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Pharmacotherapy Optimization in Older Patients by a Structured Clinical Pharmacist Assessment and Intervention

David O'Sullivan MPharm MPSI

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

June 2014

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I declare that the work contained within this thesis has not been previously submitted for a degree at this or any other university. All the work contained within this thesis is entirely my own work, apart from that indicated in the acknowledgements. I give my permission for the library to lend or copy this thesis upon request.

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Abbreviations

ACE	Angiotensin Converting Enzyme
ACE Team	Acute Care for Elderly Team
ACOVE	Assessing Care of Vulnerable Elders
ADL	Activity of Daily Living
ADR	Adverse Drug Reactions
ADE	Adverse Drug Event
AE	Adverse Event
A&E	Accident and Emergency
AOU	Assessment of underutilisation of medication
ASHP	American Society of Hospital Pharmacists
AT	Alimentary Tract
ATC	Anatomical Therapeutic Chemical
BBB	Blood Brain Barrier
BNF	British National Formulary
CCB	Calcium Channel Blocker
CCI	Charlson Co-morbidity Index
CD	Considering Diagnosis
CDSS	Computerised Decision Support Software
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CIRS	Cumulative Illness Rating Score
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CUH	Cork University Hospital
CVA	Cerebrovascular Accident
CVS	Cardiovascular System

DBI	Drug Burden Index
DRP	Drug Related Problem
DUR	Drug Utilisation Review
EQ-5D	EuroQoL-5D
FTE	Full Time Equivalent
GABA	Gamma-Aminobutyric Acid
GEM	Geriatric Evaluation and Management
GI	Gastro-Intestinal
GP	General Practitioners
HEDIS	Healthcare Effectiveness Data and Information Set
ID	Independent of Diagnosis
ICD	International Classification of Diseases
IPET	Improved Prescribing in the Elderly Tool
IQR	Inter Quartile Range
LA	Long Acting
LT	Long Term
LTC	Long Term Care
NH	Nursing Home
NHR	Nursing Home Residents
NHS	National Health Service
NI	Northern Ireland
NIC	Net Ingredient Cost
NORGEP	Norwegian General Practice
NPS	National Prescribing Service
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
M-Adm	Median at Admission
MAI	Medication Appropriateness Index

M-Fol	Median at Follow-up
MDT	Multidisciplinary Team
OR	Odds Ratio
OTC	Over The Counter
PASW	Predictive Analytics Software Statistics
PC	Primary Care
PIP	Potentially Inappropriate Prescribing
PIM	Potentially Inappropriate Medications
PPI	Proton Pump Inhibitors
PPO	Potential Prescribing Omission
PRN	Pro Re Nata
PUD	Peptic Ulcer Disease
QUB	Queens University Belfast
QOL	Quality Of Life
RCI	Resident Classification Instrument
RCT	Randomised Controlled Trial
RoI	Republic of Ireland
SC	Secondary Care
SF	Short Form
SMPA	Swedish Medical Product Agency
SPRM	Structured Pharmacist Review of Medications
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitors
STOPP	Screening Tool of Older Person's Prescriptions
START	Screening Tool to Alert doctors to Right Treatment
TCA	Tricyclic Antidepressants
UCC	University College Cork

UK	United Kingdom
US	United States
USA	United States of America
WHO	World Health Organisation
WHO-UMC	World Health Organisation - Uppsala Monitoring Centre

Publications

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O'Sullivan D., O'Mahony D., Hughes C., Parsons C., Patterson S., Byrne S., A prevalence study of potential inappropriate prescribing in Irish long term care facility older residents. *Drugs and Aging, 2013, (Jan 2013); 30 (1).*

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O'Sullivan D., O'Mahony D., Patterson S., Parson C., Hughes CM. and Byrne S., Inappropriate Prescribing in Irish Nursing Homes, CARDI Conference 2nd and 3rd November 2011; Croke Park, Dublin, Ireland-Oral Presentation

Abstract

Introduction

Presently, in Ireland older individuals constitute approximately 13% of the population and consume almost 50% of all prescription medications. Older individuals are particularly vulnerable to potentially inappropriate prescribing (PIP), drug related problems (DRPs) and adverse drug reactions (ADRs). Over the last 25 years a number of different screening tools/ criteria have been developed to address the issues of PIP and DRPs in older individuals. An area of particular focus has been on the proposed link between PIP or DRPs and ADRs. A number of different intervention types have been proposed to address the issues of PIP, DRPs and ADRs in older individuals. However to-date there is limited evidence and a paucity of well-designed trials examining the impact of such interventions in older individuals. Therefore the aim of this work was to: (i) review the literature relating to PIP in order to establish a baseline PIP prevalence both nationally and internationally, (ii) identify the most comprehensive/applicable method of assessing/addressing PIP in older individuals, (iii) develop a structured pharmacist intervention supported by a CDSS and (iv) examine the impact of this structured pharmacist intervention on the appropriateness of prescribing and the incidence of ADRs.

Methods

Initially a comprehensive review of the literature was undertaken to establish a baseline for PIP nationally and internationally. We then conducted a number of studies which examined the prevalence of PIP across different setting of care in Ireland using several different PIP screening criteria. Studies one and two examined PIP prevalence and the applicability of two PIP criteria, i.e. STOPP and Beers criteria, in older individuals residing in long term care. Study three, expanded upon

prior work examining the prevalence of PIP and the applicability of three different PIP criteria, i.e. STOPP, Beers and Priscus criteria, in isolation or in combination across three healthcare settings in Ireland. From this work we developed a structured pharmacist intervention which was supported by dedicated computerised decision support software (CDSS). Studies four and five examined the impact that the structured pharmacist intervention had on (i) the appropriateness of prescribing as defined by the medication appropriateness index (MAI) and a modified assessing care of vulnerable elders (ACOVE) and (ii) the incidence of adverse drug reactions (ADR) in acutely ill older hospitalised individuals in Ireland via the conduction of a randomised controlled trial.

Results

The literature review found that PIP was highly prevalent across all settings of care, both nationally and internationally with prevalences as high as 64.0% being reported in primary care (PC), 65.0% in secondary care (SC) and 74.0% in long term care (LTC). The variations in the rates reported between the different studies were a reflection of the different methodologies employed in the different studies. In studies one and two it was found that PIP as defined by both sets of criteria, in older LTC residents was highly prevalent in both the Republic of Ireland and Northern Ireland. PIP prevalences as high as 73.0% and 67.0% being reported in each jurisdiction respectively. The third study found that PIP was highly prevalent in Ireland across all three healthcare settings, with PIP prevalences as high as 43.3%, 70.7% and 84.7%, being reported in the PC, SC and LTC settings respectively. This study indicated that the STOPP criteria maybe the most applicable PIP criteria for assessment of PIP in older Irish individuals across all three settings, however this work did indicate that

each set of criteria possesses a number of uniquely clinically relevant criteria and to ensure that the most comprehensive assessment of PIP was undertaken it would be more appropriate to deploy an amalgamated set of criteria which contained criteria from all three criteria. However this study concluded that this combined criteria would be too cumbersome to deploy manually. Therefore for it to be effectively deployed in routine practice, it would need to be incorporated into a specially-developed CDSS. The fourth study, found that PIP and DRPs were highly prevalent in older acutely-ill individuals admitted to hospital, with 82.0% and 76.3% of patients reported to have at least one DRP or PIP instance respectively upon admission to hospital. Study four demonstrated that a structured pharmacist intervention supported by a dedicated CDSS, had a positive impact on the appropriateness of prescribing in this patient group, with a significantly reduction in pre- and post- intervention MAI scores, with a median MAI score of 15 being reported at admission and a median MAI score of 12 being reported at follow-up. This study however did not find that the intervention had a significant impact of the prevalence of potential prescribing omission as defined by the modified ACOVE criteria. Study five reported that the structured pharmacist intervention which was supported by the CDSS produced a significant reduction in the interventions patients' risk of experiencing an ADR when compared to the control patients, with an absolute risk reduction of 6.8 (95% CI 1.5% - 12.3%) and the number needed to treat = 15 (95% CI 8 - 68) being reported. However the intervention was found to have no significant effect on length of stay or the rate of mortality.

Conclusion

This thesis shows that PIP is highly prevalent in older individuals across three settings in Ireland. This work also demonstrates that a structured pharmacist intervention support by a dedicated CDSS can significantly improve the appropriateness of prescribing and reduce the incidence of ADRs in older unselected acutely ill hospitalized individuals.

Aims and Objectives

Aims

Overall, the aims of this work were to:

(i) Examine the prevalence of PIP in older individuals nationally and internationally,

(ii) Develop an intervention strategy that could improve the appropriateness of prescribing in older individuals and reduce the incidence of adverse drug reactions.

Objectives

The objectives of this research were to:

1. Undertake a comprehensive systematic review of the literature to establish the prevalence of PIP internationally.
2. Review the applicability of the STOPP, Beers and Priscus criteria in an Irish context.
3. Establish the most comprehensive and appropriate method of assessing and minimising PIP and DRPs in older Irish individuals
4. Develop a structured pharmacist intervention supported by dedicated computerised decision support software
5. Assess the impact that a structured pharmacist intervention has on the appropriateness of prescribing in older Irish hospitalised individuals and
6. Conduct a randomised control trial to assess the impact that the structured pharmacist review intervention had on the incidence of ADRs in older acutely-ill hospitalised individuals.

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Chapter 1

1. Introduction

1.1 The Ageing Population

Presently 12% of Republic of Ireland (RoI) are ≥65 years [1-3], with this figure estimated to rise over the next few decades, with it expected to almost double by 2046 (1-2). However, this is not just an Irish phenomenon; similar demographic trends have been forecasted globally (2-5). Presently it is estimated that 8% of the global population are aged ≥65 years and by 2040 it is expected to increase to 13% (6-7). Older individuals aged ≥65 years constitute just over one tenth of the population, but are reported to consume almost 50% of all the prescription medications in RoI (7-8). Similar trends have been reported across Europe, with epidemiological data indicating that older individuals aged ≥65 years take on average 2.3 times more medications than their younger counterparts (9).

Older individuals are a particularly vulnerable patient population and they display a marked heterogeneity in their health statuses; they typically suffer concurrently from multiple acute and chronic disease states, often necessitating the use of multiple concomitant medications (10-13). This heterogeneity means that the health statuses in older individuals can range from those individuals who are fit and healthy to those who are very frail, thus making generalisation of prescribing decisions across the entire older population very complicated (14-15). Advancing age is often complicated by a number of age-related physiological changes, which can lead to alterations in both the pharmacokinetic and pharmacodynamic profiles of many medications (14-17). These alterations can result in an increased risk of; (i) drug-drug interactions, (ii) drug-disease interactions, (iii) potentially inappropriate prescribing (PIP) and (iv) adverse drug reactions (ADRs) (10, 14-15, 18).

1.2 Physiological Changes

There is no definitive description of ageing; it is essentially the culmination of a number of local effects at a molecular, cellular and tissue level (17). The ageing process is characterised by a number of functional and structural changes in a variety of different organs, which is often coupled with a reduction in an individual's homeostatic capacity (17). Older individuals display a marked heterogeneity in their health statuses and generally suffer from multiple co-morbidities and for which they are frequently prescribed a variety of different medications.

Prescribing in older individuals can often prove to be challenging. When considering a new medication, a number of factors should to be considered (14, 18-21):

1. Age-related alterations in pharmacokinetics (drug absorption, distribution, metabolism and excretion) i.e. how the body affects the drug,
2. Age-related alterations in pharmacodynamics (physiological effects the drug has) i.e. how the drug effects the body and
3. Age-related changes to the body's composition and physiology.

These changes make older individuals more susceptible to the potentially toxic/adverse effects of certain prescription medications. Therefore in older patients the risk of adverse effects may potentially outweigh the potential benefits for specific medications which are used commonly in the general population (19-20, 22-25).

1.2.1 Pharmacokinetics

Pharmacokinetics is a term used to define how the body handles a drug, or how it manages the drugs movements through the body (26). Pharmacokinetics encompasses a number of different processes which describes how a drug is absorbed and distributed among the different compartments of the body, how long the drug remains therapeutically active in the body and how it is metabolised and excreted from the body (26).

An in depth understanding of the pharmacokinetic profile of each individual drug is crucial in order to effectively devise an appropriate drug regimen for a patient. Pharmacokinetics is particularly relevant when it comes to prescribing in older individuals, who are reported to undergo a variety of age-related functional and structural changes (27-28).

Pharmacokinetics can be essentially subdivided into four phases:

- Absorption,
- Distribution,
- Metabolism and
- Excretion.

1.2.1.1 Absorption

A number of studies have proposed that advancing age correlates with changes in the rate of absorption. It has been reported that ageing is associated with (17, 29-31):

- Decreased salivation, increased gastric acid pH,
- Decrease in gastric acid secretion,
- Decrease in gastric emptying,
- Decrease in gastric surface area,
- Decrease in the absorptive capacity of the small intestine and
- Decrease in splanchnic blood flow.

Even though ageing is associated with a number of changes in the gastrointestinal tract, the majority of medications are absorbed via passive diffusion and therefore most medications will only experience a slight delay, if any, in absorption, with the overall rate of absorption remaining virtually unchanged i.e. a possible initial delay to achieve maximum concentration, but in individuals on long term medications there will be little or no significant identifiable change in concentration once the steady state has been achieved.

1. 2.1.2 Distribution

There are a number of age related physiological changes in older individuals that may affect the distribution of certain medications (17, 29-31):

- A reduction in lean body mass (25-30% decrease),
- A reduction in total body water (25-30% decrease),
- Increased total body fat (25-30% increase),
- Reduction in serum albumin level and
- Slight increase in α_1-acid glycoprotein levels.

Due to a reduction in lean body mass, medications that normally distribute into muscle will exhibit a decreased volume of distribution and an increased in its initial concentration.

Hydrophilic drugs tend to exhibit a smaller volume of distribution in elderly patients, thereby resulting in higher serum levels. The body normally compensates for this reduction in total body water i.e. volume of distribution, by reducing renal clearance, resulting in little to no observable change in the plasma half-life or net effects of hydrophilic drugs in older patients.

Lipophilic drugs tend to exhibit an increased volume of distribution therefore leading to a prolongation of the half-life of certain lipophilic agents i.e. prolonging the time it takes half of the total amount of drug to be eliminated from the body. **Table 1.1** outlines examples of hydrophilic and lipophilic medications commonly prescribed in older patients.

Table 1.1 Examples of Hydrophilic and Lipophilic medications (17, 29)

Hydrophilic Medications	Lipophilic Medications
• Aminoglycosides • Digoxin • Lithium • Theophylline	• Chlordiazepoxide • Diazepam • Lidocaine

Acidic drugs principally bind to the protein known as albumin (17). The reduction in serum albumin may potentially produce a significant increase in pharmacological effects of certain highly protein bound acidic drugs. The body normally compensates for this increase in unbound drug by increasing its elimination via the liver and often this is sufficient to resolve the issue, but in certain circumstances this increase in unbound drug can result in adverse effects developing during the initial stages of drug therapy (17, 29, 31).

Basic drugs normally bind to the protein known as α_1-acid glycoprotein (17). Thus an increase in glycoprotein levels could consequentially lead to a reduction in the concentration of unbound basic drug (17). Therefore there may be a reduction in the clinical efficacy of certain medications. **Table 1.2** outlines examples of acidic and basic medications commonly prescribed in older individuals.

Table 1.2 Examples of Acidic and Basic medications (17)

Acidic Medications	Basic Medications
• Aspirin • Diazepam • Phenytoin • Warfarin	• Lidocaine • Propranolol

1. 2.1.3 Metabolism

Advancing age is associated with a reduction in hepatic blood flow (29-31). This reduced hepatic blood flow usually corresponds with a reduction in the first-pass metabolism of certain drugs (17, 31). Normally this is because the rate at which the medications are delivered to the liver to undergo first-pass metabolism is decreased and therefore prolonging the time that the medication has to interact with the body. This increase in interaction time also means that the likelihood of that medication eliciting an unwanted pharmacological effect increases (17). **Table 1.3** outlines some examples of medications which are commonly used in older individuals which undergo extensive first pass metabolism.

Table 1.3 Examples of medications that undergo extensive first pass metabolism (29)

First Pass Metabolism	
• Amitriptyline	• Pravastatin
• Atorvastatin	• Propranolol
• Levodopa	• Simvastatin
• Metoprolol	• Verapamil

Advancing age is associated with a reduction in both the mass and functionality of the liver and the kidneys. Consequentially there may be a marked decline in the metabolism of certain drugs. The true extent of hepatic changes that occurs in older individuals has not been fully elucidated too. It has been suggested that the reduction in liver mass may be as high as a 20-40% and hepatic blood flow may decrease by 35% (17, 28, 31).

It has been suggested that this reduced metabolic capacity could correspond to a reduction in Phase-1 metabolism (e.g. the addition of a polar functional group or the

modification of an existing functional group to make the drug compound more water-soluble) but as of yet the evidence is still inconclusive (29). It would however be wise for physicians to take this potential reduction in Phase-1 metabolism under consideration when prescribing for older individuals. Medications that usually undergo extensive phase-1 metabolism could display altered rates of metabolism; therefore dose adjustment may be necessary. Another option is the prescription of an alternative medication which is not reliant on phase-1 metabolism (i.e. metabolised through the glucuronidation pathway) (28-29).

A number of studies have investigated if advancing age is associated with changes in Phase 2, and these have reported that Phase-2 metabolism (e.g. conjugation type reaction, in which a polar molecule combined with a suitable functional group to further increase the water-solubility of the drug) is relatively unaffected by advancing age (29-30). **Table 1.4** lists examples of medications commonly prescribed in older individuals, which undergo Phase-1 and Phase-2 metabolism.

Table 1.4 Examples of medications that undergo Phase-1 and Phase-2 metabolism (29)

Phase 1 Metabolism		Phase 2 Metabolism
• Alprazolam • Amitriptyline • Atorvastatin • Barbiturates • Carbamazepine • Chlordiazepoxide • Citalopram • Diazepam • Diphenhydramine • Fluoxetine • Flurazepam • Ibuprofen	• Nortriptyline • Phenytoin • Propranolol • Risperidone • Sertraline • Simvastatin • Verapamil • Theophylline • Tramadol • Zolpidem • Venlafaxine	• Lorazepam • Paracetamol • Valproic acid • Zaleplon

1. 2.1.4 Elimination

Advancing age has been reported to correspond to a progressive decline in renal function. This decrease in function is believed to relate to a number of different physiological changes that occur in the ageing kidney (28-29):

- Decreased kidney size,
- Decrease in tubular secretion,
- Decreased renal blood flow and
- Decreased glomerular filtration rate (GFR).

As a consequence of this age related reduction in renal function, medications which are normally heavily dependent on renal elimination will have significantly longer half lives in older individuals. This prolongation has been reported to be quite significant and has been documented as a major contributory factor in adverse effects associated with some medications (29). **Table 1.5** list some commonly prescribed medications that normally rely on renal excretion.

Table 1.5 Examples of medications which are normally renally excreted (17, 29)

Renally-excreted medications		
• Aciclovir	• Fluconazole	• Pregabalin
• ACE inhibitors	• Gabapentin	• Sulphonamides
• Allopurinol	• Glipizide	• Telmisartan
• Aminoglycosides	• Histamine-2 Antagonists	• Tetracyclines
• Water soluble β-blockers	• Lithium	• Vancomycin
• Digoxin	• NSAIDs	
• Diuretics	• Penicillins	

Key: ACE; Angiotensin Converting Enzyme, NSAIDs; Non Steroidal Anti-Inflammatory Drugs.

1.2.2 Pharmacodynamics

Pharmacodynamics describes how a medication interacts with the body i.e. how it interacts with the receptors on a cellular level (31). It has been reported that ageing is associated with fewer pharmacodynamic changes compared to pharmacokinetic changes. Nonetheless the majority of these changes are considered to be clinically significant. These changes can result in either a decreased clinical effectiveness or alternatively an increased efficacy of certain medications (31).

The exact extent to which receptors sensitivity changes with age has not been entirely elucidated and different receptor types are considered to be affected in different ways. Some examples of the types of receptors and the drugs of concern are detailed below.

The changes in receptor sensitivity are believed to correspond to changes in:

- Receptor density/numbers,
- Receptor affinity,
- Signal transduction and
- Homeostatic mechanism.

The pharmacodynamic alterations and the heterogeneity of such alterations which develop with ageing further contribute to the complexity of therapy. Careful monitoring of treatment regimens is crucial in order to prevent the development of adverse drug events (ADEs) (29).

1.2.2.1 Cardiovascular system

Advancing age is reported to be associated with a reduction in the overall responsiveness of cardiac β-adrenergic receptors to the effect of β-adrenergic receptor agonists, however whether or not the actual number of β-adrenergic receptors decreases with age is still under investigation (26, 29). This usually means that older individuals will exhibit a decreased responsiveness to β-adrenergic receptor agonists such as adrenaline and demonstrate an increased responsiveness to β-adrenergic receptor antagonists such as metoprolol (29). This reason for this diminished responsiveness is not fully understood, however it has been proposed that it may be a result of an age-related reduction in the cardiovascular reflex effect as opposed to a decrease in β-adrenergic receptor sensitivity.

Older individuals are also at an increased risk of experiencing orthostatic hypotensive episodes, due to a reduction in arterial compliance coupled with a decrease in baroreceptor-reflex sensitivity (32). Therefore in older individuals, any medications known to impart an orthostatic hypotensive effect should be initiated at the lowest possible dose and titrated up slowly in order to minimise the risk of adverse effects e.g. tricyclic antidepressants, antipsychotic, diuretic (especially loop diuretics), angiotensin converting enzyme inhibitors, directly-acting vasodilators, opioids and calcium-channel blockers (CCBs) (29).

A number of other pharmacodynamic changes may occur in older individuals that relate to the cardiovascular system such as; (i) a reduction in the effect of verapamil on cardiac conduction and an increase in its antihypertensive effect (17) and (ii) an increase in the QT interval prolongation effects of certain medications e.g.

anticholinergics and macrolides, thereby predisposing older individuals to an increased risk of developing torsades de points (29).

Older individuals are reported to exhibit an increased responsiveness to the anticoagulant effect of warfarin and other vitamin K antagonists and this can result in older individuals exhibiting an increased inhibition in the synthesis of vitamin-K-dependant clotting factors (17, 31).

1.2.2.2 Respiratory System

Older individuals may also exhibit a reduced responsiveness to the broncho-dilatory effects of β-adrenergic agonists e.g. salbutamol, whereas there is no reported change in the responsiveness to anticholinergic broncho-dilators e.g. ipratropium. Therefore in older individuals with asthma or chronic obstructive pulmonary disease (COPD) it may be more appropriate to prescribe an anticholinergic bronchodilator as opposed to a β-adrenergic broncho-dilator (29).

1.2.2.3 Central Nervous System (CNS)

The ageing process is also reported to be associated with a number of different physiological changes in the brain. These changes are considered complex and can affect a variety of regions of the brain. They primarily relate to alterations in the number of neurons, receptors and neurochemical pathways involved in the neurotransmission process that occur in the brain. Advancing age has been reported to correlate with an increase in the permeability of the blood brain barrier (BBB). The full extent of this altered permeability is still not fully understood, but it is believed to be more prominent in individuals with vascular or Alzheimer type dementia (29). This increase in BBB permeability means that more agents can cross into the CNS and thereby could possibly elicit more CNS-related ADEs (29).

A number of different neurochemical changes have been proposed to take place in the brains of elderly individuals. Changes in the gamma aminobutyric acid (GABA) system, changes in the cholinergic systems and the dopaminergic systems have all been extensively reported in the literature (29, 31).

1.2.2.3.1 Gamma-aminobutyric acid (GABA) system

Changes in the GABA system results in older individuals exhibiting an increased sensitivity to the effects of benzodiazepines (29-30). This increased sensitivity means that older individuals may be more susceptible to the adverse effects associated with the benzodiazepine use i.e. sedation, confusion and cognitive impairment (29-30).

1.2.2.3.2 Cholinergic system

Advancing age is reported to be associated with a significant number of physiological changes relating to the cholinergic system, such as (29):

- A reduction in the number of acetylcholine neurons,
- A reduction in choline uptake from the periphery,
- A reduction in number of acetyltransferase enzymes,
- An increase in number of acetylcholinesterase enzymes,
- A reduction in number of muscarinic receptors and
- A reduction in number nicotinic receptors.

These changes can predispose older individuals to an increased susceptibility to the anticholinergic effects of certain medications e.g. postural hypotension, arrhythmias, cognitive impairment, sedation, urinary retention and constipation (33-39).

1.2.2.3.3 Dopaminergic system

Advancing age is also associated with an increase in the number of D_2 receptors. This increase in receptors is reported to correspond to an increased susceptibility of older individuals to adverse effects such as delirium, which can occur with certain anticholinergic and dopaminergic medications. A decrease in the number of dopamine receptors in the substantia nigra has also been reported with advancing age (29-30). This reduction in the dopamine receptors predisposes older individuals to an increased risk of experiencing extrapyramidal side effects from certain medications with anti-dopaminergic properties, such as antipsychotics (29).

The body maintains its postural stability through a number of short transient corrective movements that involve a number of opposing static reflexes; these reflexes involve contraction and relaxation of specific muscles groups coupled with phasic reflex responses (29). Increasing age has been reported to be associated with both an increase in the frequency and amplitude of these corrective movements. The exact reason for these age-related variations is not fully understood, but it has been suggested that it could relate to the age-related reduction in the number of D_2 receptors in the striatum region of the brain (26, 29).

This reduced ability to maintain postural stability coupled with a reduced compensatory capacity to accommodate accordingly, means that older individuals may be at an increased risk of falling. Medications which act on the D_2 receptors in the striatum region of the brain have been shown to further contribute to this increased risk of falls i.e. neuroleptics (26). The most common effects of these pharmacodynamic changes on specific drugs are summarized in **Table 1.6**.

Table 1.6 Summary of common medications which exhibit pharmacodynamic changes in older individuals (17, 26, 31)

Drug Type	Pharmacodynamic effect	Age-related change
ACE inhibitors	Antihypertensive effect, Postural hypotension	Increased effect
Anticholinergics	Postural sway, urinary retention and cognitive impairment	Increase effect
Antihypertensives	Postural hypotension	Increased effect
Benzodiazepines	Sedation, postural sway and cognitive impairment	Increased effect
CCB	Antihypertensive effect, Postural hypotension	Increased effect
Diuretics	Hypotensive effect	Increased effect
Neuroleptics	Anticholinergic effects, Postural instability, Hypotensive effect	Increased effect
NSAIDs	Gastrointestinal adverse reactions	Increased effect
Opioids	Hypotensive effect, Analgesic effect	Increased effect
TCA	Urinary retention and cognitive impairment	Increased effect
Verapamil	Acute hypertensive effect Cardiac conduction	Increased effect Decreased effect
Warfarin	Anticoagulant effect	Increased effect

Key: ACE; Angiotensin Converting Enzyme, CCB; Calcium Channel Blockers, NSAID; Non Steroidal Anti-Inflammatory Drug, TCA; Tricyclic Antidepressants.

1.2.3 Summary

Overall, there appears to be a marked difference between pharmacokinetic and pharmacodynamic profiles of elderly individuals when compared to younger healthier counterparts. This means that certain medications can prove more problematic when used in older individuals. These variations in pharmacokinetics and pharmacodynamics should always be taken into consideration when prescribing in elderly individuals. Careful selection of the most appropriate medication and dosage should in theory result in avoidance of ADRs and culminate in establishment of a successful drug regimen (14, 21, 30-31, 40).

1.3 Prescribing

Prescribing is a crucial aspect of geriatric care. The main aim of prescribing is to cure disease, eliminate or reduce symptoms relating to an underlying disease state and improve functional capacity of the patients (41).

1.3.1 Appropriate Prescribing

Appropriate prescribing is a very general concept that encompasses a variety of different aspects of prescribing (14). Prescribing is usually considered appropriate when it is (14):

- Evidence based,
- Well tolerated by the majority of patients and
- Cost effective.

However prescribing in older individuals is often complicated by a number of factors such as (15):

- Life expectancy of the patient,
- The right therapeutic approach in patients with poor prognosis and
- Selection of the pharmacotherapy with the most favourable risk/benefit ratio.

1.3.2 Inappropriate Prescribing

Inappropriate prescribing has become an area of major concern in older individuals (9, 14, 18, 25). It has been widely documented that certain medications should be used with caution in this patient population, and where possible it is generally best to completely avoid such medications, especially if safer, as effective alternatives are available (14-15, 42).

1.3.3 Potentially inappropriate Prescribing

Potentially inappropriate prescribing is usually considered to be relative rather than absolute. This relates to the fact that under certain circumstances, medications which are deemed inappropriate might in fact be indicated, so in practice the term 'potentially' inappropriate prescribing (PIP) is more commonly used (43).

PIP is a universal term often used to describe a number of different suboptimal prescribing practices such as (14, 18, 25, 43-50):

- Over-prescribing, is the prescribing of more medications than which are clinically indicated or the prescribing of medications at dosages or frequencies higher than or for longer than which are clinically indicated.
- Mis-prescribing, is the prescribing of a medication where the risks of an adverse event associated with its use outweigh the clinical benefits, especially when there are safer as effective alternatives available, i.e. prescribing of a medication with an unfavourable risk-benefit ratio or the prescribing of medications with high inherent risk of adverse drug-drug or adverse drug-disease interactions.
- Under-prescribing, is the failure to prescribe a clinically-beneficial medication to a patient for which there is no valid reason why the medication is not prescribed and for which there is no contra-indication to this medication e.g. failure to prescribe an anticoagulant for individuals with atrial fibrillation where no contra-indication exists.

