key factors affecting prescriber implementation of computer-generated medication recommendations in the SENATOR RCT have been identified across six European acute hospital sites. As with previous research, these results suggest that prescribers generally welcome computerised interventions, such as SENATOR, in the hospital setting as an aid to prescribing in complex multimorbid older adults [288]. Whilst future researchers must endeavour to improve the clinical relevance of these computer-generated medication recommendations, it is also important that they identify the most appropriate person to receive the recommendations, the best time for the intervention to occur, and to develop a greater understanding on how to best integrate these types of interventions into current healthcare systems.

Chapter 4: Computer-generated STOPP/START recommendations for hospitalised older adults: evaluation of the relationship between clinical relevance and rate of implementation in the SENATOR trial

4.1 Chapter description

In Chapter 3, one of the key factors perceived to affect prescriber implementation of the computer-generated STOPP/START recommendations in the SENATOR trial was the clinical relevance of the recommendations. In this chapter, in order to further substantiate the qualitative findings of Chapter 3, I systematically evaluate the clinical relevance of the computer-generated STOPP/START recommendations using a validated scale from the literature. In addition, I investigate if the adjudicated degree of clinical relevance of the recommendations was associated with their implementation.

The work of this chapter has been accepted in Age and Ageing, subject to revisions.

4.2 Abstract

4.2.1 Introduction

Findings from a qualitative study conducted alongside the SENATOR randomised controlled trial indicate that the perceived clinical relevance of computer-generated STOPP/START recommendations was a key factor affecting their implementation by physician prescribers caring for hospitalised older adults in the trial. The aim of the present study was to systematically evaluate the clinical relevance of these recommendations and to establish if clinical relevance significantly affected the implementation rate.

4.2.2 Methods

A pharmacist-physician pair retrospectively reviewed the case records for all SENATOR trial intervention patients at Cork University Hospital, the trial's lead recruitment site, and assigned a degree of clinical relevance for each STOPP/START recommendation based on a previously validated six-point scale. The chi-square test was used to quantify the differences in prescriber implementation rates between recommendations of varying clinical relevance, with statistical significance set at $p < 0.05$.

4.2.3 Results

In 204 intervention patients, the SENATOR software produced 925 STOPP/START recommendations. Nearly three quarters of recommendations were judged to be clinically relevant (73.6%), whilst the remainder were judged to be of '*no clinical relevance*' (21.5%) or of potential '*adverse significance*' if implemented (4.9%).

However, nearly half of the clinically relevant recommendations were judged to be of '*possibly low relevance*' (320/681; 47%). Recommendations considered to be of higher clinical relevance were significantly more likely to be implemented than those of lower clinical relevance ($p < 0.05$).

4.2.4 Conclusion

A large proportion (61%) of the computer-generated STOPP/START recommendations provided were either of potential '*adverse significance*', of '*no clinical relevance*', or of '*possibly low relevance*'. The adjudicated clinical relevance of computer-generated medication recommendations significantly affects their implementation. Meticulous software refinement is required for future interventions of this type to increase the proportion of recommendations that are of high clinical relevance. This should facilitate their implementation, resulting in prescribing optimisation and improved clinical outcomes for multimorbid older adults.

4.3 Introduction

The prescriber implementation rates of computer-generated recommendations to reduce PIP in hospitalised older adults have been found to range from 29.3% – 95% [251]. However, limited research has been conducted to identify the intervention components which significantly affect implementation. When the interim analysis from the SENATOR trial revealed that prescriber implementation was lower than anticipated, a qualitative study was conducted to explore possible reasons for non-implementation, as described in Chapter 3. The interview participants perceived that one of the key factors affecting implementation was the clinical relevance of the computer-generated recommendations, and they indicated that the SENATOR software was producing a high proportion of recommendations that were of low or doubtful clinical relevance for individual patients.

However, rather than simply accepting these qualitative findings at face value, it would be of great significance to quantitatively corroborate a clear association between the relevance of recommendations and their rate of implementation. Therefore, the aim of this study was to systematically evaluate the clinical relevance of the computer-generated STOPP/START recommendations in the SENATOR trial and examine if the relevance of recommendations was associated with their rate of implementation.

4.4 Methods

4.4.1 Context and study setting

The SENATOR RCT was conducted in six large acute teaching hospitals in six European countries. All patients recruited were multimorbid older adults (≥ 65 years) who consented to their enrolment in the trial within 60 hours of hospital admission, who were prescribed medications for ≥ 3 active chronic medical disorders, and who had an expected length of hospital stay > 48 hours. More details on patient eligibility criteria and other pertinent trial information are published elsewhere [202].

This study evaluating the clinical relevance of SENATOR's STOPP/START recommendations was conducted in the RCT's lead recruitment site only, Cork University Hospital – an 810-bed tertiary referral centre within the Munster province of the Republic of Ireland. All patients who were randomised to the intervention arm at this site were included in the present study. In Cork University Hospital, the SENATOR software generated a paper-based report detailing the STOPP/START recommendations, which was provided in each intervention patient's paper-based clinical record, and was also sent via email to the consultant with responsibility for clinical care of the patient (sample report provided in **Appendix 10**). Of the 114 STOPP/START criteria (version 2), recommendations based on 3 criteria were excluded from the analysis: STOPP A1, START I1, and START I2, with reasons for exclusion provided in **Appendix 12**.

4.4.2 Data collection

A pharmacist and physician independently and retrospectively reviewed all intervention arm patients' medical records, drug chart, laboratory test results, and STOPP/START recommendations. Through consensus agreement, the pharmacist-physician pair then assigned a degree of clinical relevance for each STOPP/START recommendation based on a previously validated six-point scale with the following categories: 0: '*adverse significance*', 1: '*no clinical relevance*', 2: '*possibly low relevance*', 3: '*possibly important relevance*', 4: '*possibly very important relevance*', and 5: '*possibly life-saving*' [289]. The pharmacist (KD) and physician (DC) were very familiar with the STOPP/START criteria and SENATOR's computerised algorithms, and, at the time of the reviews, had three years and ten years post-qualification experience respectively in optimising the pharmacotherapy of hospitalised older adults.

Inter-rater reliability (IRR) was determined among a sample of three pharmacists and three physicians (one consultant geriatrician, and two specialist registrars in geriatric medicine) in applying the scale to independently assign a degree of clinical relevance to STOPP/START recommendations from twenty randomly-selected intervention cases, each with at least three STOPP/START recommendations. The study design for this IRR assessment is provided in **Appendix 13**, with the standardised intervention case format provided in **Appendix 14**.

4.4.3 Data analysis

Statistical analysis was performed using SPSS® Version 22 and Microsoft® Excel. Data on prescriber implementation were extracted from the RCT's electronic case report form, whereby implementation was defined as the prescriber discontinuing or initiating a medication in accordance with the recommendation at any point prior to hospital discharge. The percentage prescriber implementation rates were calculated for recommendations at each degree of clinical relevance. The chi-square test was used to determine if there were any significant differences between i) the proportion of recommendations and ii) the prescriber implementation rates of recommendations at varying degrees of clinical relevance, with differences considered statistically significant at $p < 0.05$.

In the assessment of IRR, the Fleiss kappa statistic was used to determine the agreement between all raters and across the subgroups of raters (i.e. pharmacists and physicians). Cohen's kappa statistic was used to determine the level of agreement between the individual raters. The kappa statistic was interpreted according to the following ranges: slight if 0.01 – 0.2, fair if 0.21 – 0.4, moderate if 0.41 – 0.6, substantial if 0.61 – 0.8, and almost perfect if 0.81 – 0.99 [290].

4.5 Results

In Cork University Hospital, there were 204 SENATOR intervention patients (51% male), with a mean age of 77.4 years (standard deviation [SD] 6.91; range 65 – 92). In total, the SENATOR software generated 925 STOPP/START recommendations

(mean 4.5/patient; SD 2.9; range 0 – 17), which included 563 STOPP recommendations (mean 2.8/patient; SD 2.3; range 0 – 13), and 362 START recommendations (mean 1.8/patient; SD 1.5; range 0 – 7).

4.5.1 Clinical relevance evaluation

Almost three quarters (73.6%) of recommendations were deemed to be clinically relevant, i.e. assigned to categories 2, 3, or 4 – '*possibly low relevance*', '*possibly important relevance*', or '*possibly very important relevance*' (**Table 4.1**). The remaining 26.4% of recommendations were either category 1, i.e. of '*no clinical relevance*' (21.5%), or category 0, i.e. of possible '*adverse significance*' to the patient if implemented (4.9%). No recommendations were judged to be '*possibly life-saving*'.

When comparing the clinical relevance of STOPP and START recommendations in **Table 4.2**, there was a statistically significantly greater proportion of START recommendations i) of possible '*adverse significance*' (7.2% versus 3.4%; $p < 0.05$), and ii) of '*possibly very important relevance*' (12.2% versus 5.7%; $p < 0.05$). Conversely, there was a statistically significantly greater proportion of STOPP recommendations of '*possibly low relevance*' (37.7% versus 29.8%; $p < 0.05$).

Of the possible 79 STOPP and 32 START rules that were included in this study, 49 different STOPP recommendations and 24 different START recommendations triggered respectively. The clinical relevance of the recommendations based on the individual STOPP and START criteria, as well as the drug classes that were the basis for these recommendations, are displayed in **Appendix 15** and **Appendix 16**.

Table 4.1: Prescriber implementation rates of recommendations categorised according to their degree of clinical relevance

Degree of clinical relevance	0 - Adverse significance	1 - No clinical relevance	2 - Possibly low relevance	3 - Possibly important relevance	4 - Possibly very important relevance	5 - Possibly life-saving
Number of recommendations (% total)	45 (4.9%)	199 (21.5%)	320 (34.6%)	285 (30.8%)	76 (8.2%)	0 (0%)
Prescriber Implementation* (% implemented)	3/45 (6.7%)	20/171 (11.7%)	60/319 (18.8%)	119/273 (43.6%)	53/76 (69.7%)	-
Difference in implementation†	0 versus 2,3,4: $p < 0.05$‡	1 versus 2,3,4: $p < 0.05$‡	2 versus 0,1,3,4: $p < 0.05$	3 versus 0,1,2,4: $p < 0.05$	4 versus 0,1,2,3: $p < 0.05$	-
Most common type of STOPP/START recommendation within the category	START A3: *Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.* (n = 22; 48.9%)	STOPP J3: *ß-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).* (n = 40; 20.1%)	STOPP A2: *Any drug prescribed beyond the recommended duration, where treatment duration is well defined.* (n = 104; 32.5%)	START A6: *Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease.* (n = 24; 8.4%)	START A1: *Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.* (n = 13; 17.1%)	-
Possible reason for assigning this degree of relevance:	Recommendation to start an antiplatelet but patient already prescribed an anticoagulant – increased risk of bleeding.	Recommendation triggered for all diabetic patients prescribed β-blockers. Patient not presenting with frequent hypoglycaemic episodes – thus, not relevant.	Recommendation to stop long-term high-dose PPI. Not of high clinical relevance in a patient who may have a more serious acute issue to be dealt with.	Recommendation may be possibly important in reducing the risk of cardiovascular events in those with coronary artery disease.	Recommendation to start an anticoagulant in a patient with atrial fibrillation may be possibly very important in the prevention of future stroke.	

* Includes all recommendations with data available regarding prescriber † Difference in prescriber implementation rates between categories of clinical relevance; statistically significant difference observed where $p < 0.05$

‡ No statistically significant difference observed between the implementation rates of recommendations of potential 'adverse significance' (category 0) and recommendations of 'no clinical relevance' (category 1).

Table 4.2: Clinical relevance of total STOPP and total START recommendations

Category	0 - Adverse significance	1 - No clinical relevance	2 - Possibly low relevance	3 - Possibly important relevance	4 - Possibly very important relevance	Total
STOPP Recommendations (% Total STOPP)	19 (3.4%)	129 (22.9%)	212 (37.7%)	171 (30.4%)	32 (5.7%)	563
START Recommendations (% Total START)	26 (7.2%)	70 (19.3%)	108 (29.8%)	114 (31.5%)	44 (12.2%)	362
STOPP/START Recommendations (% Total STOPP/START)	45 (4.9 %)	199 (21.5%)	320 (34.6%)	285 (30.8%)	76 (8.2%)	925
Difference between proportion of START and STOPP at different categories of relevance*	$p = 0.0086$	$p = 0.1964$	$p = 0.0147$	$p = 0.7191$	$p = 0.0005$	-

* Statistically significant difference where $p < 0.05$

4.5.2 Prescriber implementation rates

Data on prescriber implementation were obtained for 884/925 (95.6%) recommendations. Data was unavailable for the following recommendations:

i) all STOPP A3 recommendations, which were later removed from the intervention (n = 20),
ii) two patients without implementation data in the electronic case report form (n = 15),
iii) all START B3 recommendations, as there were no data on oxygen prescribing (n = 5), and
iv) one STOPP N recommendation that triggered inappropriately (n = 1).

Table 4.1 illustrates the prescriber implementation rates for the recommendations according to each assigned category of clinical relevance. As the clinical relevance of recommendations increases, so too does the implementation rate, with statistically significant differences in implementation rates between recommendations of all categories identified ($p < 0.05$), the only exception being between recommendations of potential adverse significance and recommendations of no clinical relevance (6.7% versus 11.7%; $p = 0.33$).

4.5.3 Inter-rater reliability (IRR) results

When assessing IRR in choosing the same degree of clinical relevance for recommendations, the Fleiss kappa coefficient was found to be fair (0.24). Kappa was higher among pharmacists (0.27) than among physicians (0.17). The mean

Cohen's kappa coefficient between individual raters was also found to be fair (kappa = 0.24).

4.6 Discussion

This is the first study to evaluate the clinical relevance of computer-generated STOPP/START recommendations. The key finding is that increasing clinical relevance of recommendations associated with significantly higher implementation rates by prescribers. The results from this sample of acutely ill hospitalised multimorbid older patients show that nearly three quarters of STOPP/START recommendations were deemed to be clinically relevant (73.6%), whilst approximately one quarter of the recommendations were of no clinical relevance or of potential adverse significance (26.4%). Although most STOPP/START recommendations were deemed clinically relevant, it is acknowledged that nearly half of the clinically relevant recommendations were deemed to have '*possibly low relevance*', i.e. category 2 on the six-point clinical relevance scale (320/681; 47%). Whilst these recommendations were correctly triggered by the SENATOR software, they may have been addressing issues that were of minor significance at the time of hospital admission, when the focus may have been on the patient's acute illness. For example, nearly half of all benzodiazepine-related recommendations were judged to be of possibly low relevance. Although it is well-known that this drug class is a common contributing factor to ADRs (principally falls) in older adults [291], deprescribing benzodiazepines may not have been a priority at the time the recommendations were provided. Recommendations like these may have been

more clinically relevant later in the admission (such as pre-discharge), or in another setting (such as primary care or ambulatory care), where the patient may have been more stable, and it may have been easier to implement medication changes. Thus, the care setting and timing of the intervention must be key considerations for future studies.

The proportion of clinically relevant computer-generated recommendations can vary widely depending on the healthcare setting and the medications targeted [292-295]. However, there are few studies in the literature that have evaluated the clinical relevance of computer-generated recommendations concerning medication appropriateness in hospitalised older adults. One research group has previously reported findings similar to this in a pilot study, with 74.5% of computerised alerts deemed clinically relevant [293]. However, when medication alerts in one of their subsequent studies were based on a broader set of Beers criteria [296], it was found that only 30% of the alerts were clinically relevant in the intervention group [294]. In contrast, the present study has shown that the STOPP/START version 2 recommendations, i.e. another broad set of criteria, had a substantially higher proportion of clinically relevant recommendations.

Many of these previous studies have simply judged the computer-generated recommendations in a dichotomous manner - clinically relevant or not clinically relevant [293-295]. However, in the present study, it was considered important to transcend this and qualify clinical relevance in a more nuanced fashion, i.e. to assess the degree of clinical relevance, by applying a defined scale. Beaudoin *et al*. used a five-point Likert scale, ranging from 1 (not relevant) to 5 (very relevant), to

evaluate the clinical relevance of computerised rule-based alerts concerning antimicrobials [297]; however, a limitation to this Likert scale is that it does not explicitly consider the possibility that the recommendations may be potentially inappropriate, and thereby have the potential to cause harm to the patient. The scale chosen for use in this study had been previously employed to assess the clinical relevance of pharmacist recommendations in a Belgian hospital, which found low agreement between evaluators (range of kappa values: 0.15 – 0.25) [289]. Similar agreement was found between the raters in this study (kappa = 0.24). Furthermore, Bech *et al*. found only slight agreement between raters when assessing the clinical relevance of drug-related problems among older patients using a five-point scale [298]. This lack of agreement among healthcare professionals in evaluating clinical relevance highlights the complexities associated with selection of appropriate pharmacotherapy in older adults [70].

This study is important in that it was not merely indicated whether the recommendations were relevant or not, but rather their degree of clinical relevance was also qualified. If it is known that recommendations pertaining to certain criteria or particular drug classes are more likely to be clinically relevant, then one can prioritise these recommendations in future interventions. For example, in a hospitalised patient presenting with falls, the software should prioritise recommendations relating to deprescribing of benzodiazepines over those relating to proton pump inhibitors (PPIs). Provision of the most clinically relevant recommendations only, or ensuring that these recommendations appear as priorities, should help reduce the phenomenon of '*alert fatigue*' [194]. However,

designing the software to take account of competing influences on clinical decision making, and ranking the recommendations in order of priority is a significant technical challenge [299]. This study has provided evidence on which recommendations may be more clinically relevant than others, and thus may inform ranking systems within future computerised algorithms.

The present study corroborates the findings from the contemporaneous SENATOR qualitative study, which indicated that the clinical relevance of the computer-generated STOPP/START recommendations was a key influence on their implementation by prescribers [300]. These results show a clear association between these two factors – recommendations of higher clinical relevance had a greater probability of being implemented by prescribers. Previous research has shown that computer-generated recommendations that were inappropriate or erroneously triggered were unlikely to be adopted by physicians or were overridden within the software programme [301]. However, the potential risk remains that some users may blindly follow inappropriate recommendations; this increases the risk of error and possible patient harm [302, 303].

The results showed that a significantly greater proportion of START recommendations were either of '*possibly very important relevance*' or of possible '*adverse significance*' in comparison to STOPP recommendations. Thus, certain START recommendations had the potential to be of great benefit in some patients, but could have caused serious harm if implemented in other patients. This indicates a lack of specificity in the computerised algorithms, resulting in the identification of more supposed instances of PIP than actual instances [304]. However, this lack of

specificity is not purely an algorithm issue – it could also have originated from the criteria themselves. For example, previous research has highlighted that some of the STOPP/START criteria contain broad definitions, e.g. START A3 criterion (version 2) refers to "*…a documented history of coronary, cerebral or peripheral vascular disease*". Whilst this phrasing allows the criteria to be applicable to a large proportion of older adults, broad definitions such as this are more susceptible to clinician interpretation [193]. Thus, some criteria may not be as explicit as they should be for the purposes of designing computerised algorithms, and previous research groups have outlined some of the complexities encountered in this process [193, 263, 305]. Further iterations of STOPP/START criteria will likely need to be much more specific, especially if the intention is to incorporate them into computerised algorithms, which should facilitate the production of more clinically relevant recommendations that are tailored to individual patients.

However, simply producing clinically relevant STOPP/START recommendations does not guarantee their uptake; the medium through which the recommendations are delivered to prescribers also significantly affects their implementation [280]. In the present study, it was found that even the recommendations deemed to have possibly very important relevance were not implemented 30% of the time. One reason for this may have been due to the production of a high proportion of recommendations that were of potential adverse significance, not clinically relevant, or of low clinical relevance (61% of recommendations). These may, unwittingly, have undermined the trustworthiness of the SENATOR advice reports, and resulted in decreased engagement by clinicians with the most important

recommendations [300]. Increasing the proportion of recommendations of higher clinical relevance will be essential in minimising user fatigue with future computerised interventions, and enhancing the likelihood of clinically important recommendations being implemented.

As with many studies of this type, they are limited by their retrospective design, and the subjectivity of raters must be considered as a potential source of bias. This is the first study that the authors are aware of which determines the IRR among healthcare professionals in evaluating the clinical relevance of computer-generated STOPP/START recommendations. However, failure to achieve high IRR may have been due to the scale used; it has been previously shown that rating scales with poor IRR are likely to result in low estimates of IRR in subsequent studies [306]. Furthermore, a scale with fewer categories or more specific categories would allow less room for discrepancy between raters, and should produce a higher IRR kappa value. Agreement may have been affected by raters simply interpreting the scale differently [307]. Future IRR studies using this scale could consider the use of weighted kappa, using a robust method to determine appropriate weights prior to data collection.

4.7 Conclusion

This study quantifiably substantiates the findings from a recent qualitative study, which suggested that the clinical relevance of the STOPP/START recommendations in the SENATOR intervention was one of the key influences affecting their implementation. The present study shows that a large proportion (61%) of the STOPP/START recommendations provided were either of potentially adverse significance, irrelevant, or of low clinical relevance for the individual patients at the point of hospital admission. Recommendations of higher clinical relevance had significantly enhanced prescriber implementation rates. This study has also indicated the types of recommendations, based on the different physiological systems and drug classes, which are more likely to be of high clinical relevance; these findings may aid in the ranking of medication recommendations in future research. Future computerised interventions aimed at medication optimisation in multimorbid older adults must be meticulously designed to provide tailored advice specific to individual patients' pharmacotherapy, thereby minimising the number of recommendations that are irrelevant or of low clinical relevance. Achieving greater proportions of recommendations that are of high clinical relevance should facilitate implementation by prescribers, resulting in the resolution of PIP issues and improved clinical outcomes for older adults.

Chapter 5: Prescriber implementation of STOPP/START recommendations for hospitalised older adults: a comparison of a pharmacist approach and a physician approach

5.1 Chapter description

In Chapter 4, I evaluated the clinical relevance of computer-generated medication appropriateness recommendations, and the findings showed that clinical relevance was a significant factor affecting their implementation by prescribers in the SENATOR trial. However, medication appropriateness recommendations provided by a healthcare professional, such as a pharmacist or physician, are likely to be clinically relevant. Whilst the degree of relevance may still influence implementation, it is likely that there are other factors at play.

In this chapter, I compare the prescriber implementation rates of STOPP/START recommendations from similar pharmacist and physician interventions to help identify factors affecting prescriber implementation of medication appropriateness recommendations in the hospital setting, which could then be explored in depth using qualitative research methods in future.

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5.2 Abstract

5.2.1 Introduction

Two RCTs conducted simultaneously in the same acute university teaching hospital in the Republic of Ireland have shown that provision of recommendations based on STOPP/START criteria to attending prescribers can reduce in-hospital ADRs in older adults (≥ 65 years). One of the RCT interventions was conducted by a physician and the other by a pharmacist. The aims of the present study were to compare the prescriber implementation rates of STOPP/START recommendations between the physician approach and the pharmacist approach in these two RCTs and to provide a narrative summary of the comparable clinical outcomes.

5.2.2 Methods

Data were extracted from the two RCT published papers and their associated computerised databases to calculate the percentage prescriber implementation rates for the STOPP/START recommendations. The chi-square test was used to quantify the differences in prescriber implementation rates, with differences considered statistically significant where $p < 0.05$.

5.2.3 Results

Prescriber implementation rates of the STOPP and START recommendations made by the physician were 81.2% and 87.4% respectively, significantly higher than those made by the pharmacist (39.2% and 29.5% respectively), $p < 0.0001$. A greater absolute risk reduction in patients with ADRs was shown with the physician's intervention compared to the pharmacist's intervention (9.3% versus 6.8%).

5.2.4 Conclusion

This study shows that the methods of communication and the medium through which the STOPP/START recommendations are delivered significantly affect their implementation. Non-implementation of some pharmacist-delivered recommendations may be contributing to preventable ADRs in older adults. Thus, future research should aim to identify the factors influencing prescriber implementation of pharmacist recommendations in order to inform the design of more effective pharmacist interventions in optimising older patients' pharmacotherapy.

5.3 Introduction

The STOPP and START criteria are well recognised tools for aiding identification of PIP in older adults, and have been utilised in a range of healthcare settings worldwide [88, 308]. Used in tandem, the criteria can be routinely applied to older patients' pharmacotherapy and concurrent diagnoses to identify PIMs (via STOPP criteria) and PPOs (via START criteria). Studies deploying these criteria as part of the intervention routinely result in improvements in medication appropriateness [146, 174]. Two RCTs conducted in the same large acute university teaching hospital in the Republic of Ireland demonstrated a clinically significant absolute risk reduction in incident ADRs in multimorbid older adults arising from physician-delivered and pharmacist-delivered pharmacotherapy recommendations to attending prescribers [147, 148]. Both RCTs included the primary researcher (physician or pharmacist) providing recommendations based on STOPP/START criteria version 1 (**Appendix 17**) [7] to attending physician prescribers caring for hospitalised older adults.

The primary aim of the present study was to compare the prescriber implementation rates of STOPP and START recommendations from these two RCTs conducted simultaneously in the same Irish university teaching hospital, where the recommendations were delivered by a physician in one trial and by a pharmacist in the other trial [147, 148]. Secondary aims were to identify components within the interventions that may have affected prescriber implementation, to compare the prescriber implementation of the pharmacist's STOPP/START recommendations with other pharmacist-delivered recommendations, and to provide a narrative summary of comparable clinical outcomes in the two RCTs.

5.4 Methods

5.4.1 Study setting and intervention details

Both RCTs were conducted in Cork University Hospital, an 810-bed tertiary referral centre in the Munster province of the Republic of Ireland. Participants were enrolled within 48 hours of their presentation to hospital with acute illness. The interventions in both RCTs primarily aimed to reduce non-trivial in-hospital ADRs in older adults (≥ 65 years), and are briefly summarised below.

In both RCTs [147, 148], the primary researcher applied the STOPP/START criteria (version 1) [7] at a single time point to the medication list of intervention patients within 48 hours of hospital admission, and placed a printed report in the patient's clinical records with STOPP/START-based recommendations. The primary researcher in each trial verbally notified the attending prescribers of the recommendations and answered any clarifying questions that they may have had.

In RCT 1, the physician verbally notified the attending prescribers of the STOPP/START-based recommendations for all patients [148]; in RCT 2, the pharmacist verbally notified the attending prescribers of the recommendations for approximately one third of patients, but provided mobile phone contact details on the printed report in case prescribers wanted verbal clarification on the pharmacist's advice [147]. In RCT 2, the pharmacist's STOPP/START-based recommendations were provided in conjunction with recommendations based on other medication appropriateness issues, i.e. including drug-drug interactions, need for renal and hepatic dose adjustments, and other PIP instances identified utilising

Beers criteria (version 3) [309] and PRISCUS criteria [156], as well as issues based on medication reconciliation, which has been defined as the "*process of identifying the most accurate list of all medications a patient is taking - including name, dosage, frequency, and route - and using this list to provide correct medications for patients anywhere within the health care system*" and "*involves comparing the patient's current list of medications against the physician's admission, transfer, and/or discharge orders*" [310]. The medication reconciliation issues in RCT 2 were primarily due to medications omitted and incorrect doses prescribed on admission [169]. In RCT 1, the physician was a specialist registrar (i.e. senior resident) in geriatric medicine with 3 years of specialist clinical experience [148]. In RCT 2, the pharmacist was fully registered with 4 years of postgraduate experience in providing pharmaceutical care to older adults.

Both trials used a cluster randomised design. In each RCT, two lists of attending consultant prescribers were created such that the combined rates of ADRs in these groups were known to be comparable from previous work undertaken by this group [85]. Having finalised the lists, one group of attending consultant prescribers was assigned as the intervention arm of the study and the other was assigned as the control arm. The intervention clusters in both RCT 1 and RCT 2 included individuals admitted under the care of specialists in cardiology, respiratory medicine, endocrinology, renal medicine, and orthopaedics. The intervention cluster in RCT 1 also consisted of patients admitted under the care of specialists in radiation oncology, whilst the intervention cluster in RCT 2 also included patients admitted under the care of specialists in rheumatology, general and vascular surgery, and

general internal medicine. To avoid potentially biased enrolment of patients into either arm of the study, the primary researcher in each RCT approached prospective trial participants in the order of their admission to the hospital's emergency department to assess their eligibility for the trial. RCT 1 was conducted from May 2011 to May 2012. RCT 2 was conducted from June 2011 to July 2012. No patient in either RCT received the intervention from the other RCT. Patients in the intervention and control groups in both RCTs received standard medical and pharmaceutical care from physicians and pharmacists who routinely work in the hospital. Implementation of recommendations was assessed by the primary researcher at day 7 – 10 or at the point of hospital discharge (whichever came first). Further details (e.g. such as study design and patient characteristics) can be found in the published papers describing these RCTs [147, 148, 169].

5.4.2 Data extraction and analysis

As part of this secondary data analysis, data were extracted from the papers based on the RCTs [147, 148, 169], and their associated computerised databases, stored locally in Microsoft® Access. The percentage prescriber implementation rates for the STOPP and START recommendations were calculated for both RCTs. The chi-square test was used to compare the prescriber implementation rates of the STOPP and START recommendations in the pharmacist and physician intervention groups, as well as to quantify any differences between the implementation of STOPP/START recommendations and other recommendations included in the pharmacist's intervention. Differences were considered statistically significant where $p < 0.05$.

5.5 Results

5.5.1 Prescriber implementation of STOPP and START recommendations

Tables 5.1 and 5.2 show the prescriber implementation rates of STOPP and START recommendations from the physician and pharmacist respectively, divided according to the relevant physiological systems.

In 360 intervention patients in RCT 1, the physician made 292 STOPP recommendations (0.81/patient) and 159 START recommendations (0.44/patient), i.e. a total of 1.25 STOPP/START recommendations per patient. Attending prescribers implemented 237 of the physician's 292 STOPP recommendations (81.2%) and 139 of the physician's 159 START recommendations (87.4%). In 361 intervention patients in RCT 2, the pharmacist made 255 STOPP recommendations (0.71/patient), and 44 START recommendations (0.12/patient), i.e. a total of 0.83 STOPP/START recommendations per patient. Attending prescribers implemented 100 of the pharmacist's 255 STOPP recommendations (39.2%) and 13 of the pharmacist's 44 START recommendations (29.5%).

Table 5.1: Prescriber implementation rates for STOPP recommendations: physician versus pharmacist

STOPP criteria	Physician	Pharmacist	*p*-value
Cardiovascular System	**22/26 (84.6%)**	**14/26 (53.9%)**	**0.0162***
Digoxin at a long-term dose > 125µg per day with impaired renal function	1/1	-	
Loop diuretic for dependent ankle oedema only	4/6	1/2	
Loop diuretic as first-line monotherapy for hypertension	4/4	0/1	
Non-cardioselective β-blocker with COPD or asthma	9/9	2/7	
β-blocker in combination with verapamil	1/1	-	
Calcium channel blockers with chronic constipation	2/4	9/11	
Use of aspirin and warfarin in combination without histamine H_2 receptor antagonist or PPI (high risk of gastrointestinal bleeding)	-	1/4	
Aspirin at dose > 150mg day	-	1/1	
Aspirin without coronary, cerebral, or peripheral arterial symptoms or occlusive arterial event	1/1	-	
Central Nervous System	**37/46 (80.4%)**	**15/33 (45.5%)**	**0.0012***
Tricyclic antidepressants with dementia	3/3	-	
Tricyclic antidepressants with glaucoma	1/1	-	
Tricyclic antidepressants in chronic constipation	3/3	3/4	
Tricyclic antidepressants in combination with an opiate or calcium channel blocker	1/1	6/8	
Long-term (> 1 month) use of long-acting benzodiazepines	16/25	4/16	
Long-term (> 1 month) use of neuroleptics as hypnotics	4/4	-	
Long-term (> 1 month) use of neuroleptics in those with parkinsonism	2/2	1/1	
Phenothiazines in patients with epilepsy	-	0/1	
SSRIs with a history of clinically significant hyponatraemia	5/5	1/1	
Prolonged use (> 1 week) of 1st generation antihistamines	2/2	0/2	
Gastrointestinal System	**85/96 (88.5%)**	**39/118 (33%)**	**< 0.0001***
Prochlorperazine or metoclopramide with parkinsonism	-	1/3	
PPI for peptic ulcer disease at full therapeutic dose for > 8 weeks	85/96	38/115	
Respiratory System	**-**	**1/3 (33.3%)**	**-**
Theophylline as monotherapy for COPD	-	1/1	
Nebulised ipratropium with glaucoma	-	0/2	

Table 5.1 (continued): Prescriber implementation rates for STOPP recommendations: physician versus pharmacist

Musculoskeletal System	**15/20 (75%)**	**5/13 (38.5%)**	**0.0358***
NSAID with history of peptic ulcer disease or gastrointestinal bleeding unless with concurrent H_2 receptor antagonist, misoprostol or PPI	2/2	-	
NSAID with moderate-severe hypertension	4/6	3/5	
NSAID with heart failure	1/1	0/1	
Long-term (> 3 months) use of NSAIDs for symptom relief in mild osteoarthritis	6/9	1/3	
Warfarin and NSAID together	-	1/4	
NSAIDs with chronic renal failure	2/2	-	
Urogenital System	**9/12 (75%)**	**3/7 (42.9%)**	**0.1612**
Bladder antimuscarinic drugs with dementia	4/7	1/2	
Antimuscarinic drugs with glaucoma	1/1	-	
Antimuscarinic drugs with chronic constipation	3/3	2/5	
Alpha-blockers in males with frequent incontinence (≥ 1 episode daily)	1/1	-	
Endocrine System	**-**	**0/1 (0%)**	**-**
β-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes	-	0/1	
Drugs that adversely affect those prone to falls	**30/46 (65.2%)**	**12/36 (33.3%)**	**0.0042***
Benzodiazepines	19/27	10/26	
Neuroleptic drugs	3/5	1/4	
1st generation antihistamines	2/2	0/2	
Vasodilator drugs in those with persistent postural hypotension	1/1	-	
Long-term opiates	5/11	1/4	
Analgesic drugs	**16/18 (88.9%)**	**7/9 (77.8%)**	**0.4436**
Regular opiates for > 2 weeks in those with constipation without concurrent laxatives	12/14	7/9	
Use of long-term powerful opiates as first line therapy for mild-moderate pain	2/2	-	
Long-term opiates in those with dementia unless indicated for palliative care or moderate-severe chronic pain syndrome	2/2	-	
Duplicate drug class prescriptions	**23/28 (82.1%)**	**4/9 (44.4%)**	**0.0267***
Total	**237/292 (81.2%)**	**100/255 (39.2%)**	**< 0.0001***

COPD: Chronic obstructive pulmonary disease PPI: Proton pump inhibitor SSRI: Selective serotonin re-uptake inhibitor NSAID: Non-steroidal anti-inflammatory drug * Statistically significant difference observed ($p < 0.05$).

Table 5.2: Prescriber implementation rates for START recommendations: physician versus pharmacist

START criteria	Physician	Pharmacist	*p*-value
Cardiovascular System	**29/37 (78.4%)**	**4/15 (26.7%)**	**0.0005***
Warfarin with chronic atrial fibrillation	15/18	-	
Aspirin with chronic atrial fibrillation where warfarin is contraindicated	2/3	0/1	
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm	0/2	2/5	
Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg	1/1	-	
Statin therapy with history of coronary, cerebral, or peripheral artery disease without contraindication	8/9	1/3	
ACE inhibitor with chronic heart failure	3/4	1/4	
ACE inhibitor following acute myocardial infarction	-	0/1	
β-blocker with chronic stable angina	-	0/1	
Gastrointestinal System	**1/1 (100%)**	**-**	**-**
Proton Pump Inhibitor with severe gastro-oesophageal acid reflux disease or peptic stricture requiring dilatation	1/1	-	
Musculoskeletal System	**97/109 (89%)**	**6/19 (31.6%)**	**< 0.0001***
Bisphosphonates in patients taking maintenance oral corticosteroid therapy	14/18	1/10	
Calcium and vitamin D supplementation in patients with known osteoporosis, fragility fracture or dorsal kyphosis	83/91	5/9	
Endocrine System	**12/12 (100%)**	**3/10 (30%)**	**0.0004***
Metformin with type 2 diabetes mellitus +/- metabolic syndrome	1/1	-	
ACE inhibitor or angiotensin 2 receptor blocker in patients with diabetes and nephropathy	7/7	-	
Antiplatelet therapy in those with diabetes mellitus and one or more major cardiovascular risk factors	2/2	1/1	
Statin therapy in patients with diabetes mellitus and one or more major cardiovascular risk factors	2/2	2/9	
Total	**139/159 (87.4%)**	**13/44 (29.5%)**	**< 0.0001***

ACE: Angiotensin Converting Enzyme * Statistically significant difference observed ($p < 0.05$).

In total, attending prescribers implemented 83.4% of the physician's STOPP/START recommendations (376/451) compared to 37.8% of the pharmacist's STOPP/START recommendations (113/299). When comparing the physician and pharmacist interventions, there was a statistically significant difference between prescriber implementation rates of the total STOPP, total START, and total STOPP/START-combined recommendations ($p < 0.0001$).

Of the ten categories of STOPP criteria, recommendations were made by both physician and pharmacist across eight of these categories. The physician achieved higher implementation rates than the pharmacist for recommendations across all eight STOPP categories, with the absolute differences ranging from 11.1% to 55.5%. The largest absolute difference observed was for recommendations based on the gastrointestinal system. This was primarily due to the low implementation rate of pharmacist recommendations to deprescribe PPIs (38/115), which was the most common type of STOPP/START recommendation provided in both RCTs. There were statistically significant differences in the implementation rates of recommendations across six of the eight STOPP categories, with the exceptions being recommendations based on urogenital system drugs and analgesic drugs. Of the six categories of START criteria, recommendations were made by both physician and pharmacist across three of these categories. The physician achieved statistically significantly higher implementation rates than the pharmacist for recommendations across all three START categories, with the absolute differences ranging from 51.7% to 70%.

Of the 65 individual STOPP criteria, recommendations based on 22 of these were prevalent in both RCTs. The physician achieved higher implementation rates than the pharmacist for recommendations based on 19 of these 22 STOPP criteria, as shown in **Table 5.1**. The pharmacist achieved a higher implementation rate than the physician for recommendations based on one of the STOPP criteria – STOPP rule A8: "*Calcium channel blockers with chronic constipation (may exacerbate constipation)*". Of the 22 individual START criteria, recommendations based on 8 of these criteria were prevalent in both RCTs. The physician achieved higher implementation rates than the pharmacist for recommendations linked to 6 of these 8 START criteria, as shown in **Table 5.2**. The pharmacist achieved a higher implementation rate than the physician for recommendations based on one of the START criteria – START rule A3: "*Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm*".

5.5.2 Number of recommendations made and focus of intervention

Of the 360 patients randomised to the intervention arm in RCT 1, the physician made 451 recommendations in 233 patients (1.94 recommendations per patient). Of the 361 patients randomised to the intervention arm in RCT 2, the pharmacist made 1000 recommendations in 296 patients (3.38 recommendations per patient). Thus, for patients where pharmacotherapy recommendations were provided, the pharmacist provided 1.44 more recommendations per patient in comparison to the physician.

In RCT 2, the pharmacist's STOPP/START recommendations represented almost 30% of the total number of recommendations (299/1000), and 51.8% (299/577) of the medication appropriateness recommendations (i.e. including drug-drug interactions, need for renal and hepatic dose adjustments, and other PIP instances identified utilising Beers criteria version 3 [309] and PRISCUS criteria [156]) [169]. The remainder of the pharmacist's recommendations concerned issues with medication reconciliation (n = 423), of which 326 were implemented (77.1%). The implementation rate of the pharmacist's recommendations concerning medication reconciliation recommendations was approximately double the rate of those concerning STOPP/START criteria (77.1% versus 37.8%; $p < 0.0001$).

5.5.3 Pharmacist medication reconciliation recommendations based on START criteria

On initial viewing of the START recommendations in both RCTs, it is evident that the physician made 3.67 times more START recommendations per patient in RCT 1 compared to the pharmacist in RCT 2 (0.44 START/patient versus 0.12 START/patient). The physician did not conduct medication reconciliation, whereas the pharmacist did. Therefore, as part of the pharmacist's intervention, there were 322 recommendations to prescribe "*missing medications*" (i.e. medications that were prescribed prior to admission but omitted from the patient's list of medications on admission), of which 71 (22.0%) would have been identified by the START criteria based on the patients' lists of prescribed medications on admission and comorbidities (**Table 5.3**). Fifty-eight of these recommendations were implemented (81.7%). Prescribers were therefore substantially more likely to

implement a recommendation from a pharmacist to initiate a START criteria-based drug if it had previously been prescribed by a physician rather than based on the pharmacist's recommendation alone (81.7% versus 29.5%; $p < 0.0001$).

If the 71 recommendations to prescribe START criteria-based "*missing medications*" were factored in to the comparison between implementation of physician-delivered and pharmacist-delivered STOPP/START recommendations (**Appendix 18**), the physician would still achieve statistically significantly higher implementation rates for:

i) the total START recommendations: 139/159 (87.4%) versus 71/115 (61.7%); $p < 0.0001$, and
ii) the total STOPP/START recommendations: 376/451 (83.4%) versus 171/370 (46.2%); $p < 0.0001$.

Table 5.3: Pharmacist recommendations for "*missing medications*" identified by medication reconciliation that would have been identified by START criteria

START-based medication reconciliation recommendations	
Cardiovascular System	**22/27**
Warfarin with chronic atrial fibrillation	2/3
Aspirin with chronic atrial fibrillation where warfarin is contraindicated	4/4
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm	7/9
Statin therapy with history of coronary, cerebral, or peripheral artery disease without contraindication	8/9
ACE inhibitor with chronic heart failure	0/1
β-blocker with chronic stable angina	1/1
Respiratory System	**16/20**
Regular inhaled β_2 agonist or anticholinergic agent for mild to moderate asthma or COPD	5/7
Regular inhaled corticosteroid for moderate-severe asthma or COPD, where predicted FEV1 < 50%	11/13
Central Nervous System	**4/4**
Antidepressant drug in the presence of moderate-severe depressive symptoms lasting at least three months	4/4
Musculoskeletal System	**8/12**
Disease-modifying anti-rheumatic drug (DMARD) with active moderate-severe rheumatoid disease lasting > 12 weeks	0/1
Bisphosphonates in patients taking maintenance oral corticosteroid therapy	1/2
Calcium and vitamin D supplementation in patients with known osteoporosis, fragility fracture or dorsal kyphosis	7/9
Endocrine System	**8/8**
Metformin with type 2 diabetes mellitus +/- metabolic syndrome	2/2
ACE inhibitor or angiotensin 2 receptor blocker in patients with diabetes and nephropathy	1/1
Antiplatelet therapy in those with diabetes mellitus and one or more major cardiovascular risk factors	1/1
Statin therapy in patients with diabetes mellitus and one or more major cardiovascular risk factors	4/4
Total	**58/71**

ACE: Angiotensin Converting Enzyme FEV1: Forced expiratory volume in 1 second

5.5.4 Clinical outcomes

The comparable clinical outcomes from the two RCTs are displayed in **Table 5.4**. The physician's intervention resulted in an absolute reduction of 9.3% in the proportion of patients who experienced a non-trivial in-hospital ADR in comparison to the control group, compared to the pharmacist's intervention which resulted in an absolute reduction of 6.8% for this same outcome. The corresponding relative risk reductions for this outcome were 44.3% and 32.9% respectively. Neither intervention resulted in significant differences in median length of hospital stay or mortality when compared to controls.

Table 5.4: Comparable clinical outcomes between interventions

Clinical Outcome Measure	Physician	Pharmacist
Adverse Drug Reactions (ADRs):		
Control Patients with ADRs (%)	78 (21)	78 (20.7)
Intervention Patients with ADRs (%)	42 (11.7)	50 (13.9)
Absolute Risk Reduction in patients with ADRs	9.3%	6.8%
Relative Risk Reduction in patients with ADRs	44.3%	32.9%
Median Length of Hospital Stay:		
Control Patients (IQR)	8 days (4 – 14)	9 days (5 – 16)
Intervention Patients (IQR)	8 days (4 – 14)	8 days (5 – 13.5)
Significance level	Not stated	$p = 0.444$
Mortality:		
Control Patients; Intervention Patients	11; 9	17; 17
Significance level	$p = 0.6$	$p = 0.9$
	"*in-hospital deaths*"	"*died during their index hospital stay*"

IQR: Interquartile range

5.6 Discussion

There is a paucity of research comparing pharmacists and physicians in the provision of pharmacotherapy recommendations in hospitalised older adults. This is the first study to compare prescriber implementation rates of STOPP/START recommendations from one approach by a trained clinical pharmacist and another approach by a trained physician in geriatric medicine. These results have shown that the source of the STOPP/START recommendations and the communication methods through which they are provided may have a substantial impact on their implementation – it was found that physician prescribers in this particular hospital in the Republic of Ireland were statistically significantly more likely to implement STOPP/START recommendations from the physician's approach than from the pharmacist's approach in these two RCTs. There was a greater disparity between the two approaches in the implementation of START recommendations (87.4% versus 29.5%) compared to the implementation of STOPP recommendations (81.2% versus 39.2%).

A small sample size may have prevented showing statistically significant differences in the prescriber implementation rates of certain STOPP or START recommendations between physician and pharmacist. Nevertheless, this study has demonstrated that the physician obtained statistically significantly higher implementation rates than the pharmacist for 10 of the 30 individual STOPP/START recommendations present in both interventions, including recommendations to deprescribe benzodiazepines and proton pump inhibitors. In recent years, there has been extensive research on deprescribing of these drugs in particular [311-314].

The present study is consistent with previous findings that geriatricians may be more effective than other healthcare professionals with deprescribing in hospitalised older adults [313, 315].

It is acknowledged that differences between the interventions, other than the individual healthcare professionals, may have had an influence on prescriber implementation rates, such as:

i) The pharmacist provided other recommendations, not just STOPP/START recommendations like the physician did.
ii) Both the pharmacist and physician provided all of the recommendations in written form. The physician also communicated all recommendations verbally, whereas the pharmacist verbally communicated approximately one third of these recommendations.
iii) The physician had previously worked in the hospital prior to RCT commencement, whereas the pharmacist had not.

The physician-delivered intervention was narrowly focused on providing recommendations based on the STOPP/START criteria only, whereas the pharmacist's intervention involved the provision of recommendations based on STOPP/START as well as a wider range of drug-related problems. As previously stated, the pharmacist provided 1.44 more recommendations on average per patient than the research physician to attending prescribing teams. A recent systematic review suggests that computerised interventions which target a broader range of PIP issues in older adults may contribute to information overload, and consequently result in fewer recommendations being implemented [251]. Thus, in

the present study, the greater complexity of the pharmacist intervention compared to the physician intervention may have resulted in a lower implementation rate of pharmacotherapy recommendations by attending prescribers.

Previous studies have shown that pharmacists and physicians prefer the use of verbal or face-to-face recommendations when working in collaboration to review pharmacotherapy [183, 316]. Recommendations communicated in this way are usually implemented at a higher rate than those provided by written means alone [317-320]. This suggests that the pharmacist might have achieved higher implementation rates if he had provided verbal reinforcement to prescribers regarding all the recommendations in the printed report. However, the high implementation rate of the pharmacist's medication reconciliation recommendations (77.1%) suggests that the mode of delivery of the pharmacist's recommendations may not have been the primary cause of the observed difference in STOPP and START recommendation implementation rates between the pharmacist and physician. Moreover, the contrast in implementation between pharmacist medication reconciliation recommendations and STOPP/START recommendations is noteworthy. This difference suggests that there may be an impediment to prescriber implementation of pharmacist interventions relating to prescribing appropriateness in older patients, and that physicians may be more accepting of the pharmacist's role in medication reconciliation as distinct from prescribing appropriateness alterations.

Both the pharmacist and the physician were highly familiar with the STOPP/START criteria prior to the start of the two RCTs. Previous studies have demonstrated that

IRR amongst pharmacists and physicians is high when provided with the same clinical information [321, 322]. Therefore, identification of PIP by either healthcare professional should not have been different. A key factor in achieving implementation of prescribing recommendations may be *who* provides them, and *how* they are delivered to prescribers. Physicians may be more likely to implement recommendations from fellow physicians, as this is customary practice in healthcare systems worldwide. Physicians may be less likely to implement pharmacists' recommendations but the reasons for this are not fully understood. A qualitative study by Hughes *et al.* found that some pharmacists felt that doctors considered them to be subordinate on a professional level in relation to medication issues [323]. In that study, hierarchical differences were implicit in the doctors' comments as they questioned the role of pharmacists in certain areas, such as having greater involvement with prescribing decisions, which some doctors viewed to be solely within the professional domain of the doctor. The same study suggested that this may be because of some doctors' lack of awareness of pharmacist training, as well as some doctors feeling that greater pharmacist involvement would encroach on their prescribing role. Most of the studies in this area of research are focused on the relationships between pharmacists and physicians in primary care, and there appears to be limited research into exploring the factors affecting physician implementation of pharmacist recommendations in secondary care settings [323-325].

Prior to commencement of the RCTs, the research physician had previously worked in the same hospital training in geriatric medicine at specialist registrar level. As a

result, this particular physician may have already established a good professional rapport with some of the attending prescribers prior to RCT 1. This, in turn, may have contributed to an increased implementation of the STOPP/START recommendations offered by the research physician. In contrast, whilst the research pharmacist was experienced in providing pharmaceutical care for older adults, he had not previously worked in the hospital where the RCTs were conducted. Previous research has highlighted that key components to physician-pharmacist collaboration are trust and knowing each other [326], and that pharmacists who work closely with physicians are more likely to be successful in optimising geriatric pharmacotherapy [70]. These interprofessional barriers may have contributed to the observed lower implementation rate of the pharmacist's STOPP/START recommendations described in this study.

Published studies providing details on prescriber implementation of pharmacist and physician STOPP/START recommendations are limited. An earlier RCT conducted by a physician in the same hospital (where medication appropriateness was the primary outcome measure) demonstrated a very high level of prescriber implementation of both the STOPP (91%) and START (97%) recommendations [146]. Although this intervention took place in the hospital where the STOPP/START criteria were developed, it is unlikely that this is the reason for the high implementation rates as the criteria are not routinely applied to older patients there due to resource constraints. The implementation rates of the pharmacist's STOPP and START recommendations in this present study seem to be lower than those described in the literature to date (STOPP: 44% – 94% and START: 58%) [209,

327]. Therefore, these results support previous findings which indicate that a lower proportion of pharmacist-provided STOPP/START recommendations are implemented by prescribers in comparison to those provided by physicians.

There are some limitations to this study. Firstly, although both the original pharmacist and physician interventions encompass STOPP and START recommendations, they were not designed to be directly compared. Differences between the interventions cannot be ruled out as possible contributing factors to the difference in outcomes observed. Secondly, this was a single-centre comparison between the prescriber implementation rates of recommendations provided by one pharmacist and one physician. Evaluating implementation of STOPP and START recommendations from a larger sample of pharmacists and physicians in a multi-centre RCT setting would provide a more accurate comparison of the professions on this matter, as it is acknowledged that different personalities and communication styles also vary between individuals, which may impact on the implementation rates.

A cost-effectiveness analysis of the pharmacist intervention has shown that it was cost-effective [148]. However, a more recent cost-effectiveness analysis indicates that the physician intervention was unlikely to be cost-effective [328], even though it was associated with a greater absolute risk reduction in patients with ADRs compared to the pharmacist intervention. The present study suggests that a higher prescriber implementation rate of STOPP recommendations in particular is associated with lower rates of incident ADRs in hospitalised older adults. Therefore, it could be argued that the lower implementation rate of some of the pharmacist's

recommendations resulted in a higher rate of incident ADRs in the pharmacist RCT intervention cohort. Studies have consistently shown that pharmacists contribute to reductions in healthcare costs in the hospital setting [188]. If physicians are less likely to be cost-effective in conducting interventions of this type, it is important that other ways to enhance the implementation of pharmacist recommendations are identified, which reliably lead to further reductions in ADRs, and subsequently lower healthcare costs.

5.7 Conclusions

This study has shown that the methods of communication and the medium through which the STOPP/START recommendations are provided may have a significant impact on their implementation. Qualitative research is necessary to identify the key factors affecting prescriber implementation of hospital pharmacists' medication appropriateness recommendations, along with possible ideas for future intervention, as non-implementation of these recommendations may be contributing to preventable ADRs occurring in hospitalised older adults.

Chapter 6: Factors affecting prescriber implementation of hospital pharmacists' medication appropriateness recommendations in older adults

6.1 Chapter description

In Chapter 5, a significant difference was shown between the prescriber implementation rates of STOPP/START recommendations between one pharmacist approach and one physician approach in an acute hospital setting. It was highlighted that the method of communication may have been one of the primary reasons for this difference in STOPP/START recommendation implementation. However, the high uptake rate of the pharmacist's medication reconciliation recommendations suggests that there were other important factors influencing prescriber implementation of the pharmacist's STOPP/START recommendations other than the method of communication. In this chapter, I describe semi-structured interviews with hospital pharmacists and physicians which aimed to explore the principal factors affecting prescriber implementation of pharmacist recommendations concerning medication appropriateness in older adults.

6.2 Abstract

6.2.1 Introduction

Non-implementation of pharmacist recommendations by prescribers may prolong PIP in hospitalised older adults, increasing the risk of adverse clinical outcomes. The aim of this study was to ascertain the key factors influencing physician prescriber implementation of pharmacists' medication appropriateness recommendations in hospitalised older adults.

6.2.2 Methods

Semi-structured interviews were conducted with hospital pharmacists and physicians who provided care to older adults (≥ 65 years) in two acute university teaching hospitals in the Republic of Ireland. Content analysis was employed to identify the key themes that influence physician prescriber implementation of pharmacist recommendations.

6.2.3 Results

Fourteen interviews were conducted with six hospital pharmacists and eight hospital physicians between August 2018 and August 2019. Five key factors were found to affect physician implementation of pharmacist recommendations:

i) The clinical relevance and complexity of the recommendation: recommendations of higher priority and those that do not require complex decision-making are implemented more readily.

ii) Interprofessional communication: recommendations provided verbally, particularly those communicated face to face with confidence and assertion, are more likely to be implemented than written recommendations.

iii) Prescriber role and identity: the grade, specialty, and personality of the prescriber significantly affect implementation.

iv) Knowing each other and developing trusting relationships: personal acquaintance and the development of interprofessional trust and rapport greatly facilitate recommendation implementation.

v) The hospital environment: organisational issues such as documentation in the patient notes, having the opportunity to intervene, and the clinical pharmacy model all affect implementation.

6.2.4 Conclusions

This study provides a deeper understanding of the underlying behavioural determinants affecting prescriber implementation of pharmacist recommendations and will aid in the development of theoretically-informed interventions to improve medication appropriateness in hospitalised older adults.

6.3 Introduction

With their expertise in medications, pharmacists can play a vital role in recognising and resolving instances of PIP in multimorbid older patients with polypharmacy [147]. Hospital pharmacists' interventions to improve medication appropriateness in older adults have been shown in RCT studies to significantly reduce PIP, ADRs, and hospital attendances, including both emergency department visits and medication-related readmissions [147, 187, 329]. Pharmacist interventions to minimise PIP are often in the form of a recommendation, usually provided to the prescriber after reviewing patients' prescriptions. The prescriber implementation rate of these recommendations is commonly used as an indicator to measure the success of pharmacist interventions [330]. However, in order for process measures such as the rate of prescriber implementation to be clinically valid, it is essential that they correlate with positive patient outcomes [331]. Pharmacist interventions with a high proportion of medication appropriateness recommendations implemented by prescribers are more likely to result in significant improvements in patient outcomes compared to those with lower rates of implementation, which typically result in non-significant patient outcomes [186, 187, 207, 208].

It was shown in Chapter 5 that prescribers in an Irish hospital implemented a significantly greater proportion of physician-provided STOPP/START recommendations in comparison to those provided by a pharmacist (83.4% versus 37.8%; $p < 0.0001$) [280]. The physician's intervention was also associated with a greater absolute risk reduction in ADRs (9.3% versus 6.8%). This suggests that prescriber non-implementation of pharmacist recommendations may be prolonging

PIP in older adults and contributing to preventable ADRs and other adverse patient outcomes. However, only very limited qualitative research has been conducted to explore the underlying reasons for prescriber non-implementation of pharmacist recommendations. Therefore, the aim of the present study was to conduct semi-structured interviews with pharmacists and physicians in order to determine the key factors affecting prescriber implementation of pharmacist recommendations that target medication appropriateness in hospitalised older adults.

6.4 Methods

6.4.1 Context and study setting

The semi-structured interviews in this qualitative study were conducted in two acute university teaching hospitals in the Munster region of the Republic of Ireland. At the time of the interviews, pharmacists in both hospitals worked primarily according to a ward-based clinical pharmacy model, with pharmacists based on one or more assigned wards, reviewing patients under the care of multiple consultant physicians. Clinical pharmacy services in both hospitals primarily involved pharmacists performing medication reconciliation at admission and conducting prescription review throughout patients' hospital stay, without routine involvement at the time of discharge. At the time of the study, pharmacists did not have prescribing authority within either hospital.

6.4.2 Study design and recruitment

Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Cork, Republic of Ireland (**Appendix 19**). This study is reported in accordance with the COREQ checklist (**Appendix 20**) [258]. Semi-structured interviews were chosen as the preferred method of data collection in this study as they tend to evoke more in-depth accounts of participants' experiences and perspectives [259]. A sampling matrix was designed to ensure that semi-structured interviews were conducted with medical physicians and pharmacists with various levels of experience in both hospitals (as shown in **Table 6.1**). Previous studies have suggested that the level of experience of the pharmacist and the physician are important factors affecting physician implementation of pharmacist recommendations [332, 333]. Physicians were ineligible for inclusion if they had a pharmacy degree or had previously trained to be a pharmacist. Participants were recruited using a combination of convenience sampling and snowballing, and the study's information sheet and consent form were both provided to participants via email in advance of the interview.

Table 6.1: Sampling Matrix

Interview participant type	Hospital 1	Hospital 2
Pharmacist		
- Pharmacist < 3 years of hospital pharmacy experience	1	1
- Pharmacist ≥ 3 years of hospital pharmacy experience	1	1
- Pharmacist ≥ 5 years of experience with a postgraduate qualification in pharmacy	1	1
Physician		
- Intern*	1	1
- Senior House Officer+	1	1
- Registrar□	1	1
- Consultant	1	1

* < 1 year post-qualification experience.