Evidence suggests that PIP is highly prevalent in older individuals. This high prevalence of PIP is an area of major concern and may be attributable to a number of different factors, such as; age related changes in pharmacokinetics and pharmacodynamics, complex drug regimens, cognitive impairment, increasing number of prescribing physicians, increasing number of prescribing pharmacist and presence of multiple co-morbidities (14, 20, 51-53).

1.3.4 Potentially inappropriate medications

A potentially inappropriate medication (PIM) is a medication which has an unfavourable risk/benefit ratio i.e. a medication for which the risks associated with its use outweighs the benefits, especially when there are as effective safer alternatives available.

A number of medications have a propensity to cause problems in older individuals and these medications have been usually classified as high risk or potentially inappropriate for use in older individuals. Generally, these medications do not cause problems in all older individuals, but exhibit an increased potential to cause harm in this population (15, 20-21, 53-54).

In general a PIM is defined as a medication which (15):

- Has no clear evidence-based indication,
- Has a substantial higher risk of causing an ADR and
- Are not considered cost effective.

1.3.5 Consequences of Potentially Inappropriate Prescribing

PIP in older individuals is an area of major health concern and it requires considerable attention as it has been reported to be associated with (14, 20, 23-24, 40, 48, 55-59):

- Increased morbidity,
- Increased mortality,
- Increased health care utilisation,
- Increased healthcare costs and,
- Increased risk of ADRs.

1.3.6 Polypharmacy

As previously mentioned older patients are quite heterogeneous in nature and often suffer multiple co-morbidities for which they may require multiple medications.

Polypharmacy lacks a universally consistent definition, with a number of different definitions being proposed:

1. Polypharmacy is often defined by an arbitrary figure of concomitant medications; however there is no clear definitive number. Studies have proposed a variety of different cut offs for polypharmacy, ranging from >2 concomitant medications to >9 medications (41, 60-65). However generally speaking in the literature the majority of the studies report polypharmacy as the use of >5 concomitant medications (11, 13, 44, 46, 50, 66-70).
2. Polypharmacy has also been defined as unnecessary prescribing of more medications to a patient than which are clinically indicated (50, 61, 71-74).

Although the latter definition, is probably the more appropriate of the two descriptions, as it addresses the issue of potentially unnecessary prescribing. It can often prove quite subjective and difficult to apply in practice, as it is reliant on a reviewer defining what he or she believes to be necessary or unnecessary. For comparison purpose, a cut-off of >5 medications will be used to define polypharmacy in this work.

While the use of several concurrent medications is often justified in the management of multiple co-morbidities in older individuals, this type of prescribing behaviour can predispose older individuals to an increased risk of experiencing drug-drug interactions, drug-disease interactions, PIP or an ADE (18-19, 23-25, 40, 45, 52, 75-78).

Studies have identified a number of factors that may predispose patients to polypharmacy, such as (11, 14, 18, 20-21, 25, 40, 47, 52, 56, 79-82);

- Age,
- Multiple co-morbidities,
- Recent hospitalisation,
- Gender,
- Depression,
- Number of prescribing physicians and
- Number of dispensing pharmacies.

A number of studies have also reported that polypharmacy can result in reduced patient compliance, which in turn can contribute to reduced therapeutic effectiveness, resulting in major clinical consequences. Often prescribers are not aware of their patient's poor compliance (18, 83-84) and they may titrate up the dosage or consider prescribing additional medications in an attempt to try to improve the effectiveness of therapeutic regimen. This can result in an increase in both the risk and the cost of therapy (14, 18, 20-21, 25, 40, 52).

Another aspect of polypharmacy that frequently goes unrecognised is the prescribing of duplicate medications from the same therapeutic class (47, 50, 61, 85-86). Such prescribing behaviour is rarely deemed justified or appropriate.

Although the prescribing of multiple medications in older individuals is often necessary, polypharmacy can prove quite problematic in this population and can often contribute to an increase in the complexity of therapy. Polypharmacy has been

reported to be associated with PIP, an increased risk of ADRs, an increase in the prevalence of certain geriatric syndromes (i.e. as falls, fractures and urinary incontinence) and an increase in healthcare utilisation and costs (18-20, 23, 25, 40-41, 61, 71-72, 84-85, 87-90).

In summary, the more medications an individual is prescribed, the higher their risk of experiencing (i) drug-drug interactions, (ii) drug-disease interactions, (iii) PIP and (iv) ADRs (16, 18-20, 23, 25, 40-41, 61, 71-72, 84-85, 87-92).

1.3.6.1 Polypharmacy link to PIP

Throughout the literature polypharmacy has been reported to be associated with PIP. In an Irish-based study by Gallagher *et al.*, it was reported that patients who were receiving >5 medications were three times more likely to receive a PIM, than those patients on ≤5 medications (46). A number of other American and European studies have reported a similar association (20, 50-51, 93-99). Polypharmacy does not always definitely result in PIP, however due to the large number of papers which have reported on this association, a reduction in the number of medications could potentially lead to a reduction in PIP and consequentially a reduction in ADR incidence, drug-related costs and possibly an improvement in compliance (100).

1.3.7 Prescribing Cascade

Polypharmacy has also been associated with an issue known as the prescribing cascade i.e. prescribing cascade is the prescribing of any new medications to treat the symptoms of an adverse effect of another medication. The majority of individuals who experience an ADR are often treated by prescribing an additional medication rather than cessation of the causative agent e.g. the prescribing of an anticholinergic medication to treat the extrapyramidal side-effects of neuroleptics. This type of prescribing behaviour has been well documented throughout literature (40, 61, 89, 101-103) and is generally considered inappropriate and has been identified as a major contributory factor in the occurrence of polypharmacy, PIP, ADRs and increased prescribing costs (18, 25, 40, 101, 103).

1.3.8 Drug related Problems

The identification, prevention and resolution of drug related problems (DRPs) are a pivotal aspect of pharmaceutical care (104). To-date there is no universally accepted definition for DRPs, however a number of different definitions have been proposed in the literature.

A review by Van Mil and colleagues identifying as many as many as 14 different definition for DRPs (104). Some of these definitions focused specifically on the adverse consequences associated with DRPs, while others focused more on classifying/ categorising the practices that contribute to DRPs i.e. prescribing, dispensing etc. (104). Although the term DRP has been used for some time, it was not until the early 1990s, that the first actual definition of a DRP appeared in the literature, with Hepler and Strand defined it as *"an event or circumstance involving a patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome"* (105).

Hepler and Strand, also classified DRPs into several different categories based on the causes of DRPs, i.e. (i) untreated indications, (ii) improper drug selection, (iii) sub-therapeutic dosage, (iv) failure to receive drugs, (v) over-dosage, (vi) adverse reactions, (vii) drug interactions and (viii) drug use without indication (105). A number research groups have used this DRP classification system, or modifications of it, (106) to define DRPs and in 1993, the American Society of Hospital Pharmacists (ASHP) integrated this definition into their statement on pharmaceutical care. In 1998, the ASHP redefined the DRP definition, as "an event or circumstance involving medication therapy that actually or potentially interferes with an optimum outcome for a specific patient." (107).

Around the same time, Cipolle *et al.* proposed alternative DRP definition, however instead of referring to them as DRPs, they used the term *"drug-therapy problem"* (108) In this definition, a drug therapy problem was defined as *"any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with a desired patient outcome"*.

In 2000, Meyboom *et al.*, highlighted DRPs as a Pharmacovigilance issue when they published the ABC of DRPs (109). This classification system focused primarily on issues relating to side effects and adverse reactions of drugs. It separated DRPs into those that were as a result of appropriate and inappropriate prescribing.

In 2002, Mackie *et al.* (104) further adapted the DRP definition proposed by Cipolle *et al*., to produce their own DRP definition however instead of calling them DRPs they used the term *"clinical drug-related problems"*. They proposed that a clinical drug related problem *"existed when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy"*.

In a 2006, Spinewine and colleagues (48), used the Hepler and Strand definitions to define a DRP and proposed a modified DRP classification system consisting of 17 categorises i.e. (i) underuse, (ii) wrong dose, (iii) inappropriate duration of therapy, (iv) inappropriate choice of medicine, (v) no valid indication, (vi) no specific problem, (vii) inappropriate modalities of administration, (viii) adverse drug reaction suspected or confirmed, (ix) error in medication history, (x) inappropriate follow-up, (xi) prescription writing error, (xii) drug–disease interaction (including allergy),

(xiii) duplication, (xiv) less costly alternative, (xv) modalities of administration not practical for the patient, (xvi) drug–drug interaction and (xvii) other. As our "Structured Pharmacist Intervention" was based on the paradigm originally proposed by Spinewine *et al.* (48), we decided to use a modified version of the Spinewine DRP classification system to defined DRPs in this work. DRPs were divided into two categories; (i) DRPs relating to appropriateness issues and (ii) DRPs relating to reconciliation issues, i.e;

Appropriateness issues:

- Medications without a valid indication,
- Drug-drug interactions,
- Drugs that required renal or hepatic dose adjustment,
- Medications deemed potentially inappropriate as defined by the STOPP (110), Beers (111) or Priscus criteria (39),
- Potential prescribing omission as defined by the START criteria (110) and
- Miscellaneous appropriateness issues.

Medication reconciliation issues:

- Dosing errors,
- Omissions and
- Miscellaneous reconciliation issues.

1.4 Optimisation of Prescribing in the Elderly

1.4.1 Rationale for prescribing in the elderly

The prescribing of multiple medications to treat several concurrent co-morbidities is considered a fundamental component of geriatric care (14-15, 21). A number of aspects of the ageing process make the selection of an appropriate pharmacotherapy quite challenging (11, 15, 20-21, 23-24, 40, 57, 112-113). There is no doubt that the prescribing of certain medication can reduce illness, improve symptoms, prevent diseases and reduce mortality in older individuals. However achieving an optimal balance between the benefits and risks of a drug regimen can often prove quite difficult at times. This can be further complicated by the fact that advancing age is associated with an increased risk of both PIP and ADRs (19, 23-24, 40, 43, 56-57, 114).

As stated above, older individuals exhibit a marked degree of heterogeneity and it can often prove quite difficult to ensure that the most up-to-date evidence-based medical care is being effectively delivered. Healthcare professionals try to achieve a balance between minimising the number of medications i.e. to avoid polypharmacy, while simultaneously trying to optimise appropriateness of pharmaceutical care, by ensuring that all patients receive clinically indicated medications for each of their underlying co-morbidities. However, it is crucial that this does not inadvertently result in harm to the patient either as a result of under- or over-prescribing (18, 50, 102, 115). Often medication regimens may need to be individualised to the needs of patients (14, 21, 43, 52).

Over the last 25 years PIP in older individuals has become a major area of concern (14, 16, 18, 43-45, 47, 49-50, 56, 116) and has come under considerable scrutiny. Concerns regarding the appropriateness of prescribing practices in this patient population, has led to the development of a several PIP screening criteria. PIP criteria are not intended to be an all-encompassing set of prescribing rules; they are intended to be a guide of appropriateness, to supplement a physician's clinical knowledge and expertise. A number of instances of prescribing, which are deemed potentially inappropriate by the PIP criteria, may upon closer examination of a patient's medical history be the only available treatment option and in such circumstances the prescribing of PIMs may be deemed justified.

1.4.2 Assessing PIP

Appropriateness of prescribing can be evaluated using either process or outcome measures (14, 20, 40, 112). A number of different PIP screening tools have been developed; the majority of these are either explicit or implicit in nature however a number of the PIP screening tools use a combination of both. The aim of a PIP screening tool is to optimise prescribing by assisting the healthcare professional in the identification of PIP instances, thereby potentially reducing the negative outcomes associated with the ADRs that may result from PIP (14, 20, 23, 40, 52, 58, 111, 117).

1.4.2.1 Explicit Criteria

Explicit criteria are usually clearly defined statements of potential inappropriateness often developed from a variety of different sources, such as (14, 38, 46, 62, 111, 118):

- Evidence-based guidelines,
- Published reviews,
- Experts' opinions and/or
- Consensus techniques.

Explicit criteria are usually medication- or disease-orientated and typically these types of criteria require little-to-no clinical interpretation or judgement in order for them to be effectively deployed. Therefore these criteria are quick and easy to deploy and they generally exhibit a good level of inter-rater reliability (14-15, 20, 41, 119). These types of criteria usually comprise of (14, 20, 23, 40, 52, 112, 119):

- Lists of medications that should be avoided,
- Dosages of medications that should be avoided,
- Certain drug-drug combinations that should be avoided and
- Certain drug disease combinations that should be avoided.

Explicit sets of criteria have come under considerable criticism for their limited transferability between different countries due to the variability in prescribing practices between different countries and different prescribers. Another major limitation of explicit criteria is that they need to be regularly revised and updated in order to keep up-to-date with evolving clinical evidence (15, 20, 23, 38, 52, 120).

These types of criteria are usually quite inflexible and generally do not take all facets of care into consideration, nor do they consider patient preference and the majority of these criteria do not address issues relating to multiple co-morbidities (20, 25, 40).

1.4.2.2 Implicit Criteria

Implicit criteria on the other hand, are usually judgement-based and rely on healthcare professionals formulating clinical judgements relating to the appropriateness or inappropriateness of a specific treatment option based on all the available clinical evidence. This type of approach is considered to be more sensitive, as it is intended to take both the perspective and preferences of the patient into consideration. However, these criteria can often prove quite time-consuming to apply and as it is dependent on clinicians' knowledge and attitude it can often be subject to differences of opinion and therefore these types of criteria, generally exhibit a poor level of inter-rater reliability (14, 20, 23, 40).

While there is no ideal approach for assessing prescribing appropriateness, both types of approaches have their own individual advantages and disadvantages, which should be taken into consideration when devising or choosing a suitable screening tool for assessing prescribing appropriateness (14, 23, 40, 52, 57). However, due to the time consuming nature and the poorer inter-rater reliability exhibited by implicit criteria, the majority of the studies to date which have examined PIP, have used explicit criteria, even though implicit criteria are considered more sensitive (14, 20, 52, 121).

1.4.3 Potentially inappropriate prescribing criteria

A number of different screening criteria have been developed to evaluate prescribing appropriateness. These criteria incorporate either explicit or implicit measures of prescribing but some utilise a combination of both methodologies. Some examples of these tools are listed below:

- The drug utilisation review (DUR) criteria (1989, 1992 and 2002) [122-123],
- Beers criteria (1991, 1997,2003 and 2012) [42, 111, 124-125],
- Medication Appropriateness Index (MAI) (1992) [126],
- Stuck criteria (1994)[81],
- McLeod criteria (1997)[114],
- Lunn criteria (1997)[127],
- Phadke rational prescribing indicators (1998)[128],
- Improved Prescribing in the Elderly Tool (IPET) (2000)[129],
- Zhan criteria (2001)[130],
- French list of PIP criteria (2001)[131],
- Assessment of underutilisation of medication (AOU) (2001)[132],
- Assessing care of vulnerable elders (ACOVE) (2002)[133-134],
- Rancourt criteria (2004)[94],
- Swedish prescribing indicators (2004, 2008)[135],
- National Prescribing Service (NPS) prescribing indicators (2006)[136],
- Healthcare Effectiveness Data and Information Set (HEDIS) criteria (2006)[137],
- La Roche French consensus criteria (2007)[131],
- Drug burden index (DBI) (2007)[138],
- Australian prescribing indicators (2008)[139],

- Screening Tool of Older Person's Prescriptions (STOPP) (2008)[38],
- Screening Tool to Alert doctors to Right Treatment (START) (2008)[38],
- Norwegian General Practice (NORGEP) criteria (2009)[140],
- Priscus criteria (2010)[39],
- Quality indicators of In-hospital pharmaceutical care of Dutch elderly (2011)[141] and
- RASP list (2011) [142].

Table 1.7 on page 53 summaries the pertinent literature relating to the different criteria outlined above.

The criteria directly relevant to this thesis will be discussed in greater detail below.

1.4.3.1 Beers Criteria

The Beers criteria were developed in the United States of America (US) by Beers *et al.* in 1991 and was further revised and updated again in 1997, 2003 and more recently in 2012 (12, 111, 124-125).

1.4.3.1.1 Beers Criteria 2003

In 2003, the Beers criteria were further revised and updated by Fick *et al.* This update was to try to rectify some of the issues highlighted with the 1997 version of Beers in the literature.

The aims of the 2003 update were (111):

- To re-evaluate the 1997 set of criteria, so as to generate a more up-to-date, clinically-relevant information relating to the efficacy and safety of certain medications in older individual (43).
- To re-evaluate the severity rating for each of the criteria.
- To re-examine the CD section of the criteria, so as to include any other clinically relevant PIP instances which had not been included in the previous version of the criteria.

The 2003 Beers criteria outlined instances of PIP relating to the safety and effectiveness of certain medications (20, 50):

- Medications that should rarely be used or never used in the older individuals.
- Dosages of certain medications that should rarely be used or never used in older individuals.
- Drug-drug interactions that should be avoided in older individuals.
- Drug-disease interactions that should be avoided in older individuals.

As was the case with the previous two versions of the Beers criteria, an extensive literature review was undertaken and a modified Delphi-consensus validation methodology was used to establish the consensus opinion of a 12-member expert panel from different aspects of geriatric care from diverse locations across the USA and Canada. These experts were from a number of different aspects of geriatric care, including general geriatric care, clinical pharmacology and psychopharmacology (111).

Modifications to the 2003 Beers criteria entailed: (i) the removal of 11 criteria from the 1997 list of criteria (1 from the ID list and 10 from the CD list), (ii) the modification of four of the 1997 Beers list, (iv) the addition of 44 new medications to the 2003 list of PIMs (25 new PIMs were added to the ID list and 19 were added to the CD list) and (v) the addition of several new co-morbidities to the CD section of the criteria, i.e. depression, cognitive impairment, Parkinson's disease, anorexia, malnutrition, the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion and obesity (111).

Similar to the 1997 Beers criteria, the 2003 version of the Beers criteria made of two lists of criteria (18, 125):

- A list of 48 criteria that defined instances of PIP independent of diagnosis (ID), i.e. medications/ medication classes that are always deemed inappropriate in older individuals.
- A list of 43 criteria which defined instances of PIP which considers diagnosis (CD), i.e. medications/ medication classes that should be avoided in older individuals suffering from one of 20 specified conditions.

Also similar to the 1997 version of the Beers criteria, each criterion in the 2003 list of criteria was also designated a severity rating (9, 125).

1.4.3.2 The STOPP/START criteria

The Screening Tool of Older Person's Prescriptions (STOPP) criteria and the Screening Tool to Alert doctors to Right Treatment (START) were developed in Ireland by Gallagher *et al.*, in 2008 (38). The STOPP criteria are an explicit set of PIP criteria designed for assessing PIP in older individuals across all settings of care. The START criteria are also an explicit set of criteria designed to assess for potential prescribing omission (PPO) in older individuals across all settings of care. These two sets of criteria are intended to be deployed concomitantly.

The STOPP and START criteria were designed to (15-16, 18, 38):

- Be a comprehensive and valid list of the most common instances of PIP and PPO that arise in older individuals,
- Represent the most up-to-date clinical evidence,
- Be structured in an organised fashion based on physiological system to which each criterion relates,
- Capable of being applied in a time efficient manner so as it could be incorporated into routine clinical practice,
- Include a brief explanation outlining exactly why each PIM is potentially inappropriate and
- Exhibit enhanced usability, applicability and detection capabilities over previously published IP screening tools.

The original set of the STOPP and the START criteria were developed through collaboration by members of the "Care of the Elderly" research team from Cork University Hospital (CUH), Department of Medicine, University College Cork, UCC and members of the "Pharmaceutical Care" research group from the School of Pharmacy, UCC. This initial draft set of criteria were initially reviewed by a 5-

member local review panel and was then subsequently reviewed and validated via a modified Delphi consensus methodology by an 18-member expert panel from different aspects of geriatric care from diverse locations across Ireland the UK. The 18 member expert panel which included physicians in geriatric medicine, clinical pharmacologist, senior clinical hospital pharmacists, senior academic primary-care physicians and old-age psychiatrists.

This validation process involved the panel of experts reviewing the criteria and then rating their level of agreement with each criterion using a 5-point Likert scale. Full consensus was achieved after two rounds via a mailed survey. The review panel reached agreement on all of the 22 START criteria and 65 of the 68 STOPP criteria; three STOPP criteria from the initial version were subsequently removed from the final list of criteria.

When the STOPP and the START criteria are used together they address issues relating to (15-16, 18, 38):

- Drug-drug interactions,
- Drug-disease interactions,
- Potentially inappropriate duration of treatment,
- Medications which adversely affect older patients at risk of falls,
- Duplicate medications from the same therapeutic class,
- Potentially inappropriate dosages of medications based on recent biochemical data and
- Potential under-prescribing of clinically beneficial medications.

1.4.3.2.1 The Screening Tool of Older Person's Prescriptions (STOPP)

The STOPP criteria comprised of 65 criteria outlining instances where certain medications or medication classes would be considered potentially inappropriate in older individuals. The criteria are structured in an organised fashion according to the physiological system to which each criterion relates.

Thirty-three of the instances defined as PIP in the STOPP criteria are not addressed by the 2002 version of Beers (143). The STOPP criteria also include a number of criteria relating to specific dosages or durations of therapy for particular medications that should be used with caution or completely avoided in older individuals.

Each criterion is accompanied by a brief explanation, outlining why each PIM is considered potentially inappropriate. The STOPP criteria not only addresses issues relating to clinical effectiveness, but also takes cost into consideration, by including a number of criteria which highlight instances of unnecessary prescribing (100).

The STOPP criteria are subdivided into 10 categories based on the physiological system to which the criteria relates: cardiovascular, central nervous system and psychotropic drugs, gastrointestinal system, respiratory system, musculoskeletal system, urogenital system, endocrine system, drug that adversely affect fallers, analgesic drugs and duplicate drug classes.

1.4.3.2.2 The Screening Tool to Alert doctors to Right Treatment (START)

The START criteria focus on the issue of under-prescribing i.e. the omission of clinically indicated medications. Under-prescribing is an aspect of PIP that, to-date, has been underrepresented by the other PIP assessment tools.

The START tool incorporates 22 criteria relating to instances of potential prescribing omissions (PPOs) in older people. These criteria relate to potential under-prescribing of clinically beneficial medications/medication classes that should be prescribed in older individuals with certain underlying medical conditions unless otherwise contraindicated (38, 91).

Similar to the STOPP criteria, the START criteria are structured in an organised fashion according to the physiological system to which each criterion relates: cardiovascular, respiratory system, central nervous system, gastrointestinal system, musculoskeletal system and endocrine system.

1.4.3.3 The Priscus List

The Priscus list was developed by Holt *et al.* in 2010 in Germany (39). It is an explicit set of criteria for assessing PIP in all settings of care.

The Priscus criteria were developed in a four-step process;

1. A review of all the published PIP criteria for older individuals from other jurisdictions,
2. A extensive literature review,
3. Development of a preliminary draft of PIP criteria for a German market and
4. Consensus was established on the final version of the Priscus list via 2 rounds of a modified Delphi consensus methodology, based on the consensus opinions of a German-speaking 38-member expert panel.

The 38-member expert panel consisted of experts in geriatric medicine, clinical pharmacology, general practice, internal medicine, pain therapy, neurology, psychiatry and pharmacy (39).

The preliminary set of Priscus criteria outlined 131 instances of PIP relating to 24 medication classes which were deemed potentially inappropriate in older individuals and 5 medications deemed potentially inappropriate based on the type of drug release formulation.

The final version of the Priscus criteria consisted of 83 criteria relating to 18 different medication classes (39);

- 71 criteria relating to medications which are always considered potentially inappropriate in older individuals,
- 9 criteria which classify a particular medication as potentially inappropriate above a specific dose and
- 3 criteria which classify a specific formulation of a medications a potentially inappropriate.

Sixty-four of the 83 medications designated as PIMs by the Priscus list are also classified as PIMs in at least one other set of PIP criteria.

The Priscus list is intended to (39):

- Improve the appropriateness and safety of prescribing in older individuals,
- Alleviate the ADR risk associated with PIP in older individuals,
- Outline the main concerns associated with prescribing of particular PIMs,
- Provide precautionary advice that should be taken into consideration, if it is deemed necessary to prescribing the PIM and
- Recommend possible safer, as effective, therapeutic alternatives to the medications outlined as PIMs in the criteria.

1.4.3.4 Medication Appropriateness Index (MAI)

The medication appropriateness index (MAI) was developed in the USA by Hanlon and colleagues in 1992. The MAI is an implicit set of criteria which consists of a number of explicit operational instructions. The MAI is designed to be used to assess the appropriateness of prescribing (126, 144). The MAI goes beyond the boundaries of other PIP assessment criteria, by taking all facets of prescribing under consideration, when evaluating appropriateness (49).

The MAI consists of ten criteria that relate to a number of different aspects of prescribing. For each criterion there is a set of explicit operational instructions which the investigator utilises with their own clinical expertise or personal judgement to rate each of the criteria as,

1. Appropriate,
2. Marginally appropriate or
3. Inappropriate.

The rating of each criterion is then summed together and this generated a weighed score which serves as a measure of a medication appropriateness. Scores can range from 0-18, with higher scores indicating an increased level of inappropriateness (118).

The MAI evaluates the appropriateness based on ten criteria, indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost.

Three of the MAI criteria are reported to be directly related to the issue of polypharmacy i.e. indication, effectiveness and duplication.

The advantages of the MAI tool are as follows;

- It has been tested and validated in both ambulatory and inpatient setting and has demonstrated good inter-rater and intra-rater reliability as well as good face and content validity (126, 145-150).
- To-date it is considered to be the most comprehensive screening tool available for the assessment of appropriateness of prescribing in older individuals. It evaluates prescribing appropriateness on multiple levels and can be applied to every medication in a patient specific context (14, 40).

The disadvantages or limitations of the MAI tool are as follows (14, 20, 25, 40, 86, 151-153):

- Access to detailed clinical information is required for implementation of the full MAI
- It can be time consuming to apply, (approximately 10 minutes per medication),
- There are no criteria relating to the issue of under-prescribing of clinically beneficial medications,
- They do not focus on any particular medications or medication classes and
- It has only been used to evaluate the appropriateness of prescribing in a small number of studies and requires further validation in order to demonstrate its effectiveness as a screening tool across all populations and settings of care.

Although the MAI tool is regarded by many as the most comprehensive and possibly the most sensitive tool for the assessment of appropriateness of prescribing, the fact that it is quite cumbersome and time consuming to apply limits it applicability in routine clinical practice (14, 20, 25, 40, 154).

1.4.3.5 Assessing Care of Vulnerable Elders (ACOVE) Criteria

The ACOVE criteria were developed by the RAND Corporation in 2001 as part of the "Assessing Care of the Vulnerable Elders" project. The ACOVE criteria are a comprehensive set of indicators or process measures designed to evaluate the quality of care being delivered in older vulnerable individuals.

The ACOVE set of criteria include both implicit and explicit type of criteria and were based on (133-134):

- Systemic review of the published literature,
- Expert opinions and
- Guidance from specialist expert groups.

The ACOVE criteria consist of 236 indicators, 68 of which relate to the issue of PIP (25, 133-134).

The criteria relating to (25, 133-134):

- Patient education,
- Correct indication,
- Documentation of response to therapy,
- Periodic medication reviews,
- Drugs to avoid (e.g. meperidine, chlorpropamide and barbiturates),
- Drug monitoring issues (e.g. warfarin, diuretics and angiotensin converting enzyme (ACE) inhibitors) and
- Underuse of clinically beneficial medications.

The ACOVE indicators have a number of strengths (14, 25, 154):

1. The indicators simultaneously address issues relating to under-prescribing, overprescribing and mis-prescribing,
2. They include indicators which relate to a number of common occurring geriatric conditions such as falls and dementia,
3. They relate to all aspects of care in older individuals (e.g. treatment, prevention, monitoring, education and documentation) and
4. Most of the indicators can be applied to older individuals with advanced dementia or poor prognosis.

In 2007 Spinewine *et al.* developed a modified set of the ACOVE criteria. This modified ACOVE consisted of 7 criteria and focused on underprescribing of clinically beneficial medications in patients with particular underlying conditions (118) and were as follows:

1. Bisphosphonates and calcium & vitamin D_3 in patients with osteoporosis and/or fractures,
2. Anticoagulants or aspirin in patients with atrial fibrillation,
3. Aspirin in patient with ischaemic heart disease,
4. Aspirin in patients with diabetes mellitus,
5. Beta-blockers in patients with myocardial infarction,
6. Angiotensin-converting enzyme inhibitors in patients with heart failure and
7. Beta-blockers in patients with heart failure.

Table 1.7 Summary of commonly used explicit and implicit criteria (14, 20, 40-41, 119)

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
Instruments based on explicit criteria						
Beers 1991 criteria, 1991, (United States)[12]	Nursing home residents aged ≥65	Review of the literature (published 1979–1990 in English). Delphi consensus: 13 member expert panel.	30 criteria	Concise and easy to apply. Addresses the most common PIP instances in nursing home patients.	Specific to American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing	9-40.3%
Stuck criteria, 1994 (United States)[81]	Older individuals ≥65 years	Beers 1991 criteria and an extensive literature review. Delphi consensus: 13 member expert panel.	23 criteria	Concise and easy to apply. Each criterion is accompanied by a brief explanation outlining reason for inappropriateness.	Specific to American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address underprescribing.	14.0%
Lunn criteria, 1997 (United Kingdom)[127]	Nursing home residents aged ≥65	Extensive literature review. Consensus opinion: 4 member expert panel.	18 criteria	Concise and easy to apply. Addresses the most common PIP instances in nursing home patients.	Focuses on nursing home patients. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing.	53.0%
Beers 1997 criteria, 1997, (United States)[125]	Older individuals ≥65 years	Beers 1991 criteria. Review of the literature (published 1990–1995 in English). Delphi consensus: 6 member expert panel.	28 criteria	Concise and easy to apply. Addresses the most common PIP instances. Contains a rating that defines the severity of criteria.	Specific to American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing.	3.3-70.0%
McLeod criteria, 1997 (Canada)[114]	Older individuals ≥65 years	Beers 1991 criteria. Review of the literature (not defined exactly in the article) Canada's national drug formularies. Delphi consensus: 32 member expert panel.	38 criteria	Concise and easy to apply. Includes an explanation outlining inappropriateness. Contains a severity rating for each of the criteria.	A number of the criteria have become outdated by new evolving evidence e.g. beta-blocker in heart failure. Does not address the issue of underprescribing. Focuses on Canadian prescribing practices and drug formularies.	3.0-41.0%

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
Improving Prescribing in The Elderly Tool (IPET), 2000, (Canada)[129]	Older individuals ≥70 years	Based on a review of the most common instances of PIP as defined by the McLeod's criteria encountered in routine practice (not independently validated).	14 criteria	Concise and east to apply. Focuses on the most common instances of PIP in a Canadian healthcare setting.	Lacks comprehensiveness, focuses mainly on cardiovascular and psychotropic medications. Does not address the issue of underprescribing.	9.3-27.4%
French list of inappropriate medications (IM) criteria, 2001, (France)[131]	Older individuals ≥65 years	Derived from the 1997 Beers criteria and the consensus opinion of 9 member expert panel.	24 criteria	Concise and easy to apply. Addresses the most common PIP.	Focuses specifically on French prescribing practices. Does not consider underlying diagnosis in the assessment of PIP. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address underprescribing.	25.4-66.0%
Zhan criteria, 2001, (United States)[130]	Older ambulatory individuals ≥70 years	Subset of 33 drugs from Beers 1997 criteria (drugs potentially inappropriate irrespective of dose, frequency of administration, or duration of the therapy). Delphi consensus: 7 member expert panel.	33 criteria	Concise and east to apply. Less restrictive than previously published criteria in terms of 'always to avoid' drugs.	Focuses on American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing.	3.7-31.0%
ACOVE criteria, 2001, (United States)[133-134]	Older individuals ≥65 years	Derived from a systemic review of the published literature, expert opinions and guidance from specialist expert groups.	236 indicators, 68 of which relate to the issue of PIP	This set of indicators provides a comprehensive assessment which addresses all aspects of older persons care. Over a quarter of the indicators focus primarily on the issue of PIP.	Due to the comprehensive nature of this set of criteria it may prove time consuming to fully deploy. Also due to the large number of criteria the majority of studies have used modified versions of the criteria. Access to the full set of medical notes would be required to apply this set of criteria.	34.7-78.0%
Beers 2003 criteria, 2003, (United States)[111]	Older individuals ≥65 years	Beers 1997 criteria. Review of the literature (literature published 1994–2000). Delphi consensus: 12 member expert panel	68 criteria	Concise and easy to apply. Addresses the most common PIP instances. Contains a rating that defines the severity of criteria.	Focuses on American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address underprescribing.	2.8-63.8%

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
Rancourt criteria, 2004, (Canada)[94]	Older individuals aged ≥65 years in long term care	Beers criteria (1991, 1997, 2003), McLeod criteria and IPET. Review panel: 4 member expert panel.	111 criteria	Comprehensive, contains 26 criteria relating to drug-drug interactions and 10 drug duplications. Provides the ATC codes to support the criteria.	Contains a large number of criteria, specifically focusing Canadian prescribing practices and drug formularies.	54.7%
HEDIS criteria, 2006, (United States)[155]	Older individuals ≥65 years	Beers criteria ID 2003. Derived from the experience/opinions of an expert review panel.	42 criteria	Concise and easy to apply. Addresses the most common PIP instances. Full access to the medical notes is not required to fully apply this set of criteria.	Focuses on American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing. Does not consider diagnosis when assessing appropriateness of prescribing.	5.6-38.8%
La Roche French consensus criteria, 2007 (France)[131]	Older individuals ≥75 years	Beers criteria (1991, 1997, 2003) McLeod criteria and 2001 French IM criteria and guidelines of the French Medicine Agency. Delphi consensus: 15 member panel.	34 criteria	Concise explanation of inappropriateness; include drug duplication; recommended safer more effective alternatives for each criteria.	Specific to French prescribing practices and medications. Does not address drug-drug interactions Does not address the issue of underprescribing.	21.9-31.6%
Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START), 2008, (Ireland)[38]	Older individuals ≥65 years	Systematic review of the literature. Clinical experience and expertise of the investigators. Delphi consensus: 18 member expert panel.	STOPP: 65 criteria START: 22 criteria	Concise and easy to use. Easy to navigate as it is organised by physiological systems. Addresses the issue of drug-drug interactions; drug duplication; and underprescribing. Each criterion is accompanied by a concise explanation of inappropriateness.	Does not suggest safer alternatives to inappropriate medications. Does not include a severity rating. Does not address certain domains of prescribing appropriateness e.g. indications, dosage form or cost.	STOPP: 13.3-79.0% START: 11.2-74.0%.
Norwegian General Practice, 2009 (Norway)[140]	Persons aged ≥70 in general practice	Beers criteria (1991, 1997, 2003). Recent evidence from literature. Clinical experience of the investigators. Delphi consensus: 47 member expert panel.	36 criteria	Concise and easy to apply. Does not required access to the full medical notes for the full set of criteria to be applied.	Specific to Norwegian prescribing practices and medications. Does not address the issue of underprescribing; or drug-disease interactions and to-date no studies which have examined its effectiveness outside of Norway.	22.6-36.8%

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
Priscus List 2010 (Germany)[39]	Older individuals ≥65 years	Beers criteria (1991, 1997, 2003) French 2007 criteria, STOPP. Recent review of the literature. Delphi consensus: 38 member expert panel.	83 criteria	Each criterion is accompanied by an outline why the specific medications/medication classes are potentially inappropriate. Provides therapeutic alternatives; recommendations on dose adjustments and drug monitoring.	Specific to German prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing.	25.0-28.3%
RASP List 2011 (Belgium) [142]	Older individuals ≥65 years	STOPP criteria (2008). Reviewing each of the STOPP criteria for their relevance in a Belgian healthcare context and an extensive literature review was also undertaken; 10 member expert panel.	61 criteria	Concise and easy to use. Easy to navigate as it is organised by physiological systems. Valid for a Belgian healthcare setting.	Focuses primarily on Belgian prescribing practices. Does not suggest safer alternatives to inappropriate medications. Does not include a severity rating. Does not address certain domains of prescribing appropriateness e.g. indications, dosage form or cost.	None to date
Beers 2012 (United States)[124]	Older individuals ≥65 years	Beers 2003 criteria. Literature review (literature published 2001–2011). Modified Delphi consensus: 11 member expert panel.	65 criteria	Concise and easy to apply. Addresses the most common PIP instances. Incorporates the most up-to-date and clinically relevant information on PIP. Contains a grading of the quality of the evidence supporting each. Includes a list of medications that should be used with caution.	Focuses on to American prescribing practices and medications. Does not address drug-drug interactions or PIP of duplicate drugs from the same class. Does not address the issue of underprescribing.	None to date
Instruments based on implicit criteria						
DUR criteria, 1989, (United State)[122-123]	Not restricted to older adults	Based on a review of the guidelines and medications outlined in the 1988 Medicare Castrophic Coverage Act. The 2002 update was based on a review of the original 1989 criteria, the 1997 Beers criteria and the 1997 McLeod criteria.	20 criteria	Concise and easy to apply. Includes a number of criteria relating to the main areas of PIP i.e. dosage, duplication and duration of therapy and drug-drug and drug-disease interactions.	Limited evidence of effectiveness. A detailed knowledge and understanding of clinically relevant drug-drug and drug disease interactions is required. Lacks comprehensiveness, focuses on a small number of medications classes. Does not address the issue of underprescribing.	19.2-21.3%

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
MAI, 1992, (United States)[126]	Developed among persons in ≥65, but use not restricted to older adults	Based on a review published literature between 1982 and 1990. Clinical experience of the investigators.	10 criteria	The MAI allows for a comprehensive assessment of prescribing appropriateness, addresses a number of facets of prescribing. Contains a set of explicit operational instructions in order to enhance usability.	Can prove quite time consuming to apply and an in-depth clinical knowledge of prescribing is required in order to fully deploy the criteria.	44.0-96.0%
Phadke's Criteria, 1998 (India)[128]	Not restricted to older adults	Derived from the clinical experience of the investigators.	4 criteria	This set of criteria allows for a comprehensive assessment of rationale prescribing. It assesses prescribing based on a number of different aspects of prescribing.	Due to the comprehensive nature of this set of criteria it may prove quite time consuming to fully apply. The instructions for use are quite detailed and difficult to follow. Limited evidence of effectiveness and it has only been used in one study.	28.3%
Assessment of Underutilization of Medication, 1999 (United States)[132]	Older individuals ≥65 years	Derived from the clinical experience of the investigators.	26 criteria	This set of criteria addresses the instances of the most commonly under-prescribed medications in older individuals. Contains a set of explicit operational instructions in order to enhance usability.	Time consuming to apply and an in-depth clinical knowledge of prescribing is required in order for the full set of criteria to be applied. Limited to specific number of conditions and medications. Focuses on the issues of underprescribing, does not address other aspects of PIP.	37-64.0%
Australian National Prescribing Service (NPS) indicators, 2006, (Australia)[136]	Not restricted to older adults	Based on a comprehensive review of the literature and structured focus groups. Based on the experiences of GPs, other healthcare professionals, consumers and policy makers.	21 indicators	Clear, and easy to use. Reliable, reproducible and relevant to general practice. Structurally and contextually valid. Provides a comprehensive review of PIP as well as a number of other aspects of older persons care.	Focuses primarily on Australian prescribing practices. Due to the comprehensive nature of this set of criteria it may prove time consuming to fully deploy. Also limited evidence relating to its effectiveness. Focuses on more than just the PIP, therefore full access to all patient related information is required, i.e. all documentation in the medical records relating to the patient's care.	16.0%

Criteria, Publication Year (Country)	Target Group	Basis of Criteria	No. of criteria	Advantages	Disadvantages	PIP/PPO prevalence
Australian Prescribing Indicators, 2008 (Australia)[139]	Older individuals ≥65 years	Based on a review of Australian prescribing practices derived from the Australian Pharmaceutical Benefits Scheme in 2006. Most common medical conditions for which Australians aged 65 and older consult medical practitioners.	48 criteria	Provides a comprehensive review of both PIP, underprescribing and other monitoring issues relevant to prescribing in older individuals. Structurally and contextually valid.	Focuses primarily on Australian prescribing practices. Due to the comprehensive nature of this set of criteria it may prove time consuming to fully deploy. Also limited evidence relating to its effectiveness. Full access to the medical notes is required in order to fully apply this set of criteria.	95.0%
Quality Indicators for in-Hospital Pharmaceutical Care of Dutch Elderly Patients, 2011, (Netherlands)[141]	Older hospitalised individuals ≥65 years	2001 ACOVE criteria. Delphi consensus: 3 member expert panel.	87 criteria	This set of indicators addresses all aspects of PIP. Clear and easy to use. Reliable, and reproducible. Structurally and contextually valid.	Due to the comprehensive nature of this set of criteria it is time consuming to fully deploy. Also limited evidence relating to its effectiveness. Focuses on more than just the PIP, therefore full access to all patient related information is required, i.e. all documentation in the medical records relating to the patient's care.	None to date

Key: HEDIS; Healthcare Effectiveness Data and Information Set, MAI, Medication Appropriateness Index, AOU; Assessment of Underutilization, DUR; Drug Utilisation Review, NPS; National Prescribing Service, STOPP; Screening Tool of Older Person's Prescriptions, START; Screening Tool to Alert doctors to Right Treatment, PIP; Potentially Inappropriate Prescribing, PIM; Potentially Inappropriate Medication, PPO; Potential Prescribing Omission, ACOVE; Assessing Care of Vulnerable Elders, GP; General Practitioner.

1.5 Adverse Events, Adverse Drug Events and Adverse Drug Reactions

1.5.1 Terminology

The terminology relating to adverse events (AEs), adverse drug events (ADEs) and adverse drug reactions (ADRs) can often seem quite complex, complicated and interchangeable but there are differences between each.

1.5.2 Adverse Events

An adverse event is defined as an injury which results from any type of medical intervention or medical management, as opposed to adverse event which is attributable to an underlying disease i.e. anything untoward that happens to a patient e.g. bruising due to improper needle injection technique (156-157).

1.5.3 Adverse Drug Events

An adverse drug event (ADE) is any unintended injury or disability, it is AE, which occurs in an individual who is under treatment with a drug therapy i.e. after admission of a drug therapy, however there does not necessarily have to be a causal relationship between the AE and the drug treatment. The AE may be secondary to a disease, a procedure or an adverse drug reaction (ADR) (156, 158-159). Therefore all ADR are ADEs, but not all ADEs are ADRs.

1.5.4 Adverse Drug Reactions

The classification of ADRs can often prove to be quite a difficult task. A number of different ADR definitions have been proposed. However it is crucial that the most appropriate and relevant ADR definition is used, so as to ensure that the incidence of ADRs is not over or under estimated.

In 1970, the World Health Organisation (WHO) proposed that an ADR was "*any response to a medicine that is noxious or unintended attributable to a medicine, which occurs at a dose which is normally for use in human beings, for the purpose of prophylaxis, diagnosis, therapy or modification of a physiological function*" (158, 160-161). This definition did not classify AEs that are; secondary to accidental or deliberate overdoses, therapeutic failures, drug abuse, administration errors or non-compliance as ADRs.

In 1998, Laurence and Carpenter, attempted to simplify the classification of ADR and they proposed that an ADR was *"any harmful or significantly unpleasant effect caused by a drug at a dose generally considered safe for a therapeutic purpose, which warrants a dose reduction or drug withdrawal or for which hazards can be predicted from future administration"* (162). This definition was somewhat similar to the definition developed by WHO in that, it excluded therapeutic failures, accidental or deliberate overdose and drug abuse. However this definition only classified *"significant unpleasant effects"* as ADRs and therefore minor unwanted side effects, like dryness of the mouth were not considered as ADRs under this definition. Another more simplified definition of an ADR, was proposed by Bates *et al.* in 1995 which defined an ADR as *"any injury that developed as a result of any medical intervention relating to a drug"* (163).

In 2000, an alternative definition of an ADR was proposed by Edwards and Aronson. They defined an ADR as *"any harmful or unpleasant reaction as a result of use of a medicinal product, for which future hazards can be predicted on further administration which may warrant prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product"* (160). ADRs can be classified into six different types (**Table 1.8**).

Although a number of different ADR definitions have been proposed, to-date the WHO definition is the most widely cited in the literature and therefore in this thesis it is the definition used to describe adverse effects of a drug.

Table 1.8 Classifications of ADRs (103, 158, 160)

Types of ADRs	Features	Examples	Management
Type A: **(Augmented) Dose and frequency-related**	• Occur commonly • Predictable • Low incidence of ADR related mortality • ADR directly attributable to the pharmacological action of the drug	**Toxic effects:** Digoxin toxicity; serotonin syndrome with SSRIs **Side effects**: Anticholinergic effects of TCA	Reduce dose or withhold. Consider the effects of concomitant therapies.
Type B: **(Bizarre) Non-dose related**	• Uncommon • Unpredictable • High incidence of ADR related mortality • ADR not directly attributable to the pharmacological action of the drug	**Immunological reactions:** Penicillin hypersensitivity **Idiosyncratic reactions:** Acute porphyria Pseudoallergy (e.g. penicillin rash)	Withhold and avoid in future.
Type C: **(Chronic) Dose and time related**	• Uncommon • Related to cumulative doses.	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids	Reduce dose or withhold; withdrawal may have to be prolonged.
Type D: **(Delayed) Time related**	• Uncommon • Usually dose related • Can occur or become apparent some time after use of the drug	Teratogenesis: (e.g. vaginal adenocarcinoma with diethylstilbestrol) Carcinogenesis Tardive dyskinesia	Often intractable.
Type E: **(End of use) Withdrawal**	• Uncommon • Usually occur soon after a drug is withdrawn	Opiate withdrawal syndrome Myocardial ischaemia (beta-blocker withdrawal)	Reintroduce and withdraw slowly.
Type F: **(Failure) Unexpected failure of a therapy**	• Occurs frequently • Often dose related • Often a result of a drug interaction	Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers	Increase dosage. Consider effects of concomitant therapy.

Key: ADR; Adverse Drug Reaction, SSRI; Selective Serotonin Reuptake Inhibitor; TCA; Tricyclic Antidepressant.

1.5.4.1 Consequences of ADRs

Adverse drug reactions (ADRs) in hospitalised patients are considered a very important healthcare problem. ADRs have been identified as a significant contributor to increased hospital admissions and increased healthcare costs (19, 21, 23, 41, 43, 120, 164-167). ADRs have also been identified as a major contributory factor in increased health care utilisation in elderly individual and so it represents a considerable clinical and economic burden to both the patient and to society as a whole (14, 19, 21).

Over the last fifty years a number of studies have examined the incidence of ADRs in different populations across an array of healthcare settings (19, 21, 24, 56, 78, 164, 166-193). These studies have proposed a number of different factors that may predispose an individual to an ADR, i.e. longer length of hospital stay, female gender, increasing age, polypharmacy, level of co-morbidity, multiple prescribers, multiple pharmacies, and potentially inappropriate prescribing (19, 21, 23-24, 78, 112, 120, 168, 177-178, 193-196). However to-date the evidence relating to the true extent of these associations have been found to be somewhat mixed and further research is needed to establish the full extent of these associations.

1.5.4.2 Prevalence of ADRs:

A number of studies have examined ADR prevalence, however the majority of these have been retrospective in nature, making ADR detection and causality very difficult to ascertain. ADRs are reported to occur in as many as 46.0% (164, 167, 179, 184) of all hospitalised patients, with a prevalence as high as 35.0% (184) being reported in patients at admission and 46.0% in older hospital in-patients (179).

Older patients are believed to be more susceptible to ADRs with it estimated that they are four times more likely to experience an ADR compared to their younger counterparts (169, 192). The differences between the reported ADR prevalences are probably secondary to variability in the study populations and methodologies.

1.5.4.3 ADRs and Mortality:

The incidence of fatal ADRs reported in hospitalised patients ranges from 0.05-0.44% (21, 164, 167, 190). In the US, ADRs are reported to be between the 4th and 6th leading cause of death in hospitalised patients (164), while in Sweden they are reported to be the 17th leading cause of death (190).

1.5.4.4 Economic consequences of ADRs:

ADR during hospitalisation have also been associated with a significant financial burden on the health services through increased lengths of stay, increased healthcare utilisation and costs (19-21, 23, 112, 120, 166, 173-174, 178). It is estimated that patients who experience ADRs during their hospital stay will require on average 2 additional days in hospital (174). In Ireland there is limited data relating to the impacts that ADRs have on both healthcare resources and costs. However the National Health Service (NHS) closely resembles the Irish system and so it is probably the most appropriate model to extrapolate data from. In the UK it has been estimated that at any one time, ADRs in hospitalised patients resulted in the

utilisation of approximately 2000 bed days (174). The exact cost of in-hospital ADRs is often quite difficult to calculate, but crude estimates have indicated that ADRs are likely to cost in excess £171m annually (174) with the total costs of ADRs in hospitalised patients i.e. at admission or during hospitalisation, in the region of £0.5-1 billion annually (21, 167, 173, 197).

It is important to emphasise that these costs are most likely a conservative estimate, as they only focus on cost relating to length of stay and do not take the direct or indirect costs to the patients into consideration i.e. as loss of earnings due to the extended stay and increased morbidity. Also these estimates do not take the additional costs associated with treating ADRs into consideration i.e. additional medications, investigations, and involvement of additional clinician in the patient's care. All of these factors will contribute to an increase in cost and overall ADR burden. This is quite concerning as the majority of ADRs are possibly avoidable with a large proportion of these events being potentially avoidable (i.e. estimated that as high as 92% of ADRs may be preventable) (169).

1.5.5 Causality Assessment Tools

Causality assessment tools are designed to determine the probability that a specific medication is responsible for a particular ADR. Usually conventional definitions are used to describe the probability of the causal relationship i.e. certain, probable, possible, and unlikely (198-199). Establishing causal relationships between certain medications and specific ADRs in this fashion may potentially prevent a recurrence of these ADRs in the future.

Several tools have been developed to try and standardise the ADR causality assessment process (198-201). Of these tools the Naranjo (199) and the WHO-UMC causality assessment criteria (198) are the two most widely cited in the literature (103, 158). These tools require less detailed information and employ simpler methodological approaches compared with the others available (103, 158).

1.5.5.1 Naranjo ADR probability scale

The Naranjo ADR Probability Scale was developed by Naranjo *et al.*, in 1991(199). This scale was intended to standardise ADR causality assessment i.e. the likelihood of whether an ADR is actually due to a specific medications or secondary to other factors. Causality is classified from cumulative score of ten weighted questions (199) (**Table 1.9 and 1.10**).

Table 1.9 Naranjo ADR probability scale (199).

ADR Causality Assessment Yes	Yes	No	Not sure
Presence of previous conclusive report on adverse reaction?	+1	0	0
Did adverse event appear subsequent to administration of suspected drug?	+2	-1	0
Did adverse event improve on drug discontinuation or on administration of specific antagonist?	+1	0	0
Did the adverse event reappear when the drug was re-administered?	+2	-1	0
Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?	-1	+2	0
Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?	-1	+1	0
Was the incriminated drug detected in toxic concentrations in blood (fluids)?	+1	0	0
Did the adverse event worsen on increasing the dose or decreased in severity with lower doses?	+1	0	0
Past history of any similar reaction to the same or similar drugs?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Key: ADR; Adverse Drug Reaction.

Table 1.10 Summary description of Narango Causality Assessment (199).

Score	Summary
>9	A "definite" reaction was one that (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
5 to 8	A "probable" reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
1 to 4	A "possible" reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
≤0	A reaction was defined as "doubtful" if it was likely related to factors other than a drug.

1.5.5.2 WHO- Uppsala Monitoring Centre (UMC) causality assessment criteria

The WHO-UMC causality assessment system was developed by the WHO in collaboration with Uppsala Monitoring Centre (UMC) (198). This assessment system was developed because previously developed algorithms were considered to be too complex or too specific for general use. The WHO-UMC causality system takes the clinical-pharmacological aspects into consideration, while less emphasis is placed on previous knowledge of ADRs (198).

Causality is classified into one of six categories **Table 1.11**, based on a summary of answers from the 4 criteria (198);

1. Time relationships between the drug use and the adverse event,
2. Absence of other competing causes (medications, disease process itself),
3. Response to drug withdrawal or dose reduction (de-challenge) and
4. Response to drug re-administration (re-challenge).

Table 1.11 WHO–UMC causality assessment criteria (198).

Causality term Assessment criteria	Description
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

However for the purpose of this work in order to enhance applicability, a modified version of the WHO-UMC scale classifying suspected ADRs into one of four categories was utilised i.e. certain, probable, possible and unlikely **Table 1.12**.

Table 1.12 Modified WHO–UMC causality assessment criteria (198)

Categories	Time Sequence	Other Drugs/ Disease ruled out	De-challenge	Re-challenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

The WHO-UMC criteria was chosen over the Naranjo causality criteria, as it was felt that it would;

(i) Be easier to deploy in routine practice,

(ii) Require less detailed information in order for it to be applied and

(iii) Be easier to integrate into the computerised decision support system (CDSS).

1.5.6 Avoidability Assessment

A number of different approaches have been proposed for the assessment of ADR avoidability (105, 163, 202-207), however the most widely cited criteria throughout the literature is the Hallas criteria (203). This set of criteria classifies avoidability into four main categorises (**Table 1.13**).

Table 1.13 Hallas Criteria for Avoidability (203)

Classification	Descriptions
Definitely avoidable –ADR the result of drug treatment procedure inconsistent with current knowledge of good medical practice, i.e. satisfies at least one of the following;	**1-**Patient (Pt) had not taken a drug able to reduce or prevent the symptoms according to prescriptive official procedure. **2-**It was known that the pt was allergic to the drug. **3-**Pt had a pathology or condition for which the drug was contraindicated. **4-**Pt took a drug inappropriately prescribed for the diagnosed disease. **5**-Wrong drug / wrong therapeutic choice errors. **6**-Wrong dose error. **7-**Prescription of a drug associated with well established clinically important interaction.
Possibly avoidable	**8**-Prescription was not erroneous but event could have been avoided by an effort exceeding the obligatory demands of current knowledge of good medical practice.
Unavoidable	**9**-ADR could not have been avoided by any reasonable measures.
Unclassifiable	**10**-Information was contradictory or insufficient to determine avoidability.

Key: ADR; Adverse Drug Reaction.

1.5.7 Severity Assessment

Categorisation of ADR severity can often prove difficult and subjective. The American Food and Drug Administration define a serious adverse reaction as one *"one which is fatal, life threatening, prolonging hospitalisation and causing a significant persistent disability, resulting in a congenital anomaly or requiring intervention to prevent permanent damage"* (208).

A number of different ADR severity rating scales have been developed to try and standardise this rating process (195, 209-212). The most common severity rating scale cited in the literature is the Hartwig severity criteria. This set of criteria categorises ADRs into one of seven different categories with ADRs characterised as level 1 and 2 defined as mild, levels 3 and 4 defined as moderate and level 5, 6 or 7 defined as severe (211) (**Table 1.14**).

Table 1.14 Hartwig severity criteria (211)

Severity	Level	Description
Mild	1-2	• No change in treatment required with the suspected drug. • Treatment with the suspected drug temporarily withheld, discontinued or alteration in dose. No antidote or other treatment required.
Moderate	3-4	• Treatment with the suspected drug temporarily withheld, discontinued or alteration in dose and/or an antidote or other treatment was required. • As for level 3 and led to an increased hospital stay by at least one day or was the reason for admission to hospital.
Severe	5 -7	• As for level 4 and requiring intensive medical care. • Permanent harm caused to patient. • Directly or indirectly led to death of the patient.

1.5.8 Potentially inappropriate prescribing link to Adverse Drug Reactions

As stated above PIP is a major concern in older individuals and it is essentially the prescribing of a medications were the potential risks (i.e. the risk of an adverse event), outweigh the potential benefits (19).

Older individuals are reported to be especially vulnerable to both PIP and ADRs. It has been reported in the literature that older individuals have a 4 fold increased risk of experiencing an ADR when compared to their younger counterparts (183, 186, 192).

As stated above ADRs are a multifaceted problem with a number of different contributory factors (19, 23, 25, 186). Until recently there has been some disagreement and uncertainty relating to whether or not there is a causal relationship between PIP and ADRs (19, 46, 56, 120, 177-179, 181-182, 185, 213-214). However a number of recent studies have reported a clear causative relationship (19, 46, 120, 177-179, 181, 185, 214), however a number of earlier studies reported that no such association could be confirmed (56, 182, 213).

One possible explanation for this conflicting evidence, may in part relate to the methodology used to assess/quantify PIP in the different studies (19, 215). As stated above, the Beers criteria has come under considerable criticism in regards to its applicability and generalisability outside of North America. All of the studies that have failed to report an association between PIP and ADRs have used the Beers criteria to assess/quantify PIP outside of North America and therefore the reported lack of association may be reflective of the poor predictive value of the Beers criteria

(19, 215). More recent studies which have demonstrated a clear relationship have used the STOPP/START criteria to assess PIP, with one recent study by our research group demonstrating that the STOPP criteria being superior to the Beers criteria in the detection of instances PIP related ADEs in older Irish hospitalised patients (46).

This evidence indicates that the regular application of a PIP screening tool to the medication regimens of older individuals may lead to (i) improvements in the appropriateness of prescribing and (ii) a reduction in the incidence of ADRs (19, 46, 120, 177-179, 181, 185, 214). However, as stated above, it is important to emphasise that ADRs are a multi-factorial problem and any strategy focused on minimising ADRs, should address all aspects of pharmaceutical care (e.g. medication reconciliation and adherence) rather than just concentrating on PIP.

1.6 Pharmaceutical care

In 1975 the first real definition of *"Pharmaceutical Care"* was proposed by Mikeal *et al.* as *"the care that a given patient requires and receives which assure safe and rational drug usage"* (216).

In 1980, this concept was further elaborated on by Brodie *et al.* when they proposed that that the definition of pharmaceutical care should also include *"the determination of the drug needs for a given individual and the provision not only of required drugs but also the services necessary (before, during and after treatment) to ensure optimally safe and effective therapy*" (217). Brodie *et al.* were also one of the first to propose the implementation of *"feedback mechanism"* to promote safe and appropriate therapy throughout the continuity of care (217). They were also one of the first to propose taking a patient-orientated approach to pharmaceutical care rather than a medication orientated approach i.e. supply and distribution (217).

In 1988 one of the first pioneers of pharmaceutical care research, Douglas Hepler, proposed a new more philosophical definition of pharmaceutical care, he described it as "*a covenantal relationship between a patient and a pharmacist in which the pharmacist performs drug use control functions governed by the awareness of and commitment to the patient's interest"* (218).

In 1990, Hepler collaborated with another pioneer of pharmaceutical care researcher Linda Strand to publish a paper that would redefine the world of pharmaceutical care entitled *"opportunities and responsibilities in pharmaceutical care"* (105). In this paper, Hepler and Strand amalgamated the pharmaceutical care philosophies proposed by Hepler, with the practice concepts proposed by Strand *et al.* to

conceptualize pharmaceutical care as *"that component of pharmacy practice which entails the direct interaction of pharmacist with the patient for the purpose of caring for the patient's drug related needs"* (108). It is from this that the modern day definition of pharmaceutical care has evolved.

Hepler and Strand proposed that for pharmaceutical care to be effectively delivered the pharmacist must;

(i) Take the time to determine the specific wishes and needs of the patient and

(ii) Commit to continue care once it has been initiated.