+ ≥ 1 year post-qualification experience (usually 2 years in duration after internship).

□ ≥ 3 years post-qualification experience (the final stage of specialist training prior to eligibility for consultancy).

6.4.3 Data collection

Separate topic guides with a similar line of questioning were formulated for pharmacists and physicians based on the TDF [217], a literature review, and my own and my supervisors' knowledge of the research area (**Appendix 21**). Each topic guide was pilot tested with one participant each, and both were iteratively refined during the study where appropriate. All semi-structured interviews were conducted by the primary researcher (KD) between August 2018 and August 2019. One interview was conducted in a private room at the interviewer's workplace as this was the preference of the interviewee. However, all other interviews were conducted in a private room at the participants' respective hospital sites to minimise disruption to their work day. All participants provided written informed consent prior to participation. The interviews were audio-recorded and transcribed

verbatim. Field notes were documented after each interview so as to inform data analysis and topic guide refinement. Data analysis was done in tandem with data collection. It was planned in advance that if no new themes emerged in the additional three interviews after the eleventh interview (i.e. to complete the 14-participant sampling matrix), then this would confirm that data saturation had been reached [260].

6.4.4 Data analysis

All transcripts were entered into QSR NVivo® Version 11 to facilitate data analysis, which consisted of four stages. In Phase 1, transcripts were repeatedly read to ensure familiarisation with the data. Phase 2 comprised conventional content analysis, whereby open coding was utilised to inductively generate non-hierarchical codes [261]. Thereafter, these initial codes were categorised to develop the evolving themes. In Phase 3, the TDF was applied to deductively code the transcripts and identify the domains present as part of directed content analysis [261]. The predominant domains were determined by consensus agreement between two researchers (KD and AF), with three elements examined to decide this: i) the frequency of beliefs in each domain, ii) the existence of contrasting beliefs, and iii) the perceived strengths of the beliefs affecting implementation, as per Patey *et al.* [262].

Finally, the evolving themes (from Phase 2) and predominant TDF domains (from Phase 3) were evaluated further to subsequently identify the main themes, which indicate the key factors that influence prescriber implementation of pharmacists' medication appropriateness recommendations for hospitalised older adults. To

ensure validity and reliability in the data analysis, six transcripts were coded by a second researcher (AF). All members of the research group were involved in refining the final themes presented.

6.5 Results

A total of 14 interviews were conducted, as per the sampling matrix (**Table 6.1**). Both pilot interviews were included in the data analysis. With regard to hospital-based experience, half the participants had less than 5 years' experience, four participants had ≥ 5 years' experience but less than 10 years' experience, and three participants had over 10 years' experience. Ten participants were female, and the mean interview length was 33 minutes (range 18 – 47 minutes).

6.5.1 Main themes

Five main themes emerged as the key factors influencing prescriber implementation of hospital pharmacists' medication appropriateness recommendations, as described in detail below. Subthemes and quotations have been displayed under each main theme to help explain these findings, with supplementary quotations available in **Appendix 22** to provide further evidence that the themes generated were representative of the interview content.

Theme 1 – Clinical relevance and complexity of the recommendation

Clinical relevance in the hospital setting

Put simply, if it is a relevant recommendation that either clearly benefits the patient or prevents patient harm, it will be implemented.

> *"...if it's an implementation that's going to affect the patient's acute inpatient care, it'll be implemented".* [Pharmacist 6]

Priority

Participants emphasised that physicians' priorities are primarily to manage patients' acute issues. Depending on how salient the pharmacist recommendation is, and the urgency with which it must be addressed, physicians will prioritise the recommendations relative to their other work commitments.

> *"…it's probably something that mightn't be deemed particularly important or it's not going to cause any adverse effect, at least in the short term. You know, those kind of things would be slower to be acted upon, maybe because people would have graded it in their head as to how important that particular intervention is based on other jobs that they have to do that day".* [Pharmacist 3]

Complexity of decision-making

Recommendations which are not straightforward or not supported by clear evidence-based guidelines require greater knowledge and decision-making, thus hindering implementation.

"...maybe grey areas or where maybe more thought is needed, that's probably where the recommendations mightn't be followed". [Pharmacist 3]

Theme 2 – Interprofessional communication

Route of communication

Recommendations provided verbally, particularly those delivered face to face, are much more likely to be implemented than those that are written. In addition, verbal reminders are often required to reinforce the implementation of written recommendations, which may not be seen or could even be ignored on their own.

"I think verbal is better, I think it's easier to ignore something that's in the chart, as opposed to if you are face to face with someone, I think you take it on board more…" [Physician 7]

Providing recommendations verbally allows for bidirectional discussion, affording both the pharmacist an opportunity to clearly explain the rationale for their recommendation, and for the physician to clarify their reason for implementation or not, facilitating closure of the communication loop.

"I mean I think the face-to-face stuff can be useful regarding again…because there might be a bit more rationalising around why something should be changed or not". [Physician 8]

Pharmacist manner and language

Implementation is facilitated by pharmacists displaying confidence, assertiveness, and a clear rationale for the recommendation.

> *"...if they were to be more assertive in why they have made that recommendation or not then we on the medic side might be more inclined to take notice, like sit up and take notice of kind of what they're saying"*. [Physician 7]

Participants highlighted that pharmacists often play a '*corrective role*'. While most prescribers welcome this input, others may perceive this critiquing to be a challenge to their authority. For this assertiveness to not be misconstrued as arrogance, pharmacists often adjust their language to avoid conflict with or causing offence to physician prescribers, in order to facilitate implementation.

> *"...we don't want to be arrogant either by coming in and saying 'you are wrong'. My recommendations are always 'consider doing this', because the recommendations I have made are based on this guideline"*. [Pharmacist 2]

<u>Theme 3 – Prescriber role and identity</u>

Personality

Participants expressed that the physician's personality may be a factor affecting implementation, attesting that some may be open-minded and accepting of pharmacists' recommendations, while others are less receptive to pharmacist

advice as it may be perceived as a challenge to their judgement or impingement on their prescribing role.

> *"We have very supportive physicians, they're very supportive of pharmacy and are very happy to take your recommendations on board and would always thank us for flagging things. And then we would have physicians who don't like to be questioned on their treatment decisions"*. [Pharmacist 2]

Grade and experience of prescriber

Most interviewees asserted that junior prescribers would be more likely to implement pharmacists' recommendations. However, it was implied that this may be on the basis of blind trust if they are following the recommendation simply due to hierarchical influences.

> *"I remember back when I was an intern and I would have trusted everybody more senior than me, which would have been everyone. So, I might have just done it without thinking about it too much..."* [Physician 6]

Conversely, with more complex issues, participants emphasised that junior prescribers may be less likely to implement pharmacists' recommendations, either due to a lack of knowledge or skills, or because they are not in a position to decide on the patients' pharmacotherapy, thus deferring responsibility to their senior colleagues.

> *"I feel like I don't have the power to make the pharmacy decisions really. So, really, I would have to talk to the registrar or the consultant on the service…"* [Physician 7]

Participants indicated that senior physicians may be more likely to resist pharmacist input. Two participants highlighted that this viewpoint among some senior physicians may have a '*trickle-down effect*' influencing their junior colleagues to also be dismissive of pharmacist recommendations.

> *"...there'll be a trickle-down effect as well, like if a top manager is going 'Oh, pharmacy who? What are they for?' Then the intern is going to think 'Oh well, I'm fine without them. I don't need an opinion from them at all'"*. [Pharmacist 4]

Specialty

There was no unanimous agreement on how physician specialty affected implementation. Interviewees stated that some physicians were more likely to implement such recommendations as they welcomed pharmacists' expertise concerning medications outside of their specialist knowledge. Conversely, it was outlined that other specialists felt less comfortable with implementing recommendations perceived to be beyond their scope of practice, particularly when this may encroach on other prescribers' areas of expertise.

> *"I think they just don't want to step on people's toes, or it may be something they're not really familiar with and they don't want to meddle with it"*. [Pharmacist 4]

Theme 4 – Knowing each other and developing trusting relationships

Knowing each other

Participants indicated that although a physician knowing the pharmacist is not essential for implementation, it was strongly emphasised that familiarity enhances pharmacist-physician interactions, supports the development of collaborative relationships, and ultimately facilitates the routine implementation of pharmacist recommendations. However, it was clear from the interviews that pharmacists placed a greater importance on knowing each other than the physicians:

> *"…it's definitely important that…they know you I suppose, that they've seen you around, they know who you are, they know that, you know…they've had positive interactions with you before definitely I think improves the likelihood that they'll take on board what you have to say"*. [Pharmacist 5]

Relationship-building

Interviewees conveyed that greater rapport enhances the likelihood of pharmacist recommendations being implemented by physicians.

> *"…when you have an interpersonal relationship with someone, you're more likely to take on board their opinion, and subsequently maybe implement their recommendations"*. [Physician 5]

However, the recurrent medical staff changeovers hinder the longevity of pharmacists' relationships, particularly with more junior physicians. This frequent change in personnel necessitates the continual establishment of new pharmacist-physician relationships.

"…the teams change then every two or three months, and you have a whole host of new interns and SHOs and things like that but…you're kind of starting from scratch again then maybe with the medical teams a little bit…" [Pharmacist 5]

Trusting pharmacists' recommendations

It was indicated that physicians may not be that aware of pharmacists' training, skills, or roles in optimising older adults' medications, all of which influences trust in pharmacists' recommendations. Building trust usually takes substantial time; this can be achieved by pharmacists consistently providing high-quality recommendations.

"I think once you prove yourself to them a bit, they warm to you a bit. I suppose it would be the same as any new doctor. They'd be slow to trust you until there's trust there". [Pharmacist 1]

In addition, participants affirmed that when trust has been established the physician may be more likely to approach pharmacists for advice and implement their recommendations.

"…and then over time, I think, as you're there and you get to know people more that they come to you with questions…" [Pharmacist 6]

<u>Theme 5 – The hospital environment</u>

Timing and opportunity

Even though most participants expressed that face-to-face discussion was their preferred method of communication, this is not always possible in the busy hospital

environment. There can be challenges with meeting physicians in person due to busy schedules, and there is not always a clear opportunity for pharmacists to discuss recommendations face to face, thus often relying on impromptu encounters. Furthermore, many pharmacists indicated that implementation would be facilitated by pharmacists having a prescheduled time to discuss their recommendations, such as a ward round or multidisciplinary team meeting.

> *"…unless you're on a round with them, it's difficult to find* [an opportunity to meet] *afterwards. You're running around bleeping people, nosing into doctors' rooms to see if someone is in there…so it can be…it can make it difficult"*. [Pharmacist 4]

Documentation in the medical records

The medical case notes may not always contain sufficient information about the physicians' plan for the patient – this can result in pharmacists making recommendations that are of lower relevance or not in line with the physicians' treatment plan.

> *"…the pharmacist may be recommending or fairly concerned with things whereas we may not be concerned with things because our goal of care may have changed, and that sometimes doesn't come across that well in the chart. You know, it may not be clearly flagged as…we don't always write down that kind of stuff…"* [Physician 5]

Working as a team

Participants indicated that the pharmacist may often be perceived as an '*outsider*', and stated that pharmacists who work closely with physicians as part of a team would have more recommendations implemented as physicians know these pharmacists better and have had time to build trusting relationships.

> *"You know it's so much better to work with the physicians as a team rather than work with them in isolation on the ward. They don't get to know you. They don't build a relationship".* [Pharmacist 6]

Staffing levels and pharmacist presence

A common thread throughout the transcripts was pharmacist staffing levels; a greater pharmacist presence would increase accessibility to physicians and face-to-face discussions, and allow more time for collaborative teamwork.

> *"Also, the fact that we're not fully resourced; if we had more presence on the wards and more presence with teams, I think the likelihood is that we would have…recommendations would be taken up probably much more quickly and much more easily because you would be more readily available to the team to discuss matters"* [Pharmacist 3]

6.5.2 Predominant TDF domains

Six domains were identified as predominant in affecting physician prescriber implementation of pharmacist recommendations (**Table 6.2**), and these were pervasive in the five main themes depicted. Some of the supporting quotations may illustrate more than one TDF domain due to overlap between the constructs.

Table 6.2: Behavioural determinants affecting implementation of pharmacist recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Environmental Context and Resources	Urgency	"*But if it was a risk, so if there were an interaction that puts the patient at risk, they'd definitely change it more readily".* [Pharmacist 1]
	Opportunity and timing of the intervention	*"…I think meeting as opposed to opportunistically trying to find the team on the ward…"* [Physician 2] *"I think the fact that a lot of our recommendations are made retrospectively or they are very reactive, I think if you were there at the point of prescribing, the likelihood is that you would have more of an impact…"* [Pharmacist 3]
	Communication	*"Oh, face to face, they'll do it, they get your point. They'll do it straight away, and leaving a note - it can just fall by the wayside…"* [Pharmacist 4]
Social Influences	Rapport and knowing each other	"*Good rapport always helps. If you know the same pharmacist and you are working with them all the time, I think that benefits, like that definitely helps*". [Physician 1]
	Alienation – '*outsider*'	"*A lot of the time the team isn't around when you're reviewing the chart so you're leaving notes and that kind of, the communication isn't there, they might not actually recognise you when you do come up to them, so you're just, you're some outsider…*" [Pharmacist 4]
	Hierarchical influences	*"I think everything is like top-down approach like. If juniors don't see kind of their superior buying into it, if they almost see them ignoring it totally – 'oh we'll disregard that'. I'm sure that has a knock-on effect…"* [Physician 4] "*I think any of the consultants I have worked with have been very open to pharmacist intervention and discussion with them as well. So, I would have no problem ever discussing anything with the pharmacist*". [Physician 2]

Table 6.2 (continued): Behavioural determinants affecting implementation of pharmacist recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Social/Professional Role and Identity	Grade in the hierarchy	*"That may be around grade too often; a lot of this is consultant-driven. So, a registrar and SHO may not feel empowered to sort of follow a recommendation either"*. [Physician 8]
	Professional boundaries	*"…it depends then individually, if they might be very willing to listen or they might just be a little bit like 'No, you don't, this is my patient, it's nothing to do with you' so yeah, you can see that a little bit".* [Pharmacist 4]
	Personality	*"I would imagine personality may come into it here and our self-belief may come into it a bit. And you know, look I've certainly worked with doctors who pay lip service to interdisciplinary working"*. [Physician 8]
Memory, Attention, and Decision Processes	Attention to optimising medication	*"I think physicians are so busy, they…it's not something that's on their radar when a patient presents to an acute hospital setting…"* [Pharmacist 6]
	Complexity of decision	*"So I think the more straightforward ones where the guidelines are very clear are acted on probably quicker and it's easier for people to make a decision around that…"* [Pharmacist 3]
	Decision-making based on prescriber experience	*"I think someone with experience would be more able to actually be making an informed decision"* [Physician 3] *"I think it's probably the lack of experience is twofold: they can take on recommendations quite readily, but other times with more difficult decisions that have to be made that may be a little bit more difficult, they might need to go back to senior members of the team.* [Pharmacist 3]

Table 6.2 (continued): Behavioural determinants affecting implementation of pharmacist recommendations within the predominant TDF domains

Predominant TDF Domain	Determinants of Prescriber Implementation	Illustrative Quotations
Knowledge	Knowledge affects decision-making	*"I think the more knowledge that you have, in terms of pharmacology, you'd be more likely to make your own decisions".* [Physician 3]
	Procedural knowledge	*"…the pharmacy had flagged it* [i.e. the potentially inappropriate medication] *and suggested maybe we start to wean her off it but I suppose I wasn't sure how to go about weaning* [the older patient] *off it. So, in that case I kind of held off until I had spoken to somebody more senior, that kind of thing".* [Physician 6]
	Knowledge outside specialty	*"I think that, say, if you were a cardiologist, they know lots and lots about cardiology drugs but outside of that, they wouldn't really care as much".* [Pharmacist 1]
Goals	Goal of care	*"I think people are too busy, too busy to* [examine older patients' medications]*…just focusing on getting…treating the presenting complaint and getting the patient in and out".* [Pharmacist 6]
	Goal priority	*"…sometimes it's very minor discrepancies, like for example do you know like a half or a full dose PPI or something like that, that you might, you know, just put at the end of your to-do list because you're busy and you might…you know, so you don't prioritise it".* [Physician 3]

TDF: Theoretical Domains Framework SHO: Senior House Officer PPI: Proton pump inhibitor

6.6 Discussion

Even though interprofessional relationships and communication between pharmacists and physicians have been widely investigated by previous researchers [323-325], limited qualitative research has been conducted in the hospital setting, particularly when it comes to investigating the behavioural determinants underlying physicians' implementation of pharmacist recommendations. The present study is the first to explore the views of pharmacists and physicians regarding the key factors affecting physician implementation of pharmacists' medication appropriateness recommendations for hospitalised older adults.

These findings echo those of previous studies which have shown that face-to-face communication is a key facilitator to physician implementation of pharmacist recommendations [207, 334, 335]. Synchronous bidirectional discussion and face-to-face contact have been shown to be important components in developing collaborative working relationships between pharmacists and physicians [183, 336, 337]. Conversely, written communication lacks synchronicity, and is infrequently bidirectional between pharmacists and physicians, and may contribute to further ambiguity [338, 339]. This study reiterates that written recommendations from pharmacists are less likely to be implemented by prescribers [317]. However, this may be confounded by the fact that less urgent recommendations are often communicated in written form, and therefore may not be implemented as readily [340].

In line with previous research, most participants expressed a preference for face-to-face delivery of pharmacist recommendations [339]. However, this method of

communication is hampered by the difficulty in finding prescribers and speaking face to face in the busy hospital environment. Previous research has shown that interprofessional discussions in hospitals are most commonly brief, unstructured, and opportunistic interactions [341-343]. However, many of our participants emphasised the value of having scheduled times to meet (e.g. at ward rounds or multidisciplinary team meetings), rather than solely relying on spontaneous interactions, which may interrupt workflow and increase the risk of error [339, 344]. Involvement with ward rounds affords pharmacists the opportunity to proactively minimise or prevent PIP rather than the traditional reactive role, whereby pharmacists retrospectively review patients' prescriptions after the initial prescribing decisions have been made [345]. Pharmacist involvement in ward rounds has been shown to increase medication appropriateness and reduce preventable ADEs [346, 347]. However, even with face-to-face communication, implementation may be hindered if the receiver of the recommendation is not a '*decision-maker*' on the attending medical team [300].

Previous research has suggested that pharmacists' grade significantly affects physician implementation of hospital pharmacist recommendations [332]. However, the present study did not find this to be a key determinant of implementation, but it was clear from the interviews that this may be influenced by physicians' lack of awareness of the specific aspects of pharmacist training and experience [348]. In contrast, these findings have reemphasised that a physician's experience and grade, as well as some physicians' ingrained sense of the traditional hierarchy, significantly affect the implementation of pharmacist recommendations

[183, 333]. Thus, it is not surprising that '*Social Influences*' appeared as one of the predominant TDF domains throughout the interviews. Senior physicians are less likely to be interested in developing collaborative relationships with others who they perceive to be subordinate or challenging their prescribing decisions [323, 324]. In order to facilitate implementation, pharmacists often employ indirect communication strategies (e.g. gentle reminders, suggestions, questions) to avoid conflict or embarrassment and to prevent provoking defensive behaviour from physicians [183]. A hierarchical culture such as this impedes teamwork in healthcare [349]. Interprofessional education has been suggested as one strategy to enhance collaboration between healthcare professionals. However, further evidence is required to demonstrate its effectiveness in fostering the development of effective interprofessional healthcare teams with improved patient outcomes [350-352].

Participants affirmed that pharmacists working in close collaboration with physicians as part of a team would facilitate implementation of pharmacist recommendations. Successful interventions of this nature commonly involve pharmacists working closely with medical staff [182, 329, 353]. A previous study in an Irish hospital has shown that a team-based pharmacist approach was associated with a significantly higher proportion of recommendations being implemented compared with standard ward-based pharmaceutical care (95.9% versus 69.3%), and the same study also resulted in a significant improvement in medication appropriateness for the team-based pharmacist interventions only [204]. Moreover, the team-based pharmacist recommendations were also implemented

earlier compared to ward-based pharmacist recommendations, which may be vital in the prevention of ADRs [204]. However, team-based models can be less efficient with pharmacist time as in these models pharmacists may not be able to review the same number of patients, and also may affect collaboration with other healthcare professionals, such as nurses [354].

Working together as a team allows for pharmacists and physicians to get to know each other and their professional roles, to develop rapport, and to build up mutual trust in clinical judgement [326, 355]. Trust is fundamental to successful pharmacist-physician relationships [356]. The present findings reaffirm that physicians' trust in pharmacists may be developed through the consistent delivery of useful recommendations [355]. Evidence of this trust may be exhibited by physicians asking pharmacists for their particular input to patient management. However, this advice-seeking behaviour may also be facilitated by ready accessibility to pharmacists [357].

In the present study, it was reemphasised that the recurrent staff changeover in hospitals can make it challenging to develop and maintain long-lasting relationships between pharmacists and physicians [358]. Therefore, it would seem prudent for pharmacists to develop strong relationships with senior physicians who usually have a long residence time in the hospital. Senior prescribers modelling trust with pharmacists should have a '*trickle-down effect*', as two interviewees described, to influence junior prescribers to trust pharmacists and implement their recommendations [358].

Identification of the predominant TDF domains in this study has provided a greater understanding of the underlying behavioural determinants related to prescriber implementation of pharmacist recommendations. Further research is required to develop theoretically-informed interventions that aim to change the behaviour of pharmacists and physicians in order to enhance implementation of pharmacist recommendations to improve prescribing appropriateness.

6.6.1 Strengths and limitations

The TDF was utilised in formulating the topic guides and in analysing the transcripts; it has been shown that interview studies based on this framework can reveal additional themes compared to those without a theoretical basis [284, 285]. All interviews were conducted by the same researcher, which allowed for consistency in both data collection and analysis. Participants were aware that the interviewer was a pharmacist, but it was emphasised to physician participants that they should strive to see the interviewer in his role as a researcher aiming to gain a greater understanding of their views. While the risk of social desirability bias must be acknowledged, it did not seem to appear as a significant issue given the honest views and opinions provided, describing both positive and negative experiences with hospital pharmacists.

The transferability of the study findings may be questioned given that the interviews were conducted in just two acute university teaching hospitals in one geographical area of the Republic of Ireland. Given that different clinical pharmacy models or different practices exist, these findings may not necessarily reflect all the key factors affecting prescriber implementation of pharmacist recommendations in

other hospital settings in the Republic of Ireland or in other similar countries. Future work should aim to investigate this issue in settings with other clinical pharmacy models and, with the increasing prevalence of computerised systems in hospitals, further qualitative research is necessary to explore the factors affecting implementation of pharmacist recommendations communicated via electronic means [359].

6.7 Conclusion

There are a number of barriers to prescriber implementation of hospital pharmacist recommendations aiming to improve medication appropriateness in older adults. It is imperative that a high proportion of such recommendations is implemented in order to achieve better patient outcomes. This study has generated a greater understanding of the key factors affecting prescriber implementation of pharmacist recommendations, and will help inform both the design of future pharmacist interventions aimed at improving the appropriateness of prescribing in hospitalised older adults, as well as the delivery of clinical pharmacy practices in hospital settings.

Chapter 7: Discussion

7.1 Chapter description

This chapter firstly presents a summary of the thesis findings, focusing on the novel aspects of the research. Following this, an overview is provided of the key factors affecting prescriber implementation of medication appropriateness recommendations in hospitalised older adults, with a discussion of these findings in the context of the published literature. Thereafter, the overall strengths and limitations associated with this body of work will be described. Finally, the implications for practice and future research will be discussed.

7.2 Summary of findings

In the introduction to this thesis, it was highlighted that there is no accepted optimal strategy to minimise PIP in hospitalised older adults. Consequently, the prevalence of PIP remains unacceptably high, placing these older patients at significant risk of adverse outcomes. A large number of intervention studies have been conducted which involved the provision of recommendations to hospital prescribers aiming to reduce PIP in older adults. From these studies, it is evident that interventions with higher prescriber implementation rates of these recommendations are more likely to result in significant improvements in both medication appropriateness and patient outcomes [186, 187, 207, 208]. Irrespective of the impact of these interventions, most studies with low prescriber implementation rates have not investigated the reasons underlying the reduced uptake of recommendations with any rigour [207, 208]. With this gap in the literature, this doctoral research investigated the key determinants underlying prescriber implementation of medication appropriateness recommendations related to older patients' pharmacotherapy, focusing primarily on the implementation of pharmacist-provided and computer-generated recommendations.

The first novel outcome of this thesis was the production of a systematic literature review and meta-analysis on the effectiveness of computerised interventions designed to minimise PIP in hospitalised older adults [251]. Previous reviews had gathered evidence across different healthcare settings [198, 199], but the systematic review described in Chapter 2 has filled an important knowledge gap in

the literature as it was the first conducted specifically related to interventions in the hospital setting. The main finding was that these interventions can significantly reduce PIP in hospitalised older adults compared to control ($p < 0.05$). However, the systematic review also showed that computerised interventions do not routinely result in significantly improved patient outcomes. Three of the nine included studies assessed the intervention's impact on patient outcomes, with statistically significant improvements in two of seventeen patient outcomes assessed – one study showing a reduction in ADEs and the other a reduction in inpatient falls.

Five studies reported the prescriber implementation rates of the computer-generated recommendations, ranging widely from 22.5% to 95%. Interestingly, it was more common for interventions that targeted fewer PIMs to have higher implementation rates. Although not extensively investigated in any of the included studies, three articles provided reasons for prescriber non-implementation of recommendations to discontinue PIMs, including:

i) patient was tolerating the PIM,

ii) PIM was clinically indicated, or

iii) no suitable alternative available (to the PIM).

This systematic review allowed for a greater understanding of the particular research area in advance of conducting the studies related to computer-generated recommendations, as described in Chapters 3 and 4. In particular, the description of the computerised interventions and the reasons for prescriber non-implementation of computer-generated recommendations helped inform the development of the topic guides for the semi-structured interview study described in Chapter 3. This

qualitative study utilised the TDF to help ascertain the key factors that affected prescriber implementation of the SENATOR trial intervention's recommendations.

In Chapter 3, interview participants revealed that implementation of recommendations depended on some individual prescriber characteristics, such as prescriber experience, specialty, and the prescriber's attitude towards research studies. Implementation was facilitated by provision of the recommendations to a '*decision-maker*' in the prescribing team. In addition, the interviewees asserted that the hospital environment played a role in the low implementation rates. Recommendations were often not acted upon due to the patient's acutely ill status in the hospital setting, and that it may be preferable to make changes in a non-acute setting when the patient is more stable. Furthermore, the recommendations were mostly not provided to prescribers at the time of patient review, thus hindering their implementation.

The most pervasive perception among the interviewees was that the clinical relevance of the computer-generated SENATOR recommendations was a key factor affecting their implementation. Quite simply, if recommendations were not considered relevant, they would not be implemented. Furthermore, recommendations of low relevance contributed to prescriber fatigue with the intervention. This meant that even recommendations of greater relevance may have been ignored, preventing their implementation.

In comparison to the other key factors affecting implementation of the SENATOR recommendations, the clinical relevance of recommendations can be measured. Thus, the findings from Chapter 3 led us to conduct a retrospective evaluation of

the clinical relevance of computer-generated STOPP/START recommendations from the SENATOR intervention, and thereafter assess for any association between relevance and the rate of implementation. As part of this study, as described in Chapter 4, the clinical relevance of all STOPP/START recommendations that were provided to prescribers caring for the 204 intervention patients in Cork University Hospital, the lead site in the SENATOR trial, were evaluated. This study was novel in that it was the first study to:

i) evaluate the clinical relevance of computer-generated STOPP/START recommendations, and
ii) use a validated scale to assess the clinical relevance of computer-generated medication appropriateness recommendations for hospitalised older adults.

In this study, it was found that nearly three quarters of the recommendations were clinically relevant (73.6%), with the remainder judged to be either of '*no clinical relevance*' (21.5%) or of potential '*adverse significance*' (4.9%) if implemented. However, of the clinically relevant recommendations, nearly half of these were of '*possibly low relevance*' (47%). Furthermore, when examining the association between clinical relevance and implementation, it was found that recommendations of higher clinical relevance were significantly more likely to be implemented than those of lower clinical relevance ($p < 0.05$). Therefore, this chapter corroborated the qualitative findings from Chapter 3, whereby the clinical relevance of recommendations was deemed a significant factor affecting prescriber implementation.

The second aim of this thesis (as shown in **Figure 1.1**) was to identify the key determinants influencing prescriber implementation of pharmacist-provided recommendations to improve medication appropriateness in hospitalised older adults. Prior to undertaking qualitative research to investigate this issue (as detailed in Chapter 6), I compared two similar interventions – one pharmacist-led and the other physician-led – that involved the provision of STOPP/START recommendations to prescribers aiming to reduce PIP and associated ADRs in hospitalised older patients. This study, as described in Chapter 5, was the first to compare implementation rates of STOPP/START recommendations between a pharmacist and a physician [280].