From this it followed that pharmaceutical care was defined as the "*provision of responsible drug therapy for the purpose of achieving definite outcomes that improve a patient´s quality of life*" (105). Similar to the approach proposed by Brodie *et al.* (217), Hepler and Strand emphasized the importance of adopting a patient centered approach to healthcare, where concordance played a central role in treatment with the pharmacist and the patient working together to develop pharmaceutical care plans with realistic therapeutic goals *"Pharmaceutical care is responsible directly to the patient for the quality of that care. The fundamental relationship in pharmaceutical care is a mutually beneficial exchange in which the patient grants the authority to the provider and provider gives competence and commitment to the patient"* (105).

The concepts and philosophies proposed by Hepler and Strand are accepted by most, as the basis for the practice of modern pharmacy profession (108). Due to this the

profession has been redefined from a service profession (i.e. supplied and distributed of medications), to a practice profession with directly involved in patient care (108). In 1998, Cipolle *et al.* further developed this definition of pharmaceutical care, defining it as "*a practice in which the practitioner takes responsibility for patient´s drug-related needs and is held accountable for this commitment. In the course of this practice, responsible drug therapy is provided for the purpose of achieving positive patient outcomes*" (108).

Over the last forty years the philosophy and definition of pharmaceutical care has evolved, however two main ideals have remained constant (i) pharmaceutical care should be patient centered i.e. prioritisation of the needs and preference of the patient and (ii) pharmacists have a commitment/responsibility to ensure safe and appropriate delivery of care, whether it is in the supply of medications or advice (108).

1.7 Medications reconciliation

A number of different medication reconciliation definition have been proposed in the literature (219-227), however medication reconciliation is essentially *"the process of identifying the most accurate list of patient's current medications- including names, dosage, frequency, route and comparing them to the current list in use, recognising any discrepancies and documenting any changes thus resulting in a complete list of medications"* (228-230).

A medication reconciliation reviews should be seen as more than just ascertainment of the most accurate list of a patient's medications (231). It should be seen as an opportunity to optimise prescribing and in 2007, the World Health Organisation (WHO) further developed upon this concept, by suggesting that the medication reconciliation review should be accompanied by a review of appropriateness i.e. *"the medication reconciliation process provides an opportunity to reconsider the appropriateness of a patients medications"* (227).

The primary purpose of a medication reconciliation review is to establish the most accurate, up-to-date and appropriate list of a patient's medications and to ensure that this list is maintained throughout the entire continuum of care i.e. a medication reconciliation review should be undertaken at every transition in care (83, 223, 232).

1.8 Intervention strategies to improve appropriateness of prescribing and minimise adverse drug reactions

Several different strategies have been proposed in the literature to improve the appropriateness of prescribing, minimise ADRs and improve the overall quality of patient care (14, 19, 41, 57, 233-234):

- Educational interventions,
- Multidisciplinary team approaches & Comprehensive Geriatric Assessments,
- Pharmacist interventions and
- Computerised decision support systems.

1.8.1 Prescriber education

Continual medical education is one of the most important and commonly-used approaches to improve appropriateness of prescribing in older individuals (14, 19-20, 23, 25, 40-41, 80, 234-235). A number of studies describe different educational strategies, some of which take a passive approach (e.g. didactic courses, dissemination on printed material or e-learning material), while others take a more interactive approach (e.g. academic detailing, face-to-face educational sessions, computer-aided learning programmes) (14, 20, 41, 57).

These interventions are designed to educate healthcare professionals on different aspects of older person's care, i.e. providing them with up-to-date information on the range of different treatment options available (14, 19-20, 41, 233). Providing healthcare professionals with this type of information enables them to make more informed/appropriate decisions when attempting to optimise older patient's care in routine practice (14, 19-20, 41, 233). These sorts of interventions can often be quite labour intensive and costly to implement and the evidence to-date relating to their overall effectiveness is somewhat mixed, however the majority of studies have reported positive results. **Table 1.15** summarises the key findings of a number of educational intervention studies.

Table 1.15 Summary of intervention studies that used educational initiatives to optimise patient care (14, 19-20, 25, 41, 80, 233-234, 236).

Study	Study design	Intervention description	Outcome measure	Summary of findings
Avorn *et al.* (USA, 1992)[236]	Cluster RCT, 823 NHR; 12 NHs; LTC.	Geriatric psychopharmacology educational program delivered by a clinical pharmacist to physicians, nurses, and nurse's aides working in LTC.	Total use of hypnotics/ benzodiazepines/ anti-psychotics as defined by a psychoactive drug use index scores.	This study found that an educational intervention targeted at doctors and nurses, caring for older individuals in LTC can significantly reduce the usage of psychotropic medications in this patient group without adversely affecting the residents overall behaviour or functionality.
Ray *et al*. (USA, 1993)[237]	Nonrandomized controlled before-and-after, 378 NHR; 5 NHs; LTC.	Old age psychiatrist educated physicians on risks/benefits of using antipsychotics in older individuals, reference card with recommendations and flow chart for drug withdrawal also provided.	Changes in administration of psychotropic drugs, physical restraint use, frequency of behaviour problems.	In this study it was found that the intervention led to a significant reduction in the usage of antipsychotics, with no increase in the frequency of behavioural problems being reported. The study also reported that the intervention did not have any significant affect on the usage of any other psychotropic medications.
Rovner *et al*. (USA, 1996)[238]	RCT, 89 NHRs; 1 NHs; LTC.	Implementation of new prescribing guidelines according to protocol for psychotropic drug management led by study psychiatrist. Weekly educational sessions delivered by psychiatry.	Incidence of behavioural disorders measured as present/absent, antipsychotics use and restraint use.	This study found that the intervention led to a significant reduction in the number of intervention patients who exhibited behavioural problems. The study also found that the intervention resulted in a reduction in the usage of both antipsychotics and physical restraints.
Meador *et al*. (USA, 1997)[239]	Cluster RCT, 1152 NHRs; 12 NHs, LTC.	A 45–60 min visit by geriatric-psychiatrist to physicians to discuss risk and benefits of antipsychotics, physicians received reference cards with summary of key points and flow chart for antipsychotic withdrawal.	Change in days of antipsychotic use per 100 days of stay, withdrawal from antipsychotics, or reduction in antipsychotic dose by 50% or more.	This study found that a combined intervention consisting of geriatric psychiatrist visit coupled with educational material relating to withdrawal of antipsychotics led to a significant reduction the use of antipsychotics.
Lowe *et al.* (UK, 2000)[240]	RCT, 161 patients, 1 general practice, PC.	A clinical pharmacist delivered an educational session to patients about their medications and how to use them appropriately.	Assessment of patients' knowledge and their compliance with their medications.	This study found that a pharmacist led educational intervention can lead to significant improvements in patients' compliance and knowledge of their medications.
Stein *et al*. (USA, 2001)[241]	Cluster RCT, 147 NHRs; 20 NHs; LTC.	A 30 min structured training session for staff on the appropriate use of analgesics.	Use of NSAIDs and acetaminophen over seven days.	This study found that the educational intervention targeted at healthcare professionals responsible for care of older nursing home residents was effective at reducing NSAIDs usage without any significant adverse impact on pain control.
Pimlott *et al.* (2003)[242]	RCT, 374 physicians; PC.	Mailed prescribing individualised physician feedback and education materials relating to benzodiazepine prescribing.	Prescriptions of benzodiazepines alone or in combination with other psychoactive medications.	This study found that a combined intervention using prescribing feedback and educational material, led to no clinically significant effect on the appropriateness and/or the rate of benzodiazepine prescribing.
Roberts *et al.* (Australia, 2001)[243]	Cluster RCT, 2261 NHRs; 52 NHs, LTC.	Drug regimen review by clinical pharmacist in NH residents. Problem-based education sessions with nurses, provision of additional support material, telephone consultations, clinical pharmacist visits.	Mortality rate, number of ADE, hospitalisations, medication use in terms of total number of medications and prescription claims scores for each of the 14 elements comprising the RCI.	This study found that a combined intervention consisting of a pharmacist led medication review coupled with educational sessions which were focused at improving the quality of prescribing in older individuals in LTC led to a reduction in the overall drug usage without adversely affecting residents' survival or morbidity indices.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Fossey *et al*. (UK, 2006)[244]	RCT, 349 NHRs; 12 NHs, LTC.	Training and support to NH staff on alternatives to neuroleptic use and behavioural management techniques. Old age psychiatry reviewed patients' drug lists and provided recommendations to improve prescribing.	Proportion of NHR prescribed a neuroleptic.	This study found that an educational intervention focused at healthcare professionals caring for older individuals residing in LTC, can lead to significant improvements in neuroleptic usage, without leading to any significant differences in the levels of agitated or disruptive behaviour between the two groups of patients.
Monette et al. (Canada, 2007)[245]	Cluster RCT, 36 Physicians; 8 NHs, LTC.	Mailing antibiotic guidelines to physicians along with an outline of their antibiotic prescribing profile over the previous 3 months.	Proportion of prescriptions that did not adhere with the guidelines.	This study found that this educational intervention was effective at reducing the proportion of antibiotic prescriptions that were deemed not to adhere to the antibiotic guidelines.
Wessell et al. (USA, 2008)[246]	Repeated measures time series analysis, 124802 patients, 33 general practices, PC.	Three-step intervention with quarterly practice performance reports, biannual onsite visits and annual network meetings for performance review, academic detailing, and quality improvement planning.	Proportion of elderly prescribed with always inappropriate and rarely inappropriate medications.	In this study the three step intervention led to a significant reduction in the proportion of patients who were prescribed an always inappropriate medication, and the proportion of patients who were prescribed a rarely appropriate medication.
Eide *et al*. (Norway, 2010)[247]	Before-and-after study, 266 NHRs; 5 NHs, LTC.	Pharmacists held educational meetings with physicians and nurses relating to the appropriate use of hypnotics.	Change in choice, frequency and appropriateness of hypnotic medications.	This study found that the intervention led to improvements in the appropriateness, frequency and choice and administration of hypnotics in older LTC residents.

Key: RCT; Randomised controlled trial, NH; Nursing home, NHR; Nursing home resident, PC; Primary care, ADE; Adverse drug event, LTC; Long term care, SC; Secondary care, NSAID; Non-steroidal anti-inflammatory drugs, RCI; Resident Classification Instrument.

1.8.2 Multidisciplinary teams & Comprehensive geriatric assessments

The Multidisciplinary team (MDT) approach involves a group of healthcare professionals working together to review a patient treatment plan and/or patients medication regimen. This approach is designed to utilise the knowledge and expertise of each of the members of the MDT team in order to improve the overall quality of patient care, improve appropriateness of prescribing and minimise ADRs (19-20, 52).

A comprehensive geriatric assessment (CGA) is usually delivered by a MDT team consisting of a geriatrician working with a number of other specialist healthcare professionals from different aspects of geriatric medicine, i.e. nurses, physiotherapists, occupational therapists and pharmacists (14, 19-20, 25). This assessment not only focuses on prescribing, but also takes other aspects of a patient care into consideration (14, 20, 25). It provides the team with an overall summary of an older person's health status i.e. their cognitive and functional abilities, as well as an overview of the appropriateness of the patient's medication regimen (14, 20, 25). A CGA enables the MDT to make a more informed decision about a patient's care and to effectively evaluate the different treatment options available, enabling them to devise a comprehensive treatment plan (14, 20, 25). This approach is intended to address the special needs of older patients, while simultaneously attempting to improve the appropriateness of prescribing, thereby minimising the potential of PIP and/or ADRs (57). This type of intervention can prove quite resource-intensive and timely to implement, due to the fact that it involves arranging a meeting of a number of healthcare professionals so they can discuss the different aspects of the patients' care (14, 20).

A number of studies have investigated the effects that the MDT/ CGA approach has on patient's care, optimisation of prescribing and the minimisation of ADRs (19, 248-255). The majority of these studies have been small, single-site studies which used only limited measures to evaluate medication appropriateness, however, almost all of these studies report significant beneficial effects with this type of approach. **Table 1.16** summarises the key findings of a number of intervention studies that took a MDT/CGA approach to optimise patient care.

Table 1.16 Summary of intervention studies that used a multidisciplinary team approach to optimise patient care (14, 19-20, 25, 41, 80, 233-234, 236).

Study	Study design	Intervention description	Outcome measure	Summary of findings
Owens *et al.* (USA, 1990)[248]	RCT, 436 patients, 1 hospital, SC.	Multidisciplinary team approach to care; A pharmacist interviewed all experimental patients and reviewed the patient medical records and drug lists, and identified any medications of concern and presented appropriate recommendations at a team conference.	Medication use, unnecessary medication use, appropriate medication choice (Medication problem were judged as inappropriate choices if there were potential side effects that would affect patient function, and if better alternatives were available.)	This study found that the MDT intervention led to a significant reduction in the number of medications prescribed. This study also found that the intervention group were prescribed significantly fewer unnecessary medications and significantly fewer inappropriate medications.
Cavalieri *et al.* (USA, 1993)[249]	RCT, 69 NHRs, 1 NH, LTC	A Comprehensive Geriatric Assessment (CGA) Team of a geriatrician, geriatric nurse and a practitioner. The team evaluated each resident on arrival to the nursing home and was responsible for all medical treatment during the study period.	Number of drugs prescribed, Quality-of-care indices and healthcare service utilisation	This study found that the CGA intervention led to a significantly improvement in the diagnosis of conditions and the referral of patient to appropriate ancillary service. This study also reported that the intervention resulted in a non significant decrease in the rate of mortality, emergency department visits, and the number of medications prescribed. This CGA approach also led to improvements in the patients' quality of care indices.
Schmidt *et al.* (Sweden, 1998)[256]	Cluster RCT, 1854 NHR; 33 NHs, 12 months	Pharmacists arranged monthly MDT meetings, attended by nurses, physicians, pharmacists, and nursing assistants. These meetings focused on communication skills, drug use in elderly, networking and problem solving and support.	Proportion of residents with a psychotropic drug, polypharmacy or 2 or more drugs from the same therapeutic class and the proportion of residents with non-recommended or an acceptable psychotropic medications as defined by the SMPA guidelines.	This study found that the pharmacist led MDT intervention was effectively at improving prescribing practices, especially in regards to psychotropic medications, increasing staff members' knowledge about appropriateness of prescribing and improved quality of care for older nursing home residents.
Coleman *et al*. (USA, 1999)[257]	RCT, 169 patients, 9 primary care physician practices, 24 months.	Chronic care clinic involving a visit to geriatrician, nurse, and pharmacist.	Changes in self-reported urinary incontinence, frequency of falls, depressive symptoms, physical function, and satisfaction. As well as prescriptions for high-risk medications and cost/utilization data.	This study found that this intervention led to no significant improvements in the frequency of incontinence, proportion of patients with falls, patient's depression scores, patients physical function scores, or the prescribing of high risk medications. This study also reported that there was no significant difference between the frequency of hospitalization, number of hospital days, emergency and ambulatory visits, and total costs of care between the two groups.
King *et al.* (Australia, 2001)[251]	Controlled before-and-after study, 245 NHR; 3 NH, 9 months	Weekly MDT meetings attended by GP, GP project officer, pharmacist, senior nursing staff, and other health care professionals.	Number of recommendations and whether they had an effect on (i) NHR and (ii) carers, changes in number of medications prescribed, medication costs, mortality.	This study found that the MDT intervention led to a non-significant reduction in the number of medications prescribed, medication costs and the rate of mortality in the intervention group compared with the control group.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Elliott *et al*. (Australia, 2001)[252]	Ouasi-experimental Study, 1301 patients, 1 hospital, SC.	MDT review and individualised physician feedback on quality of their benzodiazepine prescribing.	Prevalence and appropriateness of benzodiazepine prescriptions.	This study found that the MDT intervention coupled with prescriber feedback led to a non-significant reduction in the proportion of patients prescribed a benzodiazepine; however it did produce a significant improvement in the appropriateness of the benzodiazepine prescriptions. These improvements in the appropriateness of prescribing were found to be maintained for up to 6 months after the intervention.
Allard *et al.* (Canada 2001)[258]	RCT, 266 patients, 1 area, PC.	Medication review and case conference by MDT including a pharmacist. Written recommendations were then mailed to the patient's physician.	Prevalence of potentially inappropriate medications (as defined by the Quebec consensus panel: drug interactions, therapeutic overlapping, and drugs of limited use).	This study found that this MDT intervention led to a significant reduction in the number of PIMs prescribed. With it reported that patients in the intervention group that received the medication review were twice as likely to be prescribed fewer PIMs.
Meredith *et al.* (USA, 2002)[259]	RCT, 259 patients, 2 large home healthcare agencies, PC.	Joint medication review by pharmacist and patient's nurse to identify DRPs; the findings of these reviews were then presented to patient's physician.	Medication use at follow-up (between 6 and 12 weeks).	This study found that the intervention led to a non-significant improvement in the overall use of medications, the intervention was found to be particularly effective at reducing the proportion of patients using duplicate drug therapies. The study also found that the intervention had no effect on appropriateness of prescribing of either psychotropic medications or NSAIDs. Also no difference was found between the two groups in terms of clinical outcomes or health care utilisation.
Schmader *et al.* (USA, 2004)[253]	RCT, 834 patients, 11 hospitals, 12 months.	Multidisciplinary geriatric team including a geriatrician, social worker and nurse providing care for older hospitalised inpatients and outpatients.	Adverse drug reactions and inappropriate drug use as defined by the MAI and Beers criteria.	This study found that the intervention led to a significant reduction in the incidence of serious ADEs in older individuals in the outpatient care setting and led to a reduction in suboptimal prescribing in this patient group in both the inpatient and outpatient setting.
Crotty *et al.* (Australia, 2004)[260]	RCT, 110 patients, 1 Hospital, SC.	Pharmacist conducted medication reviews and drafted up a medication management transfer summary. This was then discussed at a case conference with doctors and pharmacists.	Appropriateness of prescribing as defined by the MAI.	This study found that an intervention consisting of pharmacist led medication reviews coupled with MDT case conferences led a significant improvement in the appropriateness of prescribing, with improvements reported in all aspects of the MAI. At follow-up it was reported that the intervention resulted in a significant protective effect against worsening pain and hospital usage but no effect was observed in regards to ADEs, falls , worsening mobility, worsening behaviour, or increased confusion.
Crotty *et al.* (Australia, 2004)[261]	RCT, 154 NHRs, 10 NH, LTC.	Two multidisciplinary case conference (which including a geriatrician), conducted 6–12 weeks apart.	Appropriateness of prescribing as defined by the MAI.	This study found that the MDT intervention produced a significant improvement in the appropriateness of prescribing as defined by the MAI. This study also reported a significant improvement in the MAI scores for benzodiazepines and that there was no significant difference found between the two groups in regards behaviour, as defined by the nursing home behaviour problem score.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Saltvedt *et al.* (Norway, 2005)[254]	RCT, 254 patients, Hospital, SC	Multidisciplinary geriatric team approach delivered in a geriatric evaluation and management unit.	Inappropriate prescribing as defined by the Beers criteria.	This study found that the MDT intervention resulted in a significant difference in rate of discontinuation and initiation of medications between the intervention and the control groups. The study also reported that there was no significant difference between the two groups in regards the proportion of patients with PIP from admission to discharge. There was also no significant difference in the proportion of patient with polypharmacy.
Lampela *et al.* (Finland 2010) [255]	RCT 644 outpatients, 1 hospital, SC.	A medication review as part of a comprehensive geriatric assessment (CGA).	Changes to the patients' medication regimen.	This study found that the intervention consisting of a medication review coupled with a CGA resulted in more rational prescribing in older individuals in an outpatient care setting. This study reported that a more active approach to care was taken in patients who had undergone the intervention.
Hellstrom *et al.* (Sweden, 2011)[262]	Prospective, controlled study, 210 patients, 3 internal medicines wards, SC.	A clinical pharmacist working as part of a multidisciplinary team conducted a medication reconciliation review at admission and at discharge.	Prescribing appropriateness as defined by the MAI.	This study found that an intervention involving a pharmacist working as part of an MDT led to a significant reduction in the number of inappropriately prescribed medications. This study also reported that the intervention was associated with a significantly lower risk of having a medication related readmission.

Key: RCT; Randomised controlled trial, NH; Nursing home, NHR; Nursing home resident, PC; Primary care, ADE; Adverse drug event, PIM; Potentially inappropriate medication, LTC; Long term care, SC; Secondary care, MDT; Multidisciplinary team, CGA; Comprehensive geriatric assessment, GP; General practitioner, NSAID; Non-steroidal anti-inflammatory drugs, MAI; Medication appropriateness index, PIP; Potentially inappropriate prescribing, SMPA; Swedish medical product agency.

1.8.3 Pharmacists Interventions

Pharmacists are ideally positioned to address the issues of PIP and ADRs in older individuals. Throughout the literature, a variety of different pharmacist-led initiatives have been described, such as (i) pharmacist-led medications review, (ii) participation in MDTs, (iii) participation in ward rounds, (iv) medication usage reviews and (v) provision of patient counselling and (vi) delivery of educational sessions to both the patients and the prescriber (48, 52, 118, 154, 180, 240, 262-283) (**Table 1.17**).

To-date pharmacist-led interventions generally involve the delivery of pharmaceutical care either independently or as part of a MDT (48, 52, 84, 118, 154, 180, 240, 262-282). These interventions usually involve the pharmacist performing a standardised pharmaceutical assessment of an older person's prescriptions, the results of which are usually then communicated to the patient's doctor in the form of feedback or advice. These types of interventions are intended to try and influence the doctors prescribing habits in order to improve the appropriateness of therapy (14, 20, 57).

Pharmacist led interventions traditionally improved patients', physicians' and nurses' knowledge and understanding of medications (52, 153). More recently the role of the pharmacist has begun to expand and they are beginning to take a more active role in prescription monitoring and PIP assessment (84, 118, 278, 281). All of the interventions strategies outlined below utilise the experience and expertise of clinical pharmacists to try and optimise therapy and minimise the risk to the patient (14, 20, 52, 57, 153).

The majority of the studies that have assessed the effectiveness of the pharmacist-led intervention strategy have been small single site studies, with overall evidence relating to the effectiveness of these interventions being somewhat mixed (20, 52, 153). However, a number of these studies have demonstrated that the incorporation of clinical pharmacy services into older persons care can result in significant improvements in (i) compliance, (ii) the identification and resolution of instances of PIP and (ii) health related outcomes (19, 52, 118, 180, 240, 260, 262, 264, 266, 270-271, 274, 276, 279-282) (**Table 1.17**).

Implementation/creation of clinical pharmacy services can often prove quite difficult and costly (225, 284), however the majority of studies which have examined the cost effectiveness of such services, have indicated that the cost of implementation are off-set by the cost savings generated by the intervention i.e. healthcare costs associated with a reduction in the prevalence of PIP and ADRs (153, 225, 230, 235, 284-296) (**Table 1.17**). **Table 1.17** summarises the key findings of a number of pharmacist led intervention studies.

Table 1.17 Summary of intervention studies which utilised the expertise of a pharmacist to optimise patient care (14, 19-20, 25, 41, 52, 80, 233-234, 236).

Study	Study design	Intervention description	Outcome measure	Summary of findings
Thompson *et al.* (USA, 1984)[265]	Quasi-experimental design, 139 NHRs, 1 NH, LTC.	Clinical pharmacist prescribing and monitoring under the supervision of a family practitioner	Number of medications prescribed, rates of mortality, discharge destination	This study found that an intervention that involved a clinical pharmacist prescribing and monitoring patients led to a significant reduction in the number of medications prescribed and can have a positive effect on mortality and discharge rates in older individuals in LTC facilities.
Lipton *et al.* (USA, 1992)[266]	RCT, 136 patients, 1 hospital, SC.	A clinical pharmacist conducted a medication review and assessed the appropriateness of prescribing. Recommendations were then communicated to the physician either in writing or via a telephone call.	Number of clinically significant drug related problems (DRPs). DRPs were divided into six categories: 1) inappropriate choice of therapy; 2) dosage; 3) schedule; 4) drug-drug interactions; 5) therapeutic duplication; and 6) allergy.	This study found that a pharmacist based intervention led to significant improvement the appropriateness of prescribing in geriatric outpatients. With patients in the intervention group less likely to experience any type of prescribing problem or to have an appropriateness or dosage issue.
Hanlon *et al.* (USA, 1996)[180]	RCT, 168 patients, VA clinic, SC.	Medication review undertaken by a clinical pharmacist. Any issues highlighted in these review were then communicated in writing to the patients physicians. Patients were counselled about their medication regimen at each clinic visit.	Appropriateness of prescribing as defined by the MAI.	This study found that an intervention consisting of a pharmacist led medication review and patient counselling resulted in significant improvements in the appropriateness of prescribing and that it can have a positive effect on the incidence of ADEs, health related quality of life and healthcare utilisation in geriatric outpatients.
Furniss *et al.* (UK, 2000)[267]	Cluster RCT, 330 NHR; 14 NHs LTC.	Pharmacist performed a regular medication review at a GPs surgery, the nursing home (NH) or over telephone. The nursing homes were visited every 3 weeks post the review to ascertain whether the patients had any problems with medications.	Number of drugs, appropriateness of prescribing, use of primary and secondary care resources, number of accidents and deaths.	This study found that a pharmacy intervention can produce a non-significant reduction in the number of medications prescribed to older individuals residing in long term care. The intervention was also reported to have a minimal impact on morbidity and mortality.
Nazareth *et al.* (UK, 2001)[268]	RCT, 362 patients, 4 hospitals, SC.	Pharmaceutical care discharge plans provided to the patients, their caregivers and their physicians. Home visits conducted by the patients community pharmacist 1-2 weeks after discharge	Re-admission to hospital within 6 months. Number of deaths, attendance at hospital outpatient clinics, GPs and proportion of days in hospital over the follow-up period. Patients' general well-being, satisfaction, knowledge and adherence to medicine were also assessed.	This study found that the intervention resulted in no significant difference in the proportion of hospital re-admitted between the two groups. This study also reported that there was no significant differences in any of the secondary outcomes i.e. medication knowledge and adherence, general well being and satisfaction.
Zermansky *et al.* (UK, 2001)[269]	1188 patients, 4 general practices, PC.	Pharmacists conducted medication reviews of repeat prescriptions.	Number of changes to repeat prescriptions over one year, drug costs, and healthcare utilisation.	This study found that an intervention involving a pharmacist undertaking a medication review resulted in more changes in treatment than normal care and that it led to important cost savings, even after the price of the intervention was deducted.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Al-Rashed *et al.* (UK, 2002)[264]	RCT, 82 patients, 2 care of the elderly wards, SC.	Pharmacist provided pre-discharge pharmaceutical counselling to patients on their medicines.	Drug knowledge, compliance, usage of home medicine stocks and any healthcare related events.	This study found that an intervention involving a pharmacist providing pre-discharge pharmaceutical counselling resulted in significant improvement in patients' knowledge of their medications, improved compliance and the intervention was associated with fewer GP and hospital visits.
Krska *et al.* (Scotland, 2001)[270]	RCT, 332 patients, 1 general practice, primary care.	Pharmacist review of medications and related issues. The pharmacist then drafted up pharmaceutical care plan for the patients' physicians which outlining recommendations o how to optimise prescribing.	Resolution of pharmaceutical care issues. Assessment of the patients' health-related quality of life.	This study found that an intervention involving a pharmacist led medication review, resulted in a reduction in the number of pharmaceutical care issues, thereby decreasing the potential for medication related problems. This intervention however was not found to have any significant impact on medication costs, health related quality of life or healthcare utilisation.
Sturgess *et al.* (Northern Ireland, 2003)[272]	RCT, 10 community pharmacies, PC.	Community pharmacist delivered a harmonised structured pharmaceutical care programme to patients that included education on compliance, strategies to (i) optimise medication regimens and (ii) improve medication monitoring.	Health related SF-36 quality of life assessment, number of hospitalisation, patient related problems, patients' knowledge of medications, drug use, number of medications changes, compliance and number of contacts with healthcare professionals.	This study found that a pharmaceutical care intervention can lead to improvements in compliance, a reduction in the number of patient related problems and costs. However the intervention was found to have little impact on health related quality of life, knowledge of medications or healthcare utilisations.
Sellors *et al.* (Canada, 2003)[263]	RCT, 889 patients, 48 general practices, PC.	A clinical pharmacist conducted face-to-face medication reviews with the patients and then provided their physicians with written recommendations focused on resolving any of identified drug-related problems.	Number of drug-related problems identified, proportion of recommendations implemented by the physicians.	This study found that this pharmacist intervention had no significant effect on the number of medications prescribed, healthcare utilisation or cost, or on health related quality of life. However the study did illustrate that physicians were quite receptive to pharmacist's recommendations, with it reported that the physicians implemented or attempted to implement 72.3% of the interventions.
Brown *et al.* (United States, 2004)[274]	Retrospective case series, 99 patients, 1 Hospital, SC.	Acute Care for Elderly (ACE) team pharmacist reviewed patients.	Number of medications prescribed and appropriateness of prescribing as defined by Beers.	This study found that an intervention involving an ACE team pharmacist can lead to a significant improvement in the appropriateness of prescribing, from admission to discharge. The intervention did not however result in a decrease in the number of medications prescribed.
Holland *et al.* (UK, 2005)[275]	RCT, 872 patients, 6 hospital, SC.	A pharmacist conducting 2 home-based medications reviews after discharge.	Emergency readmissions to hospital at six months. Mortality and quality of life as defined by the EQ-5D.	This study found that this pharmacist intervention led to no improvements in the patients' quality of life, as defined by the EQ-5D. The study did however report fewer deaths in the intervention group, however this was not found to be significant. This study also reported that the intervention appeared to be associated with an increased risk of hospital re-admission.
Spinewine *et al.* (Belgium, 2006)[48]	Before and after study, 101 patients, 1 hospital, SC.	A clinical pharmacist delivered pharmaceutical care from admission to discharge. The pharmacist participation on ward round; and the patients were provided with written instructions about their medications.	Number of drug related problems (DRPs) and rate of uptake of intervention recommendations.	This study found that involving a clinically trained pharmacist in a geriatric team can lead to improvements in the appropriateness of prescribing and the identification and resolution of DRPs. This study also reported that the majority of the pharmacist recommendations were accepted by the medical teams and were deemed clinically relevant.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Zermansky *et al*. (UK, 2006)[276]	RCT, 661 patients; 65 homes (13 nursing, 38 residential and 14 mixed), LTC.	A clinical pharmacist conducted a medical review of the patient's clinical record. The pharmacist also conducted an interview with the patient and/or their carer. The recommendations generated from this review were then forwarded in writing to the patients' GPs.	Number of changes to a patient's medication regimen. Number of and cost of repeat medicines; mortality rates, falls, hospital admissions, GP consultations, activity of daily living (ADL) and cognitive function.	This study found that the intervention resulted in the generation of a number of clinically relevant recommendations which are generally well accepted. The intervention also produced a substantial change to a patient's medication regimen without resulting in a significant change in drug costs. This study also indicated that the intervention may have an effect on the incidence of falls.
Spinewine *et al.* (Belgium, 2007)[118]	RCT, 203 patients, 1 acute care of the elderly ward, SC.	Clinical pharmacist provided pharmaceutical care from admission to discharge in patients admitted to a geriatric evaluation and management (GEM) unit.	Appropriateness of prescribing as defined by the MAI and ACOVE.	This study found that an intervention involving a pharmacist working as part of a GEM team can lead to significant improvements in the appropriateness of prescribing i.e. overuse, misuse and underuse of medications, during admission and post discharge. The study however also reported no difference in the rates of emergency visits, hospital readmission or mortality between the two groups.
Lenaghan *et al.* (UK, 2007)[277]	RCT, 136 patients, 1 general practice, PC.	A community pharmacist conducted a home based medication review/medication educational sessions and the recommendations from these review were then communicated to the patients' GPs.	Total number of non-elective hospital admissions within 6 months. Mortality rate, care home admissions and quality of life as defined by the EQ-5d. Number of medications prescribed.	This study found that the pharmacist intervention had no significant impact on hospital admissions, mortality, care home admissions or health related quality of life. The intervention did however result in a significant reduction in the number of prescribed medications.
Gillepsie *et al*. (Sweden, 2009)[278]	RCT, 368 patients, 1 acute internal medicine ward, SC.	Pharmacists provided pharmaceutical care from admission to discharge, plus a follow-up calls after discharge.	Frequency of hospital visits (emergency department and readmissions [total and drug-related]) during the 12-month follow-up period.	This study found that the pharmaceutical care intervention was associated with a reduction in all hospital visits, emergency department visits and drug related readmissions. This study also found that the intervention resulted in substantial cost savings.
Koehler *et al*. (USA, 2009)[279]	RCT, 41 patients, 2 hospitals, SC.	A clinical pharmacist conducted a reconciliation review combined with medication counselling at admission and discharge. Patients were also given condition specific education/ enhanced discharge planning which was delivered by a discharge coordinator and was followed up 5-7 days after discharge.	Emergency department/hospital readmission rates.	This study found that an intervention involving a pharmacist performing a medication reconciliation review led to a significantly fewer readmissions or ED visits post discharge in the intervention group at the 30 day follow-up, however no significant difference was found at the 60 day follow-up. This study also reported that when unscheduled readmission did actually occur the time to event was longer in the intervention patients.
Murray *et al*. (USA 2009)[280]	RCT, 800 outpatients, 1 hospital, SC.	Pharmacists dispense patients' medications and provide them with ongoing oral and written instructions on how to use their medications. The pharmacist conducted ongoing reviews of the patients' prescriptions and medical records using an electronic medical record system.	Incidence of adverse drug events and medication errors according to a specially developed trigger list.	This study found that the pharmacist intervention led to patients in the intervention group being exposed to a reduced risk of ADEs or medication errors.