Prescriber implementation of physician-provided STOPP/START recommendations was found to be significantly higher than those provided by a pharmacist (83.4% versus 37.8%; $p < 0.0001$). Furthermore, these results suggested that higher implementation rates of recommendations may be associated with better patient outcomes – the physician's intervention had a higher proportion of STOPP/START recommendations implemented and resulted in a greater absolute risk reduction in patients with ADRs in comparison to the pharmacist's intervention (9.3% versus 6.8%). This study also identified intervention components that may have influenced the prescriber implementation rates of pharmacist recommendations, namely the method of communication utilised, the type of the recommendation made, and personal acquaintance with the prescriber. These findings were used to inform the topic guide development for the semi-structured interviews with hospital pharmacists and physicians conducted in Chapter 6.

Although several studies have explored interprofessional relationships between pharmacists and physicians [323-325], the final research chapter is novel in that it describes the first study to explicitly elucidate the factors affecting prescriber implementation of hospital pharmacist medication appropriateness recommendations. The findings in this study echo some of those described in Chapter 3, reaffirming that environmental barriers (e.g. communications methods utilised and intervention timing), individual prescriber characteristics (e.g. experience, specialty, and personality), and the clinical relevance of the prescribing advice all significantly affect the implementation of medication appropriateness recommendations by hospital physician prescribers.

It was suggested in Chapter 5 that one reason contributing to non-implementation of pharmacist recommendations was lack of personal acquaintance with the physician. This hypothesis was supported by interviewees in Chapter 6, who indicated that although knowing each other is not essential, it does however greatly enhance rapport and the likelihood of recommendation uptake. In addition, the findings in Chapter 6 emphasised the important influence that the medical hierarchy has on implementation of pharmacist recommendations. Junior physicians are likely to seek advice from their senior physician colleagues as part of the decision-making process to implement pharmacist recommendations. This implies that physicians often trust their colleagues' advice over that of pharmacists, which perhaps further explains the significantly lower implementation rate of pharmacist-provided recommendations in comparison to physician-provided recommendations found in Chapter 5.

Six TDF domains appeared as predominant in influencing prescriber implementation of medication appropriateness recommendations in each of the qualitative studies (Chapters 3 and 6). Five of these predominant domains were common to both studies, namely: '*Environmental Context and Resources*', '*Social/Professional Role and Identity*', '*Memory, Attention and Decision Processes*', '*Knowledge*', and '*Goals*'. By mapping these predominant domains to the BCW, this may help identify intervention functions that could be utilised to enhance prescriber implementation of recommendations to improve medication appropriateness.

The '*Social Influences*' domain appeared as predominant in influencing prescriber implementation of pharmacist recommendations, but this was not the case for the computer-generated SENATOR recommendations. This is perhaps unsurprising due to the importance that has been previously attributed to the interpersonal processes between pharmacists and physician prescribers [360, 361]. Conversely, the '*Intentions*' domain appeared as predominant in affecting prescriber implementation of the SENATOR recommendations, but not for the pharmacist recommendations in Chapter 6. As highlighted in Chapter 3, this may be due to prescribers' lack of intrinsic motivation to engage with a research trial intervention, whereas there may be greater intentions to engage with pharmacist interventions as they have been proven to be effective in improving the appropriateness of prescribing in hospitalised older adults [184].

7.3 Key factors affecting prescriber implementation of medication appropriateness recommendations in hospitalised older adults

The factors identified by this body of doctoral research to be key in affecting prescriber implementation of medication appropriateness recommendations are as follows:

i) Clinical relevance of the recommendation.

ii) Method of communication and integration into prescriber workflow.

iii) The hospital environment.

iv) Prescriber identity.

v) Source of the recommendation.

Whilst the quantitative research components of this thesis allowed us to make statistical inferences on specific factors affecting implementation, the deeper insights into these issues are primarily underpinned by the two qualitative studies described in Chapters 3 and 6. Given the complexity associated with prescribing for older adults in the hospital setting, this thesis aimed to robustly identify the salient factors affecting implementation of these recommendations, as it would be impossible to detail each underlying determinant of this issue. The factors outlined above contain elements that are inextricably interlinked, and will now be discussed as to how each of these elements affects implementation.

7.3.1 Clinical relevance of the recommendation

Participants in both qualitative studies (Chapters 3 and 6) emphasised that the clinical relevance of the recommendations was key to implementation. Recommendations that are important in the clinical context of the patient are more likely to be implemented; for example, if they are related to the acute admission and/or would undoubtedly prevent or ameliorate medication-related harm. Similarly, it was suggested that the low implementation rate observed in the pharmacist intervention described in Chapter 5 may have been due to recommendations that were of low relevance at the time of the intervention [169]. Whilst previous studies have assessed the clinical relevance of pharmacist recommendations or computer-generated recommendations [289, 293-295, 307], very few studies actually prove that clinical relevance is the likely reason for non-implementation. However, in this thesis, the participant insights from the interview studies have been corroborated by the novel quantitative findings in Chapter 4, whereby the clinical relevance was shown to significantly influence the implementation rate, i.e. recommendations of higher clinical relevance were significantly more likely to be implemented than those of lower clinical relevance ($p < 0.05$).

However, recommendations of low clinical relevance can also have an effect on the implementation of recommendations of high clinical relevance. Large numbers of recommendations of low relevance may cause prescribers to experience fatigue with the intervention – for computerised interventions, this is a well-documented phenomenon called '*alert fatigue*' [194], possibly resulting in clinically important

recommendations being ignored. This may have been the case with the findings in Chapter 4, as it was observed that even recommendations judged to be of '*possibly very important relevance*' were still not implemented approximately 30% of the time.

7.3.2 Method of communication and integration into prescriber workflow

As indicated above, these factors affecting implementation are often interconnected. With regard to pharmacist interventions, it should be noted that the clinical relevance of the recommendation often dictates the method of communication used to contact the prescriber [317]. Recommendations of high importance that require urgent resolution will necessitate swift communication, usually using verbal methods – via telephone, or preferably face to face if the prescriber is present. There is less urgency to resolve issues of lower relevance; this may result in the pharmacist providing the recommendation in writing or delaying the recommendation until the next opportunity to discuss with the prescriber. As written recommendations usually have lower implementation rates than verbal recommendations [317, 318], this may be a confounding factor affecting the implementation of recommendations of lower relevance. Thus, one reason postulated for significantly reduced implementation rates for recommendations of lower relevance may be the method of communication used.

In Chapter 5, it was suggested that the proportion of the pharmacist's recommendations implemented was significantly lower than the physician's due to the method of communication used. Only one third of the pharmacist's

recommendations were communicated verbally, whereas all the physician's recommendations were communicated in this manner. This theory was supported by interviewees in Chapter 6, who affirmed that not only did face-to-face communication enhance the rate of implementation, but it was also the preferred method of communication by both pharmacists and physicians as it facilitated synchronous bidirectional discussion [111, 355, 362-364]. Face-to-face communication is usually deemed the most effective method to facilitate implementation of these recommendations [360, 365].

Whilst the method of communication used appears to be important, it is also paramount that provision of prescribing recommendations is integrated into prescriber routine workflow. In Chapter 6, interviewees emphasised that better integration of pharmacists' recommendations into prescribers' workflow may require the organisation of scheduled discussions between pharmacists and physicians (e.g. as part of multidisciplinary team meetings) or pharmacist involvement in physicians' ward rounds. Research has shown that pharmacist participation in consultant physician-led ward rounds can significantly add to the implementation rates of pharmacist recommendations [366]. Furthermore, the findings in Chapter 3 emphasised the importance of the timing of the recommendations – those provided to prescribers at a time when they are not reviewing the patient are much less likely to be implemented [333]. Thus, computer-generated pharmacotherapy recommendations within an EHR should ideally be provided at the point of prescribing or at the time of patient review to facilitate implementation [367].

7.3.3 The hospital environment

Environmental barriers within the hospital setting can prevent the review and implementation of recommendations to optimise medication appropriateness. As previously mentioned, face-to-face communication usually achieves the highest implementation rates, but this is not always possible in busy acute hospital wards [368]. Pharmacists and physicians may not be physically present on the ward at the same time to discuss recommendations face to face. Furthermore, there can be difficulties in contacting prescribers via telephone, and written recommendations in the patients' clinical notes may be overlooked [369].

The implementation of pharmacist recommendations can be influenced by the type of pharmaceutical care model that exists in individual hospital settings. In Chapter 6, it was clear that both pharmacists and physicians felt that pharmaceutical care models with pharmacists and physicians working together on the same clinical care team were likely to have higher implementation rates of pharmacist recommendations compared to those without pharmacists integrated into the team. Previous research has shown that this team-based pharmacist approach not only increases the implementation rate significantly, but it can also result in earlier implementation of recommendations [204]; swifter implementation may be vital in the prevention of particular ADRs.

Participants in Chapters 3 and 6 questioned whether the hospital environment was the right place to optimise the appropriateness of prescribing for older adults, as the acute setting does not always facilitate the review of patients' chronic medications [76]. Certain types of recommendations may be less likely to be

implemented in hospital; for example, recommendations to discontinue or taper benzodiazepines may be more appropriate for a setting where the patient is clinically stable, e.g. in primary care. In the qualitative studies, patient preference did not appear as one of the key factors affecting implementation. However, in a non-acute environment, such as the general practice setting, patient preference and involvement are likely to be much more influential [370, 371].

From this doctoral research, it is evident that prescribers do not always view recommendations addressing medication appropriateness as a priority in the acute hospital setting. Hospital prescribers' busy workload, which is often characterised by severe time constraints, may prevent a thorough medication review being performed for every patient [111]. In addition, many indicated that there is a culture within hospital settings for prescribers to primarily focus on the patients' acute illness and/or issues related to their own particular specialty [372, 373]. In Chapter 6, participants indicated that senior prescribers' compliance with such prescribing norms has a substantial influence on junior prescribers' behaviour [374]. Junior prescribers are less likely to implement recommendations that contravene the prescribing norms within their specialty team or within their hospital setting [375]. This lack of a holistic approach to older patients' care in hospital settings is a fundamental barrier to implementing these recommendations and optimising pharmacotherapy.

7.3.4 Prescriber identity

In this thesis, it was clear that that the roles of individual prescribers and their professional identity have a significant effect on the implementation of medication

appropriateness recommendations. Interview participants in Chapters 3 and 6 asserted that prescriber specialty is an important determinant of implementation; specialists who do not have specific expertise in geriatric pharmacotherapy may be hesitant to make changes to medications that are outside their specialist field of knowledge. Similar to previous research, participants stated that some prescribers believe that they are responsible for managing medications solely within their specialty, and that dealing with other prescribing issues is not within their remit [376]. Furthermore, interviewees described specialists' reluctance to interfere with medications that had been prescribed by a colleague or other specialist [377, 378].

It was clearly evident that prescriber experience is an important factor affecting the implementation rate of recommendations aimed at optimising medication in older adults, which concurs with previous research [379]. However, conflicting views were expressed by interviewees regarding this issue. Some participants suggested that higher implementation rates may be seen amongst junior prescribers as they are more likely to trust the source of the recommendations to be reliable – a lack of clinical knowledge may prevent them from distinguishing between clearly correct and incorrect recommendations [375]. Contrastingly, another common belief was that junior prescribers were less likely to implement recommendations. Irrespective of their knowledge or skills, it was indicated that junior prescribers may be more hesitant to change pharmacotherapy independently – either because they do not accept the role as the '*decision-maker*', or because of fear of negative patient consequences or criticism from their senior colleagues, often resulting in no action being taken in response to particular recommendations [273].

This sense of clinical inertia was also indicated in the systematic review (Chapter 2), whereby the most common reason for non-implementation of computer-generated recommendations was that the patient was already tolerating the PIM [251]. Previous qualitative research has conveyed this '*don't rock the boat*' approach when it comes to making changes to older patients' pharmacotherapy [380, 381]. Furthermore, in accordance with existing research, my findings accentuate the importance of providing medication recommendations to a '*decision-maker*' [271], i.e. usually a senior member of the prescribing team. However, this '*decision-maker*' status is not simply a function of experience and hierarchy [375]; it is also a reflection of prescriber knowledge, training, and self-efficacy [273].

7.3.5 Source of the recommendation

It was evident from this thesis that the source of medication appropriateness recommendations has a substantial impact on the implementation rate. This was distinctly conveyed by the marked contrast in implementation rates of physician-provided recommendations and pharmacist-provided recommendations demonstrated in Chapter 5. A previous study by Axon *et al*. has indicated that junior physicians are more likely to follow senior physicians' prescribing recommendations rather than those from pharmacists [333]; as highlighted in Chapter 6, this is likely influenced by the medical hierarchy within hospital settings [375].

Prescribers having trust in the recommendation source is of paramount importance. A major theme from Chapter 6 was that knowing and trusting the pharmacist was a key facilitator to prescribers implementing the recommendations, which is commonly reported in the literature [326, 360, 361]. Trust is vital to

collaborative pharmacist-physician relationships [355, 382], as with any professional relationship [383]. Building trust can take time [384, 385], and some pharmacists in the interviews felt that they had to prove their competence to some physicians before they were trusted and their recommendations implemented. The need for trust has previously been explained by physicians' lack of awareness of the pharmacists' knowledge, skill set, and role within the healthcare team [323, 324]. Building and maintaining interprofessional trust can be achieved by the provision of valued recommendations consistently over time [355]. However, the findings in Chapter 6 are in line with previous published research in suggesting that high staff turnover may affect collaboration, and thus impact negatively on maintaining these trusting relationships between pharmacists and physicians over time [336, 341].

Similarly, trust in computerised interventions emerged as a subtheme in Chapter 3, whereby interviewees stressed that whilst they regarded computer-generated recommendations to be a potential aid to better quality prescribing, they would not trust them unquestionably. Previous research has shown that prescribers with higher levels of trust in CDSSs are significantly more likely to implement computer-generated recommendations [386]. However, as shown in Chapter 4, some CDSS-generated recommendations may be of potential adverse significance if implemented. Therefore, it is important that prescribers do not implicitly trust all computer-generated recommendations without using their clinical judgment [302].

7.4 Strengths and limitations

The specific strengths and limitations of each study have already been described in the individual research chapters (Chapters 2 – 6). However, the main overall strengths and limitations of this work will be discussed below.

One particular strength of this thesis was the complementary use of quantitative and qualitative research, whereby the results of one study either helped explain findings from previous studies or contributed to the development of research questions in subsequent investigations. For example, the quantitative results from Chapter 4 provided data to substantiate the qualitative findings from Chapter 3, supporting the argument that the clinical relevance of computer-generated recommendations was a significant factor affecting their implementation.

Using the TDF as a robust framework in the directed content analysis phase of both qualitative interview studies allowed me to make comparisons between the findings in Chapters 3 and 6, and subsequently to ascertain the key factors affecting prescriber implementation common to both studies [217, 261]. In addition, the interview transcripts in both qualitative studies also underwent conventional content analysis [261]. Using these methods in tandem was more time-consuming compared to standard approaches of qualitative analysis. However, this allowed me to convey the themes openly without the constraints of specifically reporting according to the TDF, whilst still identifying the predominant TDF domains which can be mapped to suitable intervention functions [226].

Where possible, the studies in this thesis were reported in accordance with best-practice guidelines. The PRISMA Statement was used to report the conduct of the systematic review and meta-analysis described in Chapter 2 [236]. Furthermore, the COREQ checklist guided reporting of the semi-structured interview studies in Chapters 3 and 6 [258]. It is important to emphasise that all five research chapters in this thesis are novel and have either been published in peer-reviewed journals, are currently under review, or are in preparation for submission for publication. Finally, the findings within this thesis have been presented at conferences locally, nationally, and internationally – indicating substantial interest in this body of work and the quality of the research conducted. Further endeavours shall be made to disseminate these findings and to use them to develop interventions which can sustainably minimise PIP in hospitalised older adults.

There are also a number of limitations within this thesis that must be acknowledged. Although the qualitative study in Chapter 3 included participants from six countries, it is acknowledged that the interviews were based around one single computerised intervention (i.e. the CDSS intervention in the SENATOR RCT) [202]. Therefore, some of the findings specific to this intervention may not be as transferable to other hospital settings with different software systems. Additionally, whilst the qualitative study described in Chapter 6 did assess the views of pharmacists and physician prescribers from two hospital sites, it is likely that some findings may not be generalisable across all hospital settings in the Republic of Ireland or in other countries. However, I contend that the context of the study sites

has been described in sufficient detail to allow readers to decide if the findings are transferable to their own setting.

Lastly, this thesis did not involve the development of a novel intervention. However, design and testing of a theoretically-informed intervention was beyond the scope of this body of work. It was deemed more important to firstly gain a greater understanding of the underlying factors that prevent medication optimisation for older adults in the hospital setting. Nonetheless, the findings in this thesis will inform the design of interventions targeting prescriber behaviour aimed at reduction of PIP in hospitalised older adults in future.

7.5 Implications of findings

The findings in this thesis have provided evidence to inform changes to practice that facilitate the implementation of recommendations to improve medication appropriateness in hospitalised older adults. Furthermore, the research described in this thesis has created a foundation to build on the evidence provided as well as yielding directions for new research.

7.5.1 Implications for practice

These findings suggest that a change to the specialty culture in hospitals is required. With the growing proportion of older adults in secondary care, many specialists will have responsibility for increasing numbers of these patients more frequently [387]. Specialists taking a more holistic approach to optimising medications for older adults must become the norm in hospital practice [388]. If PIP is identified and a

recommendation is made, the onus is on these specialists to ensure that PIP is reviewed promptly and implemented if deemed appropriate, rather than clinical inertia which perpetuates PIP, thereby potentially increasing the risk of patient harm [272].

The findings from this thesis concur with previous research in demonstrating that prescribers perceive their knowledge to be suboptimal with regard to prescribing in older adults [111], emphasising that further education and training in geriatric pharmacotherapy is required at both undergraduate and postgraduate level [389, 390]. These educational interventions have been shown to be acceptable to implement and effective in improving prescriber knowledge [143], and may therefore be one solution to overcome prescribing inertia and low self-efficacy with optimising geriatric pharmacotherapy when PIP issues are identified [391].

A key component for interventions to improve medication appropriateness is how the recommendations are provided, who receives them, and at what time during the hospitalisation of an older person. In line with several previous research studies, the research described in this thesis indicates that pharmacists should strive to deliver their recommendations face to face, where possible, in order to facilitate higher implementation rates. It is important to reiterate this point as suboptimal communication methods continue to prevail, which can contribute to adverse patient outcomes [339]. Furthermore, rather than relying on impromptu discussions with prescribers, hospital pharmacists should be afforded opportunities for regular structured face-to-face communication with attending physician prescribers when the patient's case is being reviewed, e.g. such as on ward rounds

or at multidisciplinary team meetings. In addition, when pharmacists are confident that their recommendations can reduce PIP, they can show appropriate assertiveness with regard to proposed medication changes [392]. Previous studies have shown that a lack of pharmacist assertiveness results in medication errors going uncorrected [363].

It was evident from the interviews in Chapter 6 that physicians' awareness of pharmacists' training was an issue [323]. Increased interprofessional education between pharmacists and physicians is warranted to facilitate greater understanding of each profession's knowledge and skills, as well as to promote collaboration [393, 394]. As with previous research, the findings in this thesis advocate greater use of pharmacist-physician collaborative practice models to facilitate implementation of pharmacists' medication recommendations [187, 204, 353]. Team-based pharmacist models may not be feasible in all institutions [204], but it is advisable that pharmacists have good engagement with other multidisciplinary team members, and, where possible, integrate with the attending physician's team.

Pharmacist-physician team-based collaborations should begin with defined introductions – either formal or informal – to open the channels of communication and clarify roles [316, 395]. Given the high turnover of junior medical staff in hospitals, it would seem prudent for future collaborative models to have strong trust-based relationships between pharmacists and senior physician prescribers, particularly consultants. Having senior prescribers collaborating with pharmacists to

optimise pharmacotherapy in multimorbid older adults should serve as role models to junior prescribers and improve their prescribing habits [396].

With the advancement of technology, it is likely that computerised interventions will become much more widely used for prescribing optimisation in the coming decades [88]. Concerns have been expressed about their integration into hospital settings, including being costly to design and integrate into hospital settings, and the possibility of new types of clinical error [249]. However, most computerised systems designed to reduce medication errors are both clinically effective and cost-effective [250, 397, 398]. The systematic review in this thesis established that computerised interventions can significantly reduce PIP in hospitalised older adults. As systematic reviews are widely viewed as the '*gold standard*' in evidence synthesis to inform practice [399], this systematic review adds justification for their use in hospitals, where possible, to reduce PIP and improve patient outcomes. In Chapter 3, it was highlighted that the timing and location of the computer-generated SENATOR recommendations was a key barrier to implementation. Provision of these recommendations in future must be seamlessly integrated into prescriber workflow, ideally in EHRs or EPRs.

Lastly, my findings indicate that the hospital environment may not always be conducive to making changes to long-term medications in acutely unwell older adults [76], and that it may be preferable to do this in primary care post-hospitalisation. However, for this to be achieved, better information exchange is required between primary and secondary healthcare settings in order to facilitate comprehensive medication reviews by GPs and pharmacists [400, 401]. As

described by the interview participants in Chapter 3, prescriber implementation of recommendations may be hindered by patient resistance to deprescribing certain medications, which is commonly reported in the literature for medications such as hypnotics and PPIs [402-404]. Therefore, better patient education is necessary to explain the harms of PIP; previous RCTs with patient education interventions have been proven to significantly reduce PIP in older adults [275, 276].

7.5.2 Implications for future research

Future research into this area should consider the measurement of '*prescriber implementation*' rather than the commonly used term '*prescriber acceptance*', as prescribers may agree with the recommendation at face value but not necessarily act on the recommendation. Nonetheless, prescriber implementation is merely a process measure (i.e. it assesses what prescribers do). To be valid in a clinical setting, process measures must correlate with important patient outcomes [331]. In Chapter 5, the physician-driven intervention was associated with a higher implementation rate for STOPP/START recommendations and a greater absolute risk reduction in ADRs in comparison to the pharmacist's intervention. This prompts two further research questions. Firstly, future studies should examine if improved prescriber implementation of STOPP/START recommendations, as a process measure, correlates with improved patient outcomes (e.g. reduced ADRs). This may have ultimately proved to be a key shortcoming of the SENATOR intervention, whereby low implementation of the recommendations resulted in no difference in the proportion of patients with ADRs between the intervention and control groups [281]. Secondly, future research should aim to test in a multi-centre RCT setting if

there are statistically significant differences in prescriber implementation between physicians' recommendations and pharmacists' recommendations with a larger sample size of pharmacists and physicians to help account for interindividual differences.

This thesis underlines the importance of using qualitative research alongside RCTs in future – not only to explain the quantitative results associated with the trial, but also to help inform the research and development of future interventions [256, 257]. The qualitative findings in Chapter 3 and quantitative findings in Chapter 4 have together confirmed that the clinical relevance of the computer-generated recommendations in the SENATOR RCT significantly affected their implementation. Therefore, this body of work has reaffirmed that future researchers should consider mixed-methods approaches to answer complex research questions.

This thesis shows that meticulous software refinement is required for future computerised interventions to minimise inappropriate or irrelevant recommendations [304, 405], thus increasing the proportion of clinically relevant recommendations. In addition, it was suggested by interviewees that it is fundamentally important to provide the most clinically relevant recommendations first to reduce prescriber fatigue with these types of interventions [194]. Therefore, it is imperative for future researchers to consider developing an in-built ranking system within the software algorithms to prioritise prescribing recommendations with the highest clinical relevance. Furthermore, given the low inter-rater reliability with the scale used in Chapter 4, it would be worthwhile for future researchers to

consider developing a new validated scale to assess the clinical relevance of computer-generated pharmacotherapy recommendations.

As highlighted throughout this thesis, there is an urgent need to develop theoretically-informed interventions with enhanced prescriber implementation of recommendations to optimise medication appropriateness in older adults. Of the fourteen possible TDF domains, five appeared predominant in both qualitative studies in this thesis. As demonstrated in Chapters 3 and 6, mapping these predominant TDF domains to the BCW helped identify what intervention types may be successful in enhancing prescriber implementation rates. However, even though all nine intervention functions described in the BCW may be suitable in theory, all options may not be feasible in routine clinical practice. When designing future intervention strategies, it may be warranted to employ the APEASE criteria (Acceptability, Practicability, Effectiveness/cost-effectiveness, Affordability, Safety/side effects, Equity) [227]. This set of criteria can be used to help decide on the intervention content and delivery in a particular context, but should be applied in a systematic manner in combination with expert judgment. Even though the research in this thesis has been focused on secondary care, there is a clear need for further research to determine the best way to integrate these types of interventions into clinical workflows not only in hospitals but also in other settings, such as general practice, ambulatory care clinics, long-term care facilities, as well as in community pharmacies.

7.6 Conclusion

Optimising pharmacotherapy for multimorbid older adults is a complex process. The research described in this thesis was conducted in the context of a continuing high prevalence of PIP in hospitalised older adults. Prescriber implementation rates of recommendations to reduce PIP vary widely between interventions. Non-implementation increases the risk of medication-related harm, but the reasons for non-implementation in individual studies are often not clear or not reported.

This thesis has made a substantial contribution to the literature by achieving its aim of providing a comprehensive and detailed body of research exploring the key factors affecting prescriber implementation of recommendations to improve medication appropriateness in hospitalised older adults.

This work has provided evidence that prescriber implementation is primarily influenced by the clinical relevance of the recommendations, the method of communication, the identity of the prescriber, the source of the recommendation, and the acute hospital environment. Therefore, prescriber implementation of these recommendations is not attributable to one easily identifiable cause, and it is likely that a multi-faceted approach will be required in future interventions. The studies described in this thesis have laid the groundwork for the development of theoretically-informed interventions that could result in enhanced prescriber implementation of these recommendations, ultimately assisting with the aim of significantly reducing PIP and improving health outcomes for older adults.

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Appendices

Appendix 1: STOPP/START criteria version 2

Screening Tool of Older People's Prescriptions (STOPP) version 2.

The following prescriptions are potentially inappropriate to use in patients aged 65 years and older.

Section A: Indication of medication

1. Any drug prescribed without an evidence-based clinical indication.
2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined.
3. Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent).

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit).
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
3. β-blocker in combination with verapamil or diltiazem (risk of heart block).
4. β-blocker with bradycardia (< 50/min), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side effects than β-blockers, digoxin, verapamil or diltiazem)
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K^+ < 3.0 mmol/l), hyponatraemia (i.e. serum Na^+ < 130 mmol/l) hypercalcaemia (i.e. corrected serum calcium > 2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).

9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).
11. ACE inhibitors or Angiotensin Receptor Blockers (ARBs) in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACE inhibitors, ARBs, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K^+ should be monitored regularly, i.e. at least every 6 months).
13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic blood pressure < 90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).

Section C: Antiplatelet/Anticoagulant Drugs

1. Long-term aspirin at doses greater than 160mg per day (increased risk of bleeding, no evidence for increased efficacy).
2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).
3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors with concurrent significant bleeding risk, i.e. uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding) (high risk of bleeding).
4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy).
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin).
6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in patients with stable coronary, cerebrovascular, or peripheral arterial disease (No added benefit from dual therapy).
7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side effects).

8. Vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g. thrombophilia) for > 6 months, (no proven added benefit).
9. Vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g. thrombophilia) for > 12 months (no proven added benefit).
10. NSAID and vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding).
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease).

Section D: Central Nervous System and Psychotropic Drugs

1. Tricyclic antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
2. Initiation of TCAs as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
4. Selective serotonin re-uptake inhibitors (SSRIs) with current or recent significant hyponatraemia i.e. serum Na^+ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).
5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).
6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms).
7. Anticholinergics/antimuscarinics to treat extra-pyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity).
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).

10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/minute), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as β-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant antimuscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).
13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy).
14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

Section E: Renal System. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m^2 (risk of digoxin toxicity if plasma levels not measured).
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m^2 (risk of bleeding).
3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m^2 (risk of bleeding).
4. NSAIDs if eGFR < 50 ml/min/1.73m^2 (risk of deterioration in renal function).
5. Colchicine if eGFR < 10 ml/min/1.73m^2 (risk of colchicine toxicity).
6. Metformin if eGFR < 30 ml/min/1.73m^2 (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with parkinsonism (risk of exacerbating parkinsonian symptoms).
2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).

3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).
4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: Respiratory System

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side effects of systemic corticosteroids and effective inhaled therapies are available).
3. Antimuscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).
4. Non-selective β-blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm).
5. Benzodiazepines with acute or chronic respiratory failure i.e. pO_2 < 8.0 kPa ± pCO_2 > 6.5 kPa (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H_2 antagonist (risk of peptic ulcer relapse).
2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).
3. Long-term use of NSAID (> 3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).
4. Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side effects).
5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side effects).

6. Long-term NSAID or colchicine (> 3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).
9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

Section I: Urogenital System

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).
2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J. Endocrine System

1. Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Thiazolidinediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure).
3. β-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).
4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence).
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity; no proven benefit outside of the hypogonadism indication).

Section K: Drugs that predictably increase the risk of falls in older people

1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
2. Neuroleptic drugs (may cause gait dyspraxia, parkinsonism).
3. Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, ARBs) with persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls).
4. Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).

Section L: Analgesic Drugs

1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first-line therapy for mild pain (WHO analgesic ladder not observed).
2. Use of regular (as distinct from *prn*) opioids without concomitant laxative (risk of severe constipation).
3. Long-acting opioids without short-acting opioids for break-through pain (risk of persistence of severe pain).

Section N: Antimuscarinic/Anticholinergic Drug Burden

Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g. bladder antispasmodics, intestinal antispasmodics, TCAs, first-generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity).

Screening Tool to Alert to Right Treatment (START) version 2.

Unless an elderly patient's clinical status is end-of-life and therefore requiring a more palliative focus of pharmacotherapy, the following drug therapies should be considered where omitted for no valid clinical reason(s). It is assumed that the prescriber observes all the specific contraindications to these drug therapies prior to recommending them to older patients.

Section A: Cardiovascular System

1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.
2. Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated.
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral, or peripheral vascular disease.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg and/or diastolic blood pressure consistently > 90 mmHg; if systolic blood pressure > 140 mmHg and /or diastolic blood pressure > 90 mmHg, if diabetic.
5. Statin therapy with a documented history of coronary, cerebral, or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.
6. ACE inhibitor with systolic heart failure and/or documented coronary artery disease.
7. β-blocker with ischaemic heart disease.
8. Appropriate β-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.

Section B: Respiratory System

1. Regular inhaled β2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 < 50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
3. Home continuous oxygen with documented chronic hypoxaemia (i.e. pO_2 < 8.0 kPa or 60 mmHg or SaO_2 < 89%).

Section C: Central Nervous System & Eyes

1. Levodopa or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability.
2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms.
3. Acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine).
4. Topical prostaglandin, prostamide, or β-blocker for primary open-angle glaucoma.
5. SSRI (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning.
6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded.

Section D: Gastrointestinal System

1. PPI with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation.
2. Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation.

Section E: Musculoskeletal System

1. Disease-modifying anti-rheumatic drug (DMARD) with active, disabling rheumatoid disease.
2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy.
3. Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).
4. Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores more than -2.5 in multiple sites) and/or previous history of fragility fracture(s).
5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).

6. Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout.
7. Folic acid supplement in patients taking methotrexate.

Section F: Endocrine System

1. ACE inhibitor or ARB (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (> 30mg/24 hours) with or without serum biochemical renal impairment.

Section G: Urogenital System

1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.
2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.
3. Topical vaginal oestrogen or vaginal oestrogen pessary for symptomatic atrophic vaginitis.

Section H: Analgesics

1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective.
2. Laxatives in patients receiving opioids regularly.

Section I: Vaccines

1. Seasonal trivalent influenza vaccine annually.
2. Pneumococcal vaccine at least once after age 65 according to national guidelines.

Reference: *O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015 Mar;44(2):213-8.*

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Appendix 2: Theoretical Domains Framework (version 2)

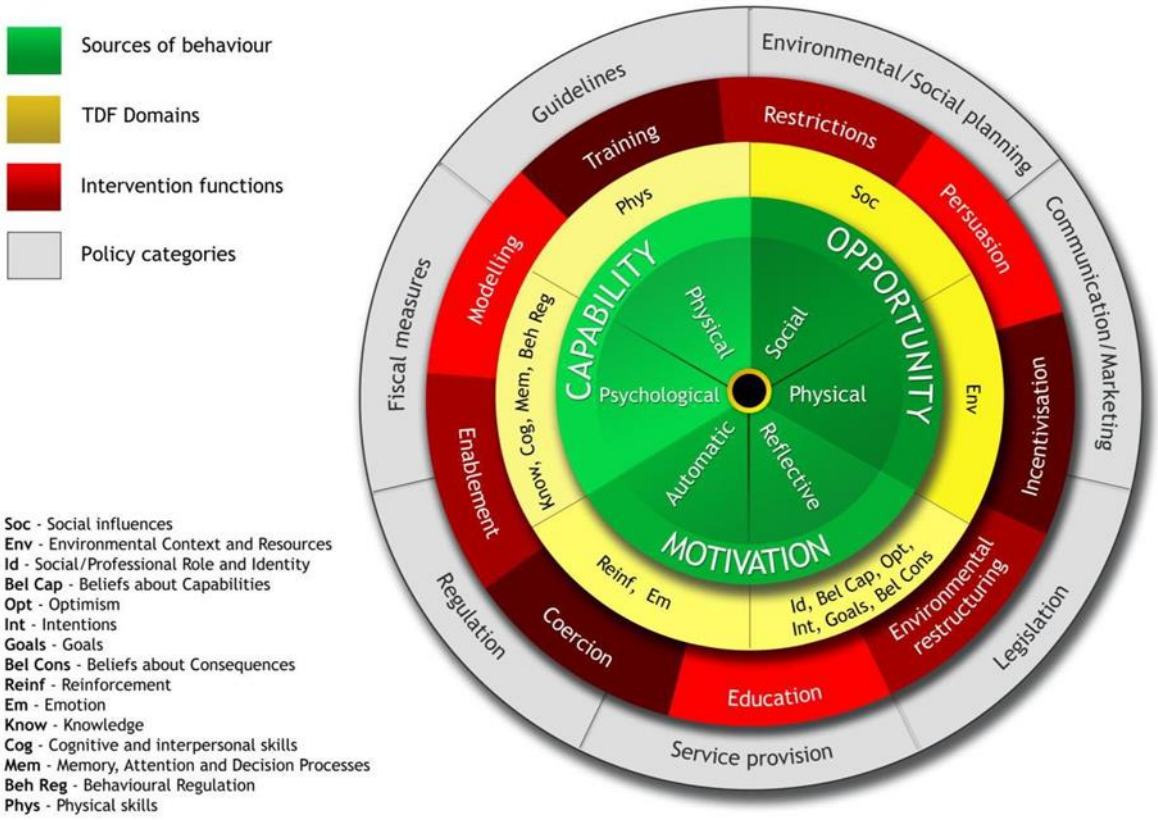
Domain (definition)	Constructs
1. Knowledge (An awareness of the existence of something)	Knowledge (including knowledge of condition /scientific rationale) Procedural knowledge Knowledge of task environment
2. Skills (An ability or proficiency acquired through practice)	Skills Skills development Competence Ability Interpersonal skills Practice Skill assessment
3. Social/Professional Role and Identity (A coherent set of behaviours and displayed personal qualities of an individual in a social or work setting)	Professional identity Professional role Social identity Identity Professional boundaries Professional confidence Group Identity Leadership Organisational commitment
4. Beliefs about Capabilities (Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use)	Self-confidence Perceived competence Self-efficacy Perceived behavioural control Beliefs Self-esteem Empowerment Professional confidence
5. Optimism	Optimism Pessimism Unrealistic optimism Identity
6. Beliefs about Consequences	Beliefs Outcome expectancies Characteristics of outcome expectancies Anticipated regret Consequents
7. Reinforcement (Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus)	Rewards (proximal / distal, valued / not valued, probable / improbable) Incentives Punishment Consequents Reinforcement Contingencies Sanctions

Domain (definition)	Constructs
8. Intentions	Stability of Intentions
(A conscious decision to perform a behaviour or a resolve to act in a certain way)	Stages of change model
	Transtheoretical model and stages of change
9. Goals	Goals (distal / proximal)
(Mental representations of outcomes or end states that an individual wants to achieve)	Goal priority
	Goal / target setting
	Goals (autonomous /controlled)
	Action planning
	Implementation intention
10. Memory, Attention and Decision Processes	Memory
(The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives)	Attention
	Attention control
	Decision making
	Cognitive overload / tiredness
11. Environmental Context and Resources	Environmental stressors
(Any circumstance of a person's situation or environment that discourages, or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour)	Resources / material resources
	Organisational culture / climate
	Salient events / critical incidents
	Person x environment interaction
	Barriers and facilitators
12. Social Influences	Social pressure
(Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours)	Social norms
	Group conformity
	Social comparisons
	Group norms
	Social support
	Power
	Intergroup conflict
	Alienation
	Group Identity
	Modelling
13. Emotion	Fear
(A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event)	Anxiety
	Affect
	Stress
	Depression
	Positive / negative affect
	Burn-out
14. Behavioural Regulation	Self-monitoring
(Anything aimed at managing or changing objectively observed or measured actions)	Breaking habit
	Action planning

Reference: *Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci. 2012 Apr 24;7:37.*

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Appendix 3: Behaviour Change Wheel



Soc - Social influences
Env - Environmental Context and Resources
Id - Social/Professional Role and Identity
Bel Cap - Beliefs about Capabilities
Opt - Optimism
Int - Intentions
Goals - Goals
Bel Cons - Beliefs about Consequences
Reinf - Reinforcement
Em - Emotion
Know - Knowledge
Cog - Cognitive and interpersonal skills
Mem - Memory, Attention and Decision Processes
Beh Reg - Behavioural Regulation
Phys - Physical skills

The domains of the TDF are presented in yellow here. Depending on which domains are identified, they can be mapped to intervention functions, shown here in red, which may be suitable components in the design of future interventions.

Reference: *Michie S, Atkins L, West R. The behaviour change wheel: a guide to designing interventions: London: Silverback Publishing; 2014.*

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Appendix 4: PRISMA checklist for systematic review

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	48
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.	49/50; Registration Number: 52
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	51
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	51/52
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.	52
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.	53
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.	52/53
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 5

Section/topic	#	Checklist item	Reported on page #
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).	53
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.	53
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made.	53
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.	54
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	54
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.	54
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).	54
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
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.	54/55
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.	57-59 Appendix 6
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).	60/61

Section/topic	#	Checklist item	Reported on page #
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.	57-59, 62-63
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	62
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	60-61
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
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).	67-70
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).	68-69
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	70
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.	Published review [251]

Appendix 5: Search strategy for systematic review

Inappropriate prescribing OR potentially inappropriate prescribing OR inappropriate prescription* OR overprescribing OR underprescribing OR inappropriate polypharmacy OR inappropriate medicine* OR inappropriate medication* OR inappropriate drug* OR optimize prescribing OR improve appropriateness of prescribing

AND

aged OR elder* OR geriatric OR older person* OR older patient* OR older adult*

AND

Computer* OR software OR software intervention OR clinical decision support OR CDSS OR CDS

Note: This search strategy was developed in the PubMed database. For each of the remaining databases, the search strategy was modified to suit their specific search capabilities if necessary.

Appendix 6: Supplementary details about the included studies in the systematic review

Author Year (Country)	Study design	Duration of study	Number of patients	Target medications	Intervention aimed at	Prescriber involved with intervention	Intervention
Agostini *et al.* 2007 (USA) [211]	Before-after study	Pre- and post-intervention periods were both 12 months.	C: 12,356 I: 12,153 Total: 24,509	The sedative hypnotics diazepam and diphenhydramine.	Patients aged ≥ 65 years admitted to the adult inpatient service.	Physician	Computerised reminder in a CPOE system aiming to minimise use of diphenhydramine and diazepam, and directing physicians to either a non-pharmacological sleep protocol or to an alternative medication, such as trazodone or lorazepam.
Boustani *et al.* 2012 (USA) [240]	RCT	Twenty-one months.	C: 225 I: 199 Total: 424	Eighteen medications with moderate to severe centrally-acting anticholinergic properties, selected by an interdisciplinary team (which included a geriatrician, a geriatric nurse practitioner, a pharmacist, a social worker, a physical therapist, an occupational therapist, and an administrative assistant).	English-speaking patients ≥ 65 years hospitalised on a medical ward, with cognitive impairment at the time of hospital admission. Patients excluded if they had previously been enrolled in the study, were aphasic, or unresponsive at the time of screening.	Physician	If a physician ordered any one of 18 inappropriate anticholinergic medications in a CPOE system, a CDSS interruptive alert recommended to discontinue the medicine, dose modification, or suggested an alternative.
Ghibelli *et al.* 2013 (Italy) [238]	Before-after study	Two months for both phases.	C: 74 I: 60 Total: 134	PIMs according to the 2003 Beers criteria, as these were the explicit criteria in INTERcheck®.	Inpatients ≥ 65 years – only exclusion criteria were severe malignancy (life expectancy less than 6 months) or terminal illness.	Physician	The physician utilised a computerised prescription support system (INTERcheck®) to identify PIMs and potential drug-drug interactions, as well as aiming to reduce anticholinergic load and adjust doses in patients with renal impairment.

Author Year (Country)	Study design	Duration of study	Number of patients	Target medications	Intervention aimed at	Prescriber involved with intervention	Intervention
Griffey *et al.* 2011 (USA) [201]	Interrupted time series	Alternated OFF, ON, OFF, ON. First two blocks were 6 weeks long and last two blocks were 7 weeks long.	C: 668 I: 739 Total 1,407	Benzodiazepines, NSAIDs, opiates, sedative-hypnotics. These were selected by an expert panel including a geriatrician, a general psychiatrist, a pharmacist, two general internists, and an anaesthesiologist specialising in pain management, as had previously been done in Peterson *et al.* [200].	All persons aged ≥ 65 years who had an order for a medication in one of the targeted drug classes during the study period. The study excluded patient orders in which qualifying medication orders were subsequently cancelled and any orders with missing data.	Physician	When one of the study medications was ordered in a CPOE system for patients ≥ 65 years, a clinical decision support tool modified one or more of the following parameters: medication selection, default dosage, or default frequency. The physician could then choose to accept or override the recommendation. The tool was alternated 'OFF' and 'ON' in consecutive blocks during the study period.
Lester *et al.* 2015 (USA) [241]	Before-after study	Four years: 2010 to 2013. Results are from the second quarters of each year.	C: 3,259 I: 9,591 Total: 12,850	Diphenhydramine, metoclopramide, and all antipsychotics.	Patients aged ≥ 65 years.	Prescribers – doesn't specify.	Informational alerts popped up when a PIM was ordered in the CPOE system. The physician was required to acknowledge the alert, before deciding on whether to cancel their order or continue prescribing the medication.
Mattison *et al.* 2010 (USA) [242]	Before-after study	Pre-alert: 6 months. Post-alert: 37 months.	Number of patients is not stated	A list of Beers 2003 criteria medications selected by a geriatrician and pharmacist, and then revised by the hospital's Pharmacy and Therapeutics Committee.	All hospitalised inpatients aged ≥ 65 years.	Physicians	The CPOE system alerted prescribers when a PIM was ordered by providing a medication-specific warning that advised alternative medication or dose reduction.

Author Year (Country)	Study design	Duration of study	Number of patients	Target medications	Intervention aimed at	Prescriber involved with intervention	Intervention
Peterson *et al.* 2005 (USA) [200]	Interrupted time series	Four consecutive 6-week study periods. 1st and 3rd were control periods (usual CPOE). 2nd and 4th periods were intervention periods.	C: 2,515 patient visits I: 2,647 patient visits Total: 5,162	Seventy-two psychotropic medications decided on by a panel of experts, including a geriatrician, a geriatric psychiatrist, a pharmacist, 2 internists, and an anaesthesiologist specialising in pain management.	All patients ≥ 65 years prescribed one of the targeted medications and admitted to any of the medical, surgical, neurology, and gynaecology services were evaluated. General ward and intensive care patients were eligible for analysis. Only those patients whose admission was entirely contained within 1 of the 6-week study periods were included.	Physicians	A decision support tool altered the default dose and frequency for psychotropic medications for patients ≥ 65 years, and suggested an alternative medication when prescribers ordered one of 12 psychotropic medications known to be poorly tolerated in older patients. The support tool was activated for 2 of 4 six-week study periods in an off-on-off-on pattern.
Terrell *et al.* 2009 (USA) [210]	RCT	Thirty months.	C: 1,925 I: 1,793 Total: 3,718	Nine high-use and high impact PIMs, selected by an expert panel consisting of two doctors of pharmacy, two physician information technology experts, three geriatricians, and three emergency physicians.	The intervention was aimed at emergency department physicians. C: 31 physicians I: 32 physicians	Physicians	Physicians in the intervention group were provided decision support when they attempted to prescribe a PIM for patients ≥ 65 years who were being discharged from the emergency department. The computerised reminder provided recommendations for alternatives which the physician could accept or reject.

USA: United States of America C: Control group; I: Intervention group; CPOE: Computerised physician order entry; RCT: Randomised controlled trial; CDSS: Clinical decision support system; PIM: Potentially inappropriate medication; NSAID: Non-steroidal anti-inflammatory drug.

Appendix 7: Ethical approval for Chapter 3

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

ECM 4 (m) 05/09/17

5th September 2017

Professor Stephen Byrne
School of Pharmacy
University College Cork
Room UG06
Cavanagh Building
College Road
Cork

Re: Acceptability and delivery of computer-generated recommendations regarding medication optimization in a multi-centre randomized controlled trial.

Dear Professor Byrne

Approval is granted to carry out the above study at University College Cork and Cork University Hospital.

The following documents have been approved:

- Cover Letter dated 9th August 2017
- Application Form signed 9th August 2017
- Participant Information Letter
- Consent Form Version 1.0 dated August 2017
- Study Protocol
- Topic Guide
- Evidence of Insurance.

We note that the co-investigators involved in this study will be:

- Professor Denis O'Mahony, Consultant in Geriartic Medicine, Shane Cullinan, Lecturer in Pharmacy Practice and Kieran Dalton, PhD Researcher.

The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

4. Notify CREC of discontinuation of the study

5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospital

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 8: COREQ checklist for qualitative interview study from Chapter 3

Domain 1: Research Team and Reflexivity

Personal characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	KD conducted the interviews.
2.	Credentials	What were the researcher's credentials (e.g. PhD, MD)?	At the time of undertaking the interviews, KD's credentials were BPharm, MPharm, MPSI.
3.	Occupation	What was their occupation at the time of the study?	KD is an Irish registered pharmacist who was undertaking a PhD in Clinical Pharmacy research when this study was conducted.
4.	Sex	Was the researcher male or female?	Male.
5.	Experience and training	What experience or training did the researcher have?	KD completed training in utilisation of QSR NVivo® software, and received training in analysis of qualitative interviews at Oxford University, United Kingdom.
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	The interviewer had established a rapport with some of the primary researchers prior to the qualitative study due to trial commitments (i.e. annual general meetings, teleconferences, communication via email), but no relationship between the interviewer and prescriber participants was established prior to study commencement.
7.	Participant knowledge of the interviewer	What did the participants know about the researcher (e.g. personal goals, reasons for doing the research)?	KD had disclosed to all participants that he was a pharmacist undertaking this study as part of his PhD, prior to conducting the interviews.
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? (e.g. bias, assumptions, reasons and interests in the research topic)	KD is a registered pharmacist who was working as a primary researcher as part of the SENATOR trial, and was conducting this study as part of his PhD exploring factors affecting prescriber implementation of medication recommendations in hospitalised older adults. This information was disclosed to participants ahead of the interview.

Domain 2: Study Design

Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study (e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis)?	Content analysis was used in this study to analyse the data from the interview transcripts. Conventional content analysis was used to identify the conventional themes, which were attributed as factors that influenced implementation of the SENATOR recommendations. The Theoretical Domains Framework (TDF) was used to structure the interview topic guides, and directed content analysis was used to identify the relevant TDF domains.
Participant selection			
10.	Sampling	How were participants selected (e.g. purposive, convenience, consecutive, snowball)?	Primary researchers involved with the SENATOR trial were recruited using purposive sampling as there were limited numbers of primary researchers at each site. Snowball sampling was used to recruit prescribers, whereby the SENATOR primary researchers and their colleagues referred the interviewer to prescribers in their site who would participate in the study.
11.	Method of approach	How were participants approached (e.g. face-to-face, telephone, mail, email)?	Participants were contacted via email, and were provided with an information sheet and consent form in their native language in advance of the interview.
12.	Sample size	How many participants were in the study?	24.
13.	Nonparticipation	How many people refused to participate or dropped out? Reasons?	None.
Setting			
14.	Setting of data collection	Where was the data collected (e.g. home, clinic, workplace)?	All interviews took place in the participant's workplace, or in their workplace when previously working as part of the SENATOR trial.
15.	Presence of nonparticipants	Was anyone else present besides the participants and researchers?	No.
16.	Description of sample	What are the important characteristics of the sample (e.g. demographic data, date)?	Table 3.1 provides details of where the participants were sampled from, whilst Table 3.2 provides demographic details of the participants. The interviews took place between November 2017 and May 2018.

Data collection

17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Two separate topic guides comprising a similar line of questioning (with prompts where appropriate) were formulated for both prescribers and primary researchers, and these were based on a review of the literature, the TDF, and my own and my supervisors' knowledge of the research area of the randomised controlled trial and research area. Careful consideration was given to the language used, knowing that English would not be the first language for all participants. Interviewees were provided with a sample of a SENATOR report in their native language during the interview as a reminder of the report design and the types of recommendations provided. The topic guide for interviewing prescribers was piloted with a prescriber who had received SENATOR recommendations in the lead trial site, and this interview was included in the data analysis. The topic guide for interviewing primary researchers was piloted with a primary researcher working with a similar randomised controlled trial (OPERAM study), who was very familiar with the SENATOR trial procedures. The topic guides were iteratively refined during the study to ensure that emerging themes were explored in subsequent interviews.
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No.
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio-recorded.
20.	Field notes	Were field notes made during and/or after the interview or focus group?	Field notes were recorded after each interview, and were used to refine topic guides and inform data analysis.
21.	Duration	What was the duration of the interviews or focus group?	The average interview length was 24 minutes (range 18 – 64 minutes).
22.	Data saturation	Was data saturation discussed?	Data analysis coincided with data collection, and sampling continued until no new themes emerged. As per the Francis *et al.* method, an additional three interviews were conducted without any new themes appearing to confirm that data saturation had been reached.
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No.

Domain 3: Analysis and Findings

Data analysis			
24.	Number of data coders	How many data coders coded the data?	Two (KD and SC).
25.	Description of the coding tree	Did authors provide a description of the coding tree?	A description of the process is provided, whereby initial, non-hierarchical codes were categorised, and subsequently developed to generate themes and subthemes as part of conventional content analysis. The TDF was the chosen framework for directed content analysis, and was used as the basis for a coding tree here.
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Conventional content analysis comprised open coding to inductively create initial, non-hierarchical codes. These initial codes were subsequently categorised to generate the evolving themes and subthemes. Directed content analysis was then employed whereby the transcripts were deductively coded using the TDF to identify the domains present.
27.	Software	What software, if applicable, was used to manage the data?	QSR NVivo® Version 11
28.	Participant checking	Did participants provide feedback on the findings?	No.
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Yes.
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Quotations are presented in a manner consistent with findings.
31.	Clarity of major themes	Were major themes clearly presented in the findings?	Major themes are clearly presented in the results section.
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Subthemes are presented under each of the major themes.

Appendix 9: Final version of topic guides for Chapter 3

Topic guide for SENATOR primary researchers

1. As we know, the SENATOR engine analysed patients' information and made recommendations to optimise patients' medications. Here is an example of a report that was generated. What are your thoughts on the design of the report?
   - Structure, layout, colours, font size, information provided
   - Location of report
2. When a prescriber was looking at a SENATOR report for the first time, what do you think they would have thought of it?
   - Do you think that they knew what the report was asking them to do?
3. What are your thoughts on the quality of the recommendations?
   - Thoughts on the relevance of the recommendations?
   - Would you change anything about the recommendations/report?
4. What are your thoughts on the timing of the intervention?
   - Would it have been better to have the report at the original point of prescribing/admission?
5. What are your thoughts on conducting this intervention in the hospital setting?
   - Do you think there is a more appropriate setting this could take place?
6. Whose role is it to make recommendations to optimise older patients' medications in your hospital?
   - How would these recommendations be communicated (do you know)?

7. How do you communicate the presence of the report and the recommendations?
   - Were there any barriers to this communication?
8. What are your thoughts on the methods of communication of the report's recommendations in this hospital?
   - What method of communication did you find most successful when providing the recommendations to the prescribing team, e.g. face-to-face or via telephone?
9. Given your professional background, how do you feel your role may affect the number of recommendations implemented?
   - The role/status of the primary researcher
10. How do you feel when discussing the report with the prescribing team?
11. Did you have any particular rewarding or negative experiences in your role in carrying out the intervention?
12. What was the reaction of prescribers in your hospital to the SENATOR report/recommendations?
   - Was there a positive or negative reaction?
   - Do you think that prescribers saw it as a priority to review the SENATOR report recommendations?
13. In your opinion, whose role should it be to review computer-generated recommendations like this in the hospital setting?
   - Do you think there should be someone to screen the recommendations before reaching the prescriber?

14. The prescriber implementation rates for the SENATOR recommendations were lower than expected – why do you think that may be?
15. How do you think that we could achieve higher implementation rates of the recommendations?
16. Do you foresee any problems for implementing an intervention like this routinely in future?
    - Resources (money, electronic prescribing)
    - Having a defined role for someone to lead/deliver the intervention
17. Do you think there is anything more you could have done to enhance the acceptance rates of the recommendations?
    - Anything more that your Principal Investigator could have done?
    - Anything more that the lead site (Cork) could have done?
18. How could SENATOR (or a similar intervention) be done better in future?
    - What resources would be required?
    - What information would you want to be provided by the computer?
    - How should the information to be provided?

That brings us to the end of the interview. Do you have any additional comments that you would like to make, or any points you would like to expand on?

Topic guide for prescribers

The SENATOR trial involves a computer programme analysing older patients' medications, medical conditions, and other information with the aim of optimising prescribing. The programme then generates a report for the prescribing team to review with recommendations to address potentially inappropriate medications or potential prescribing omissions.

1. Firstly, what are your thoughts on the SENATOR intervention overall?
2. Do you think that automated programmes can help reduce potential inappropriately prescribing in hospitalised older adults?
   - Why? / Why not?
3. What is your role in reviewing the appropriateness of medications an older patient is prescribed during their hospital stay?
   - Is this a priority of yours on a daily basis?
4. How confident do you feel in prescribing for this patient group?
   - Do you think that your prescribing decisions would benefit from regular automated support/feedback/advice?
   - How do you feel about trusting recommendations from an automated programme?

As I said, the SENATOR intervention produced a report highlighting potentially inappropriate medications or potential prescribing omissions. Here is an example of a report generated.

5. How did you receive the report or how were you made aware of the recommendations?
   - What are your thoughts on the method of communication for this intervention?
   - What about the timing of the intervention?
6. When you looked at the SENATOR report for the first time, what did you think of it?
   - Did you understand what the report was aiming to do or what it asked of you?
   - What do you think of the design of the report? (e.g. layout, font size, length, colours, data / information contained within the report etc.)
7. When looking at the report, how easy or difficult was it for you to identify which of the recommendations were relevant for each patient?
   - Do you think all of the recommendations that you have reviewed have been relevant for your patients' needs?
   - If you saw irrelevant recommendations, would it make you question the validity / relevance of the other recommendations?
8. What influence, if any, did the SENATOR report have on your decision-making?
9. Is there anything that may have prevented you from acting upon the SENATOR recommendations?
   - Patient's acute medical presentation / Lack of information to hand / Work environment / Resources / Time / Your role / Role of others

10. In your opinion, whose role should it be to review these computer-generated recommendations in the hospital setting?
    - Do you think someone should screen the recommendations before reaching the prescriber (e.g. doctor, pharmacist, nurse)?
11. The prescriber implementation rates for the recommendations were lower than anticipated – what do you think are the reasons for this?
    - How do you think that we could achieve higher implementation rates of the computer-generated recommendations?
12. What problems, if any, do you foresee in implementing this intervention into routine clinical practice?
    - Resources (e.g. money to cover the cost, electronic prescribing, having a person to review the recommendations)
13. Do you have any suggestions for how we could enhance the implementation of this type of intervention in future?
    - What resources would be required? Electronic prescribing?
    - What information would you want to be provided by the computer?
    - How would you like this information to be provided? Information box/report/alert?

That brings us to the end of the interview. Do you have any additional comments that you would like to make, or any points you would like to expand on?

Appendix 10: Sample SENATOR report

SENATOR Trial Id: [redacted]

SENATOR

If Available Please Affix Local Patient Identifier here

Gender: Female
Date of Birth [redacted]

Date of arrival: [redacted]
Age: 73

The recommendations below are based on medications prescribed at the time of assessment and do NOT include those on hold.

SENATOR provides generic recommendations but cannot account for all the individual characteristics for any given patient, this remains the sole responsibility of the prescribing clinician in deciding to use or not use the recommendations below.

Routine Daily Drugs prior to Senator Assessment as of [redacted]

(Please consider stopping the drugs in orange, see explanation in STOPP recommendations that follow)

#	Generic Name
1	pantoprazole
2	furosemide
3	lercanidipine hydrochloride
4	oxycodone hydrochloide
5	nebivolol
6	metronidazole

PRN Drugs:

#	Generic Name
1	ondansetron
2	oxycodone hydrochloide

STOPP Recommendations (The following prescription is potentially inappropriate for the following reason)	
Please check that all prescribed drugs are clearly indicated. Please also check for any inappropriate duplicate drug class prescription (e.g. two ACE inhibitors, two selective serotonin reuptake inhibitors).	
furosemide	Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
oxycodone hydrochloide	Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first line therapy for mild pain (WHO analgesic ladder not observed). Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation).
pantoprazole	Any drug prescribed beyond the recommended duration, where treatment duration is well defined.