Study	Study design	Intervention description	Outcome measure	Summary of findings
Richmond *et al.* (UK, 2010)[194]	Multiple interrupted time-series, 551, 62 community pharmacies, 24 genera practices, PC.	Shared pharmaceutical care for older people between patients' GPs and their community pharmacists, coupled with home visits by patients' community pharmacists which focus on improving patients adherence and knowledge of their medications.	Appropriateness of prescribing as defined by the UK MAI, quality of life as defined by the SF-36 Health Survey, and prevalence of serious adverse events.	This study found that this shared care intervention resulted in no significant improvements in the appropriateness of prescribing, in the number of hospital admissions, in the patients quality of life or in the incidence of adverse events.
Patterson *et al.* (UK, 2010)[281]	Cluster RCT, 334 NHRs, 22 NHs, LTC.	A pharmacist conducted a medication review on a monthly basis for 12 months. The pharmacists applied an algorithm relating to the use of psychoactive medications in consultation with the patients' GPs.	Proportion of residents prescribed one or more inappropriate psychoactive (anxiolytic, hypnotic or antipsychotic) drugs, change in number of inappropriate psychoactive drugs, rate of falls per 100 resident months.	This study found that the pharmacist intervention led to a marked reduction in the number of older long term care residents that were receiving one or more inappropriate psychotropic medication. This study also reported that the reduction in psychotropic medications was associated with a non-significant increase in the incidence of falls in the intervention group.
Lisby *et al.* (Denmark, 2010)[282]	RCT, 100 patients, 1 acute internal medicine ward, SC.	A clinical pharmacist undertook a patients' medication history which was followed by discussion about their treatment with a clinical pharmacologist.	Length of in-hospital stay. Readmission rates, mortality, contact with primary healthcare services and quality of life.	This study found that the pharmacist intervention resulted in no measurable change in short-term morbidity or in long term morbidity and mortality.

Key: RCT; Randomised controlled trial, NH; Nursing home, NHR; Nursing home resident, PC; Primary care, ADE; Adverse drug event, LTC; Long term care, SC; Secondary care, NSAID; Non-steroidal anti-inflammatory drugs, GP; General practitioner, SF; Short form, ACE; Acute care for elderly, PIP; Potentially inappropriate prescribing, UK; United Kingdom, DRP; Drug related problems, GEM; Geriatric evaluation and management, MAI; Medication appropriateness index, ACOVE, Assessing care of vulnerable elders, MDT; Multidisciplinary team, EQ-5D; EuroQoL:-5D, ADL; Activity of daily living.

1.8.4 Computerised decision-support systems

A number of different computerised decision support systems (CDSS) have been developed which focus on a number of different aspects of the prescribing i.e. drug interaction, drug monitoring, dosing errors and PIP issues (20, 25, 57, 233, 297-301).

These systems often prove quite difficult, time-consuming and costly to develop and implement (14, 25). However, these systems are quite promising and once successfully implemented they can prove to be a very powerful resource that can be utilised at any stage of the prescribing process to assist healthcare professionals in the identification of PIP, drug-related problems (DRPs) or ADRs (14, 19-20, 25, 57, 233, 297-301). The key to the success of any CDSS is its ability to able to link patient specific clinical information with a set of explicit or implicit criteria, in order to effectively screen for PIP (14, 25).

The majority of the studies that used a CDSS reported that the implementation of such systems is associated with a positive impact on the appropriateness prescribing in older individuals (297-299, 301), however to-date there is little evidence relating to their impact on the incidence of ADR in older individuals (19). **Table 1.18** summarises the key findings of intervention studies that used computerised decision support software to optimise patient care.

Table 1.18 Summary of intervention studies that used computerised decision support software to optimise patient care (14, 19-20, 25, 41, 80, 233-234, 236).

Study	Study design	Intervention description	Outcome measure	Summary of findings
Tamblyn *et al.* (Canada, 2003)[298]	RCT, 12560 patients, 107 family doctors, PC.	Physician provided with computerized decision support software (CDSS).	Initiation and discontinuation rates of inappropriate prescriptions.	This study found that a CDSS intervention led to a significant reduction in the initiation of PIMs in older community dwelling individuals, however this study also reported that there was no significant difference observed in regards the rate of discontinuation of already prescribed PIMs.
Monane *et al.* (USA, 1998)[297]	Cohort study, 23269 patients, 1 pharmaceutical benefits manager, PC .	Computerized drug utilisation review (DUR) which includes alerts relating to potential prescribing issues. These alerts notify the pharmacist to contact the physician.	Contact rate with physician and changes to drug regimen over 1-year period.	This study found that the computerised drug utilisation review led to improvements in both the appropriateness of prescribing and quality of care in older community dwelling individuals.
Raebel *et al.* (USA, 2007)(299)	RCT, Intervention 59680 patients, 12 months	Computerized system which alerted pharmacists when PIMs are prescribed and then the pharmacists telephones the prescribers to recommend a safer alternative.	Number of inappropriate medications dispensed to elderly patients during intervention period of 1 year.	This study found that the CDSS intervention was effective at improving appropriateness of prescribing, with a significant reduction in the initiation and/or dispensing of medications considered potentially inappropriate in older individuals being reported.
Gurwitz *et al.* (USA and Canada, 2008)[300]	Cluster RCT, 1118 NHRs; 2 NHs, 6 months to1 year.	Clinical decision-support system designed for preventing ADEs. Programmed to identify more than 600 potentially serious drug-drug interactions and to display alerts	Number of ADEs that could have been prevented by CDSSs, number of ADEs preventable by any means, and severity of the events	This study found that the CDSS intervention led to no significant reduction in the occurrence of (i) all type ADEs or (ii) preventable ADEs, in older nursing home residents.
Field *et al.* (Canada, 2009)[301]	Cluster RCT, 833 NHRs; 1 NHs, 12 months.	Clinical decision-support system designed to improve prescribing for residents with renal insufficiency.	Proportion of alerts that led to an appropriate final drug order, overall rate of prescribing of 'drugs that should be avoided in older individuals with renal insufficiency.	This study found that a CDSS intervention designed to improve prescribing in older long term care residents with renal insufficiency can lead to improvement in several different aspects of prescribing. However it is reported that this intervention did not lead to an improvement in the rate at which physicians order dosages of particular medications which are deemed inappropriate in older individuals with renal insufficiency.

Key: RCT; Randomised controlled trial, CDSS; Computerised decision support software, DUR; Drug utilisation review, NH; Nursing home, NHR; Nursing home resident, PC; Primary care, ADE; Adverse drug event, PIM; Potentially inappropriate medication

1.9 Summary

Although the evidence to supporting the effectiveness of each of these different types of interventions appears somewhat mixed, there is little or no doubt that these approaches could potentially play a crucial role in reducing PIP, optimising patient care and minimising ADRs (14, 19-20, 57).

Chapter 2

2. Potentially inappropriate prescribing, 25 years on.

In this study, I was involved in developing the study's design. I was the lead researcher and I performed the review of the literature. I decided which studies were to be included based on the inclusion and exclusion criteria. I reviewed the 180 papers that were identified for inclusion and extracted all the relevant information as outlined below.

2.1 Introduction

Presently, approximately 7% of the world's population (506 million), is aged ≥65 years, with this forecasted to increase to approximately 14% (1.3 billion) by 2040 (5). Older individuals are a particularly vulnerable patient population and they display a marked heterogeneity in their health status. Older individuals commonly suffer from one or more acute and/or chronic disease states concurrently, which often necessitate the use of multiple concomitant medications (10-13). Advancing age is often complicated by a number of age-related physiological changes, which can lead to alterations in both the pharmacokinetic and pharmacodynamic profiles of many medications (15-16, 18). Prescribing of multiple concomitant medications in this fashion can potentially result in an individual being exposed to an increased risk of drug-drug interactions, drug-disease interactions, potentially inappropriate prescribing (PIP) and adverse drug reactions (ADRs). PIP is essentially the prescribing of (/or lack thereof) a particular medication for which the relative risks associated with its use (/or lack thereof) outweigh the potential benefits, especially when there are safer/as effective alternatives available (14, 18, 43, 48-49, 94, 125, 302-303).

The aim of this paper is to conduct a systematic review to summarise the available PIP criteria in order to provide an overview of the PIP prevalence in older individuals aged ≥60 years over the last 25 years.

2.1.1 PIP screening Tools

A number of different screening tools have been developed to evaluate prescribing appropriateness (**Table 2.1**). The criteria within these tools may incorporate explicit or implicit measures to assess prescribing appropriateness, with some using a combination of both (14, 20, 40, 57, 119, 126, 139, 141).

Explicit criteria are usually clearly defined statements of inappropriateness often developed from a variety of different sources, such as evidence-based guidelines, published reviews, expert opinion and consensus techniques. These criteria are usually drug or disease oriented, and typically require little or no clinical judgement in order to be effectively applied. They usually consist of lists of medications, doses of particular medications, drug-drug combinations and/or drug-disease interactions that should generally be avoided in specific patient groups (14, 38, 46, 62, 111, 118). Explicit criteria have been criticised for their limited transferability between different countries, due to variations in prescribing practices both at prescriber and national level. Another major limitation of explicit criteria is that they require regular revision and updating in order to remain up-to-date with evolving clinical evidence (15, 18, 23, 25, 40, 80, 215).

Implicit criteria are usually judgement-based; they require the healthcare professional to formulate a clinical judgement relating to the appropriateness or inappropriateness of a specific treatment, based on the patient-specific information and the available clinical evidence available to them. In contrast to explicit criteria, implicit criteria are usually patient centred as opposed to being medications or disease focused (14, 20, 41), however, these types of criteria can prove quite time-consuming to apply and are dependent on clinicians' knowledge and attitude and they are subject to differences of opinion.

A number of other reviews have been previously been published on PIP in older individuals, however the majority of these have used narrower search strategies and have focused on (i) older individuals in a specific care settings (10, 40, 234) or (ii) specific PIP criteria (98, 304).

2.1.2 Objectives

The objective of this systematic review was to quantify the extent of potentially inappropriate prescribing (PIP) in older individuals across different healthcare settings and different jurisdictions of care.

Table 2.1 Breakdown of each PIP criteria and the corresponding PIP/PPO prevalence reported with each criteria

Criteria, Publication Year	Country	Target Group	No. of criteria	Basis of Criteria	No. of studies	PIP/PPO prevalence
Drug Utilisation Review (DUR) criteria, 1989 [122-123]	United States	Not restricted to older adults	20 criteria	Based on a review of the guidelines and medications outlined in the 1988 Medicare Castrophic Coverage Act. The 2002 update was based on a review of the original 1989 criteria, the 1997 Beers criteria and the 1997 McLeod criteria.	2	19.2-21.3%
Beers 1991 criteria, 1991 [12]	United States	Nursing home residents aged ≥65	30 criteria	Based on a literature review (literature published in English between 1979 and 1990). Delphi consensus: 13 member expert panel.	6	9-40.3%
Medication Appropriateness index (MAI), 1992 [126]	United States	Developed in older individuals ≥65 years, but not restricted to older individuals	10 criteria	Based on a review published literature between 1982 and 1990. Clinical experience of the investigators.	9	44-96%
Lunn criteria, 1997 [127]	United Kingdom	Nursing home residents aged ≥65	18 criteria	Based on an extensive literature review. Consensus opinion: 4 member expert panel.	1	53%
Beers 1997 criteria, 1997 [125]	United States	Older individuals ≥65 years	28 criteria	Based on the Beers 1991 criteria Literature (published 1990–1995 in English). Delphi consensus: 6 member expert panel	49	3.3-70.0%
McLeod criteria, 1997 [114]	Canada	Older individuals ≥65 years	38 criteria	Based on the Beers 1991 criteria, a literature review (not defined exactly in the article), and the Canadians' national drug formularies. Delphi consensus: 32 member expert panel	5	3-41%
Phadke's Criteria, 1998 [128]	India	Not restricted to older adults	4 criteria	Derived from the clinical experience of the investigators.	1	
Assessment of Underutilization (AOU) criteria, 1999 [132]	United States	Older individuals ≥65 years	26 criteria	Derived from the clinical experience of the investigators.	3	37-64%
Improving Prescribing in The Elderly Tool (IPET), 2000 [129]	Canada	Older individuals ≥70 years	14 criteria	Based on a review of the most common instances of PIP as defined by the McLeod's criteria encountered in routine practice (not independently validated).	6	9.3-27.4%
French list of inappropriate medications criteria, 2001 [131]	France	Older individuals ≥65 years	24 criteria	Derived from the 1997 Beers criteria and the consensus opinion of 9 member expert panel.	3	25.4-66.0%
Zhan criteria, 2001 [130]	United States	Older ambulatory individuals ≥70 years	33 criteria	Based on a subset of 33 drugs from Beers 1997 criteria (drugs potentially inappropriate irrespective of dose, frequency of administration, or duration). Delphi consensus: 7 member expert panel.	8	3.7-31%
Assessing Care Of Vulnerable Elders (ACOVE) criteria, 2001 [133-134]	United States	Older individuals ≥65 years	236 indicators, 68 of which relate to the issue of PIP	Derived from a systemic review of the published literature, expert opinions and guidance from specialist expert groups.	2	34.7-78%
Beers 2003 criteria, 2003 [111]	United States	Older individuals ≥65 years	68 criteria	Based on the Beers 1997 criteria Literature (published in English 1994–2000). Delphi consensus: 12 member expert panel.	93	2.8-63.8%

Criteria, Publication Year	Country	Target Group	No. of criteria	Basis of Criteria	No. of studies	PIP/PPO prevalence
Rancourt criteria, 2004 [94]	Canada	Older individuals ≥65 years in long term care	111 criteria	Based on the Beers criteria (1991, 1997, and 2003), McLeod criteria and IPET. Review panel: 4 member expert panel.	1	54.7%
Swedish Prescribing Indicators, 2004 [135]	Sweden	Older individuals ≥65 years	33 criteria	Based on a review of the Beers 1997 and Beers 2003 criteria.	1	74.0%
Healthcare Effectiveness Data and Information Set (HEDIS) criteria, 2006 [155]	United States	Older individuals ≥65 years	42 criteria	Based on the Beers criteria ID 2003. Derived from the experience/opinions of an expert review panel.	5	5.6-38.8%
Australian National Prescribing Service (NPS) indicators, 2006 [136]	Australia	Not restricted to older adults	21 indicators	Based on a comprehensive review of the literature and structured focus groups. Derived from the experiences of GPs, other healthcare professionals, consumers and policy makers.	1	16%
Drug Burden Index (DBI), 2007 [138]	United States	Not restricted to older adults	N/A	The DBI evaluates prescribing appropriate based on the calculated the overall cumulative effects of medications with anticholinergic or sedative effects.	1	39.8-60.5%
La Roche French consensus criteria, 2007 [89]	France	Older individuals ≥75 years	34 criteria	Based on a review of the Beers criteria, the McLeod criteria, the 2001 French IM criteria and guidelines of the French Medicine Agency. Delphi consensus: 15 member expert panel.	2	21.9-31.6%
Screening Tool of Older Person's Prescriptions (STOPP), 2008 [38]	Ireland	Older individuals ≥65 years	65 criteria	Based on a systematic review of the literature. Clinical experience and expertise of the investigators. Delphi consensus: 18 member expert panel.	21	13.3- 79.0%
Screening Tool to Alert doctors to Right Treatment (START), 2008 [38]	Ireland	Older individuals ≥65 years	22 criteria	As with the STOPP criteria the START criteria are based on a systematic review of the literature. Clinical experience and expertise of the investigators. Delphi consensus: 18 member expert panel.	14	11.2- 74.0%
Australian Prescribing Indicators, 2008 [139]	Australia	Older individuals ≥65 years	48 criteria	Based on a review of Australian prescribing practices derived from the Australian Pharmaceutical Benefits Scheme in 2006. Derived from the most common encountered medical conditions in Australians aged 65 and older.	1	95.0%
Norwegian General Practice (NORGEP), 2009 [140]	Norway	Older individuals ≥70 years in general practice	36 criteria	Based on the Beers criteria (1991, 1997 and 2003), a literature review and the clinical experience of the investigators. Delphi consensus: 47 member expert panel.	2	22.6-36.8%
Priscus List, 2010 [39]	Germany	Older individuals ≥65 years	83 criteria	Based on the Beers criteria (1991, 1997 and 2003), French 2007 and the STOPP criteria. Recent review of the literature. Delphi consensus: 38 member expert panel	1	25-28.3%

Key: HEDIS; Healthcare Effectiveness Data and Information Set, MAI, Medication Appropriateness Index, AOU; Assessment of Underutilization, DUR; Drug Utilisation Review, NPS; National Prescribing Service, STOPP; Screening Tool of Older Person's Prescriptions, START; Screening Tool to Alert doctors to Right Treatment (START). PIP; Potentially Inappropriate Prescribing, PIM; Potentially Inappropriate Medication, PPO; Potential Prescribing Omission , ACOVE; Assessing Care of Vulnerable Elders

2.2 Methods

2.2.1 Data Sources and Search Strategy

An initial search of the EMBASE, Medline (through OVID) and PubMed databases was performed to establish a list of the most commonly used PIP/PPO screening tools. These databases were then systematically reviewed for any relevant studies which have reported on PIP prevalences in older individuals in primary, secondary and long term care between January 1988 and March 2013. The following search terms were used, (Beers Criteria) OR (STOPP Criteria) OR (START Criteria) OR (HEDIS) OR (Zhan criteria) OR (IPET) OR (McLeod Criteria) OR (AOU) OR (ACOVE) OR (MAI) OR (French Consensus Criteria) OR (Australian Criteria) OR (Priscus) OR (NORGEP) AND ((Elderly) OR (Aged)) AND ((inappropriate prescribing) OR (prescribing omissions)). The search of the databases was performed in March 2013.

The references of the relevant papers were subsequently reviewed to identify any relevant papers that were not captured from the initial search. Abstracts and conference proceedings were also excluded from this review. All retrieved papers were initially reviewed for duplicates between the different databases then title, abstracts and the full article were reviewed for relevance.

2.2.2 Inclusion Criteria

Selected papers were assessed against the following inclusion criteria: (i) patients ≥60 years, (ii) reported on PIP or PPO prevalence, (iii) published in English. Studies published only as abstracts were excluded. **Figure 2.1** below outlines the process.

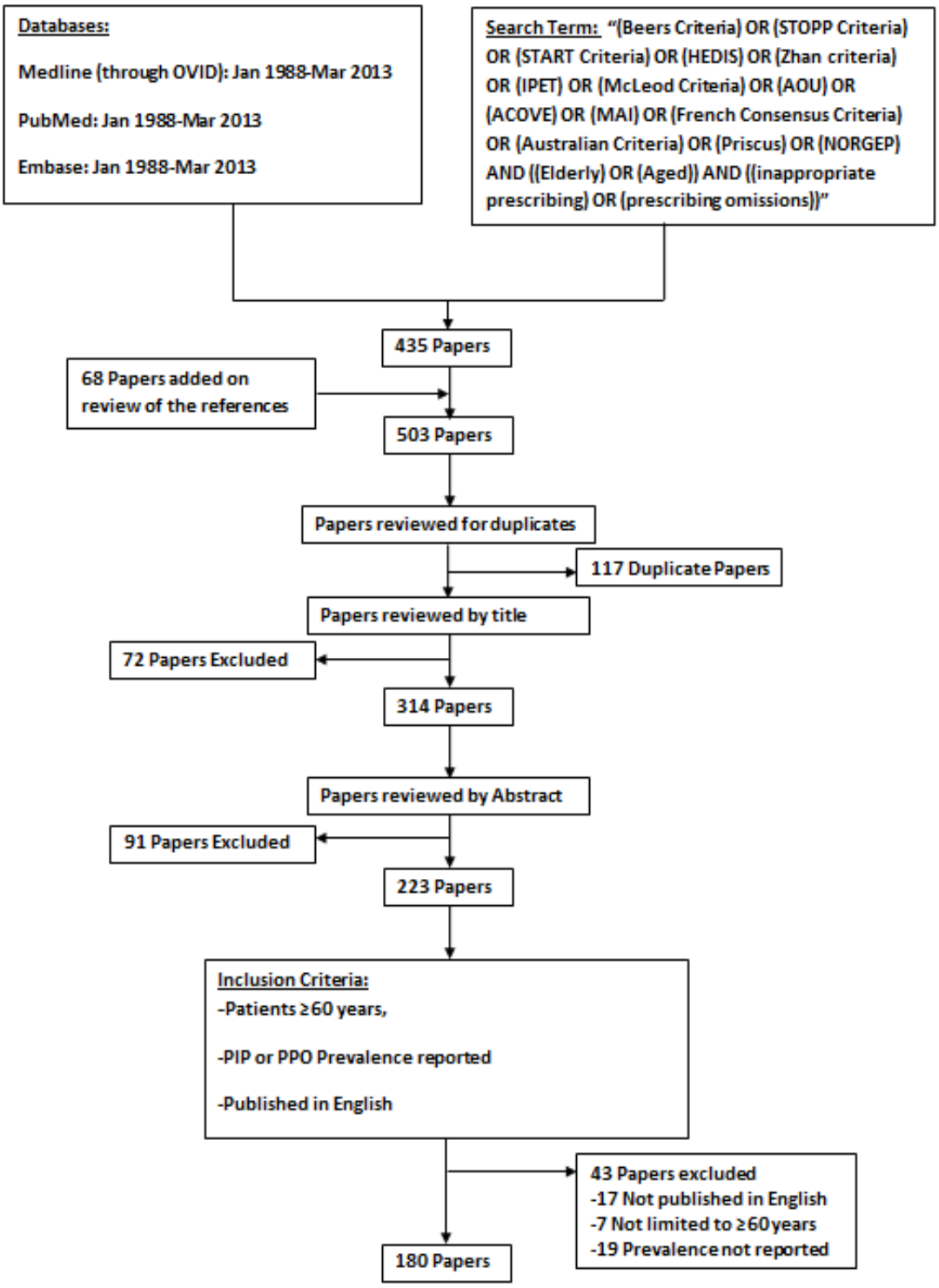


Figure 2.1 Schematic diagram of Literature Search

2.3 Results

This review subdivides the studies down by jurisdiction, setting of care and criteria employed, in order to (1) give a detailed, easy to navigate summary of PIP prevalence and (2) enhance comparability with other studies in the future.

2.3.1 PIP Prevalences

Over the last 25 years, a number of studies have reported on PIP prevalence determined by a variety of different tools across a number of different jurisdictions and healthcare settings (**Electronic Appendix Tables 2.3-2.39**).

This literature review identified 180 papers which have reported on PIP prevalence. These papers reported on 24 different PIP screening tools. These tools were applied to datasets of varying size, ranging from as low as 53 to as high as 8,213,147 older individuals, located across three main healthcare settings, primary care (community-dwelling), secondary care (hospital) and long term care (residential homes, nursing homes and community hospitals). This review identified PIP prevalences of 2.8-96% and PPO prevalence of 11.2-65%.

A number of other reviews have been previously been published on PIP in older individuals, however the majority of these have used narrower search strategies and have focused on (i) older individuals in a specific care settings (10, 40, 234) or (ii) specific PIP criteria.

2.3.2 Setting of Care

2.3.2.1 Primary Care

In the primary care setting, 64 studies examined PIP prevalence and reported prevalences of 9.0 to 94.3%. Three studies included in the review examined PPO in primary care and have reported prevalences of 22.7-64% (**Electronic Appendix Table 2.4**).

2.3.2.2 Secondary Care

Sixty three studies examined PIP in secondary care and reported prevalences of 3.7-96%. Nine studies included in the review examined PPO in secondary care and reported prevalences of 11.2-65.0% (**Electronic Appendix Table 2.5**).

2.3.2.3 Long term Care

Twenty nine of the studies in the long term care (LTC) setting examined PIP and have reported prevalences of 2.8-79.0%. Three studies included in the review examined PPO in LTC setting and reported PPO prevalences of 42.2-74 (**Electronic Appendix Table 2.6**).

2.3.3 Jurisdiction

2.3.3.1 United States

The majority of the studies examining PIP prevalence have been undertaken in the US (n=70), with PIP prevalences of 4.2-91.9% being reported in this jurisdiction. Four US based studies examined PPO prevalence, with prevalences of 35.0-64.0% being reported (**Electronic Appendix Table 2.8**).

2.3.3.2 Europe

Sixty eight European studies (n=68), have also examined PIP and have reported prevalences of 2.8-96.0%. While 13 European studies examined PPO and have reported prevalences of 11.2-74.0% (**Electronic Appendix Table 2.9**).

2.3.3.3 Asia

Twenty five studies have examined PIP in Asia, with PIP prevalences of 7.0-70.0% being reported and 1 study has reported on PPO prevalence in this jurisdiction, with a prevalence of 41.9% being reported (**Electronic Appendix Table 2.10**).

2.3.3.4 Australia

Six studies from Australia have examined PIP prevalence and have reported prevalences of 16-60.5%, no study from Australia reported on PPO prevalence (**Electronic Appendix Table 2.11**).

2.3.3.5 Canada

Four studies from Canada have reported PIP prevalences of 12.5-54.7%, no studies from this jurisdiction have reported on PPO (**Electronic Appendix Table 2.12**).

2.3.3.6 Africa

Two studies from Africa have reported on PIP prevalence with prevalences of 11.4-30.0% being report, no studies from Africa examined PPO prevalence (**Electronic Appendix Table 2.13**).

2.3.3.7 South America

Only one study examining PIP was included in this review was from South America with a PIP prevalence of 34.5% being reported, no studies examining PPO in South America were included in the review (**Electronic Appendix Table 2.14**).

2.3.4 PIP/PPO assessment tools

A number of different tools or modifications of these tools have been used to examine PIP and PPO prevalence across different healthcare settings. The PIP/PPO prevalences corresponding to each of these assessment tools are outlined in **Table 2.1** and **Electronic Appendix Table 2.3-2.39**.

2.3.5 Intervention Studies

Of the 180 studies include in this review, 10 (5.6%) studies reported on some type of intervention strategy being used to improve appropriateness of prescribing (**Table 2.2**). All ten of the studies, reported that the interventions produced a positive effect on the appropriateness of prescribing. Of the ten studies, three used a randomised controlled design, while the other seven used the intervention group prior to the intervention as their baseline for prescribing appropriateness.

Three of the studies used a multidisciplinary team approach to optimise prescribing appropriateness (254, 305-306). While five of studies used a pharmacist-led medication review approach (118, 271, 307-309), one of the studies used a nurse-led medication review approach (310), and utilised the knowledge and expertise of a research physician to try and improve prescribing appropriateness (177).

Two of the studies used the 2003 Beers criteria as the intervention tool (309, 311), while two others used the 1997 Beers criteria (271, 307), with another using the STOPP/START criteria (312) and another using the IPET criteria (306).

In terms of outcome measures, two studies used the 2003 Beers criteria (309, 311), four used the 1997 Beers criteria (118, 254, 271, 307), two used the STOPP/START (305, 313), three used the MAI (118, 308, 313), one used the ACOVE criteria (118), one used the AOU criteria (313) and one used the IPET criteria (306).

Of the ten intervention studies, five of these studies used the same set of criteria as their intervention tool and their primary outcome measure (271, 306-307, 309-310) (**Table 2.2**).

Table 2.2 Summary of Intervention Studies

Study	Study design	Intervention description	Outcome measure	Outcome
Spiker *et al.* (United States 2001) (307)	Cross-sectional study, 146 patients, 6 primary healthcare clinics, PC, **pharmacist intervention.**	A clinical pharmacist carried out a medication review using a modified version of the 1997 Beers criteria to define prescribing appropriateness. Based on this review, written recommendations were then communicated to each patients prescribing physician	Appropriateness of the prescribing as defined by the 1997 Beers criteria.	This study found that 35.6% of the patients had at least one potentially inappropriate medication with the potential to cause an adverse drug event. Recommendations were made on 60% of these potentially inappropriate prescribing instances with 60% of these recommendations being accepted by the patient's physicians.
Gill *et al.* (Canada, 2001)(306)	Before and after study, 355 patients, 1 long term care facility, LTC, **multidisciplinary team intervention.**	A multidisciplinary team made up of a geriatrician, a family physician and a pharmacist conducting a medication review using the IPET criteria. Based on this review, written recommendations were then communicated in writing to each patients prescribing physician	Appropriateness of prescribing as defined by the IPET criteria.	This study found that patients seen by the multidisciplinary team had significantly fewer instances of potentially inappropriate prescribing (P<0.001). It was reported that 37.9% of the instances of potentially inappropriate prescribing that were intervened on were changed for safer alternatives. The follow-up letters were rated as "somewhat" or "very" helpful by 92% of the physicians.
Rhoads *et al.* (United States, 2003)[271]	Prospective case series, 456 patients, 1 assisted living facility, LTC, **pharmacist intervention**	A consultant pharmacist conducted a medication review, identified any PIMs and faxed a list of recommendation letters to the physician	Prevalence of PIP based on Beers criteria and physician acceptance rate of recommendations	This study found that 31.6% of the residents had one or medication considered potentially inappropriate and 16.7% of these instances were discontinued and 2.5% were changed to lower dosages post the pharmacist's intervention.
Saltvedt *et al.* (Norway, 2005)[254]	RCT, 254 patients, 1 hospital, SC, **multidisciplinary team intervention.**	Multidisciplinary geriatric team approach delivered in a geriatric evaluation and management unit	Inappropriate drug prescribing according to Beers criteria	This study found that the proportion of patients with polypharmacy did not differ significantly between the intervention and the control group. While a significant difference was reported between the median number of scheduled medications withdrawn per patient between the intervention and the control group (p=0.005). There was no significant difference in the proportion of patients that had an improvement in prescribing appropriateness as defined by Beers, from admission to discharge between the intervention and the control groups (6% in the intervention vs. 3% in the control).
Spinewine *et al.* (Belgium, 2007)[118]	RCT, 203 patients, 1 acute care of the elderly ward, SC, **pharmacist intervention.**	Clinical pharmacist provided pharmaceutical care provided from admission to discharge in patients in a geriatric evaluation and management unit	Appropriateness of prescribing as defined by the MAI and ACOVE	This study found that intervention patients in the intervention group were significantly more likely to exhibit improvement in the appropriateness of prescribing as defined by the MAI and ACOVE underuse criteria compared with the patients in the control group from admission to discharge (odds ratio (OR)=9.1, 95% confidence interval (CI)=4.2-21.6 and OR=6.1, 95% CI=2.2-17.0, respectively). Bothe groups had comparable improvements in terms of the Beers criteria. This study also found that at 12 months there was no difference in the rates of emergency visits, hospital readmission or mortality.

Study	Study design	Intervention description	Outcome measure	Outcome
Bergkvist *et al.* (Sweden, 2009)[308]	Non-randomised prospective controlled study, 43 patients, 1 hospital, SC, **pharmacist intervention.**	Introduction of a clinical pharmacist conducting a medication review at admission. Any drug related problems identified during this review were communicated to the medical team.	Appropriateness of prescribing as defined by the MAI.	This study found that there was a significant decrease in the number of inappropriate medications prescribed in the intervention group compared with the control group (p = 0.049). This study also found that there were no differences in the change in mean MAI-score between the groups during hospital stay (P = 0.335) or from admission to 2 weeks after discharge (P = 0.326).
Blozik *et al.* (Switzerland, 2010)[311]	Before and after study, 181 patients, 1 nursing home, LTC, **nurse intervention.**	The intervention involved a medication review based on a Swiss adaptation of the Beers criteria coupled with a staff training session.	Appropriateness of prescribing as defined by a Swiss adaption of the 2003 Beers criteria	This study found that the prevalence of potentially inappropriate prescribing decreased from 14.5% prior to the intervention to 2.8% post-intervention (relative risk [RR] = 0.2; 95% CI 0.06, 0.5). This study also found that there was a non-significant increased risk of a patient being prescribed a potentially inappropriate medication after one year compared with post intervention (RR = 1.6; 95% CI 0.5, 6.1).
Lang *et al.* (Switzerland, 2011)[314]	Non-randomised prospective before after study, 150 patients, 1 hospital, SC, **multidisciplinary team intervention.**	A multidisciplinary team approach involving a geriatrician and psychiatrist.	Appropriateness of prescribing as defined by the STOPP and START criteria	This study found that the intervention resulted in a significant reduction in the total number of medications prescribed between admission and discharge (1347 vs. 790; P < .0001) and that there was a significant reduction in both the incidence rates for potentially inappropriate prescribing (77% vs. 19%; P < .0001) and potential prescribing omission (65% vs. 11%; P < .0001) during the same period.
Dunn *et al.* (United States, 2011)[309]	Non-randomised prospective before and after study, 120 charts, 1 medical centre, PC, **pharmacist intervention.**	A clinical pharmacist conducted a medication review using the Beers 2003 criteria. Any recommendations were then communicated to the patient's physicians.	Appropriateness of prescribing as defined by the Beers criteria.	This study found that the intervention resulted in a significant reduction in the mean number of potentially inappropriate medications prescribed per patient between admission and follow-up (0.52 (±0.84) vs. 0.45 (±0.78), 95% CI 0.067, 0.006-0.013; p=0.032). Post-intervention the patient's physicians had discontinued 12.7% of the medications identified as potentially inappropriate.
Gallagher *et al.* (Ireland, 2011)[177]	RCT, 400 patients, 1 hospital, SC, **physician intervention.**	A trained physician conducted a medication review using the STOPP/ START criteria to define prescribing appropriateness. The interventions were then communicated to the prescribing physicians in oral and in written format.	Appropriateness of prescribing as defined by the medication appropriateness index (MAI) and the assessment of underutilization (AOU) criteria	This study found that the intervention produced a significant reduction in unnecessary polypharmacy, prescribing of medications at incorrect doses, and potential drug-drug and drug-disease interactions in the intervention group at discharge compared with the controls, with 71.1% of the intervention compared with 35.4% of the control group showing and improvement in their MAI scores (absolute risk reduction 35.7%). The intervention also resulted in a reduction in the underutilisation of clinically indicated medications, with 31.6% of the interventions compared with 10.4% of the controls showing an improvement in the AOU scores (absolute risk reduction 21.2%). These significant improvements in terms of the MAI and the AOU were maintained for up to 6 months post discharge.

Key: PC; Primary care, SC; Secondary care. LTC; Long term care, STOPP; Screening Tool of Older Person's Prescriptions, START; Screening Tool to Alert doctors to Right Treatment, MAI; Medication Appropriateness Index, ACOVE; Assessing Care Of Vulnerable Elders, AOU; Assessment of Underutilization, IPET; Improved prescribing in the Elderly Tool , PIM; Potentially inappropriate medications, PIP; potentially inappropriate prescribing, RCT; Randomised controlled trial.

2.4 Discussion

In the last 25 years, PIP in older individuals has come under considerable scrutiny and a number of PIP screening tools have been developed to try and quantify and resolve this issue. Despite the increased attention on the matter, PIP still remains highly prevalent across all healthcare settings.

The findings of this review are consistent with the existing literature, which indicates, that as the complexity of care increases i.e. PC to LTC, so too does the prevalence of PIP. This finding was not unexpected, as older individuals in SC and LTC are usually sicker and frailer than their community dwelling counterparts. This increased level of co-morbidity usually necessitates the prescribing of increasing number of medications and a number of studies have shown an association between the number of medications and PIP.

In this review there was a marked variation in the PIP prevalences reported, this may be attributable to a number of reasons; (i) differences in prescribing practices/approaches to prescribing between care setting, countries and jurisdictions, (ii) differences in both the number of and/or types of criteria utilised in the screening tools, (iii) difference in the availability of certain medications between countries and jurisdictions and (iv) difference in the methodologies employed in the different studies. Aside from these differences, one fact that still remains constant is that across all care settings and jurisdictions, PIP is highly prevalent and appears to be as, if not more prevalent now as it was 25 years ago. This may be due to the fact that detection of PIP is far superior now, however if detection has progressed so much, one must ask the questions (i) what is being done to resolve each of the individual

instances of PIP which are being detected and (ii) why have the interventions to combat PIP not advanced to the same extent.

The screening tools appear to be effective at highlighting PIP, but there appears to be very little research relating to their impact on resolving the issue of PIP. In this review, less than 10% of the studies included, focused on the development of appropriate intervention strategies to try and reduce PIP. Maybe future work should concentrate less on PIP prevalence and more on developing viable/efficient intervention strategies to prevent/reduce PIP.

2.4.1 Limitations

There are a number of limitations associated with this review, the 180 studies that were included in this review, were undertaken in a variety of different healthcare settings and across seven different jurisdictions. Due to the heterogeneity between the studies in terms of design, sample population, prescribing practices, drug availability and outcome measures, it was not possible to directly compare each of the studies.

A small number of the studies included in this review were interventions, with the majority of these studies being observational in design. For the majority of the studies, the sample size was quite small however there was a wide variation in the number of individuals included, with the sample size reported to range from 53 to 8,213,147.

Twenty four different criteria were used throughout the 180 studies, however, modified or truncated version of these criteria were also often used, therefore further limiting the comparability between the studies, even the ones that reported using the same criteria.

Recruitment and sampling methodologies varied considerably between the studies, with some studies reporting that they consecutive sampling/recruitment, some using randomisation and other studies on large pharmacy claims dataset which employed no sampling methodology at all.

These limitations should be borne in mind when interpreting the results. This study tried to capture as many papers as possible, but it is acknowledged that it was not possible to capture every paper relating to PIP prevalence.

2.5 Conclusion

This review provides an overview of PIP prevalences over the last 25 years. It is intend to be an updated, robust reference source of international PIP prevalence. This review also examined the small number of interventional type studies which focus on addressing the issues relating to PIP. The limited amount of interventional type studies found in this review, further highlights the need for future research to focus less on PIP prevalence and more on interventional strategies to improve prescribing appropriateness, which would in turn hopefully lead to a reduction in ADR, healthcare utilisation and medication related morbidity and mortality.

Chapter 3

3. A Prevalence Study of Potentially Inappropriate Prescribing in Long Term Care Residents: An Irish Perspective

In this study, I was involved in the development of the study's design, the drafting of the research proposal and the application for ethical approval. I was the lead researcher in this study and undertook the data collection for the 732 patients. I applied the different PIP criteria to the data of the 732 patients and I undertook all of the statistical analysis in this study.

3.1 Introduction

Potentially inappropriate prescribing (PIP) is defined as the prescribing of a pharmacotherapy for which the potential risks of use outweigh the potential clinical benefits. It may involve prescribing of a potentially inappropriate medication (PIM) or the prescribing of a medication where a safer but equally effective alternative is available (12, 94, 302). PIP also encompasses the omission of any potentially beneficially medications which are clinically indicated and for which no clear contraindication exists (38, 177).

It has been reported that 11% of the Irish population is 65 years or older, and that 4.6% of older Irish individuals reside in long term care (LTC) facilities, which comprise nursing and residential homes (315). Furthermore these percentages are expected to rise (8, 315-316). Older individuals residing in LTC facilities are generally considered to be a vulnerable population. They are often more frail and exhibit a higher degree of physical, functional and cognitive dependency when compared to their community-dwelling counterparts (13, 302, 317) which usually results in these individuals being prescribed more medications than older individuals in the community (10-13, 317).

Recently, prescribing practices in LTC facilities have come under considerable scrutiny, with concerns being raised about the appropriateness of prescribed medications to this population (10-11, 59, 302, 318).

A number of different screening criteria have been developed to evaluation prescribing appropriateness. These criteria incorporate either explicit or implicit measures of prescribing but some utilise a combination of both.

Explicit criteria are usually clearly defined statements of inappropriateness often developed from a variety of different sources, including evidence-based guidelines, published reviews, expert opinion and consensus techniques. These criteria are usually drug or disease oriented, and typically require little or no clinical judgement in order to be effectively applied. They usually comprise lists of medications, certain doses of particular medications, certain drug-drug combinations and/or certain drug-disease interactions that should be avoided (14, 38, 46, 62, 111, 118). Explicit criteria have come under criticism for having limited transferability between different countries, due to variations in prescribing practices both at prescriber and national levels. A further major limitation of explicit criteria is that they require regular review and updating so as to remain current with evolving clinical evidence (15, 23, 38, 120).

In contrast, implicit criteria are usually judgement-based. The healthcare professional uses patient-specific information and the available clinical evidence to formulate a clinical judgement relating to the appropriateness or inappropriateness of a specific treatment. In contrast to explicit criteria, implicit criteria focus on the

patient as opposed to the drugs or the disease process. However, it can prove quite time- consuming to apply as it is dependent on clinicians' knowledge and attitude, which can often be subject to differences of opinion.

Two sets of criteria have gained international recognition, i.e. Beers criteria (12, 111, 125) and "Screening Tool of Older Person's Prescriptions" (STOPP) (38).

The Beers criteria was the first set of criteria developed to assess PIP in older individuals and it was originally developed in 1991 (12) and were revised and updated on several occasions, in order to make them more generalisable to all elderly patients, independent of their level of frailty or setting of care (15, 18, 81, 111, 125).

To date the 2003 version of Beers is the most cited version in published literature, and this version of the criteria was used in this study (111). The criteria consist of two lists of PIP criteria, (i) consisting of twenty criteria relating to medications which are deemed potentially inappropriate for use in an individual suffering from a specific condition i.e. considering diagnosis (CD) and (ii) consisted of forty eight criteria relating to medications which are deemed potentially inappropriate regardless of co-morbidity i.e. independent of diagnosis (ID) (111).

A number of studies have used the Beers criteria to assess PIP in older individuals across different settings of care, with prevalence as high as 49% being reported in community-dwelling individuals, 56% in older individuals in secondary care and 55% in LTC (13-14, 18, 23, 48, 68, 70, 81, 94, 120, 177, 319-337).

A number of studies have highlighted a range of limitations relating to the Beers criteria applicability and reliability outside of the US (38, 46, 91, 100, 177, 338). These limitations relate to the Beers criteria failure to address instances of potentially inappropriate (i) drug-drug interactions, (ii) therapeutic duplication, (iii) under prescribing, while also the criteria have been criticised for its designation of certain medications as always inappropriate in older individuals i.e. amiodarone, nitrofurantoin, amitriptyline and doxazosin (38, 46, 91, 100, 177, 338).

In 2008, a new set of PIP criteria known as the STOPP criteria were developed and validated for use in an Irish and European care setting (38). The STOPP criteria were based on the most up-to-date clinical relevant evidence. The STOPP criteria consist of 65 explicit criteria, outlining instances where certain medications/medication classes are deemed potentially inappropriate. These criteria were designed to incorporate the most common encountered instances of PIP which arise in older individuals (38, 46, 91, 100, 120, 177).

A number of recent studies have used the STOPP criteria to assess PIP prevalence across different setting of care settings, i.e. primary and secondary care, with a prevalence as high as 36% being reported in older individuals in primary care (91) and a prevalence as high as 77% being reported in secondary care (338).

In 2008, our research group carried out a pilot study which retrospectively examined the prevalence of PIP in 313 older individuals residing in six LTC facilities in the greater Cork area. This study reported that 59.8% of the residents had at least one instance of PIP as defined by STOPP (318).

In order to ensure both the accuracy and generalisability of the prevalence reported in this pilot study, it was felt that a larger study in a LTC population in the greater Cork area was needed, in which data collection would be conducted by a postgraduate researcher using a specially formulated electronic proforma as opposed to the methodology used in the previous study, in which data were collected by three undergraduate student researchers, using a paper based data collection proforma. This would clarify the true prevalence of instances of PIP in LTC facilities and identify the most applicable PIP screening tool, prior to the design and implementation of a more robust pharmaceutical care intervention in this population.

3.1.1 Aims

The aims of this study were (1) to conduct a prevalence study of PIP in LTC facilities in the greater Cork area by applying both the STOPP and the Beers criteria, (2) to evaluate the applicability of STOPP criteria and Beers criteria in the Irish LTC population and compare the prevalence of PIP obtained using these two screening tools and, (3) to investigate the association between the occurrence of PIP as determined by STOPP and Beers criteria and number of drugs prescribed, age, gender and Charlson Co-morbidity Index (CCI) score.

3.2 Methods

3.2.1 Study population

Fifteen publicly funded LTC facilities (including nursing homes and long stay community hospitals) in the greater Cork area were invited to participate in the study; fourteen of these agreed to take part. The 15 LTC facilities approached to participate in this study represented all of the publically funded facilities located in the greater Cork region.

These facilities care for older individuals who suffer from an array of multiple co-morbidities and who exhibit varying levels of dependency. In regards to the capacity of the facilities, there was some variability in the number of resident beds per facility, i.e. bed capacity range from 22 to 153 beds. There was a degree of variability in staffing levels (i.e. nurses and care assistants), however the exact number of staff members was not recorded in this study. While all facilities were under the medical supervision of a consultant geriatrician who visited on a monthly basis, facilities varied in terms of additional access to medical services, with some facilities indicating that they had daily visits from a medical practitioner, while others hade bi-weekly or weekly visits. In all facilities, emergency access to medical services was available if required. The physicians caring for the residents in these facilities were usually allocated to the residents at the point of admission, however in certain situations the physicians that care for an individual in the community continued to care for that individual after admission into the facility.

In the 14 LTC facilities that agreed to participate in the study, there were a total of 867 resident, 732 (84.4%) of whom were eligible for inclusion. All participants in the study were aged ≥65 years. Terminally ill residents and residents receiving respite care were excluded from the study, because their medication lists did not, in general, reflect their stable, longer-term prescription orders.

Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals and University College Cork, Cork Ireland. As this was an observational study, patient specific consent was not required, however consent was sought and by each of the LTC facilities that participated in the study.

3.2.2 Data collection

The medical records and medication prescription Kardex details of all eligible older individuals residing in the participating facilities were reviewed at one time point. Data collection took place between December 2009 and September 2010. A database was developed using Microsoft Access™ based on a proforma which was designed and developed by the Department of Geriatric Medicine, Cork University Hospital, and the Schools of Pharmacy at University College Cork (UCC) and Queen's University Belfast (QUB).

Data collection took approximately 25 minutes per patient. Details of residents' demographics, medical co-morbidities, blood pressure, heart rate, complete blood count and serum biochemistry were extracted from their medical and nursing records where available. All data were anonymised at the point of data collection. If necessary, additional resident-related information which was not available in the

clinical records was gathered from a consultation with the nursing staff, the attending medical officer or the clinical pharmacist within each LTC facility.

Medication data including name, dose, frequency and total number of medications, were recorded from the most recent medication Kardex. Both regular and 'as required' / *pro re nata* (PRN) prescription medications were recorded to ensure comprehensiveness of the medication data collection. All medications were supplied by prescription only, so non-prescription/over-the-counter medications were not considered in this study.

Medications were coded according to the World Health Organisation's Anatomical Therapeutic Chemical (ATC) classification system (339) and all medical diagnoses were coded according to the International Classification of Diseases, 10th edition (ICD-10), second level (340). Co-morbidity burden was quantified using the Charlson Co-morbidity index (CCI), which is a weighted score that address both number as well as severity of commonly occurring co-morbid conditions (35, 341). For this study polypharmacy was defined as >5 medications (41, 43).

3.2.3 Potentially Inappropriate Prescribing

To assess the potential appropriateness of the medications being prescribed, two sets of PIP screening criteria were applied to patient data; The full set of STOPP criteria (n=65) (38) and the full set of Beers criteria ID and CD (n=68) were applied to the medication profiles of the 732 residents (111). These tools were applied by the postgraduate researcher, who was experienced in the application of each of the screening tools. The application of tools took the researcher approximately 3-4 minutes per patient.

3.2.4 Data analysis

Statistical analysis was performed using PASW (Predictive Analytics SoftWare) (SPSS Inc. Chicago, Illinois, USA) version 18.0. The data were determined to be non-parametric (not normally distributed) based on a review of skewness and kurtosis of the distribution histograms, a review of the box plots, and by performing Kolmogorov-Smirnov and Shapiro-Wilk tests for age and number of medications.

Tests of association were performed using a chi-square test and multivariate logistic regression analysis to assess the impact of a number of variables such as gender, age, and number of medications on occurrence of PIP as defined by both sets of criteria. Based on a review of the literature the following variables were chosen for inclusion in the model: age, gender, CCI score and number of medications, as these variables were most commonly cited as being associated with the occurrence of PIP (69-70, 93, 100, 320, 322, 333, 338, 342-345). Specific disease states or medication classes were not included in the model as it was deemed that the model was not sufficiently powered to include all of these variables and inclusion of such variables may have resulted in multiple comparisons. A probability value of $p < 0.05$ was considered statistically significant for all tests.

3.3 Results

3.3.1 Demographics

A total of 732 residents were recruited from the 14 participating LTC facilities. The median age (IQR) of the residents was 86 (80-91) years and 70.2% of the residents were female. The median CCI score was 1 (IQR1-3). The background demographic details and the ten most prevalent disease states affecting residents are listed in **Table 3.1**.

Table 3.1 Background patient demographic details (n=732).

Variable	Total (732)	Men (218)	Women (514)
Mean age [±SD]*	83.9 [±7.7]	80.6 [±7.1]	85.3 [±7.6]
Age range*	65-102	65-97	65-102
Median age*	85	81	86
IQR age range*	79-89	75-86	80-91
Age groups			
65-74 years (%)	98 (13.4)	45(20.6)	53 (10.3)
75-84 years (%)	266 (36.3)	103 (47.3)	163 (31.7)
≥85 years (%)	368 (50.3)	70 (32.1)	298 (58.0)
Medical Conditions/Problems			
Hypertension (%)	340 (46.5)	94 (43.1)	246 (47.9)
Dementia/long term cognitive impairment (%)	315 (43.0)	80 (36.7)	235 (45.7)
Incontinence (%)	245 (33.5)	71 (32.6)	174 (33.9)
Cerebral Vascular Accident (CVA) (%)	234 (32.0)	81 (37.2)	153 (29.8)
Depression (%)	231 (31.6)	44 (20.2)	187 (36.4)
Osteoarthritis (%)	209 (28.6)	53 (24.3)	156 (30.4)
Chronic constipation (%)	205 (28.0)	67 (30.7)	138 (26.9)
Agitation (%)	193 (26.4)	52 (23.9)	141 (27.4)
History of fractures (%)	192 (26.2)	37(17.0)	155 (30.2)
Atrial fibrillation (%)	161 (22)	57 (26.1)	104 (20.2)

Key: SD; Standard Deviation, IQR; Inter quartile range, CVA; Cerebrovascular accident. *Calculated in years

The median number of prescription medications per resident was 11 (IQR 9–14), when PRN medications were included and 8 (IQR 6-10) when they were excluded (**Table 3.2**). Polypharmacy was prevalent in just over three-quarters of residents (77.2%).

Table 3.2 Frequency of medications prescribed for residents (n=732).

Medications	Total (732)	Men (218)	Women (514)
Number of prescribed medications	8325	2468	5857
Median (IQR)	11 (9-14)	12 (8-13)	11 (9-14)
Mean [±SD]	11.4 [±3.7]	11.3 [±3.7]	11.4 [±3.7]
Range	2-25	2-24	3-25
Number of regular medications	5902	1807	4095
Median (IQR)	8 (6-10)	8 (6-10)	8 (6-10)
Mean [±SD]	8.1 [±3.2]	8.3 [±3.2]	8.0 [±3.2]
Range	0-18	1-17	0-18
Number of "PRN*" medications	2423	661	1762
Median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)
Mean [±SD]	3.3 [±2.0]	3.0 [±1.7]	3.4 [±2.1]
Range	0-12	0-9	0-12

Key: SD; Standard Deviation, IQR; Inter quartile range, PRN; as required / *pro re nata*/ as needed

3.3.2 Identification of PIP using the Screening Tool of Older Person's Prescriptions (STOPP)

When the full set of STOPP criteria were applied a total of 1,280 instances of PIP relating to 1,140 PIMs (13.7 %) in 518 residents (70.8 %) were identified. Almost 30% of the residents (209; 28.6%) were taking one PIM, 124 (16.9%) were taking two PIMs and 185 (25.3%) were taking three or more PIMs. However only 45 of the full 65 STOPP criteria (69.2%) were utilised in the identification of PIP.

When PRN medications were excluded, PIM detection rates reduced; there were 955 instances of PIP relating to 836 PIMs (14.2%) in 466 patients (63.7%) (**Table 3.3**). Forty-three of the 65 STOPP criteria (66.2%) were utilised in the identification of PIP.

The medications most commonly implicated in PIP included (1) medications which adversely affect fallers (n=392) [in particular, benzodiazepines and neuroleptics], followed by (2) medications acting on the gastrointestinal system (n = 176) [in particular, proton pump inhibitors (PPIs)], (3) medications acting on the central nervous system (n = 166) (**Table 3.3**).

Of the 1,280 instances of PIP, 874 (68.3%) were attributable to eight groups of medications: benzodiazepines (20.2%), neuroleptics (14.4%), PPIs (13.0%), opioids (7.6%), nonsteroidal anti-inflammatory medications (NSAIDs; 7.1%), tricyclic antidepressants (TCAs) (3.6%), bladder antimuscarinics (2.7%) and calcium channel blockers (2.0%).

3.3.3 Identification of PIP using the Beers criteria

When the full set of Beers criteria [ID and CD] were applied, 831 instances of PIP relating to 575 PIMs (6.9%) in 392 patients (53.5%) were identified and 617 instances of PIP relating to 424 PIMs (7.2%) in 314 (42.9%) of patients were identified when PRN medications were excluded (**Table 3.3**).

Application of the Beers criteria identified that 188 residents (25.7%) were taking one PIM, 85 (11.6%) residents were taking two PIMs and 119 (16.3%) residents were taking three or more PIMs. As with the STOPP criteria, Beers PIP prevalence decreased when PRN medications were excluded (**Table 3.3**).

3.3.3.1 Beers [Independent of diagnosis (ID)]

When the full Beers ID criteria were applied 240 instances of PIP relating to 240 PIMs (2.9%) in 204 residents i.e. 27.9% were identified. Fourteen of the 48 medication categories available were utilised, with the most being chlordiazepoxide and diazepam (n = 70); gastrointestinal antispasmodic medications (belladonna alkaloids-hyoscine; n=27); and anticholinergics and antihistamines (chlorphenamine, hydroxyzine, promethazine; n=25).

When PRN medications are excluded, Beers ID criteria identified 178 instances of PIP using just 14 of the 48 medication, with the most common instances relating to chlordiazepoxide and diazepam (n = 41), amitriptyline (n=20) and fluoxetine (n = 17).

3.3.3.1 Beers [Considering diagnosis (CD)]

When the full Beers CD criteria were applied 591 instances of PIP relating to 459 PIMs (5.5%) in 326 patients (44.5%) were identified. Similar to the Beers ID prevalence, the prevalence of Beers CD PIP declined when PRN medications were excluded.

The most commonly implicated Beers CD criteria when PRN medications were included, were (i) falls/syncope with short to intermediate acting benzodiazepines or tricyclic antidepressants (n = 208), (ii) depression with long-term benzodiazepine use, methyldopa, reserpine and guanethidine (n = 87) and (iii) constipation with calcium channel blockers and tricyclic antidepressants (n = 81). Similar Beers CD PIP instances were identified when PRN medications were excluded.

Fourteen of the 19 available Beers CD criteria (73.7%) identified 591 instances of PIP when PRN medications were included, and 13 identified 591 instances of PIP when PRN medications were excluded.

Table 3.3 Prevalence of PIP identified using the STOPP and Beers criteria.