START Recommendations (Unless an older patient's clinical status is end-of-life and therefore requiring a more palliative focus of pharmacotherapy, the following drug therapies should be considered where omitted for no valid clinical reason(s). It is assumed that the prescriber observes all the specific contraindications to these drug therapies prior to recommending them to older patients. The following prescription is appropriate for the following reason)
Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation. OR Aspirin (75 mg – 160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated
Laxatives in patients receiving opioids regularly.
Seasonal trivalent influenza vaccine annually.
Pneumococcal vaccine at least once after age 65 according to national guidelines.

Potentially Adverse Medication Interactions

Potentially Important Drug-Disease Interactions

Non pharmacological therapies that may help your patient
(ONTOP)

SURGICAL PATIENTS: In patients aged 65 years hospitalized with acute surgical illness, there is a significant risk of developing delirium.
The following interventions are evidence-based and have been shown to prevent delirium in this at-risk population when implemented together, as a multi-component intervention.

Ambulate early
a) Get the patient out of bed on postoperative day 1 and for several hours each day
b) Administer physical therapy daily; administer occupational therapy, as needed

Hydrate and feed
a) Restore serum sodium, potassium and glucose to normal levels (glucose < 16.67 mmol/L (300 mg/dl) for diabetics)
b) Treat dehydration or fluid overload
c) Ask the patient to use dentures and position him/her properly for meals
d) If the patient is unable to eat, consider other means of feeding

Oxygenate
a) Supplement oxygen to maintain blood oxygen saturation >90%, preferably >95% (with caution in patients with COPD)
b) Correct systolic blood pressure to a level of >2/3 of baseline or >90 mmHg

Control pain
a) Follow national, local or hospital guidelines for the treatment of pain
d) Assess the underlying causes of the pain

Regulate bladder and bowel function
a) Check for bowel movement by postoperative day 2 and every 48 hours afterwards
b) Actively prevent and treat constipation
c) Remove urinary catheter by postoperative day 2 and screen for retention or incontinence afterwards

d) Employ a skin care program for patients with established incontinence

Prevent, detect early, and treat major postoperative complications

a) For suspected myocardial infarction/ischemia, perform an electrocardiogram and analyze cardiac enzymes
b) For supraventricular arrhythmias/atrial fibrillation, ensure appropriate ventricular rate control, balanced electrolytes, and administer anticoagulants in cases of persistent atrial fibrillation.
c) Prevent pulmonary embolus with appropriate doses of prophylactic anticoagulants
d) For pneumonia/chronic obstructive pulmonary disease, screen and treat as needed
e) Screen for and treat urinary tract infection
f) Transfuse blood if hemoglobin levels are <8 g/dl.

Contraindications

There are no established contraindications to the use of non-pharmacological interventions for the prevention of delirium

Disclaimer: Whilst every effort has been made to ensure that the information provided by SENATOR is accurate, up-to-date and complete, no guarantee is made to that effect. In addition, the drug information contained herein may be time-sensitive and should not be utilized as a reference resource beyond the date hereof. SENATOR's drug information is a reference resource designed as supplement to, and not a substitute for, the expertise, skill, knowledge, and judgement of healthcare practitioners in patient care. The absence of a warning for a given drug or drug combination in no way should be construed to indicate that the drug or drug combination in question is safe, effective, or appropriate for any given patient. The information contained herein is not intended to cover all possible uses, directions, precautions, warnings, drug interactions, allergic reactions, or adverse treatment effects. Clanwilliam Health Ltd. does not assume any responsibility for any aspect of healthcare administered with the aid of information contained herein. Whilst the prescription advice generated by SENATOR software is evidence-based and correct as far as can be determined, it is emphasized that this advice should not supersede careful clinical judgement in individual cases. It is further emphasized that the final decision to accept or reject SENATOR-generated treatment advice rests primarily with the patient's attending medical staff.

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Appendix 11: Supplementary quotations for Chapter 3

Theme	Descriptor	Illustrative Quotations
1. Computerised Output	Aid to prescribing, but cannot be trusted blindly	*"…essentially what they're doing is giving us guidance and as clinicians it's up to us to decide what we do about it".* **Surgical Prescriber 1** *"I think they can be very helpful. They can't do it automatically but I think they can give very good hints, so I think in general they're helpful as assisting".* **Medical Prescriber 3** *"I think it's a useful resource. Also, I think that we make mistakes when we're prescribing because there's too much information we have to attend to and sometimes we just can't handle everything, and so I think it's a very good thing that we can have a computer or someone who can supervise what we are doing. So it's like, it helps us to do our job better".* **Medical Prescriber 10** *"I don't think you can look at the advice alone. Em…like I said sometimes there are a bit of errors, which I think is normal. Em…you have to think about it yourself and not just read like the advice and put it into eh…put it into practice but really think about it as well".* **Medical Prescriber 2** *"I think…the human intelligence, at least as it is today, computers haven't taken that over…that we use them as assisting us but not relying on it completely so if there comes, you know if there's something that we think sounds funny we can always take over and correct that".* **Medical Prescriber 12** *"If it comes out with something that is completely opposed to my views then I would also then be looking into that to find out then, okay, I wouldn't have perceived that as an interaction. Is there other stuff to back it up? I don't think I would be blindly led by a computer".* **Medical Prescriber 6** *"I wouldn't implicitly trust automated recommendations I suppose is what I'm trying to get at".* **Medical Prescriber 8** *"…you cannot trust the programme blindly, i.e. you have to still think about the medication".* **Medical Prescriber 4** *"I mean I wouldn't ever rely solely on a computer, but I think it's kind of helpful to have that, that initial maybe…em…notification from a computer programme, and you can work with that then".* **Medical Prescriber 1**
	Lack of specificity	*"…it's not specific to the particular patient because it does…it did not take into account the complexity of that particular patient".* **Primary Researcher 9** *"…the decision support software says that for a thousand people, that's the right thing to do. It may not be the right thing to do for that person".* **Surgical Prescriber 2** *"…the computer cannot take into context the human aspect of the patient and therefore they cannot they cannot advise on the individual, they can advise on the, on the actual drugs".* **Medical Prescriber 9**

Theme	Descriptor	Illustrative Quotations
1. Computerised Output (continued)	Recommendations of low relevance contributing to prescriber fatigue	*"I think absolutely for sure, em, the fact that a lot of the recommendations were simply not relevant or appropriate, I think that's very very very very important. Em, and…obviously explains part…at least partly explains the low uptake".* **Primary Researcher 7** *"I had recommendations that were irrelevant and even, even dangerous."* **Medical Prescriber 4** *"So I think there's potential for benefit, but you need to make sure it's not information overload and people aren't just getting dismissive of it".* **Medical Prescriber 6** *"…if we could filter out the irrelevant or inappropriate recommendations, I think that the whole value of the report would go upwards very significantly. Because undoubtedly there is a fatigue as well when you get lots and lots of recommendations".* **Primary Researcher 7** *"…it seems that if there's been a negative one then they're not so receptive the next time".* **Primary Researcher 4** *"Well if you have some not very specific recommendations, you can see that they are…the second time you go they are…or the third time they are less interested in the study. So I already had physicians who start laughing when I go there again. So it's definitely a barrier to the adherence".* **Primary Researcher 1** *"…some consultants were really interested and over time when I repeatedly met the same consultant, they kind of lost interest because some of the recommendations were too broad, too generic. They were not tailored to that particular patient".* **Primary Researcher 9**
	Provision of the recommendations: Report Layout and Length	*"…well this is rather clear. Stop these. Start these. So em I don't know if you can get any more clearer than that".* **Medical Prescriber 12** *"There's a lot of text in it so if people are very busy, they might think it's too big, too big a file. But having this in colour – STOPP and START – this is very good, very clear yeah".* **Primary Researcher 8** *"I'd try and keep it a little bit shorter, so make sure the report (you know) only has recommendations that really are relevant to the setting".* **Primary Researcher 2** *"…if it could be a one-page document I think that would be better because I think we all have short attention spans…"* **Primary Researcher 7** *"…it's probably a little bit too long and a bit too detailed (you know), and that maybe just focusing on the smaller number of maybe significant…significant STOPP or START recommendations might make more sense".* **Medical Prescriber 1**
	Provision of the recommendations by the primary researcher	*"…if you've had a chance to speak to the researchers, you've get…you've got a better understanding".* **Medical Prescriber 6** *"…their interest would be higher if I was a doctor who would give the report to them".* **Primary Researcher 1**

Theme	Descriptor	Illustrative Quotations
2. Acute hospital environment	Right setting for the intervention	*"It's the right place to do it, absolutely. Here we are starting a lot of new drugs. Here we have the possibility to monitor the response and the side effects".* **Medical Prescriber 12** *"…the inpatient services are very specialty-driven. And probably the only people who've really got a whole overview of the person, to me, is the general practitioners and they're the ones who are having to, who are being asked to, continue prescriptions".* **Medical Prescriber 6** *"I mean they, these recommendations are relevant to the patient, but they're not particularly relevant to a patient in hospital at that particular time".* **Primary Researcher 2** *"In the ward, I'm often just dealing with the acute issues. And I probably don't see it so much as my role to start stopping what other people have done. I think when the SENATOR trial first came out I wondered why it wasn't being targeted in general practice".* **Medical Prescriber 6**
	Unfamiliar intervention in a busy environment	*"So unless they actually become part of the fabric of a health service, then you're gonna have a situation where you're gonna have a few enthusiastic early uptakers, and then you're gonna have everyone else who kind of (you know) will uptake, take them up for a period of time and then will drift out of consciousness".* **Surgical Prescriber 2** *"I think just by repeating this I think people will get more eh…yeah familiar with this kind of program".* **Medical Prescriber 4** *"I think so yeah, and also (you know) this is something new. People are not used to this".* **Medical Prescriber 12** *"…any trial would probably suffer from similar…you know similar challenges in a really busy hospital where people just are kind of too busy to give an awful lot of time to a research project".* **Primary Researcher 2** *"…they were rushed, they were busy doing something else, and the recommendations that I would have highlighted to them would not have been seen as a priority, it would have been something that they would have come back to at a later stage".* **Primary Researcher 7** *"…it's very busy busy mornings we have here but so it is easy to get lost. So in order for it to be used in the everyday rounds, it has to become more established so that (you know) it's a part of that, that everyday work, not just something that (you know) you hear about once a week, or every other week, or something like that, then you forget about it".* **Medical Prescriber 12**

Theme	Descriptor	Illustrative Quotations
2. Acute hospital environment (continued)	Timing of the intervention and location of the recommendations	*"…if it was present right at the time where they're dealing with the patient, where they're focused on the patient, I think that could absolutely have improved uptake of the recommendations".* **Primary Researcher 7** *"The intervention of getting the information may not have been the best time. The patient isn't on your mind - you're not thinking about the patient, you're not doing a chart review".* **Medical Prescriber 8** *"I'd say it was more the timing and…you know it was hit or miss if you got somebody who was in the middle of doing a hundred things and you're interrupting them to tell them about this report you've placed, they're not going to be very receptive to…to hearing about it".* **Primary Researcher 2** *"…certainly from me the big issue was just the timing of getting the report versus when I saw the patient, when I was probably most invested in (you know) their, their care pathway".* **Medical Prescriber 1** *"…it is a little bit of an interruption and especially you may be dealing with another patient's case and so to to to sort of think back on…on a different patient and their prescription I think it's hard to really grasp and take in the recommendations at that particular time".* **Primary Researcher 7** *"…it might just be around kind of timing actually more than anything else, and that maybe the route of the information just being a bit disconnected. You know a patient's in one place, you get your information in a different place…"* **Medical Prescriber 8** *"I think it's location. I think simply if we saw it we'd have gone 'oh yeah, that's sensible'. So, putting it physically in where we're writing our notes".* **Medical Prescriber 11** *"If instead having it inside the history, it was em…it appeared with the programme, with the prescription programme, because you have to use it - there's no other way, and probably they would pay more attention".* **Medical Prescriber 10** *"I suppose one of the other things is that this came into me by email, and em…it, it, it maybe wasn't immediate enough in terms of the patient interaction to take it on board, you know that you would…probably the best time to get this is actually the first time you see the patient on the ward round".* **Medical Prescriber 1** *"I find the eh, the email a bit better for me personally, because eh if it's filed in the notes it can get lost amongst all the pages and I wouldn't necessary know that the patient would have that type of recommendations".* **Medical Prescriber 9** *"Ill often the time when you'll come, when you'll actually open this email will be a couple of days later after you've gotten it and at that stage the patient is well gone home and that window is kinda missed you know".* **Surgical Prescriber 2**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity	Responsibility	*"But I'm not the prescribing clinician. You know because a lot of the time, and you can say it well yes you are because they've come into hospital and you've, you or a member of your team have physically prescribed them, but really you're not. You're, you're carrying on a prescription on a decision that's been made by somebody else. You're honouring their decision".* **Surgical Prescriber 2** *"Well I think it's my responsibility to do so as a doctor and I'm the one who has to decide which medicines I give to someone".* **Medical Prescriber 10** *"They don't feel it's their place. They feel it's a GP's job so they don't want to get involved or they're not confident enough to get involved".* **Primary Researcher 4** *"…really it needs to be targeted at the people who are making the decisions to initiate the medications in the first place rather than me, who is seeing them on a very casual basis. I might see somebody's prescription chart once in their entire relationship with me (you know), whereas you're talking about a general practitioner who is seeing them on a very regular basis".* **Surgical Prescriber 2**
	Prescriber Inertia	*"…if it's related, if someone's come in with a fall and then it's related to the admission, I'd be much more likely to look at the SENATOR recommendations in detail. So if they've come in with something which I perceive to be something completely unrelated, and they're on lots of complex cardiac medicines for heart failure which is stable, I'll be much more reluctant to fiddle around with things, and I suppose in sort of the thought process is: well if it's not broken, don't…don't try to fix it…"* **Medical Prescriber 6** *"…the doctors that don't want to make a change, they're not going to make a change…"* **Primary Researcher 4** *"I'm not gonna start interfering with somebody's medications unless there's a glaring danger in them or I see something that's absolutely contraindicated…"* **Surgical Prescriber 2**
	Prescriber outlook towards research studies	*"…so when the doctors are enthusiastic about the study, they will read it, and they will take it…they will see it more as a priority but if the doctor isn't interested in the study, they will not see it as a priority".* **Primary Researcher 6** *"I think it depends on the person itself if they are open-minded for studies. Sometimes physicians are not really…they can have the impression that not all the physicians are very open-minded to studies, and others are…eh…open-minded so I think it also depends on it".* **Primary Researcher 1** "So I guess while it's part of a study, we'll take on that responsibility". **Medical Prescriber 6** *"I appreciated the work they did so I was receptive to em…doing this and receiving the information because I think it's important, and I think that before they did it I already thought that we needed something like this so I was very ready to have it and I wanted to see it and I don't know if the rest of the people who participated had the same feeling".* **Medical Prescriber 10**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Prescriber specialty and fear of encroachment	*"…we would kind of just, probably just intervene on the ones that are within our area of specialty. We leave the other ones generally alone".* **Surgical Prescriber 2** *"One thing you'll find I suppose with consultants is their kind of, their particular area is what they would focus on, so if they're admitted under cardiology, they may look at cardiology meds, and you know if they're on a high dose of a PPI it's not something they're really gonna review".* **Primary Researcher 2** *"…a number of the recommendations would be out of my comfort zone of what I manage".* **Surgical Prescriber 1** *"…it comes down to what I'm prescribing…em…and I suppose your confidence with prescribing certain medications wanes the longer you're away from a certain specialty".* **Medical Prescriber 8** *"They have conditions that are out of my range of knowledge, and their treatment often…their treatment of one condition might collide with another condition that I'm not an expert in".* **Medical Prescriber 12** *"I clearly understand that there are certain specialist fields that I'm capable of dealing with, and that's that acute surgical problem".* **Surgical Prescriber 1** *"I probably don't see it so much as my role to start stopping what other people have done".* **Medical Prescriber 6** *"So medications started by one specialist doctor, the other specialist doctor is a bit reluctant to change em…or is not happy to deal with this medication. It looks like instead of holistic treatment of the patient, each consultant is treating their part".* **Primary Researcher 9** *"…you may have a patient admitted under you or you see the patient but you're not the only person involved in their care so you may be reluctant to stop a medication that somebody else started. You may not have all the information why the medication was started".* **Medical Prescriber 1** *"I think especially if you're meeting a patient for the first time and they're on a number of different medications em…you will not want to interfere with medications that you didn't start or certainly medications that are outside of your own specialty".* **Primary Researcher 7** *"…you're carrying on a prescription on a decision that's been made by somebody else. You're honouring their decision. So, in honouring their decision, you're dishonouring their decision by changing that, and without due regard to them for doing it".* **Surgical Prescriber 2**
	Prescribers forgetting about the intervention	*"I think the team has to be given a…a real nudge – 'read the STOPP medications!' – not because they won't, because I think we just forget".* **Medical Prescriber 11** *"I think it was usually something that they would put on the long finger, that they would intend to come back to".* **Primary Researcher 7** *"…it's all about reminders. I think people are well-intentioned, I think they just forget".* **Medical Prescriber 11**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Prescriber experience and the need for a '*decision-maker*'	*"…if you're just started as a doctor…em I think you're also a bit hesitant to, to stop certain medications than if you've years of experience".* **Medical Prescriber 12** *"…if you have a lot of years of work, it's possible that you tend to consolidate your ideas so SENATOR could be less effective in changing your prescription".* **Medical Prescriber 7** *"I mean it definitely has to be somebody with senior clinical decision-making power. Em…most interns won't really have the kind of experience to go tinkering with people's medications and they shouldn't be".* **Medical Prescriber 8** *"The junior doctors, like interns – they are maybe…do not have the eh…they're not that independent or they (you know) don't take many decisions without consulting their seniors".* **Medical Prescriber 12** *"I think it's probably more important that it's targeted at the actual decision-maker".* **Surgical Prescriber 2**
4. The patient	Acute status of the patient	*"The primary reason is I think they are not (the physicians here) are not worried about the chronic medications, they focus on the acute conditions".* **Primary Researcher 5** *"…when the patients are admitted in secondary care in hospital, the clinical team only deals with the acute problem. They are not interested in looking into the other medications…"* **Primary Researcher 9** *"I think the mindset on a busy clinical job is to sort out the acute issue and the long term medications oftentimes I would imagine physicians don't feel that they're the ones that should have to em…em…change or interfere or sort of adjust the long term medications".* **Primary Researcher 7** *"…the priority to that patient may have been focused on, on more acute issues around that you know, you know do I need to operate or not? So that's probably why there's been a slight, a lower em acceptance of some of the recommendations".* **Surgical Prescriber 1** *"…personally my focus would be on the acute pathology, which shall be the abdominal pain and...and it's rare that we have in the past made any meaningful alterations to certain medication".* **Surgical Prescriber 1** *"…from a surgery point of view, it's a...(you know)…you're very much focused on an interventional situation".* **Surgical Prescriber 2** *"…we know when they're surgical if it is a…like fracture, the focus is on the fracture, not all the other medication, so they are not willing to change many things".* **Primary Researcher 8** *"…surgeons most of the time don't care about these things, well some of them at least, because they are really focused on the surgery, and it's like this is someone else's job".* **Medical Prescriber 10** *"The benzodiazepine one - again if the patient's unwell and they've been on a long-term sleeping tablet, my impression would be let's sort the acute issue. If they're drowsy or something like that, then that's a different issue".* **Primary Researcher 7**

Theme	Descriptor	Illustrative Quotations
4. The patient (continued)	Knowing the patient	*"I'm not sure the grade is affected, it's more who is in charge of the patient and who knows the patient best".* **Primary Researcher 8** *"I think doctors that meet the patient for the first time at the hospital admission, they don't know…they don't know him so much. Eh…and maybe they don't investigate any more than what they need for the acute problem".* **Primary Researcher 10** *"…they didn't have a complete picture of the patient when I discussed the recommendation. So, I'm thinking that also is one of the reasons why they don't adapt the change".* **Primary Researcher 9** *"They don't want to get involved…em…you know making big changes. They think that's a job for the GP that knows the patient better and knows what they've been taking long-term and the reasons why".* **Primary Researcher 4**
	Patient involvement	*"…give more information to the patient itself, like go to the patients and then say like "this medication we can stop, this medication we can stop", like we inform the patients as well and then em…maybe it would work a bit better".* **Medical Prescriber 2** *"The patient in theory could affect the number of recommendations. I think that good communication between prescriber, pharmacist, and patient is the good way, is the good way to…because, because, because patients should be, should be the centre role, centre role. In my experience, patient have in part, a little part in influencing the recommendation".* **Primary Researcher 3**
	Patient preference	*"So, eh…and then there's of course patient preference factors. Some of them really prefer to have some drugs".* **Medical Prescriber 3** *"I think, again, if a patient is very positive and keen for changes to be made, and speaks to the doctor then that seems to help".* **Primary Researcher 4** *"A lot of the recommendations involved taking patients off sleeping tablets and benzos and things, which you're gonna get resistance to".* **Primary Researcher 2** *"I wouldn't stop some things, someone's medications, without explaining to them why".* **Medical Prescriber 6**

STOPP: Screening Tool of Older People's Prescriptions START: Screening Tool to Alert to Right Treatment

SENATOR: Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older peRsons GP: General practitioner

Appendix 12: Reasons for criterion exclusion in evaluation of clinical relevance

As part of the intervention, recommendations START I1 and START I2 (suggesting to ensure patients received influenza and pneumococcal vaccinations) appeared on all SENATOR reports. These recommendations were excluded from the assessment of clinical relevance and implementation as it was not documented if all these patients had been vaccinated or not. STOPP A1 (a recommendation suggesting to stop *"Any drug prescribed without an evidence-based clinical indication"*) was also written on the report but this too could not be assessed for clinical relevance or implementation, as the indication was not clear for all medications. Therefore, of the 114 STOPP/START criteria (version 2), recommendations based on 3 criteria were excluded from the analysis.

However, it should also be noted that two slight software modifications were made a few weeks into patient recruitment:

i) START A2 (*"Aspirin [75 mg – 160 mg once daily] in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated"*) was initially triggering as a stand-alone recommendation, but later appeared as a joint recommendation along with START A1 (*"Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation"*). Therefore, relevance and implementation data are only available for START A1 from that point on.

ii) STOPP A3 (a recommendation to stop “Any duplicate drug class prescription”) was initially appearing on reports. However, due to high numbers of STOPP A3 recommendations being produced that were not clinically relevant, this recommendation trigger was ceased by trial researchers.

Appendix 13: Inter-rater reliability assessment

A convenience sample of three pharmacists and three physicians (one consultant geriatrician, and two specialist registrars – i.e. senior residents – in geriatric medicine) were invited to participate. Raters were purposively selected on the basis of their involvement with the SENATOR project and/or the OPERAM project.

Twenty intervention cases were selected at random, representing approximately 10% of intervention patients recruited at Cork University Hospital. Details of this random selection can be found below. The study's objectives were explained to each rater, and all raters were supplied with instructions on how to assess the clinical relevance of the recommendations, whereby the rater had to independently assign a code of 0 – 5 for each SENATOR-generated STOPP/START recommendation based on the clinical relevance categories. Three sample cases (all based on real intervention patients) were provided with the clinical relevance codes already assigned to the recommendations, and with a rationale given as to why each code was chosen by the pharmacist-physician pair for each patient. The twenty clinical cases were presented in a standardised format (**Appendix 14**) to include age, sex, comorbidities, medications prescribed at the time of randomisation, laboratory test results, and any other important information required to facilitate the raters in evaluating the clinical relevance of the STOPP/START recommendations.

For the random selection of the twenty intervention cases, a list of all intervention patients in the study site was divided into four according to the date of recruitment to ensure patient cases were obtained from different times during the RCT.

An independent researcher (external to the study) rearranged the four lists of patient numbers into a random order. The first five patients with at least three STOPP/START recommendations in each list were chosen as the cases in the inter-rater reliability assessment. Thus, twenty intervention patient cases were selected at random.

Appendix 14: Standardised case format for inter-rater reliability assessment

Age: 80

Sex: Female

Date of recruitment: 11/2017

Presenting Condition: Patient presenting with urosepsis. Patient fell during the night before admission to hospital when on her way to the toilet with bruising to right arm and leg, but no fracture.

Medical History:

1. Hypertension
2. Hypercholesterolemia
3. Chronic ischaemic heart disease
4. Osteoarthritis
5. Osteoporosis
6. Neck of femur fracture 2014

Medications:

1. Tinzaparin 3500 units od SC	On since admission
2. Piperacillin/Tazobactam 4.5g tds IV	On since admission
3. Aspirin 75mg od po	
4. Ramipril 2.5mg od po	
5. Atorvastatin 20mg od po	
6. Zolpidem 10mg nocte po	On for 6 – 12 months
7. Paracetamol 1g qds po/IV prn	

Laboratory Parameters:

Sodium (mmol/L)	140
Potassium (mmol/L)	4.1
Corrected calcium (mmol/L)	2.31
Creatinine (µmoles/L)	63
eGFR (MDRD) ml/min/1.73m^2	113
Haemoglobin (g/dl)	-
Platelets x 10^9	370
INR	-

Other relevant information:

- Blood Pressure: 124/79 mmHg.
- Heart Rate: 76 beats/minute.
- Patient does not have a history of recurrent falls.
- On at home but not charted: Calcium/Vitamin D_3 500mg/400 units 1 tablet bd po and Risedronate sodium 35mg once weekly po.

STOPP Recommendations:

Drug	Recommendation	Clinical Relevance
Zolpidem	Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia).	
	Any drug prescribed beyond the recommended duration, where treatment duration is well defined.	

START Recommendations:

Recommendation	Clinical Relevance
β-blocker with ischaemic heart disease.	
Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).	
Bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (Bone Mineral Density T-scores more than -2.5 in multiple sites) and/or previous history of fragility fracture(s).	

Appendix 15: Clinical relevance of individual STOPP and START recommendations

Rule	Adverse significance	No clinical relevance	Possibly low relevance	Possibly important relevance	Possibly very important relevance	Total
STOPP A2	1	8	104	17	4	134
STOPP A3	-	20	-	-	-	20
STOPP B1	-	2	-	-	-	2
STOPP B3	-	2	-	1	-	3
STOPP B5	-	5	1	-	-	6
STOPP B6	2	2	-	1	-	5
STOPP B7	7	10	6	3	-	26
STOPP B8	-	-	3	2	1	6
STOPP B9	-	1	-	-	-	1
STOPP B11	-	-	2	1	1	4
STOPP B12	-	-	2	-	-	2
STOPP C3	3	8	1	5	-	17
STOPP C5	2	-	-	2	-	4
STOPP C6	1	4	-	1	-	6
STOPP C10	-	-	-	1	5	6
STOPP C11	-	-	-	-	1	1
STOPP D2	-	1	1	1	-	3
STOPP D4	-	1	1	-	-	2
STOPP D5	-	-	13	9	2	24
STOPP D8	-	-	5	13	-	18
STOPP D9	-	1	-	-	-	1
STOPP D10	-	2	1	1	1	5
STOPP D11	-	4	-	-	-	4
STOPP D12	-	-	-	9	-	9
STOPP D14	-	-	1	20	-	21
STOPP E3	-	1	1	-	-	2
STOPP E6	-	-	-	-	1	1
STOPP F2	1	-	15	-	-	16
STOPP F3	-	-	3	2	3	8
STOPP G1	-	1	-	-	-	1
STOPP G2	-	-	1	-	-	1
STOPP G4	-	-	1	-	-	1

Rule	Adverse significance	No clinical relevance	Possibly low relevance	Possibly important relevance	Possibly very important relevance	Total
STOPP H4	-	2	1	-	-	3
STOPP H5	-	2	-	1	-	3
STOPP H6	-	-	1	-	-	1
STOPP H7	-	-	-	1	-	1
STOPP H8	-	-	-	7	-	7
STOPP H9	-	-	-	2	-	2
STOPP I1	-	-	-	10	-	10
STOPP I2	-	1	-	4	-	5
STOPP J3	-	40	1	-	-	41
STOPP K1	-	-	13	10	8	31
STOPP K2	-	1	2	3	1	7
STOPP K3	1	1	3	11	-	16
STOPP K4	-	-	10	5	1	16
STOPP L1	-	4	5	2	-	11
STOPP L2	1	2	4	10	2	19
STOPP L3	-	2	6	4	1	13
STOPP N	-	1	4	12	-	17
START A1	1	-	1	12	13	27
START A2	-	1	-	1	1	3
START A3	22	15	3	4	3	47
START A4	-	5	4	4	3	16
START A5	-	6	12	11	4	33
START A6	-	2	21	24	3	50
START A7	2	1	5	5	-	13
START A8	-	-	8	5	1	14
START B1	-	1	1	-	2	4
START B2	-	1	1	2	2	6
START B3	-	5	-	-	-	5
START C1	-	-	-	-	1	1
START D2	-	-	1	-	-	1
START E1	-	3	3	1	-	7
START E2	-	-	-	-	1	1
START E3	-	-	-	5	2	7
START E4	-	2	6	5	1	14

Rule	Adverse significance	No clinical relevance	Possibly low relevance	Possibly important relevance	Possibly very important relevance	Total
STOPP E4	-	-	-	8	3	11
START E6	-	-	1	2	-	3
START F1	-	1	1	10	1	13
START G1	-	8	-	1	-	9
START G2	-	12	8	1	-	21
START H1	-	4	3	-	1	8
START H2	1	3	29	13	2	48
All rules	**45**	**199**	**320**	**285**	**76**	**925**

Appendix 16: Clinical relevance of recommendations based on drug class

Drug Class	Adverse significance	No clinical relevance	Possibly low relevance	Possibly important relevance	Possibly very important relevance	Total
Antithrombotics	29	33	6	32	17	117
PPIs	2	8	96	-	-	106
Benzodiazepines	-	-	37	27	11	75
ACE inhibitors and/or ARBs	1	3	25	38	5	72
β-blockers	2	41	14	10	1	68
Opioids	1	13	19	16	7	56
Laxatives	1	5	29	13	2	50
Diuretics	9	13	11	6	1	40
Antihistamines	-	-	3	35	-	38
Statins	-	6	12	11	4	33
Antipsychotics	-	4	3	21	2	30
Z-drugs	-	-	18	8	2	28
Bone anti-resorptive, anabolic agents	-	2	7	11	2	22
5-alpha reductase inhibitors	-	12	8	1	-	21
Alpha-1 Receptor blockers	-	10	-	9	-	19
Vitamin D +/- Calcium	-	-	-	13	5	18
Drugs for obstructive airways disease	-	9	2	2	4	17
Antihypertensives (START A4)	-	5	4	4	3	16
Anticholinergics	-	1	3	11	-	15
Miscellaneous cardiac drugs	-	8	2	2	-	12

Drug Class	Adverse significance	No clinical relevance	Possibly low relevance	Possibly important relevance	Possibly very important relevance	Total
Other miscellaneous agents	-	1	4	3	3	11
Antidepressants	-	3	4	1	-	8
Corticosteroids	-	4	3	1	-	8
NSAIDs	-	-	-	2	6	8
Calcium channel blockers	-	2	2	3	-	7
DMARDs	-	3	3	1	-	7
Anti-diabetic drugs	-	4	-	-	1	5
Drugs to treat gout or hyperuricaemia	-	-	3	2	-	5
Oxygen	-	5	-	-	-	5
Anti-dementia drugs	-	4	-	-	-	4
Drugs for urinary frequency or incontinence	-	-	2	2	-	4
All classes	**45**	**199**	**320**	**285**	**76**	**925**

PPI: Proton pump inhibitor ACE: Angiotensin Converting Enzyme ARB: Angiotensin Receptor Blocker
NSAID: Non-steroidal anti-inflammatory drug DMARD: Disease-modifying anti-rheumatic drug

Appendix 17: STOPP/START criteria version 1

STOPP (Screening Tool of Older People's potentially inappropriate Prescriptions).

The following prescriptions are potentially inappropriate in persons aged ≥ 65 years of age.

A. Cardiovascular System

1. Digoxin at a long-term dose > 125µg/day with impaired renal function* *(increased risk of toxicity).*
2. Loop diuretic for dependent ankle oedema only i.e. no clinical signs of heart failure *(no evidence of efficacy, compression hosiery usually more appropriate).*
3. Loop diuretic as first-line monotherapy for hypertension *(safer, more effective alternatives available).*
4. Thiazide diuretic with a history of gout *(may exacerbate gout).*
5. Non-cardioselective β-blocker with chronic obstructive pulmonary disease (COPD) *(risk of bronchospasm)*.
6. β-blocker in combination with verapamil *(risk of symptomatic heart block).*
7. Use of diltiazem or verapamil with NYHA Class III or IV heart failure *(may worsen heart failure).*
8. Calcium channel blockers with chronic constipation *(may exacerbate constipation).*
9. Use of aspirin and warfarin in combination without histamine H_2 receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (PPI) *(high risk of gastrointestinal bleeding).*
10. Dipyridamole as monotherapy for cardiovascular secondary prevention *(no evidence for efficacy).*
11. Aspirin with a past history of peptic ulcer disease without histamine H_2 receptor antagonist or PPI *(risk of bleeding).*
12. Aspirin at dose > 150mg day *(increased bleeding risk, no evidence for increased efficacy).*
13. Aspirin with no history of coronary, cerebral, or peripheral arterial symptoms or occlusive arterial event *(not indicated).*
14. Aspirin to treat dizziness not clearly attributable to cerebrovascular disease *(not indicated).*
15. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration *(no proven added benefit).*
16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration *(no proven benefit).*

17. Aspirin, clopidogrel, dipyridamole, or warfarin with concurrent bleeding disorder *(high risk of bleeding).*

* GFR < 50ml/min.

B. Central Nervous System and Psychotropic Drugs

1. Tricyclic antidepressants (TCAs) with dementia *(risk of worsening cognitive impairment).*
2. TCAs with glaucoma *(likely to exacerbate glaucoma).*
3. TCAs with cardiac conductive abnormalities *(pro-arrhythmic effects).*
4. TCAs with constipation *(likely to worsen constipation).*
5. TCAs with an opiate or calcium channel blocker *(risk of severe constipation).*
6. TCAs with prostatism or prior history of urinary retention *(risk of urinary retention).*
7. Long-term (i.e. > 1 month), long-acting benzodiazepines, e.g. chlordiazepoxide, flurazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam *(risk of prolonged sedation, confusion, impaired balance, falls).*
8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics *(risk of confusion, hypotension, extra-pyramidal side effects, falls)*.
9. Long-term neuroleptics (> 1 month) in those with parkinsonism *(likely to worsen extra-pyramidal symptoms)*.
10. Phenothiazines in patients with epilepsy *(may lower seizure threshold)*.
11. Anticholinergics to treat extra-pyramidal side effects of neuroleptic medications *(risk of anticholinergic toxicity)*.
12. Selective serotonin re-uptake inhibitors (SSRIs) with a history of clinically significant hyponatraemia *(non-iatrogenic hyponatraemia < 130mmol/l within the previous 2 months)*.
13. Prolonged use (> 1 week) of first-generation antihistamines, i.e. diphenydramine, chlorpheniramine, cyclizine, promethazine *(risk of sedation and anti-cholinergic side effects)*.

C. Gastrointestinal System

1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause *(risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis)*.

2. Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis i.e. bloody diarrhoea, high fever or severe systemic toxicity *(risk of exacerbation or protraction of infection)*.
3. Prochlorperazine or metoclopramide with parkinsonism *(risk of exacerbating parkinsonism)*.
4. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks *(earlier discontinuation or dose reduction for maintenance/prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated)*.
5. Anticholinergic antispasmodic drugs with chronic constipation *(risk of exacerbation of constipation)*.

D. Respiratory System

1. Theophylline as monotherapy for COPD *(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)*.
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD *(unnecessary exposure to long-term side effects of systemic steroids)*.
3. Nebulised ipratropium with glaucoma *(may exacerbate glaucoma)*.

E. Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H_2 receptor antagonist, PPI, or misoprostol *(risk of peptic ulcer relapse)*.
2. NSAID with moderate-severe hypertension (moderate: 160/100mmHg – 179/109mmHg; severe: ≥ 180/110mmHg) *(risk of exacerbation of hypertension)*.
3. NSAID with heart failure (risk of exacerbation of heart failure).
4. Long-term use of NSAID (> 3 months) for relief of mild joint pain in osteoarthtitis *(simple analgesics preferable and usually as effective for pain relief)*.
5. Warfarin and NSAID together *(risk of gastrointestinal bleeding)*.
6. NSAID with chronic renal failure* *(risk of deterioration in renal function)*. * estimated GFR 20 – 50ml/min.
7. Long-term corticosteroids (> 3 months) as monotherapy for rheumatoid arthrtitis or osterarthritis *(risk of major systemic corticosteroid side effects)*.
8. Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol *(allopurinol first choice prophylactic drug in gout)*.

F. Urogenital System

1. Bladder antimuscarinic drugs with dementia *(risk of increased confusion, agitation)*.
2. Bladder antimuscarinic drugs with chronic glaucoma *(risk of acute exacerbation of glaucoma)*.
3. Bladder antimuscarinic drugs with chronic constipation *(risk of exacerbation of constipation)*.
4. Bladder antimuscarinic drugs with chronic prostatism *(risk of urinary retention)*.
5. Alpha-blockers in males with frequent incontinence i.e. one or more episodes of incontinence daily *(risk of urinary frequency and worsening of incontinence)*.
6. Alpha-blockers with long-term urinary catheter *in situ*, i.e. more than 2 months *(drug not indicated)*.

G. Endocrine System

1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus *(risk of prolonged hypoglycaemia)*.
2. β-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes i.e. ≥ 1 episode per month *(risk of masking hypoglycaemic symptoms)*.
3. Oestrogens with a history of breast cancer or venous thromboembolism *(increased risk of recurrence)*.
4. Oestrogens without progestogen in patients with intact uterus *(risk of endometrial cancer)*.

H. Drugs that adversely affect those prone to falls (≥ 1 fall in past three months)

1. Benzodiazepines *(sedative, may cause reduced sensorium, impair balance)*.
2. Neuroleptic drugs *(may cause gait dyspraxia, parkinsonism)*.
3. First generation antihistamines *(sedative, may impair sensorium)*.
4. Vasodilator drugs known to cause hypotension in those with persistent postural hypotension i.e. recurrent > 20mmHg drop in systolic blood pressure *(risk of syncope, falls)*.
5. Long-term opiates in those with recurrent falls *(risk of drowsiness, postural hypotension, vertigo)*.

I. Analgesic Drugs

1. Use of long-term powerful opiates e.g. morphine or fentanyl as first line therapy for mild-moderate pain *(WHO analgesic ladder not observed)*.
2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives *(risk of severe constipation)*.
3. Long-term opiates in those with dementia unless indicted for palliative care or management of moderate/severe chronic pain syndrome *(risk of exacerbation of cognitive impairment)*.

J. Duplicate Drug Classes

Any regular duplicate drug class prescription e.g. two concurrent opiates, NSAIDs, SSRIs, loop diuretics, Angiotensin Converting Enzyme (ACE) inhibitors *(optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug)*. This excludes duplicate prescribing of drugs that may be required on a *prn* basis e.g. inhaled β_2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain.

START: Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatment.

These medications should be considered for people ≥ 65 years of age with the following conditions, where no contraindication to prescription exists.

A. Cardiovascular System

1. Warfarin in the presence of chronic atrial fibrillation.
2. Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin.
3. Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral, or peripheral vascular disease in patients with sinus rhythm.
4. Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg.
5. Statin therapy with a documented history of coronary, cerebral, or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is > 5 years.
6. ACE inhibitor with chronic heart failure.
7. ACE inhibitor following acute myocardial infarction.
8. β-blocker with chronic stable angina.

B. Respiratory System

1. Regular inhaled β_2 agonist or anticholinergic agent for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where predicted FEV1 < 50%.
3. Home continuous oxygen with documented chronic type 1 respiratory failure (pO_2 < 8.0kPa, pCO_2 < 6.5kPa) or type 2 respiratory failure (pO_2 < 8.0kPa, pCO_2 > 6.5kPa).

C. Central Nervous System

1. Levodopa in idiopathic Parkinson's disease with definite functional impairment and resultant disability.
2. Antidepressant drug in the presence of moderate-severe depressive symptoms lasting at least three months.

D. Gastrointestinal System

1. Proton Pump Inhibitor with severe gastro-oesophageal acid reflux disease or peptic stricture requiring dilatation.
2. Fibre supplement for chronic, symptomatic diverticular disease with constipation.

E. Musculoskeletal System

1. Disease-modifying anti-rheumatic drug (DMARD) with active moderate-severe rheumatoid disease lasting > 12 weeks.
2. Bisphosphonates in patients taking maintenance oral corticosteroid therapy.
3. Calcium and Vitamin D supplement in patients with known osteoporosis (radiological evidence or previous fragility fracture or acquired dorsal kyphosis).

F. Endocrine System

1. Metformin with type 2 diabetes +/- metabolic syndrome (in the absence of renal impairment*).
2. ACE inhibitor or Angiotensin Receptor Blocker in diabetes with nephropathy i.e. overt urinalysis proteinuria or microalbuminuria (> 30mg/24 hours) +/- serum biochemical renal impairment*.
3. Antiplatelet therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present (hypertension, hypercholesterolaemia, smoking history).
4. Statin therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present.

   * GFR < 50ml/min

Reference: *Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008 Feb;46(2):72-83.*

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Appendix 18: Prescriber implementation rates for START recommendations (including START-based recommendations to prescribe "*missing medications*")

START-based Recommendations	Physician	Pharmacist	*p*-value†
Cardiovascular System	**29/37**	**26/42**	**0.1121**
Warfarin with chronic atrial fibrillation	15/18	2/3	
Aspirin with chronic atrial fibrillation where warfarin is contraindicated	2/3	4/5	
Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral, or peripheral vascular disease in patients with sinus rhythm	0/2	9/14	
Antihypertensive therapy where systolic blood pressure consistently > 160 mmHg	1/1	-	
Statin therapy with history of coronary, cerebral, or peripheral artery disease without contraindication	8/9	9/12	
ACE inhibitor with chronic heart failure	3/4	1/5	
ACE inhibitor following acute myocardial infarction	-	0/1	
β-blocker with chronic stable angina.	-	1/2	
Respiratory System	-	**16/20**	**-**
Regular inhaled β_2 agonist or anticholinergic agent for mild to moderate asthma or COPD	-	5/7	
Regular inhaled corticosteroid for moderate-severe asthma or COPD, where predicted FEV1 < 50%.	-	11/13	
Central Nervous System	-	**4/4**	-
Antidepressant drug in the presence of moderate-severe depressive symptoms lasting at least three months.	-	4/4	
Gastrointestinal System	**1/1**	**-**	**-**
Proton Pump Inhibitor with severe gastro-oesophageal acid reflux disease or peptic stricture requiring dilatation.	1/1	-	

START-based Recommendations	Physician	Pharmacist	*p*-value†
Musculoskeletal System	**97/109**	**14/31**	**< 0.0001***
Disease-modifying anti-rheumatic drug (DMARD) with active moderate-severe rheumatoid disease lasting > 12 weeks	-	0/1	
Bisphosphonates in patients taking maintenance oral corticosteroid therapy	14/18	2/12	
Calcium and vitamin D supplementation in patients with known osteoporosis, fragility fracture or dorsal kyphosis	83/91	12/18	
Endocrine System	**12/12**	**11/18**	**0.0136***
Metformin with type 2 diabetes mellitus +/- metabolic syndrome	1/1	2/2	
ACE inhibitor or Angiotensin Receptor Blocker in patients with diabetes and nephropathy	7/7	1/1	
Antiplatelet therapy in those with diabetes mellitus and one or more major cardiovascular risk factors	2/2	2/2	
Statin therapy in patients with diabetes mellitus and one or more major cardiovascular risk factors	2/2	6/13	
Total START Recommendations	**139/159**	**71/115**	**< 0.0001***
Total STOPP/START Recommendations	**376/451**	**171/370**	**< 0.0001***

ACE: Angiotensin Converting Enzyme COPD: Chronic obstructive pulmonary disease FEV1: Forced expiratory volume in 1 second

†p-value calculated using chi-squared test. * Statistically significant difference observed ($p < 0.05$).

Appendix 19: Ethical approval for Chapter 6

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

CREC Review Reference Number: ECM 4 (l) 03/07/18

Date: 3rd July 2018

Professor Stephen Byrne
School of Pharmacy
Cavanagh Pharmacy Building
Room UG06
College Road
Cork

Study Title: To identify factors affecting prescriber implementation of hospital pharmacists' medication recommendations.

Approval is granted to carry out the above study at:

Acute hospitals under the remit of the UCC Cork Teaching Hospitals.

The following documents have been approved:

Document	Approved	Version	Date
Cover Letter	Yes		Dated 12th June 2018 (received 18th June 2018)
Application Form	Yes		12th June 2018
CV for Chief Investigator	Yes		
Evidence of Insurance	Yes		
Study Protocol	Version	1.0 dated June 2018	
Data Collection Sheet	None		
Participant Information Sheet	Yes	1.0 dated June 2018	
Garda Vetting Forms	None		
Consent Form	Yes	1.0 dated June 2018	
Study Questionnaire/Survey	None		
Interview Guides	Yes	1.0 dated June 2018	

We note that the co-investigator(s) involved in this project will be:

Name	Occupation
Professor Denis O'Mahony	Consultant Geriatrician
Aoife Fleming	Lecturer
Kieran Dalton	PhD Researcher

The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.

4. Notify CREC of discontinuation of the study

5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 20: COREQ checklist for qualitative interview study from Chapter 6

Domain 1: Research Team and Reflexivity

Personal characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	KD conducted the interviews.
2.	Credentials	What were the researcher's credentials (e.g. PhD, MD)?	At the time of undertaking the interviews, KD's credentials were BPharm, MPharm, MPSI.
3.	Occupation	What was their occupation at the time of the study?	KD is an Irish registered pharmacist, who was undertaking a PhD in Clinical Pharmacy research when this study was conducted.
4.	Sex	Was the researcher male or female?	Male.
5.	Experience and training	What experience or training did the researcher have?	KD completed training in utilisation of NVivo software, and received training in analysis of qualitative interviews at Oxford University, United Kingdom.
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	The interviewer had no previous relationship or established rapport with any of the interviewees prior to study commencement.
7.	Participant knowledge of the interviewer	What did the participants know about the researcher (e.g. personal goals, reasons for doing the research)?	KD had disclosed to all participants that he was a pharmacist undertaking this study as part of his PhD, prior to conducting the interviews.
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? (e.g. bias, assumptions, reasons and interests in the research topic)	KD is a registered pharmacist who was conducting this study as part of his PhD exploring factors affecting physician prescriber implementation of medication appropriateness recommendations in hospitalised older adults. This information was disclosed to participants ahead of the interview.

Domain 2: Study Design

Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study (e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis)?	Content analysis was used in this study to analyse the data from the interview transcripts. Conventional content analysis was used to identify the conventional themes, which were attributed as factors that influence physician prescriber implementation of hospital pharmacist recommendations. The Theoretical Domains Framework (TDF) was used to structure the interview topic guides, and directed content analysis was used to identify the relevant TDF domains from the interview transcripts.
Participant selection			
10.	Sampling	How were participants selected (e.g. purposive, convenience, consecutive, snowball)?	Participants were identified and recruited through a combination of convenience sampling and purposive sampling. Of the pharmacists, the pilot participant was recruited face to face by KD at their place of work, three were identified via a colleague of KD, and two were recruited via snowballing (i.e. identified from a pharmacist who had already participated in the study). Of the physicians, two were identified through a colleague of KD, three via snowballing, and three were identified via pharmacists who had not already participated in the study (note: these pharmacists were identified through a colleague of KD).
11.	Method of approach	How were participants approached (e.g. face-to-face, telephone, mail, email)?	Nine participants were recruited via email, three participants were approached face to face by KD at their place of work, and two were contacted via text message.
12.	Sample size	How many participants were in the study?	14.
13.	Nonparticipation	How many people refused to participate or dropped out? Reasons?	None.
Setting			
14.	Setting of data collection	Where was the data collected (e.g. home, clinic, workplace)?	One interview was conducted in a private room at the interviewer's workplace as this was the preference of the interviewee. However, all other interviews were conducted in a private room in the participant's respective hospital site to minimise disruption to their work day.

15.	Presence of nonparticipants	Was anyone else present besides the participants and researchers?	No.
16.	Description of sample	What are the important characteristics of the sample (e.g. demographic data, date)?	Ten participants were female. With regard to hospital-based experience, half the participants had less than 5 years' experience, four participants had ≥ 5 years' experience but less than 10 years' experience, and three participants had over 10 years' experience. The interviews took place between August 2018 and August 2019.
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Two separate topic guides comprising a similar line of questioning (with prompts where appropriate) were formulated for the pharmacist and physician participants. The topic guides were based on a review of the literature, the TDF, and my own and my supervisors' knowledge of the research area. Each topic guide was pilot tested with one participant each, and both of these interviews were included in the study. The topic guides were iteratively refined during the study where appropriate to ensure that emerging themes were explored in subsequent interviews.
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No.
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio-recorded.
20.	Field notes	Were field notes made during and/or after the interview or focus group?	Field notes were recorded after each interview, and were used to refine topic guides and inform data analysis.
21.	Duration	What was the duration of the interviews or focus group?	The mean interview length was 33 minutes (range 18 – 47 minutes).
22.	Data saturation	Was data saturation discussed?	Data analysis coincided with data collection. It was as planned in advance that if no new themes emerged in the additional three interviews after the eleventh interview (i.e. to complete the 14-participant sampling matrix), then this would confirm that data saturation had been reached.
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No.

Domain 3: Analysis and Findings

Data analysis			
24.	Number of data coders	How many data coders coded the data?	Two (KD and AF).
25.	Description of the coding tree	Did authors provide a description of the coding tree?	A description of the process is provided, whereby initial, non-hierarchical codes were categorised, and subsequently developed to generate themes and subthemes as part of conventional content analysis. The TDF was the chosen framework for directed content analysis, and was used as the basis for a coding tree here.
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Conventional content analysis comprised open coding to inductively create initial, non-hierarchical codes. These initial codes were subsequently categorised to generate the evolving themes and subthemes. Directed content analysis was then employed whereby the transcripts were deductively coded using the TDF to identify the domains present.
27.	Software	What software, if applicable, was used to manage the data?	QSR NVivo® Version 11.
28.	Participant checking	Did participants provide feedback on the findings?	No.
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Yes.
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Quotations are presented in a manner consistent with findings.
31.	Clarity of major themes	Were major themes clearly presented in the findings?	Major themes are clearly presented in the results section.
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Subthemes are presented under each of the major themes.

Appendix 21: Final version of topic guides for Chapter 6

Topic guide for pharmacists

1. What do you see as the main roles that pharmacists have in the multidisciplinary care of older adults in the hospital setting?
2. How aware do you think physicians are of the pharmacist's role in the hospital setting?
   - What do you think doctors' opinions are of hospital pharmacists' roles?
3. How would you compare your knowledge and skill set with that of a physician when it comes to medication appropriateness in hospitalised older adults?
   - Are there any gaps in the knowledge or skill set of physicians that pharmacists can help with in particular?
   - Are there any gaps in the knowledge or skill set of pharmacists?
4. To what extent do pharmacists and physicians share the same goals in terms of reducing potentially inappropriate prescribing in older adults?
5. How would you describe your day-to-day interactions with physicians?
6. How do you inform physicians of medication appropriateness issues in older adults?
   - How do you decide what method of communication to use?
   - Do you use different communication methods for different types of recommendations?
   - Do you find any methods of communication more effective than others?
   - If the most effective method is not the most commonly used, ask why.

7. What factors might make it more likely for a physician to implement recommendations from a pharmacist?
8. What factors might make it less likely for a physician to implement recommendations from a pharmacist?
9. Are there any specific types of recommendations that you think are more likely or less likely going to be implemented by physicians?
   - e.g. recommendations regarding medication reconciliation, medication appropriateness, drug interactions, renal dose adjustment etc.
10. How does the experience of a pharmacist affect the number of recommendations implemented by physicians?
11. How do the characteristics of an individual pharmacist affect the implementation of recommendations?
    - Personality? Knowledge? Mindset? Approach from pharmacist? Confidence?
12. How does the grade or experience of physician affect the number of recommendations implemented?
13. How does the specialty of physician affect the number of recommendations implemented?
    - Are some specialties more likely or less likely to implement the recommendations?
    - How do you feel about making a recommendation to a specialist concerning their area of expertise?
14. How do the characteristics of an individual physician affect the number of recommendations implemented?
    - Personality? Knowledge? Mindset? Approach from doctor? Confidence?

15. How important do you think it is for the physician to know you or be familiar with you when it comes to implementing your recommendations?
16. On a scale of 1 to 10, how would you, as a pharmacist with *(insert number)* years of experience, rate your confidence in discussing medication appropriateness with physicians, 1 being not confident at all and 10 being very confident?
17. You identify that an older patient under the care of a hospital physician has been prescribed a potentially inappropriate medication long-term by another prescriber, and make a recommendation to stop this medication. How likely is it that this will be implemented?
18. What are the organisational barriers to pharmacists providing medication recommendations?
19. How does the hospital environment affect the implementation rate of pharmacist recommendations?
    - Is there enough time/opportunity to address these issues?
20. Does the patient have any impact on the number of pharmacist recommendations implemented?
21. Are pharmacist recommendations audited or reviewed by your department? Any quality improvement initiatives?
22. Do you think that the culture within this particular hospital has any impact on i) the relationship between pharmacists and physicians and/or ii) physicians' implementation of pharmacist recommendations?

23. Do you have experience from another hospital that is relevant? Were the means of communicating with physicians different and what was the effect on the implementation of recommendations?
24. If you could change how pharmacists make recommendations or interventions for older adults in your hospital setting, what would you suggest?
25. In some jurisdictions, pharmacists prescribe as part of the hospital multidisciplinary team. How do you feel about pharmacists having some form of prescribing (or deprescribing) role in the care of older adults?
26. A study by our research group has suggested that physicians are more likely to implement recommendations from fellow physicians than from pharmacists when it comes to recommendations addressing older patients' medications. What are your thoughts on this?

That brings us to the end of the interview. Do you have any additional comments that you would like to make, or any points you would like to expand on?

Topic guide for physicians

1. What do you see as your role in identifying and addressing issues of potentially inappropriate prescribing in hospitalised older adults?
   - How do you feel about making changes in older patients' medications?
2. What do you see as the main roles that pharmacists have in the multidisciplinary care of older adults in the hospital setting?
3. How would you compare your knowledge and skill set with that of a pharmacist when it comes to medication appropriateness in hospitalised older adults?
   - Are there any gaps in your knowledge or skill set that pharmacists can help with?
   - Are there any gaps in the knowledge or skill set of pharmacists?
4. To what extent do pharmacists and physicians share the same goals in terms of reducing potentially inappropriate prescribing in older adults?
5. How would you describe your relationship or day-to-day interactions with pharmacists?
6. At present, how do you receive recommendations from pharmacists in hospital?
   - e.g. face to face, over the telephone, written, or a combination?
   - How do you most commonly receive these recommendations?
   - What method do you find most effective? Why?
   - If the most effective method is not the most commonly used method, why do you think that is the case?
7. What factors might make it more likely for you implement a recommendation from a pharmacist?

8. What factors might make it less likely for you to implement a recommendation from a pharmacist?
9. Are there any specific types of recommendations from hospital pharmacists that you find most beneficial?
   - e.g. recommendations regarding medication reconciliation, medication appropriateness, drug interactions, renal dose adjustment etc.
10. How does the experience of a pharmacist affect the number of their recommendations that you implement?
11. How do the characteristics of an individual pharmacist affect the implementation of pharmacist recommendations?
   - Personality? Knowledge? Mindset? Approach from pharmacist? Confidence?
12. How does the grade or experience of physician affect the number of pharmacist recommendations implemented, do you think?
13. How does the specialty of physician affect the number of pharmacist recommendations implemented?
   - Are some specialties more likely or less likely to implement the recommendations?
14. How do the characteristics of an individual physician affect the implementation of pharmacist recommendations?
   - Personality? Knowledge? Mindset? Approach from doctor? Confidence?
15. How important is it for you to know or be familiar with the pharmacist you are receiving recommendations from?

16. On a scale of 1 to 10, how would you, as a(n) *(insert grade of doctor)* rate your confidence in discussing medication appropriateness with a hospital pharmacist, 1 being not confident at all and 10 being very confident? Why?
17. Can you describe an instance where a pharmacist made a recommendation that you did not implement.
    - What are reasons you did not implement the recommendation?
18. How does the hospital environment affect the implementation rate of pharmacist recommendations?
    - Is there enough time/opportunity to address these issues?
19. Does the patient have any impact on the number of pharmacist recommendations implemented?
20. A pharmacist makes a recommendation to you to stop a potentially inappropriate medication that an older patient has been taking long-term under the care of another physician. What would you do?
21. If pharmacist recommendations are not implemented, what clinical impact (if any) does this have on older patients?
22. If you could change how pharmacists make recommendations or interventions for older adults in your hospital setting, what would you suggest?
23. In some jurisdictions, pharmacists prescribe as part of the hospital multidisciplinary team. How do you feel about pharmacists having some form of prescribing (or deprescribing) role in the care of older adults?

24. A study by our research group has suggested that physicians are more likely to implement recommendations from fellow physicians than from pharmacists when it comes to recommendations addressing older patients' medications? What are your thoughts on this?

That brings us to the end of the interview. Do you have any additional comments that you would like to make, or any points you would like to expand on?