Description	Total (732)
Residents with at least one instance of STOPP PIP	518 (70.8%)
Excluding PRNs	*466 (63.7%)*
Residents with one instance of STOPP PIP	209 (28.6%)
Excluding PRNs	*228 (31.2%)*
Residents with two instances of STOPP PIP	124 (16.9%)
Excluding PRNs	*121 (16.5%)*
Residents with three or more instances of STOPP PIP	185 (25.3%)
Excluding PRNs	*117 (16.0%)*
Residents with at least one instance of Beers PIP	392 (53.6%)
Excluding PRNs	314 (42.9%)
Residents with one instance of Beers PIP	188 (25.7%)
Excluding PRNs	161 (22.0%)
Residents with two instances of Beers PIP	85 (11.6%)
Excluding PRNs	70 (9.6%)
Residents with three or more instances of Beers PIP	119 (16.3%)
Excluding PRNs	83 (11.3%)

Key: PRN; as required / *pro re nata,* PIP; potentially inappropriate prescribing

3.3.4 Test of association

A chi-square test for independence indicated a statistically significant association between polypharmacy and STOPP PIP (χ^2=7.67: $p < 0.05$) and Beers PIP (χ^2=10.36: $p < 0.05$)

Multivariate regression analysis taking age, gender, disease burden and number of medications into consideration, showed a statistically significant association between number of medications and PIP as defined by STOPP (OR: 1.30, 95% CI: 1.22-1.37: $p < 0.001$) and Beers criteria (OR: 1.26, 95% CI: 1.20-1.33: $p < 0.001$) respectively.

Significant negative associations between CCI score and the occurrence of PIP as defined by STOPP (OR: 0.86, 95% CI: 0.76-0.97: $p < 0.05$) and the occurrence of PIP as defined by the Beers criteria were also identified (OR: 0.84, 95% CI: 0.75-0.94: $p < 0.05$).

Table 3.4 Multivariate analysis of variables associated with PIP as defined by the STOPP and Beers criteria.

STOPP criteria PIP			
Factor	**OR**	**95% CI**	**p-value**
Number of medication	1.295	1.223-1.372	<0.001
Female	1.340	0.900-1.994	0.149
CCI Score	0.857	0.760-0.966	<0.05
Age	1.001	0.978-1.024	0.940
Beers criteria PIP			
Factor	**OR**	**95% CI**	**p-value**
Number of medication	1.263	1.201-1.327	<0.001
Female	1.260	0.881-1.802	.205
CCI Score	0.843	0.754-0.943	<0.05
Age	1.002	0.981-1.024	0.846

Key: OR: odds ratio; CI: Confidence intervals; CCI: Charlson co-morbidity index, STOPP: Screening Tool of Older Person's Prescriptions.

Table 3.5 Contingency table of PIP occurrences as determined by the STOPP and Beers criteria (n=732).

			Beers PIP		
			No	**Yes**	**Total**
STOPP PIP	**No**	Count	171	43	214
		% of Total	23.4%	5.9%	29.2%
	Yes	Count	169	349	518
		% of Total	23.1%	47.7%	70.8%
Total		Count	340	392	732
		% of Total	46.4%	53.6%	100.0%

Key: STOPP: Screening Tool of Older Person's Prescriptions.

3.4 Discussion

A high prevalence of PIP was determined using STOPP and the Beers criteria in this LTC population. **Table 3.5** shows that both sets of criteria identified an instance of PIP in approximately 50% of the population, with over three quarters (76.6%), having at least one instance of PIP as defined by each either set of criteria. However the screening tools identified differing prevalence of PIP among participating residents; 70.8% / 63.7% (including / excluding PRN medications respectively) using STOPP criteria and 53.4% / 42.8% (including / excluding PRN medications respectively) using the Beers criteria. The PIP prevalence reported in this study are similar to those found in an earlier pilot study (59.7% with STOPP criteria and 37.1% with Beers criteria) (318).

Apart from this pilot study, there are no other published data examining the prevalence of PIP using STOPP criteria in LTC facilities nationally or internationally with which to compare our results. However, several studies have been undertaken which examine prevalence of PIP in older Irish individuals in primary and secondary care; these have reported significantly lower PIP prevalence than those reported in this study of up to 21.4% (primary care) and 36% (secondary care) (46, 91, 120, 177). However, this is not surprising, given the frailer profile of the LTC population in the present study. North American and European studies have examined prevalence of PIP in LTC settings using modified versions of the Beers criteria (2003) and have reported widely varying PIP prevalence between 15% and 70% (10-12, 59, 302). **Table 3.5** also shows that the Beers criteria can identify two thirds of the individuals with a STOPP PIP instance, while the STOPP criteria can indentify almost 9 out of 10 individuals with a Beers PIP instance.

A number of studies have examined the relationship between the number of medications an individual is prescribed and prevalence of PIP (11, 18, 46, 91, 328). These studies have reported that polypharmacy is a significant contributory risk factor for PIP. In this study, 96.6% / 77.2% of residents were prescribed > 5 medications (including / excluding PRN medications respectively). This finding further confirms that older individuals in LTC are prescribed significantly more medications than their community-dwelling counterparts. Previous studies in Ireland have reported a prevalence of polypharmacy of 45%-66% in primary and secondary care respectively (46, 91, 120, 177).

Bivariate analysis and chi-square test of association showed a significant correlation and association between number of medications and occurrence of PIP as defined by STOPP and the Beers criteria. No such association was observed for age, gender or CCI score and occurrence of PIP as determined by either sets of criteria (data not shown).

A multivariate logistic regression, taking age, gender, disease burden and number of medications into consideration, found a significant positive association between the number of medications and occurrence of PIP as defined by the STOPP and the Beers criteria. Therefore for each additional medication added to an individual's medication list, their risk of being exposed to an instance of PIP as determined by STOPP criteria increased by 30%, and their risk of being exposed to an instance of PIP as defined by the Beers criteria increased by approximately 26%.

Also a statistically significant negative association was found between CCI score and occurrence of PIP as defined by the STOPP and the Beers criteria were identified. Therefore as an individuals' CCI score increased, there was a 16% decrease in their risk of being exposed to the PIP instance as determined by STOPP and a 19% decrease in their risk of being exposed to a PIP instance as defined by the Beers. The full explanation for this negative association was unclear; however it may reflect a more cautious attitude on behalf of the prescribers in older individuals with higher disease burdens. However this hypothesis is somewhat flawed, because if this was the case, patients on higher number of medications would have exhibited a similar trend, as number of medications has been highlighted repeatedly as a major contributory factor in PIP.

Although both sets of criteria contain comparable numbers of PIP criteria (65 STOPP criteria and 68 Beers criteria), only 69.2% of the STOPP criteria compared with 41.2% of Beers criteria were utilised in the identification of PIP in this study and when PRN medications were excluded, only 66.2% of the STOPP criteria and 39.7% of the Beers criteria where utilised, thus suggesting that STOPP may be more relevant to the medication profiles of Irish LTC residents.

The majority of instances of PIP determined using the STOPP criteria were attributable to a small proportion of medications /medication classes, with almost 70% of instances the PIP attributable to eight categories of medications: PPIs, benzodiazepines, neuroleptics, NSAIDs, TCAs, opioids, bladder antispasmodics and calcium channel blockers.

Similarly, approximately 90% of the instances of PIP determined using the Beers criteria were attributable to eight categories of medications; benzodiazepines, antidepressants, antihistamines, bladder antispasmodics, gastro-intestinal antimuscarinics, calcium channel blockers, muscle relaxants, anticholinergics and anti-arrhythmics.

The medications most commonly implicated in PIP using the STOPP criteria were PPIs at maximum therapeutic dose for longer than eight weeks without a valid indication. It has been estimated that PPI expenditure constitutes approximately 10% of the annual drugs budget in the Republic of Ireland (100, 346-347). Aside from obvious financial implications of long-term prescribing of this class of medications at doses in excess of that which is clinically indicated, prescribing in such a fashion may expose older individuals to an increased risk of adverse effects such as reduced absorption of calcium, vitamin B_{12}, iron or increased risks of fractures and osteoporosis (348-351).

The second most common instance of PIP identified using the STOPP criteria involved use of long-acting benzodiazepines in those at risk of falls. In addition to the increased risk of falls, this patient population may also be at an increased risk of both psychological and physical dependency with this medication class (15-16, 91, 111, 182, 352-354). Despite these risks, benzodiazepines continue to be widely prescribed for older individuals, both nationally and internationally (91, 242, 353).

A number of instances of PIP identified using the STOPP criteria relating to neuroleptics were also identified in this study. Adverse effects relating to the long-

term use of neuroleptics has been widely documented in the literature, particularly in relation to gait/balance disorders, sedation/cognitive impairment and increased stroke risk (182, 355-357).

As with the STOPP criteria, the Beers criteria frequently identified residents with at least one instance of PIP relating to benzodiazepines in the LTC population (32.2%). Furthermore, application of the Beers criteria identified that 7.8% of LTC residents were taking potentially inappropriate antidepressants (the majority [61.6%] of which were directly attributable to TCAs) and 5.3% were taking potentially inappropriate first generation antihistamines.

The higher prevalence of PIP identified using STOPP compared to the Beers criteria, coupled with the findings from previous Irish studies, indicate that the STOPP criteria may be more appropriate than the Beers criteria for detection of PIP in older individuals across all care settings in Ireland (16, 46, 91, 120, 177). There are several possible reasons for the lower PIP prevalence using the Beers criteria e.g. issues relating to the applicability of Beers criteria outside North America (15-16, 18, 23, 38, 43, 46, 56, 62, 112, 337), as well as issues relating to the true inappropriateness of several medications defined as potentially inappropriate such as amitriptyline, doxazosin and amiodarone in older people (15-16, 46). Since the conduction of this study an updated version of the Beers criteria have been published, which may address some of the issues identified above (124). The Beers criteria were originally formulated for use in the United States and were primarily based on expert opinion rather than clinical evidence (15-16, 46). Furthermore, almost 50% of the medications listed in the Beers criteria are not authorised in drug formularies in

European countries (15-16, 62, 112). It is therefore not surprising that less than 50% (n=28) of the Beers criteria were utilised in the identification of PIP in this study. Similar findings have been reported in previous Irish studies (16, 38, 47, 62, 91, 120, 143, 177).

3.4.1 Limitations

This present study has a number of potential limitations. The order in which data were compiled in medical notes varied considerably from patient to patient and from one LTC facility to another. This could have affected the quality of the data recorded, and may have led to higher instances of PIP identified. The information was compiled and analysed by a single investigator; a number of drug indications and patient complications recorded in the medical records were open to interpretation and thus introduced a degree of subjectivity e.g. an individual suffering from regular intermittent constipation which required regular laxatives may be diagnosed with chronic constipation by one individual and diagnosed as intermittent constipation by another.

It was not possible to apply the START criteria to dataset due to the retrospective nature of this work. Due to data collection taking place in the greater Cork region one, may question the generalisability of the data across the island of Ireland.

Non-prescription over the counter (OTC) medications were not considered in the PIP assessment, as the study population under review are LTC residents and it is was felt that it would be unlikely that they would receive an OTC medication unless they were prescribed/charted for it on their medication Kardex.

Numerous studies have highlighted limitations relating to explicit criteria in the assessment of PIP, with a number of studies specifically criticising the Beers for its lack of comprehensiveness and generalisability outside of the US. However it is important to re-iterate that these PIP criteria are intended to serve as a guide for appropriateness, not to replace clinical judgement.

Although the prevalence of PIP reported in this study are high, it is important to emphasise that both STOPP and the Beers criteria were designed to identify the proportion of medications considered to be *potentially* inappropriate in older individuals. These PIMs may not always be detrimental to the patient in question. Such tools were designed to complement professional clinical judgement, not to replace it, and to highlight the most common instances of PIP in order to facilitate informed decision making in review of older persons' medications (18, 62, 120, 177, 358).

3.5 Conclusion

PIP has become a major area of concern and has been identified in the literature as a considerable burden to health services nationally and internationally. In this study, both STOPP and the Beers criteria confirmed a high prevalence of PIP in this sample of frail older residents of LTC facilities. Over three-quarters of the residents reviewed had at least one instance of PIP. The higher prevalence of PIP determined using STOPP criteria than using the Beers criteria is of uncertain relevance, but may be because the STOPP criteria were designed and validated for use in an Irish setting, whereas the Beers criteria were formulated for application in a US healthcare setting.

The findings that the STOPP criteria indentifies almost 90% of individuals with a Beers instance of PIP, while the Beers criteria only identifies two thirds of the individuals with a concurrent STOPP instance of PIP, indicates that the STOPP criteria may be a more suitable tool for the approximation of individuals with Beers PIP instances, than the Beers criteria would be at approximating individuals with STOPP PIP instances.

Ideally both sets of criteria would be deployed concomitantly to ensure comprehensiveness of the screening process, however if time constraints are present and only one tool could be deployed, then the STOPP criteria would probably be the most appropriate option for this population. This has direct relevance for all healthcare professionals working in this setting, given that recent data have shown a significant causal relationship between PIP and adverse drug events (ADEs) (56, 78, 120, 177). Polypharmacy (>5 medications) was highly prevalent in this population

and the number of medications was significantly associated with an increased risk of experiencing PIP.

Therefore interventions which focus on optimising prescribing by addressing the issues relating to the most common instances of PIP should yield a reduction in ADEs. Such interventions may involve the routine application of an explicit set of criteria such as the STOPP criteria. By their nature, these types of criteria are generally inexpensive and time efficient and they have the potential to yield significant improvements in prescribing appropriateness. To date, the application of STOPP in routine clinical practice has been limited and its true clinical and financial value has not been fully established.

Further prospective randomized controlled trials are needed to determine the benefits (if any) of applying the STOPP criteria routinely to medication lists for older people residing in the LTC setting in terms of prevention of ADEs and cost-savings.

Chapter 4

4. A comparison of potentially inappropriate prescribing in older residents of long term care facilities in both Northern Ireland and the Republic of Ireland.

In this study, I was involved in the development of the study design, the drafting of the research proposal and the application for ethical approval. I was the lead researcher in this study and I undertook the data collection for the Republic of Ireland arm of this study and I undertook the age and gender matching. I also applied the PIP criteria and did all the statistical analysis in both jurisdictions in this study.

4.1 Introduction

Presently 12% of the Republic of Ireland (RoI) (359) and 14% of the Northern Ireland (NI) population are ≥65 years (360). It is estimated by 2030 that this proportion of individuals ≥65 years, will increase to 16% and 18.2% in the RoI and NI respectively (2). Similar demographic trends have been forecasted globally (2-4). Currently, approximately 4.6% of the older individuals living in the RoI and 4.0% living in NI reside in long term care (LTC) (i.e. nursing and residential homes), with these populations expected to rise in line with the projected growths above (3, 360-361).

Older individuals in LTC are an especially vulnerable patient population as they typically exhibit a high level of physical and functional dependency (10-11, 13, 302, 317). Advancing age is often complicated by a number of age-related physiological changes, which can lead to alterations in both the pharmacokinetic and pharmacodynamic profiles of many drugs (15-16, 18), exposing them to an increased risk of adverse drug reactions (ADRs), drug-drug and drug-disease interactions and potentially inappropriate prescribing (PIP) (10, 14-15, 18).

Over the last 20 years or so, concerns regarding the appropriateness of prescribing practices in older individuals have led to a number of different screening criteria being developed (12, 38, 111, 125, 129, 131, 147, 362-363). Two sets of criteria have gained international recognition, the Beers criteria (12, 111, 124-125) and the STOPP criteria (38).

The Beers criteria were the first explicit set of criteria developed to assess PIP in older individuals and to-date is the most widely-cited in the literature. It was originally developed in 1991 (12) and were subsequently revised and updated on several occasions (38, 81, 111, 124-125). The most recent version of the Beers criteria were published in 2012 (124). However, at the time this study was conducted, the 2003 Beers criteria were the most up-to-date and widely cited version (111). A number of studies have utilised the Beers criteria to assess PIP in older individuals in LTC and prevalence of up 70.0% have been reported (336, 364-365). However a number of studies have highlighted limitations relating to the Beers criteria's applicability and reliability outside of the United States (US) (15-16, 38, 62).

In 2008, a new set of criteria to determine PIP arising in older individuals (35, 52), known as the STOPP criteria, were developed for use in an Irish and European care setting (38). A number of recent studies have used the STOPP criteria to assess prevalence of PIP in LTC and have reported rates as high as 79% (318, 366-368). Evidence to date seems to suggest that, of the two sets of criteria, the STOPP criteria exhibits superior applicability and reliability, as a PIP detection tool for use across all care settings (16, 44, 46, 62, 91, 112, 120, 143, 177, 366).

To date only two studies have examined the prevalence of PIP determined using the Beers criteria and the STOPP criteria in an Irish context they reported PIP prevalences ranging from 59.8-70.8% (318, 366), however to date these studies have primarily focused on LTC facilities in the Republic of Ireland. To our knowledge none have assessed the prevalence of PIP determined using the STOPP and the Beers criteria in LTC facilities in the RoI and NI or compare the prevalence of PIP as determined by both tools between the two jurisdictions.

4.1.1 Objectives

The objectives of this study were to:

1. Assess the prevalence of PIP in LTC residents ≥65 years in both NI and RoI using both the STOPP and the Beers criteria
2. Compare the prevalence of PIP determined using both screening tools in both populations.

4.2 Methods

The data for the RoI arm of the study were collected prospectively for 732 LTC residents aged ≥65 years is described elsewhere (366).

The data for the NI arm of the study was extracted from a database of 334 older individuals residing in LTC that had been previously compiled in a dataset using Microsoft Access® 2007 as part of the Fleetwood Northern Ireland Study. This study was conducted from March 2006 to June 2007 and it used a cluster randomised controlled trial design to examine the impact that a modified Fleetwood model of care could have on the appropriateness of psychoactive prescribing in older Northern Irish nursing home residents (281). The nursing homes selected for this study were selected from all of the registered nursing homes in Northern Ireland (n=254), however it was limited to facilities with more than 30 resident beds (n=175) (281).

These included facilities for general nursing category residents and facilities that cared for specific patient groups, such as patients with dementia (281). Facilities that cared exclusively for terminally ill patients were excluded. Of the 175 eligible facilities, 29 agreed to participate in the study. These facilities were then paired based on nurse staffing levels, type of ownership (i.e. private or other), number of doctors' practices that provided care to the facilities and location (i.e. urban or rural) (281). Fourteen pairs were successfully made, with the one outlier being removed (281). An independent researcher then selected 11 of 14 pairs of facilities at random to participate in the study (281). The homes within the matched pairs were then randomly assigned to one of 2 groups, intervention and control using a computer-generated table of random numbers, by an independent researcher blinded to the identity of the homes (281).

Of the 22 facilities selected for participation in the study in NI jurisdiction, 19 of them were privately owned (281). In the intervention facility the mean number of full-time equivalent (FTE) nurses (± standard deviation) per facility was 9.2 ± 2.8 and the mean number of FTE care assistants was 20.1 ± 6.9 (281). While in the control facilities the mean number of FTE nurses per facility was 9.2 ± 3.4 and the mean number of FTE care assistants was 20.1 ± 6.9 (281). Full details of the methods and procedures used in this study have been published previously (281).

The datasets for RoI and NI were stratified by age and gender using Predictive Analysis Soft-Ware Statistics version 18.0 (PASW, SSPS Inc. Chicago, IL.). A total of 315 residents from each dataset were successfully matched on the basis of age and gender.

All disease states were coded to the using the World Health Organisation's (WHO) International Classification of Diseases (ICD-10) (2010) (340) and medications prescribed were coded using the WHO hierarchal Anatomical Therapeutic Chemical (ATC) Classification System (2011) (339). Co-morbidity burden was quantified using the Charlson Co-morbidity index (CCI) (35, 341).

Ethical approval for this study was sought and granted from the Clinical Research Ethics Committee of the Cork Teaching Hospital and University College Cork, Ireland.

4.2.1 Main outcome measure

Prevalence of PIP was determined in both jurisdictions by applying the STOPP and the Beers criteria to the patient profiles of all matched residents in each dataset. A PIP instance refers to each instance/occurrence of PIP observed and a potentially inappropriate medication (PIM) refers to each medication considered potentially inappropriate, i.e. a PIM could potentially contribute to more than one PIP instances.

4.2.2 Statistical Analysis

The results were analysed using Microsoft Excel® 2007 and Predictive Analysis Soft-Ware (PASW, SSPS Inc. Chicago, IL.) version 18.0. The data for both datasets were determined to be non-parametric based on a review of the distribution histograms and box plots for age and number of medications.

Mann-Whitney U tests were performed to evaluate if there was any statistical significant difference between the prevalence of PIP and the number of medications in both jurisdictions. A chi-square analysis was conducted for the categorical data.

Contingency tables were used to show the combined distribution of PIP prevalence according to both sets of criteria. These tables also illustrated how either tool can approximate the occurrence of PIP of the other. A p-value <0.05 was deemed to be statistically significant.

4.3 Results

4.3.1 Demographics

The median age of 630 residents (315 in each dataset) was 84 (IQR 78-89) years and three-quarters were female (**Table 4.1**). A total of 7,124 medications were prescribed with 3,730 and 3,394 being prescribed in the RoI and NI datasets respectively. The overall median number of medications prescribed per resident for the combined datasets was 11 (IQR 8-14; RoI median=11; IQR 9-13 and NI median=10; IQR 7-13). A Mann-Whitney U test revealed that there was a small but significant difference between the number of medications in the RoI (median=11, n=315) and the NI (median=10, n=315) ($z=-3.515$, $p< 0.001$, $r=0.14$).

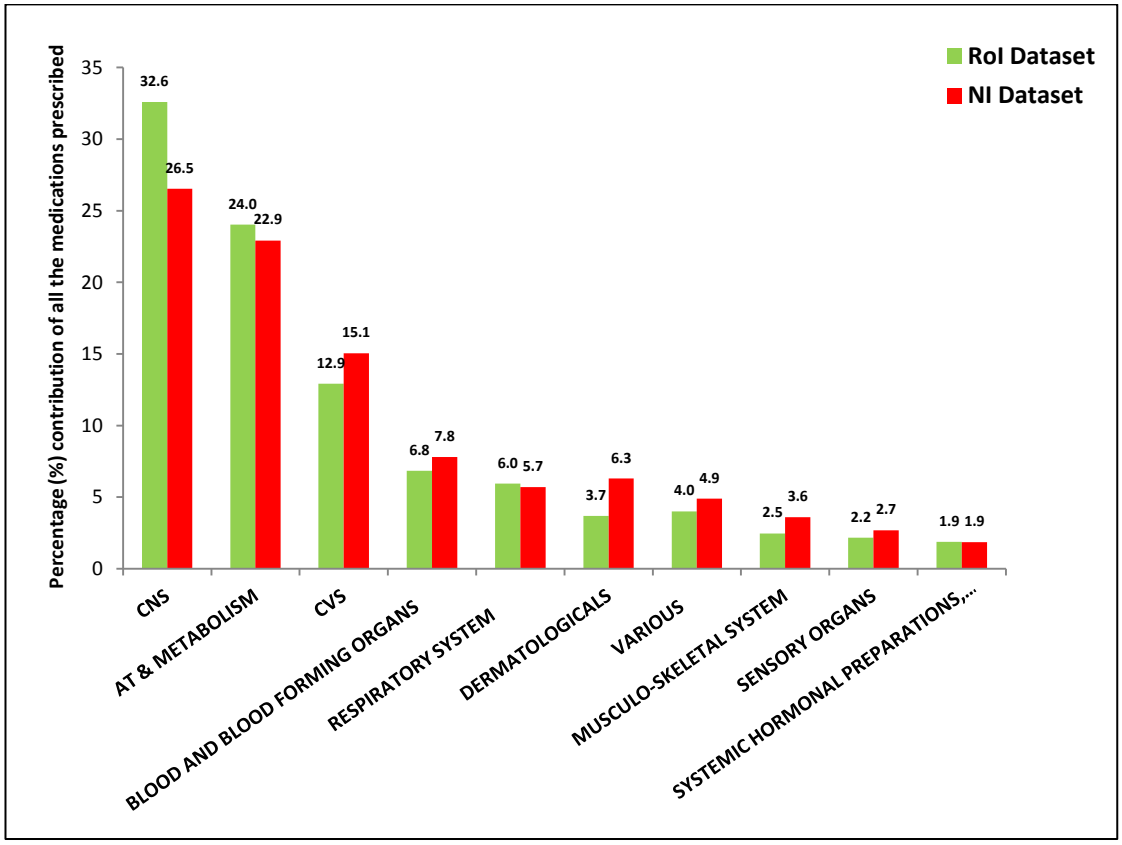
Table 4.1 Demographics of the age and gender matched populations.

Demographics	RoI Dataset (n=315)	NI Dataset (n=315)	Matched Dataset (n=630)
Male	79 (25.1%)	79 (25.1%)	158 (25.1%)
Female	236 (74.9%)	236 (74.9%)	472 (74.9%)
Median Age* (IQR)	84 (78-89)	84 (78-89)	84 (78-89)
Age Range*	65-99	65-99	65-99
No. of medications prescribed	3,730	3,394	7,124
No. of regular medications prescribed	2,683	2,246	4,929
No. of "*prn*" medications prescribed	1,047	1,148	2,195
Median number of medications prescribed (IQR)	11 (9-14)	10 (7-14)	11 (8-14)
Median number of regular medications (IQR)	8 (6-10)	7 (5-9)	8 (5-10)
Median CCI score (IQR)	2 (1-3)	1 (1-2)	2 (1-3)

Key: RoI; Republic of Ireland, NI; Northern Ireland, PRN; as required / *pro re nata*, IQR; Inter Quartile Range, CCI; Charlson Co-morbidity Index. *Calculated in years

4.3.2 Prescribing patterns

In both datasets medications for the Central Nervous System (CNS) were the most commonly prescribed, with a higher percentage prescribed for residents from the RoI dataset than for residents from the NI dataset (RoI: 32.6%, NI: 26.5%) (**Figure 4.1**). Medications classified for the alimentary tract (AT) and metabolism system were the second most commonly prescribed category, with a higher percentage again being prescribed in the RoI dataset compared to NI dataset (RoI: 24% and NI: 22.9%) (**Figure 4.1**).



Key: CNS: Central nervous system, CVS: Cardiovascular system, AT: alimentary tract.

Figure 4.1 Breakdown of the top 10 medication categories prescribed based on the Anatomical Therapeutic Chemical (ATC) classification system, across both datasets.

4.3.3 Prevalence of PIP measured per dataset as defined using the STOPP and Beers criteria

4.3.3.1Application of the STOPP criteria to the RoI and NI datasets

In the RoI dataset the STOPP criteria identified a total of 568 instances of PIP relating to 500 PIMs in 230 (73.0%) residents and in the NI dataset STOPP identified a total of 478 instances of PIP relating to 420 PIMs in 211 (67.0%) residents (**Table 4.2**) (**Figure 4.2**). A Mann-Whitney U test showed that there was no statistically significant difference in the number of instances of PIP between the two datasets (RoI: Md=1, n=315; NI: Md=1, n=315, z=-1.892, p=0.58, r= 0.08). In both datasets the full 65 STOPP criteria were deployed 39 (60.0%) of the 65 criteria and 30 (46.15%) of the 65 criteria were utilised in RoI and NI datasets respectively.

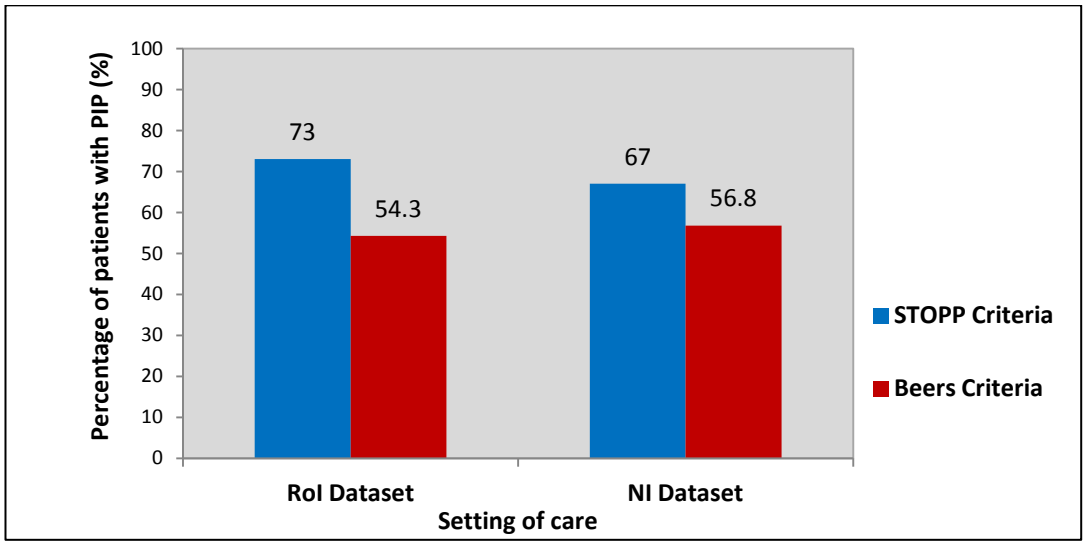


Figure 4.2 The prevalence of PIP calculated per dataset.

Table 4.2 Prevalence of PIP calculated per dataset using the STOPP and Beers criteria (n=315 per dataset).

Tool	% Residents ≥ 1 PIP instances	No. of instances of PIP	No. of PIMs	No. of Residents with PIP	No. Residents with 1 PIP instances	No. Residents with 2 PIP instances	No. Residents with ≥3 PIP instances
RoI STOPP	73.0	568	500	230	87	59	84
RoI Beers	54.3	384	259	171	69	45	57
NI STOPP	67.1	478	420	211	86	56	69
NI Beers	56.8	381	265	179	69	58	52

Key: NI; Northern Ireland, ROI; Republic of Ireland, STOPP; Screening Tool of Older Person's Prescriptions.

The most common instances of PIP in both jurisdictions identified by the STOPP criteria are outlined in **Table 4.3**.

Table 4.3 The number of instances of PIP identified by the STOPP criteria in the RoI and NI datasets.