Appendix 22: Supplementary Quotations for Chapter 6

Theme	Descriptor	Illustrative Quotations
1. Clinical relevance and complexity of the recommendation	Clinical relevance in the hospital setting	*"I don't think they'll really do much about long-term medicines because – like here's an acute setting, so they might only have them for a week. But like tapering a person off like long-term benzos is a long-term project, so I don't think they have the time for it here to be honest".* **Pharmacist 1** *"I think physicians are so busy, they…it's not something that's on their radar when a patient presents to an acute hospital setting, and I suppose if you stand back and look at it – is it the role of a hospital, an acute hospital, to optimise pharmacotherapy on a, on, on a…in older…is that the best time to do it? Is it not the best time for that to be done in primary care?"* **Pharmacist 6** *"…maybe if they press too hard on the what we would may consider the less important issues, you know that might kind of annoy you a little bit. You might feel like, you know, that's a minor issue compared to what's actually going with the patient. We need to focus on the bigger things".* **Physician 5** *"…I suppose is it relevant to the patient's clinical picture at the time of admission? So, for example, if it's something to do with a sleeping tablet and it's not relevant to the patient's admission at the moment, they might feel that the GP might be a better person, you know, to review those type of medications".* **Pharmacist 3** *"I suppose you would grade them in some sort of way, you would grade them on importance as well as to if something is very minor or very important. So like some absolute contra-indications or double-prescribing of anticoagulants like things that have potential serious side effects would be taken very seriously".* **Physician 3** *"I find that interactions, even especially if they're theoretical interactions and they're not going to affect the patient too much, I don't think they are really considered. They're not really intervened on too much".* **Pharmacist 2** *"I suppose it depends on what the recommendation is, like say if someone had A Fib* [atrial fibrillation] *and a high CHA_2DS_2-VASc score, then if the pharmacist has recommended anticoagulation and they weren't anticoagulated, that obviously has a big impact. I think the higher impact things tend to be implemented…"* **Physician 2** *"I suppose if it's more urgent. Like, if they saw a patient and the patient was on Calcichew® D3 at home and they're on just Calcichew® now, they might not think of that as a problem. But if it was a risk, so if there were an interaction that puts the patient at risk, they'd definitely change it more readily".* **Pharmacist 1**
	Priority	*"…maybe they're in a very stressful day or they're very busy and they're not that interested in hearing about medication for a particular patient or they might feel they have more pressing issues to deal with".* **Pharmacist 3**

Theme	Descriptor	Illustrative Quotations
1. Clinical relevance and complexity of the recommendation (continued)	Priority (continued)	*"But if you're on a completely different ward dealing with an emergency and like you're going to say 'Yeah, I'll do it at some point' and you might not actually do it. So, they're kind of smaller errors that you wouldn't pay that much attention to and I think it's just how you prioritise the…like perceived problem with the prescription".* **Physician 3** *"…things like benzos not being stopped in your older people. Like you know that does have an effect for sure but it's not going to be a priority for a patient. You know it's not going to be one of the priorities for an inpatient during their stay here…"* **Pharmacist 6** *"…it's an acute setting here. So, there's always someone more sick than the patient they're at. So, maybe towards the end of a patient's admission when you can actually have the time to sit down and review it, their medicines on discharge. There's always another 10 patients that are sicker than them. So, it even might fall through the cracks then towards the end".* **Pharmacist 1**
	Complexity of decision-making	*"…it's the ease of doing it as well. So like if you take that example of a PPI: if someone tells you they're on 15 and not 30 at home and give you the kardex and it's in front of you, yeah that's easy to do".* **Physician 3** *"…someone comes in and they're on glaucoma eye drops – yeah prescribe that. There's no thinking about it – it's black and white".* **Pharmacist 6** *"I would always, unless it was something very benign, like I don't know Chloromycetin® eye drops or something and their eye is fine, then I would be happy to cancel that, but I would usually always call and ask the registrar if it was appropriate to stop or not".* **Physician 7** *"I think the experience part comes in when it's more grey areas…"* **Pharmacist 3** *"They probably interact more with the intern and the SHO on the team in person, you know, with recommendations or with issues, who in turn may have to pass it up to me then if they're not sure what to do".* **Physician 5** *"I think the most junior of doctors I'd say, the interns or the SHOs, I think are more likely to ask for advice regarding more complex stuff".* **Physician 8** *"So I think the more straightforward ones where the guidelines are very clear are acted on probably quicker and it's easier for people to make a decision around that because there's no 'oh maybe I need to check with a senior member of the team' or 'that needs to be discussed maybe with the GP'…"* **Pharmacist 3** *"More evidence-based things, they'd be more quick to change".* **Pharmacist 1** *"Well like if they tell us more information about why we should change it. Kind of like their back up info about why are they making that recommendation".* **Physician 1** *"But I think if you can present your case and give them good evidence, they'll do it. Like, don't just say that there's an interaction there. Tell them where you got the interaction and what kind of – like, what it could cause if you don't change it. So, give them plenty of information".* **Pharmacist 1**

Theme	Descriptor	Illustrative Quotations
2. Interprofessional communication	Route of communication	*"…I think face-to-face communication of the changes is the easiest way to actually get them implemented…"* **Physician 3** *"I suppose to meet with the doctors is always easier, so if you can like face to face have a discussion when you have the information in front of you - so when you have the patient's kardex or the patient's notes, it's always easier to explain something rather than doing it through a phone call".* **Pharmacist 3** *"I think face-to-face when you're both there and you can look at the drug chart if necessary and you can pull the notes and you can say 'look, this is the issue', whereas I think if you're relying on…the least effective probably is like our notes that we leave on the drug chart, because I don't think that a lot of the time, you know, during a ward round, they don't look at the drug chart…"* **Pharmacist 5** *"…other methods of communication are not as effective as face-to-face and getting you to do it right in front of them…"* **Physician 1** *"Sometimes it could be acted upon incorrectly if you're not there to look at what, you know…so I think like definitely face-to-face communication on a ward is the most effective".* **Pharmacist 5** *"I think for serious things, face-to-face is great. You can kind of talk back and forth sometimes you know. Written things – you know, you may…people may not understand the reason something's being prescribed or the reason for maybe going outside the license…"* **Physician 5** *"Oh, face to face, they'll do it, they kind of get your point. They'll do it straight away, and leaving a note - it can just fall by the wayside…"* **Pharmacist 4** *"…I guess one thing is the written recommendations on the front of the kardex, it's usually on the green piece of paper. We would follow their recommendations but a lot of the times it can get missed. So, I guess that's one factor that makes us less likely to implement it. If we just miss it".* **Physician 1** *"…if you talk to the person face to face, I think they'd do it. They're more inclined to take up your recommendations than if you left a note".* **Pharmacist 1** *"I think if it's not communicated well. Like definitely the best way of communicating it is by saying it, whereas sometimes you can look at what they have written especially if it is in the notes and say, as I said like, are they telling us just to use it with caution or are they telling us to absolutely stop it? So, I think verbal is better than written communication".* **Physician 2** *"…if I think it's an urgent issue, I will bleep them and talk to them verbally, because they'll just respond to it a lot quicker that way. If I leave a note, they might not see it till the next ward round or they might not be looked at at all".* **Pharmacist 2** *"…I suppose more pharmacy time would useful, because I think the sort of rather cold abstracts or the way we deal with a lot of it is, it's written in the notes, it's sort of vague almost anonymous green script…"* **Physician 8**

Theme	Descriptor	Illustrative Quotations
2. Interprofessional communication (continued)	Route of communication (continued)	*"If they just write a note in a book, in the notes, I'd say they'd be less likely to implement them. Possibly if they didn't get (I suppose) the reasoning behind them…"* **Pharmacist 4** *"I find that a verbal communication is much more effective than a written communication regarding an intervention I want to make because you can explain it better verbally and I think they are more likely to take it on board. That's kind of just what I found. So I would be inclined to bleep them and talk to them through the issue and I think they are more inclined to take it on board then".* **Pharmacist 2** *"…I've worked in places where you get a phone call maybe after your ward round with the big list of recommendations verbally that you'd be trying to write down and like the serious potential for information to be lost there…"* **Physician 5** *"I don't really see much difference in over the phone or face-to-face in terms of them getting, them following through on the intervention I think. Yeah I think they would follow through just as much if I talk to them over the phone than I did face to face yeah".* **Pharmacist 2**
	Combination of communication methods	"*…the most effective way of doing, getting stuff implemented is both by writing in the notes, and verbally contacting them. So, if you just write it in the notes, it may not happen. Em…you have to speak to somebody. It's really important that you speak to somebody*". **Pharmacist 6** *"…and then both verbal and written communication because sometimes we need reminders".* **Physician 3** *"I could say well I also put it in writing on the intervention slip, just to kind of have a back-up there and just in case the SHO didn't discuss it with the team, that somebody might see it then written as well".* **Pharmacist 2** *"You know, coming to meet somebody is much more difficult. So, I think the note is probably the most important but, like if you were to maybe make a verbal kind of reference to the fact that 'I have made a note on this person' that might be helpful as well".* **Physician 7**
	Pharmacist manner, language, and assertiveness	*"Definitely, I think if you've got a nice manner, and you approach in a less accusatory fashion, you'll get things I think a little bit easier, or explain better rather than going up and saying 'That's wrong, that's dangerous, don't do that'. But then I've also seen (I suppose) a couple of pharmacists who might be quite reluctant to counteract anything that a doctor has done. Like 'Oh, they may know. So, I'm not saying anything', or 'I don't really write in the patients notes because the team might get offended', that kind of way. So, I think there is kind of that still hierarchy system - can still be there sometimes and can affect people. But definitely, the way you approach it will definitely affect it".* **Pharmacist 4** *"…we shouldn't just go in and say 'you are wrong. This is what you should be doing'. I would always say 'maybe think about doing this instead'. So I suppose we shouldn't be arrogant either".* **Pharmacist 2**

Theme	Descriptor	Illustrative Quotations
2. Interprofessional communication (continued)	Pharmacist manner, language, and assertiveness (continued)	*"I think experience…I think you…if you have a lot of experience, and you're confident in what you're saying to physicians, they're gonna trust you then, and they're gonna trust you. I think I can say confidently that the doctors trust me…"* **Pharmacist 6** *"I guess just being friendly to be honest. Nothing much to it. As long as they are friendly and nice and smile and are nice to you about it and not condescending, like you'd do anything for anyone who is nice to you".* **Physician 1** *"But most of the time I'll just say 'this is the guidance. Consider changing x to y' because the guidance states this. So, again, I'm not telling them what to do, but just what I know and what I have found and to maybe review it again".* **Pharmacist 2** *"I suppose if it's more direct, like 'please consider stopping', as opposed to 'the guidelines state…' If it's an actual like 'I think you should consider stopping it', as opposed to just this kind of abstract concept".* **Physician 2** *"They're making these decisions, but I feel like sometimes they think 'Oh you know, I'm writing this as a kind of an FYI' but no one pushes it to say that you know you need to…can you have a look at my note or, what do you think about this? I feel like the individual pharmacist doesn't approach it kind of even verbally…"* **Physician 7** *"…you need to be assertive and confident, but not overly arrogant in what you are saying".* **Pharmacist 2**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity	Experience/Grade	*"I feel my knowledge at intern level of pharmacology and therapeutics is so much less than it should be, and that pharmacists have this really in-depth knowledge and understanding of a lot of different drugs…"* **Physician 7** *"I find if you go to interns, they won't change things realistically, especially now. They're only about four months in now. They won't change – I won't really go to interns too often because they'll just bounce it back off their SHOs and registrars".* **Pharmacist 1** *"Well I suppose I'm at an SHO level, I mightn't always be sure whether this can be stopped…"* **Physician 6** *"I think usually their clinical experience plays a huge part in their decision to change* [referring to senior physicians]*".* **Physician 1** *"I suppose it's probably twofold: when they don't have that much experience, they are probably more likely to take on the advice that you are giving them sometimes, so you know they mightn't…like a lot of the time if I was making a recommendation on a patient's medications, they would probably take on face value what I was saying as correct because they mightn't have the experience behind them or they mightn't be familiar with the medication".* **Pharmacist 3** *"I think you may find that as you get older you are more likely to say, I know it all and continue on. So I think the grade is you may find the lower the grade the more likely they are to take on board pharmacists recommendations and more open to it I think. Like lots of things as we get older, we are maybe a bit more sure of ourselves and less likely to take on advice".* **Physician 8** *"…if you take someone more experienced, while you might not always follow the recommendation, I think someone with experience would be more able to actually be making an informed decision and not following it for a reason…"* **Physician 3** *"…maybe the more old school consultants would've been more dismissive of pharmacist input…"* **Pharmacist 5** *"…senior doctors have kind of disregarded what the pharmacist's opinion has been and from like, for no valid reason that I could see at that point in time"*. **Physician 7** *"I would kind of generalise and see that kind of the younger generation are a lot more accepting, a lot more encouraging of your involvement. I think personally that's because they, a lot of them would have been trained with us. The older generation would have been completely separate…"* **Pharmacist 4** *"I think when you first start off as an intern you would be scared of making changes by yourself even if the pharmacist tells you that it is the correct dose or that there's a kind of interaction - we would always go to our, let's say registrar first before we make any changes. But as you get more experienced you become more comfortable making the changes on your own".* **Physician 1** *"…it might be that the SHO or the registrar has charted that particular medication and, you know, a more junior member of the team mightn't feel confident in discontinuing it on the advice of pharmacy or they might feel that again, it might need further discussion before they discontinue it or amend the prescription".* **Pharmacist 3**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Less experienced physicians implementing on the basis of blind trust in their seniors	*"I suppose the lower…I suppose they would probably be more likely to accept their recommendations as kind of more gospel, whereas we might use our own experience to weigh up the pros and cons of taking the advice, and you know saying what are…and looking at the (kind of) goals, and make our own decision on whether we want to follow the advice…"* **Physician 5** *"…when they don't have that much experience, they are probably more likely to take on the advice that you are giving them sometimes, so you know they mightn't…like a lot of the time if I was making a recommendation on a patient's medications, they would probably take on face value what I was saying as correct because they mightn't have the experience behind them or they mightn't be familiar with the medication".* **Pharmacist 3** *"I think we probably take on board what anyone senior would say. So, if it's a senior pharmacist you probably take it on board, whereas I don't know maybe the more senior physicians would have their own opinions on whether it's appropriate or not".* **Physician 2** *"I think that interns and SHOs, well especially interns, or less experienced doctors would be more likely to just do what they were told or what they are asked to do without taking the clinical context into account. So, I think they would be less able to know the importance of doing or not doing something".* **Physician 3**
	Hierarchical influences	*"…because medicine is quite hierarchical, you're really…it's followed by a rigid structure, so maybe they feel like going to the more junior person and letting them pass on the message if needed is the appropriate way to do it".* ***Physician 5*** *"That may be around grade too often, a lot of this is consultant-driven. So, a registrar and SHO may not feel empowered to sort of follow a recommendation either".* **Physician 8** *"…whereas if it's something that like their registrar has told them to do this or the SHO did it, and they're slower then to change the work that another member of their team has done, you know, without checking, without checking with them, or they just don't know".* **Pharmacist 5** *"…you're always going to go through your consultant or the senior registrar to make a kind of a medication prescribing decision".* **Physician 7** *"Maybe sometimes, they were just told 'oh prescribe this' or whatever, so they're not really sure do they…who is correct? Is it their registrar or is it you?"* **Pharmacist 5** *"…maybe junior doctors don't change immediately if someone else has told them to prescribe something, but they might question it with the rest of the team".* **Physician 4** *"I might approach maybe the SHO rather than the registrar because I think the SHO would be more willing to listen to me and would be likely to discuss it with the rest of the team, and would be grateful for the interaction. Whereas in my experience talking to registrars, if I query something, it's…the reply that I get is 'well that's what I want, so don't question it' basically. They might not say don't question it, but that's implied".* **Pharmacist 2**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Hierarchical culture and the '*trickle-down effect*'	*"I feel like there is probably a bit of a 'Well the doctor knows best' kind of thing, you know".* ***Physician 7*** *"…there can be moments of conflict and it probably is to do with a personality clash or that they, maybe sometimes they perceive that they have got more important things to be dealing with than answering or talking about recommendations or answering a query from a pharmacist".* **Pharmacist 3** *"I think any of the consultants I have worked with have been very open to pharmacist intervention and discussion with them as well. So, I would have no problem ever discussing anything with the pharmacist".* **Physician 2** *"I kind of feel sometimes that the pharmacists make comments or write a note about potential you know, adverse effects or have you considered X, Y or Z but that the like senior doctors especially tend to just kind of fluff that off, and they say 'Oh well, we're the doctor making the prescribing decision, we have already kind of considered what the pharmacist is saying'…"* ***Physician 7*** *"I suppose there's a power thing. So, do you know, like someone telling you something…and maybe held in a position of power, I've no doubt maybe has an effect, do you know. Because that's quite sizeable really, and then that might be that kind of trickle-down effect too of ignoring…"* **Physician 4**
	Personality	*"Like obviously you're gonna have surgeons or doctors who are way more abrupt and not as warm, or as friendly…but at the end of the day, it shouldn't matter what their characteristics are, as long as the recommendation is sound from an experienced pharmacist, and is of benefit to the patient".* **Pharmacist 6** *"I feel like some characters are probably more inclined to be kind of open-minded about most things".* **Physician 7** *"…the personality of the person will obviously dictate how well they take that advice up or how they perceive that or how helpful they perceive that advice to be".* **Pharmacist 3** *"…some would be more receptive to maybe perceived criticism or to a perceived challenge of their own prescribing".* **Physician 3** *"There are some people that would, you know, think they are always right and they don't want to take advice from other people".* ***Physician 5*** *"…the reply that I got from the physician was 'I've prescribed it like that because that's how I want it done'. Rather than 'okay thanks for your query. This is why I'm doing this way and this is the evidence behind it'. It was just 'this is why I'm doing it because I want it this way'. So I suppose maybe arrogance might come into it a little bit".* **Pharmacist 2** *"Probably more arrogant physicians are less likely to take up recommendations".* **Physician 1**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Specialty	*"I think the specialty is hugely influential on taking up recommendations".* **Physician 7** *"And then some would be, wouldn't want to prescribe medicines that they aren't familiar with. So I think like knowledge of the drugs themselves would probably be the biggest factor as to what you do and you don't, and I think that some doctors will be fairly set in their ways of using certain medications only and then not deviating from that".* ***Physician 3*** *"…if you take surgeons or like specialties that maybe aren't very medical and would have a lot less pharmacology knowledge, would be more likely to just take up anything. I'm not saying this is good or bad but would be more likely to just follow any recommendation made by someone else because they have less knowledge about the subject".* **Pharmacist 6** *"…especially medicines that might be outside the far, day-to-day prescribing practice, we may not know as much…"* **Physician 5** *"So, I feel like in the context of a specialty, that those physicians probably would be very protective of their specialty drugs whereas the other non-kind of specialty drugs, so non-cardiac drugs for example in cardiology patients, I feel like recommendations would be both helpful and pretty well respected in that context really".* **Physician 7** *"If you were making a recommendation…maybe a recommendation about the specialty…so, a cardiology drug, the cardiologist, they might not listen to you as fast. But if it was about another type of drug, they'd probably take it up faster".* **Pharmacist 1** *"…you'd be more likely to agree with recommendations outside your specialty, and in your specialty, you may have more knowledge or more of that soft knowledge…"* **Physician 5** *"The pharmacist can kind of look at it as a whole, whereas you'll see now you go into a cardiac ward, a cardiologist will never touch a mental health drug, 'That's not - I didn't prescribe it'".* **Pharmacist 4** *"So, we would normally not, unless you get psychiatry input, we wouldn't have the background of the appropriateness of antipsychotics in particular".* **Physician 4** *"You might find cardiologists might be reluctant to fiddle around with respiratory drugs or respiratory physicians might be slow enough to fiddle around with psychiatry drugs. So I think geriatricians are probably a group that are sort of happy to fiddle around with most medications".* **Physician 8** *"I think it depends on the team, you know. We'll say your geriatricians probably would be quite welcoming of pharmacist involvement and quite aware of the roles that they play, say other teams, not as much…"* **Pharmacist 5** *"I think as geriatricians we would be more likely to want to make our own decisions about medication management and sort of taking the patient's own like context into account".* **Physician 3** *"I think the geriatric teams are probably very supportive of pharmacists and there does seem to be… You do you get the feeling that there is a shared care there between geriatricians and pharmacists. Em…and I think geriatricians are trained to be very aware of the patient as a whole and kind of a holistic view".* **Pharmacist 2**

Theme	Descriptor	Illustrative Quotations
3. Prescriber role and identity (continued)	Professional boundaries / Encroachment	*"…he was involved with the patient initially, he saw me as coming in and almost interfering, and just being overly cautious".* ***Pharmacist 4*** *"…if they're confident in their own ability, they feel maybe that they don't need the advice of a pharmacist and that they've made their decision and that it's not our place to question their decision retrospectively".* ***Pharmacist 3*** *"…if it's something that's very specialty-based - do you know like certain like, I don't know, rheumatological drugs or cardiac drugs that I don't use that frequently that they're under someone else's specialist care for, I would be a lot less likely to stop it".* **Physician 3** *"…some people would be I suppose less keen to stop medications that they felt if they haven't started it, sometimes they'd be less keen to stop it. Whereas I think geriatricians would kind of take ownership for just stopping it".* **Physician 2** *"Again, it comes down to: does a doctor who might be only seeing the patient, you know, on this presentation stop the medication that was started by another colleague".* **Pharmacist 3** *"…what importance they do place on the role of the pharmacist because a lot of the role of the pharmacist would overlap with what they might have considered that they've done anyway…"* **Pharmacist 5**

Theme	Descriptor	Illustrative Quotations
4. Knowing each other and developing trusting relationships	Knowing each other	*"I think definitely in terms of uptake of recommendations, if you have a very good relationship with the team, you're more likely…it's more likely because they know you".* **Pharmacist 3** *"I suppose like if you were just a random person coming up…because I think that's what happens a lot. They don't know… If you can't put a face to the name, they don't know you really".* **Pharmacist 1** *"…if you don't know the team or you don't know the doctor you're kind of going 'Oh God, I have to walk up there now and approach this', but yeah, I'd say I wouldn't be meek about it anyway".* **Pharmacist 4** *"But I suppose if you're just leaving a note to a team that you don't know, how do they even know who you are?"* **Pharmacist 1** *"I think it would be extremely beneficial if we knew them at a kind of a deeper level".* **Physician 7** *"So I think it's not essential. But I think like any bit when you are working as part of a team if you know somebody it probably makes interactions a little bit better".* **Physician 8** *"…if they see an intervention from you, you know, because they know you, they are more likely to act on that intervention, which I suppose is natural".* **Pharmacist 3**
	Outsider	*"So you're kind of back in the mist".* ***Pharmacist 5*** *"Outside the loop sometime yeah. Certainly…that probably is one of the main sources of miscommunication, or not picking up recommendations in that they may not be….yeah inside the exact loop with the train of thought or the goal of care…"* **Physician 5**
	Relationship-building	*"…when you have an interpersonal relationship with someone, you're more likely to take on board their opinion, and subsequently maybe implement their recommendations".* **Physician 5** *"I suppose you build up a sort of relationship with some pharmacists too where you know that you have worked with them before and you know that their advice is very good and solid. So sometimes when maybe newer people or younger people are in the ward, you may be less sure as to what their sort of experience is…"* **Physician 8** *"I think I'd have a good relationship with the SHOs and registrars because the interns change every three months and the SHOs kind of change as well, but you kind of have more exposure to them because they'd actually be kind of the main people you see on the team, so they might get used to you more as well…a lot better relationship with them".* **Pharmacist 1** *"I think if they were like again like a cardiology pharmacist that if they mentioned something on the ward round, I think they would have built up a rapport with the consultants who were there obviously more long-term than we are, and it probably would be implemented easier, if they had already built up that rapport".* ***Physician 2***

Theme	Descriptor	Illustrative Quotations
4. Knowing each other and developing trusting relationships (continued)	Relationship-building (continued)	*"Good rapport always helps. If you know the same pharmacist and you are working with them all the time, I think that benefits, like that definitely helps. If the pharmacist was to change every single day, I don't think that should be a reason to not implement their recommendations anyway".* **Physician 1** *"I think, as you're there and you get to know people more that they come to you with questions and things like that. You do need to put in a bit of time and effort, I suppose, into building up those kinds of relationships".* **Pharmacist 5**
	Trusting pharmacists' recommendations	*"…if you build up a relationship, a working relationship, then it helps massively and there's much more trust and you even get to know why one person is doing one thing and one person is doing another".* **Physician 5** *"…like any relationship, like if you build up, if you make a few recommendations that were good, they kind of trust you more, so I think it's very important..."* **Pharmacist 1** *"Because you know the pharmacist, and you have a personal relationship with them, and you trust their opinion…"* **Physician 3** *"…when you're working in a particular area, you get to know the different doctors that work in that particular area and they're more familiar with you, even just seeing your face kind of repeatedly then, I think you have more I suppose credence in their eyes or credibility in their eyes, because you know they've seen you at work and they've seen you, you know review patients' medications and review patients' charts".* **Pharmacist 3** *"I suppose they're less experienced* [referring to more junior physicians] *and they have more trust in other healthcare professionals that might have more experience than them. So I suppose the less experienced they are…the more trust they would have that other people will guide them".* **Pharmacist 2**

Theme	Descriptor	Illustrative Quotations
5. Hospital environment	Opportunity for intervention	*"…I think meeting as opposed to kind of opportunistically trying to find the team on the ward…"* **Physician 2** *"I suppose when I'm on the wards, it's probably more ad hoc interactions…"* **Pharmacist 3** *"…if you miss the team when they are around on a ward round, you are relying on, you know, if it's extremely urgent, you're bleeping and waiting for them to ring you back".* **Pharmacist 5** *"You know it was just easier when the pharmacist was there on the ward round to flag things with the consultant and then you'd get an answer straight away".* ***Physician 2*** *"…the pharmacist went on a round once a week and that was very good and it helped the…again, the knowledge passing and for new doctors…"* **Physician 4**
	Busy	*"At the same time, they could be very busy, so they might not think that doing them is important as well* [referring to pharmacist recommendations]*".* **Pharmacist 1** *"I think when you're on a busy service you mightn't necessarily do it straight away* [the pharmacist recommendation]. *So, I think that's probably one of the biggest factors is if you have a long patient list and if it's not something say particularly pressing, then you might not do it straight away".* **Physician 2** *"…it is all a bit chaotic, and that doesn't lend to safe prescribing really and the overall hospital environment and workload could all impact on it certainly, and that will also then impact on following the guidance".* **Physician 5** *"I think time is a huge thing. I think all of the teams are very time-poor. They don't really have the time to look at the drug chart, they don't have the time to look up what it is the issue is or why it should be changed…"* **Pharmacist 5**
	Timing	*"I suppose one of the issues is that when you do bleep an intern or bleep an SHO about a medication issue, you know, they could be having a really busy incident on another ward or they could be, I suppose dealing with something pressing on another ward and you are trying to explain to them about a patient on your particular ward".* **Pharmacist 3** *"…get a bleep, find a phone, ring the number back… You know, maybe that's engaged and, you know, you can play what they call phone tag for all that - so that can be an issue".* **Physician 5** *"…at the moment we either leave a note or we bleep the team and we are always kind of going 'why have you done this?' and 'can you review it?', rather than at the time of prescribing we could have discussed it and you'd already have your answers and you wouldn't have to go querying it because you'd know why it has been done".* **Pharmacist 2** *"Ideally, at the point of prescribing or at the bedside or when the doctors have the kardex and the medication notes, that would be the time to raise any issues…"* **Pharmacist 3**

Theme	Descriptor	Illustrative Quotations
5. Hospital environment (continued)	Documentation in the medical notes	*"…the written notes can sometimes be a disaster, because even like the binding holes rip and the pages either are in the wrong position or they fall out or they're shoved into the back of the chart".* **Physician 7** *"So if you are not on a ward round, I suppose some things can be omitted from the notes sometimes and so I suppose when I'm reviewing medication, I don't assume that I have all the information to hand".* **Pharmacist 2** *"…I suppose you have to take into consideration that there's other factors that mightn't be, you know, maybe particularly clear in the notes, so you know, from a pharmacist's point of view, I think it's always very prudent to, you know, to discuss any issue you have rather than just kind of dictating what you think the dose might be".* **Pharmacist 3**
	Working as a team	*"…I think being on their team would make it* [would make implementation more likely]. *You are their team, you're kind of in their specialty, they know you - I think that's much better rather than random pharmacists kind of approaching them on the ward..."* **Pharmacist 4** *"…well if you're part of the team then I feel like people know you at a kind of deeper, like behind the professional level you know, and you get to know people…"* **Physician 7** *"I think you've a better relationship with the doctors if you have a team-based approach and I think if you're familiar with the team and you have maybe more easier methods of communication where you are seeing each other more frequently or you're catching up with each other at certain points of the day, then I think that makes the likelihood that interventions can be acted on much more likely…"* ***Pharmacist 3***
	Staffing levels	*"I think staffing levels is a big thing here, like we don't have enough pharmacists here to cover every ward, so like I said, if you have screened a drug in the dispensary and you have to go up to the ward that you're not familiar with - the team isn't familiar with you. So, if we had more staff levels I think that, and that they actually see your face, they'd be more inclined to implement it…"* **Pharmacist 1** *"I think it may be as simple as sort of more face time, more pharmacists, more clearly a role and understood role among doctors…"* **Physician 8** *"I think we don't have sufficient staff to expand our roles and really develop relationships. It's all about developing relationships with the physicians, particularly the consultants and I don't think we're able to do that with what we have at the moment to develop relationships with the consultants".* **Pharmacist 6** *"It's really really variable depending on what hospital you're in. I really don't see a lot of them here* [referring to day-to-day interactions with pharmacists]*".* **Physician 3** *"…I suppose there is that thing there's so few of us, many of them* [physicians] *won't even know that we're around…"* **Pharmacist 4**

GP: General practitioner CHA_2DS_2-VASc: a scoring system to calculate stroke risk in non-valvular atrial fibrillation patients based on Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, history of Stroke or transient ischemic attack, Vascular disease, Age 65-74, and Sex category. PPI: Proton pump inhibitor SHO: Senior house officer FYI: For your information