Criteria	RoI Instances of PIP	NI Instances of PIP
Central Nervous System		
Long term long half life benzodiazepine	29	32
Neuroleptics as long-term hypnotics i.e. > 1 month	13	29
>1 week 1st generation antihistamines	9	22
Gastro Intestinal System		
PPI for PUD at full therapeutic dosage for > 8 weeks	74	66
Musculoskeletal System		
NSAID & hypertension	30	4
Falls		
Benzodiazepines	94	107
Neuroleptic drugs	57	55
1st generation antihistamines	7	26
Long term opiates	31	16
Duplicate class	85	50
Total PIMs	***568***	***478***

Key: NI; Northern Ireland, ROI; Republic of Ireland, PPI: Proton Pump Inhibitor, PUD: Peptic Ulcer Disease, NSAID: Non Steroidal Anti-inflammatory.

4.3.3.2 Application of the Beers criteria to the RoI and NI datasets

In the RoI dataset, the Beers criteria identified 384 instances of PIP (108 independent of diagnosis (ID) and 276 considering diagnosis (CD)) relating to 259 PIMs in a total of 171 (54.3%) residents. In the NI dataset the Beers criteria identified 381 instances of PIP (183 ID and 198 CD) relating to 265 PIMs in a total of 179 (56.8%) residents (**Table 4.2**) (**Figure 4.2**). A Mann-Whitney U test showed that there was no statistically significant difference between the number of instances of PIP determined by STOPP between the two datasets (RoI: Md=1, n=315; NI: Md=1, n=315,z=-0.457, p=0.65, r= 0.02).

The full set of the Beers criteria were applied to both datasets. In the RoI dataset, 28 (12 CD and 16 ID) (41.2%) of the 68 Beers criteria were utilised in the identification of instances of PIP. In the NI dataset 26 (7 CD and 19 ID) (38.2%) of the criteria were utilised. The most common instances of PIP identified by both the Beers CD and Beers ID criteria are outlined in **Table 4.4**.

Table 4.4 The 5 most common instance of PIP identified by Beers criteria independent of diagnosis and considering diagnosis

Criteria	RoI Instances of PIP	NI Instances of PIP
Independent of Diagnosis		
Diazepam & Chlordiazepoxide	37	68
Fluoxetine	5	31
Chlorpheniramine	8	19
Amitriptyline	9	14
Temazepam *>15mg*	5	16
Total Independent of Diagnosis	108	183
Considering Diagnosis		
Benzodiazepines and or TCAs in individuals with a high risk of falls	100	127
Depression & Long term benzodiazepine	44	22
Cognitive Impairment & Anticholinergics and/or muscle relaxants and/or Barbiturates	24	29
Incontinence & TCAs and/or Benzodiazepine and/or Anticholinergics and/or Alpha blockers	36	7
Constipation & CCBs and/or Anticholinergics and/or TCAs	40	1
Total Considering Diagnosis	276	198
Total Independent of Diagnosis & Considering Diagnosis	384	381

Key: NI; Northern Ireland, ROI; Republic of Ireland, CCBs: Calcium Channel Blockers, TCAs: Tricyclic Antidepressants.

Table 4.5, shows in the RoI dataset, the Beers criteria identifies 68.6% (22.9/73x100=31.4%; 100-31.4) of the individuals with a concurrent STOPP PIP instance, while the STOPP criteria indentifies 93.4% (4.1/54.3x100=7.6%; 100-7.6) of individuals with a concurrent Beers PIP instance.

While **Table 4.5**, shows in the NI dataset, that the Beers criteria identifies 73.4% (17.8/67x100=26.6%; 100-26.6).of the individuals with a STOPP PIP instance, while the STOPP criteria indentifies 86.6% (7.6/56.8x100=13.4%; 100-13.4) of individuals with a concurrent Beers PIP instance.

Table 4.5 Contingency table of potentially inappropriate prescribing (PIP) occurrences [count (% of total count)] as determined by the STOPP criteria and Beers criteria for RoI dataset (n=315) and NI dataset (n=315).

RoI (n=315)			
		Beers PIP	
	No	**Yes**	**Total**
STOPP PIP			
No	72 (22.9)	13 (4.1)	85 (27.0)
Yes	72 (22.9)	158 (50.2)	230 (73.0)
Total	144 (45.7)	171 (54.3)	315 (100.0)
NI (n=315)			
		Beers PIP	
	No	**Yes**	**Total**
STOPP PIP			
No	80 (25.4)	24 (7.6)	104 (33.0)
Yes	56 (17.8)	155 (49.2)	211 (67.0)
Total	136 (43.2)	179 (56.8)	315 (100.0)

Key: NI; Northern Ireland, ROI; Republic of Ireland, STOPP; Screening Tool of Older Person's Prescriptions

4.4 Discussion

A high prevalence of PIP was determined using the STOPP and the Beers criteria in both datasets. **Table 4.5** shows that in the both jurisdictions, a PIP instance was determined concurrently with the STOPP and Beers criteria in approximately 50% of the residents and approximately three quarters of the resident had a PIP instance determined by either set of criteria. In both datasets differing prevalences of PIP were determined (**Figure 4.2**).

The PIP prevalences reported in this study are consistent with PIP prevalences reported previously in LTC residents in Ireland (318). Several other studies have examined the prevalence of PIP in other healthcare settings in Ireland and have reported lower PIP prevalence, with prevalence of up to 21.4% and 56.2% being reported in primary and secondary care respectively (15, 91, 120, 177). The lower prevalences of PIP reported in these other healthcare settings is not surprising, given the frailer nature of the LTC population in the present study. A number of North American and European studies have examined PIP prevalence in LTC settings using modified versions of the Beers criteria (2003). They have reported widely varying prevalences ranging between 15% and 79% (10-12, 59, 302, 367). Although there is a high rate of PIP identified in this study, it is important to remember that the medications identified as potentially inappropriate by each set of criteria, are only "potentially" inappropriate. Under certain circumstances, use of such medications may often be appropriate and justified.

Similar to previous studies conducted in Ireland, the STOPP criteria identified a higher prevalence of PIP than the Beers criteria in both jurisdictions. Although the STOPP and Beers criteria are not directly comparable they do contain similar

numbers of criteria i.e. STOPP, n=65 and Beers, n=68. In this study more of the STOPP criteria (RoI n=39, NI n=30) were utilised in the determination of PIP compared with the Beers criteria (RoI n=28, NI n=26). **Table 4.5** also indicates that the STOPP criteria may be a more suitable tool for the approximation of individuals with Beers PIP instances, than the Beers criteria would be at approximating individuals with STOPP PIP instances. There was a slightly more noticeable effect observed in the RoI dataset compared with the NI dataset. This is not surprising, as the STOPP criteria were originally formulated for use in a RoI context and are based on primarily on RoI prescribing practices and medications. There are some subtle differences between the two jurisdictions that may account for both the variations in the number of instances of PIP determined between the two jurisdictions. In order to ensure comprehensiveness, both sets of criteria should ideally be applied concomitantly, however this may not always be possible, due to times constraints and limitations of the data, it is the authors' opinion that then the STOPP criteria may be the most appropriate option in both jurisdictions.

Similar prescribing patterns were observed across all categories of medications in both jurisdictions (339) (**Figure 4.1**). Of note, slightly more medications for the CNS were prescribed in the RoI dataset than in the NI dataset, whereas slightly more medications for the CVS were prescribed in the NI dataset compared to the RoI dataset. The high level of prescribing of CNS-related medications is an area of particular interest, as over half of the overall instances of PIP identified by both the STOPP and the Beers criteria in both jurisdictions are directly attributable to CNS medications (data not shown). Several other studies have reported similar trends relating to the PIP of CNS medications (317, 355, 369-370).

Specific strategies such as (i) nationally developed consensus guidelines relating to appropriate selection of pharmacotherapies for the treatment of certain psychological conditions and (ii) clear recommendations to assist prescribers on how to withdraw/ taper psychotropic medications appropriately, could significantly improve appropriateness of prescribing in older individuals, reduce the incidence of ADEs relating to these types of medication, and subsequently reduce the financial implications associated with these types of ADEs.

PIP instances relating to CVS also featured quite prominently in both jurisdictions and a number of studies have indicated that CVS medications may be one of the leading causes of preventable drug related hospitalisation in older individuals (21, 165, 371-372). Strategies focused on ensuring appropriate selection of the most effective CVS medications and consensus guidelines on initiation, dose adjustments and withdrawal of these pharmacotherapies in older individuals could lead to a marked reduction in CVS related hospital admissions in this population.

Not only was the prevalence of STOPP PIP found to be similar between the two datasets, the most common instances of PIP were also found to be similar (**Table 4.3**). The most commonly encountered instance of PIP in both jurisdictions related to the use of benzodiazepines in older individuals with a history of recurrent falls (RoI n=97 and NI n=107). Benzodiazepines may also expose individuals to an increased risk of fractures, sedation, confusion and both psychological and physical dependency (16, 62, 91, 111, 182, 352-354). Despite these risks, benzodiazepines continue to be widely prescribed, both nationally and internationally across all settings of care (91, 242, 353).

The second most commonly encountered instances of PIP identified using the STOPP criteria in both jurisdictions, related to the long-term use of a proton pump inhibitor (PPI) at full therapeutic dosage (RoI n=74 and NI n=66). Several studies have identified a number of relatively rare but significant ADEs associated with long-term use of this class of medications e.g. reduced absorption of calcium, vitamin B12, iron or increased risks of fractures, osteoporosis and increased risk of Clostridium difficile infections (348-351). PIP of this class of medications can also incur significant financial costs.

Similar instances of PIP identified using Beers criteria were also reported between the two jurisdictions. The most common instance of PIP in both jurisdictions related to the PIP of benzodiazepines and/or tricyclic antidepressants in individuals with a history of / high risk of falls (RoI n = 100, NI n=127). The second most common instance of PIP related to the PIP of long-acting benzodiazepines such as diazepam and chlordiazepoxide (RoI n = 37, NI n=68). Long-acting benzodiazepines have a long half-life in older individuals (often several days) and consequentially can produce prolonged sedation and increased risk of falls and/or fractures. Use of these types of medications in older individuals should generally be avoided or should be used conservatively and low-dose short-acting benzodiazepines are generally preferred (242, 353, 370, 373).

The differences in the frequency of certain PIP instances between the two datasets (**Tables 4.3 and 4.4**) may be due to slight variations in prescribing practices/guidelines between the two jurisdictions. Alternatively it might be secondary to variations in both the quality and detail of the medical data collected. In

the RoI, the data collection for all 315 patients was carried out by a single investigator, while the data for the NI dataset was compiled as part of the Fleetwood Study (281) and was collected by 9 pharmacists this may have introduced a certain degree of variation.

The lower prevalence of PIP identified using the Beers criteria; may in part be explained by the fact that almost 50% of the medications listed in the Beers criteria are not authorised in drug formularies in European countries (16, 62, 112). Similar findings have been reported in previous Irish studies (16, 38, 45, 47, 62, 91, 120, 143, 177).

4.4.1 Limitations

A limitation of this study relates to the differences in the data collection periods. In the NI study, the data were collected between March 2006 and June 2007, whereas in the ROI study the data were collected between December 2009 and September 2010. During this 3 year period there may have been changes in prescribing guidelines or availability of certain medications that may have impacted on the prevalence of PIP observed. However, the NI Fleetwood study dataset was selected for this study, as at the time of the study it was the only NI LTC dataset available.

Another major limitation of this study related to the differences between the facilities sampled in the ROI and NI. In the ROI, the LTC facilities were all publically funded facilities, whereas the majority of the facilities in the NI were privately owned facilities. The difference in the type of ownership may or may not have impacted on the quality care and the appropriateness of prescribing within these facilities. Although there were differences between the facilities included in the studies, the types of individuals that reside in these facilities appear similar, that is the facilities in both the NI and ROI care for patients with multiple co-morbidities, varying degrees of dependency and cognitive impairment.

There was also some variation in the size (i.e. number of resident beds) of the facilities included in the study, with facilities with as low as 22 resident beds being included in the ROI, whereas in the NI facilities, a lower limit of 30 or more residents was used. The number of residents residing (i.e. cared for) in a LTC facility may impact on the quality of care being delivered, however this effect would usually be offset by ensuring adequate levels of staff are present to care for the numbers of patients residing in the facility.

Within each jurisdiction and between the two jurisdictions there was variability in the number of nurses and care assistants working in the LTC facilities. However in the ROI, the exact levels of nursing/ care assistant staff was not recorded and therefore it is not possible to compare it with the levels reported in the NI. However, it is important to note that staffing levels have been reported in the literature to have a substantial influence on the quality of care being delivered in LTC facilities (374-376).

Also access to medical services i.e. frequency of doctors' visits, also has a substantial impact on quality of care and appropriateness of prescribing in LTC. Again, in the ROI dataset, the exact extent to which each patient or facility had access to medical services was not recorded and therefore it was not possible to directly compare it with the level of physician input in NI.

On review, it may have been more appropriate to recorded staffing levels and details of medical services in each facility and to have matched the ROI and NI facilities based on type of facilities, number of residents, staffing levels and access to medical services as opposed to stratify it on a patient level, based on age and gender.

Another limitation of this work was that the medications identified as inappropriate according to the criteria, were potentially inappropriate and the residents were not actually examined to determine if there was any level of harm evident.

A number of issues were also identified relating to the interpretation of different diagnoses/conditions between the two datasets. As the two datasets were collected by a number of different researchers, the detail of information recorded (medical diagnosis, biochemical data) may have varied between both datasets e.g. a resident has a history of constipation but requires long term laxative therapy, one researcher could report that this resident suffers from long term constipation, while another may not have recorded this as an on-going problem because a physician has not diagnosed the resident with chronic constipation. This variation could significantly influenced the PIP occurrence rate as a number of the criteria in the STOPP and Beers CD list of criteria take diagnosis into consideration.

4.5 Conclusion

This study found that a high proportion of older residents in both datasets had at least one instance of PIP defined using either set of criteria. PIP prevalences determined by each set of criteria was found to be similar between the two jurisdictions and were consistent with prevalences reported in two previous studies conducted in this care setting in Ireland (318, 366) and with PIP prevalence reported internationally (10-12, 59, 367-368). A larger, randomised controlled trial is necessary to investigate the true economic and clinical impact of a structured pharmacist intervention on outcomes such as ADE reduction.

Chapter 5

5. Potentially Inappropriate Prescribing in Ireland across Three Settings of Care.

In this study, I was involved in the development of the study design. I undertook the data collection for the secondary care and the long term care aspects of the study as previous described. I applied the different PIP criteria to all three datasets and carried out all of the statistical analysis in this study.

5.1 Introduction

As the population ages, the prevalence of chronic conditions increases and the number of prescribed medicines increases in parallel. Advancing age is often complicated by age-related physiological changes, which can lead to significant alterations in pharmacokinetics and pharmacodynamics, making older patients more susceptible to drug-related problems, including potentially inappropriate prescribing (PIP) (15, 18, 47).

PIP is a universal term used to describe a number of different suboptimal prescribing practices, which encompasses the prescribing of medications that are not clinically indicated, have a high inherent risk of adverse drug interactions, are likely to exacerbate a clinical problem, and where there is a more favourable alternative available (14, 16, 18, 44, 47, 49, 56). PIP has become an area of concern in the older population (14, 16, 44, 47, 49, 56).

A number of evidence-based screening tools have been developed, with the aim of improving prescribing appropriateness for older individuals. The most commonly cited screening tools are the Beers criteria (US based) and Screening Tool of Older Person's Prescriptions (STOPP) (European base) (111, 125). As Beers criteria is US based, a number of non-US studies have raised concerns regarding the applicability

of this set of criteria outside of the US (15-16, 18, 43, 56, 62, 377). STOPP is the first evidence based, Delphi-validated European PIP screening tool, developed to address some of perceived deficits of Beers criteria (44, 46, 62, 112, 177). Further European screening tools have since become available e.g. the Priscus list, which was Delphi validated by a panel of 38 German experts in geriatric pharmacotherapy and outlines 83 medications considered potentially inappropriate in this cohort (39).

Varying degrees of PIP have been reported, depending on the setting, the country of study and the methods of detection of PIP employed. Studies using Beers criteria have reported PIP prevalences of 3.3-63.8% in primary care (PC), 7.8-56.1% in secondary care (SC) and 14.5-70.0% in long term care settings (LTC) (43, 311, 336, 364, 378). Studies that have used the STOPP criteria have reported PIP prevalences of 21.4-36.0% for PC, 18.6-77.3% for SC and 50-79.0% for LTC (44, 91, 100, 112, 314, 338, 358, 367, 379). Studies using the Priscus criteria have reported PIP prevalences of 17.0-31.9% in PC, and rates up to 60.4% in LTC (380-382). There are no published studies using Priscus specific to the SC setting. A further two studies have examined PIP using the Priscus criteria in larger mixed datasets of health insurance claimants have reported PIP prevalences of 24-25% (380, 383).

Unsurprisingly, to-date the STOPP criteria has shown favourable applicability when compare with Beers criteria in all Irish health-care settings. Each set of the three PIP criteria includes a number of clinically relevant criteria relating to specific instances of PIP that may or may not be addressed by either of the other two sets of criteria.

A number of papers have reported that computer decision support systems (CDSS) can enhance the screening and resolution of PIP in older individuals (19-20, 40, 298-301).

Therefore the authors felt that a CDSS that incorporated an amalgamated/hybrid set of all three sets of criteria would provide the most comprehensive and thorough evaluation of PIP. To-date, no study has examined the potential applicability of CDSS utilising a combination of all three sets of criteria.

The objectives of this study were to:

1 Compare and contrast prescribing patterns across the three healthcare settings,

2 Determine and compare the prevalence and applicability of a combined set of PIP criteria made up of the STOPP, Beers and Priscus criteria with each set of criteria individually across three healthcare settings i.e. PC, SC and LTC.

5.2 Methods

5.2.1 Data Collection

Three hundred patient files were randomly selected from three large datasets (n=2418) of patients in PC, SC and LTC. These databases were compiled in similar studies, conducted independently in each care setting; all were conducted in the greater Cork region of Ireland and are described in greater detail elsewhere (91, 382, 384). Similar methods and inclusion/exclusion criteria were used for each study. All patients were ≥ 65 years and were not terminally ill.

The same information was recorded in each study: patients' age, sex, medical diagnosis, relevant medical history (coded according to the World Health Organisation's (WHO) International Classification of Diseases (ICD-10) (340)), current medications (regular and as required (prn) medications (coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System); over the counter medicines were excluded), and biochemical data.

The PC database contained a total of 1329 patient profiles and was compiled between January 2007 and July 2008 from patients attending three general practices (91). The SC database contained a total of 357 patient profiles, all of whom were admitted to a university teaching hospital between May 2011 and January 2012 (384). The LTC dataset was derived from 732 residents living in fourteen publically funded nursing homes/community hospitals between December 2009 and September 2010 (382). All datasets were entered in a specially developed CDSS which was created in Microsoft Access ® (2007 & 2010). Each patient's co-morbidity burden was quantified using a computerised Charlson Co-morbidity Index (CCI) (35, 341).

PIP was assessed using the STOPP, Beers (2003) and Priscus criteria individual and in combination all of which were incorporated into a CDSS. The 2003 version of the Beers criteria was used as the updated version of Beers (2012) criteria was not published at the time that this study was undertaken. The combined set of criteria was made up of all three sets of criteria with criteria directly overlapped only being counted once, the resultant criteria contained 175 criteria.

The Clinical Research Ethics Committee of the Cork Teaching Hospital and University College Cork granted ethical approval for these studies.

5.2.2 Statistical Analysis

Statistical analysis was performed using Predictive Analytics SoftWare Statistics (PASW) (SPSS^{TM}, Inc Chicago, IL, USA) version 18. Data for each patient group were non-parametric.

The Krustal-Wallis test was used to investigate for significant statistical difference between continuous variables (e.g. age, number of medicines, instances of PIP) and the chi-square test for differences between categorical variables (e.g. gender). A p value of <0.05 was deemed to be statistically significant.

5.3 Results

5.3.1 Demographics

The median age of the combined dataset (n=900) was 80 years (IQR 74-86) (**Table 5.1**); over half of the patients were female (57.4%) (**Table 5.1**). The overall total number of medications prescribed was 7,706 (6,249 regular, 1,457 PRN) with median number of 8 medications per patient (IQR 5-12) (**Table 5.1**).

Table 5.1 Patient Demographics (n=300 per dataset).

Demographics	Overall (n=900) (n; %)	PC (n=300) (n; %)	SC (n=300) (n; %)	LTC (n=300) (n; %)	p*
Male	383 (42.6)	121 (40.3)	170 (56.7)	92 (30.7)	0.000
Female	517 (57.4)	179 (59.7)	130 (43.3)	208 (69.3)	0.000
Median age (IQR) years	80 (74-86)	77 (73-83)	77 (72-83)	85 (79-89)	0.000
Total Medications	7706	1466	2838	3402	0.000
Total Regular Medications	6249	1412	2438	2399	0.000
Total *PRN* Medications	1457	54	400	1003	0.000
Median Medications per patient (IQR)	8 (5-12)	5 (3-7)	9 (7-12)	11 (9-13)	-
Median Regular Medications per patient (IQR)	7 (4-9)	4 (3-7)	8 (5-11)	8 (6-10)	-
Median *PRN* Medications per patient (IQR)	1 (0-3)	0	1 (0-2)	3 (2-4)	-
Median CCI score (IQR)	1 (0-2)	0 (0-2)	1 (1-2)	1(1-3)	0.000

Key: IQR; Inter Quartile Range, PRN; *pro re nata* ('when required'), PC; Primary Care, SC; Secondary Care, LTC; Long Term Care, CCI; Charlson Co-morbidity Index. (* Krustal-Wallis test for continuous variables and the chi-square test for categorical variables).

5.3.2 Prescribing patterns

Table 5.2 outlines the prescribing patterns according to the ATC categories across all three setting of care. In the PC setting, the top three medication classes were (i) lipid lowering agents (n= 152; 10.4%), (ii) antithrombotic agents (n= 134; 9.1%), (iii) beta blocking agents (n= 102; 7%). In the SC setting, the top three medication classes were (i) antithrombotic agents (n= 335; 11.8%), (ii) drugs for peptic ulcer and gastro-oesophageal reflux disease (n= 178; 6.3%), (iii) analgesics and antipyretics (n= 167; 5.9%). While in the LTC setting, the top three medication classes were (i) laxatives (n= 480; 14.1%), (ii) analgesics and antipyretics (n= 294; 8.6%), (iii) drugs for peptic ulcer and gastro-oesophageal reflux disease (n= 176; 5.2%).

Table 5.2 Breakdown of the prescribed medication categories based on the Anatomical Therapeutic Chemical (ATC) classification system, across all three healthcare settings.

Medication category	PC	SC	LTC	Total (% of Total Medications) (n;%)	p*
Nervous system	184	572	1093	1849 (24.0)	0.000
Cardiovascular system	564	781	387	1732 (22.5)	0.000
Alimentary tract and metabolism	199	502	870	1571 (20.4)	0.000
Blood and blood forming organs	153	375	214	742 (9.6)	0.000
Respiratory system	98	161	218	477 (6.2)	0.000
Musculo-skeletal system	96	82	84	262 (3.4)	0.315
Anti-infectives for systemic use	10	167	51	228 (3.0)	0.000
Various	3	17	152	172 (2.2)	0.000
Genito-urinary system and sex hormones	51	58	55	164 (2.1)	0.859
Dermatologicals	14	30	119	163 (2.1)	0.000
Sensory organs	36	31	82	149 (1.9)	0.000
Systemic hormonal preparations, excl. Sex hormones and insulins	41	41	58	140 (1.8)	0.251
Antineoplastic and immune-modulating agents	12	16	11	39 (0.5)	0.52
Anti-parasitic products, insecticides and repellents	5	5	8	18 (0.2)	0.601

Key: PC; Primary Care, SC; Secondary Care, LTC; Long Term Care. (* Krustal-Wallis test for continuous variables)

5.3.3 Potentially Inappropriate Prescribing

When the combined criteria was applied to each dataset, 211 instances of PIP relating to 185 medications in 130 (43.3%) patients were identified in the PC dataset, 475 instances of PIP relating to 384 medications in 212 (70.7%) patients in the SC dataset and 902 instances of PIP relating to 665 medications in 254 (84.7%) patients in the LTC dataset (**Table 5.3**). **Figure 5.1** and **Table 5.3** illustrate the PIP prevalences determined by the combined criteria and each of the PIP criteria independently. The most frequent instances of PIP as determined by the STOPP, Beers and Priscus criteria in all three health care settings are outlined in **Tables 5.4, 5.5 and 5.6**.

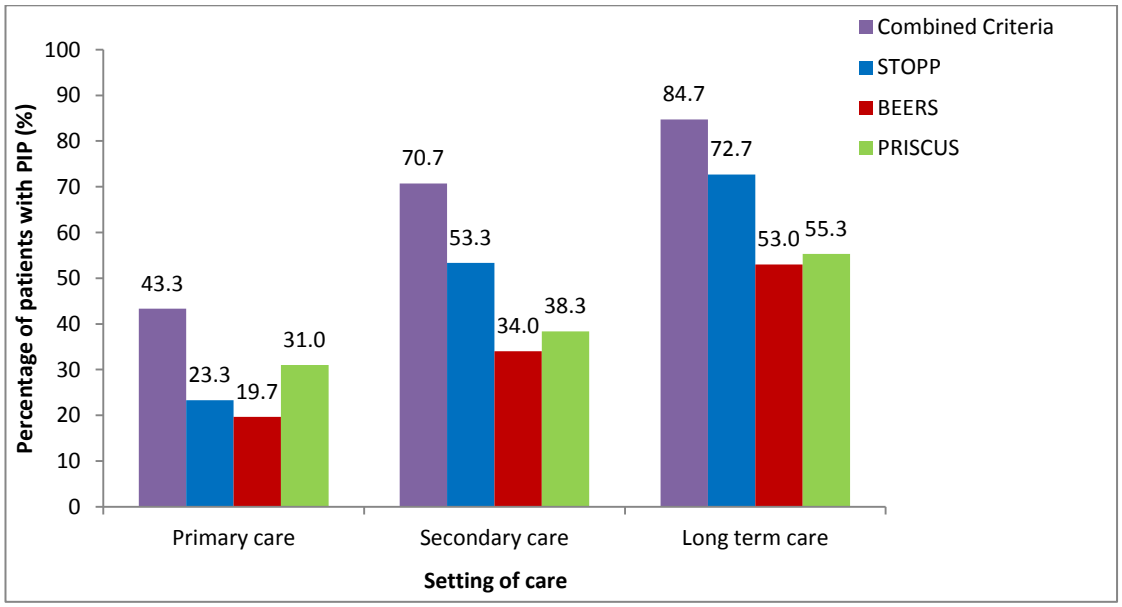


Figure 5.1 PIP prevalence determined by the Combined, STOPP, Beers and Priscus criteria across the three care settings.

Table 5.3 Number and percentage of Patients with PIP identified by the STOPP, Beers and Priscus criteria (n=300 per dataset).

Primary Care (n=300)				
PIP Frequency	**Combined criteria**	**STOPP criteria**	**Beers criteria**	**Priscus criteria**
	No. of patients (%)	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**
1	83 (27.7)	60 (20.0)	45 (15.0)	75 (25.0)
2	25 (8.3)	9 (3.0)	12 (4.0)	17 (5.7)
≥3	22 (7.3)	1 (0.3)	2 (0.7)	1 (0.3)
Total	*130 (43.3)*	*70 (23.3)*	*59 (19.7)*	*93 (31.0)*
No. of PIP instances	211	82	76	112
Secondary Care (n=300)				
PIP Frequency	**Combined criteria**	**STOPP criteria**	**Beers criteria**	**Priscus criteria**
	No. of patients (%)	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**
1	97 (32.3)	95 (31.7)	57 (19.0)	92 (30.7)
2	45 (15.0)	34 (11.3)	25 (8.3)	22 (7.3)
≥3	70 (23.3)	31 (10.3)	20 (6.7)	1 (0.3)
Total	*212 (70.7)*	*160 (53.3)*	*102 (34.0)*	*115 (38.3)*
No. of PIP instances	475	273	178	139

		Long Term Care (n=300)		
PIP Frequency	**Combined criteria**	**STOPP criteria**	**Beers criteria**	**Priscus criteria**
	No. of patients (%)	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**
1	59 (19.7)	84 (28.0)	83 (27.7)	108 (36.0)
2	53 (17.7)	44 (14.7)	29 (9.7)	45 (15.0)
≥3	142 (47.3)	90 (30.0)	47 (15.7)	13 (4.3)
Total	*254 (84.7)*	*218 (72.7)*	*159 (53.0)*	*166 (55.3)*
No. of PIP instances	902	551	339	239

Key: PIP; potential inappropriate prescribing, PRN; pro re nata ('when required'), STOPP; Screening Tool of Older Person's Prescriptions.

Table 5.4 PC, SC and LTC Top 10 STOPP PIP instances.

Instances of PIP	PC	SC	LTC	Total (% of Total PIP) (n;%)	p *
PPI at full therapeutic dosage for > 8 weeks	31	97	82	210 (23.2)	0.000
Benzodiazepines in those with recurrent falls	0	22	89	111 (12.3)	0.000
Benzodiazepines in those with recurrent falls	0	22	89	65 (7.2)	0.000
LT LA benzodiazepines with LA metabolites	11	15	30	56 (6.2)	0.003
Long term opiates in those with recurrent falls	0	14	36	50 (5.5)	0.000
NSAID with moderate-severe hypertension	6	14	24	44 (4.9)	0.013
CCB in those with chronic constipation	1	13	13	27 (3.0)	0.004
Non cardioselective β blocker with COPD	9	14	0	23 (2.5)	0.001
Long term neuroleptics as long term hypnotics	5	4	9	18 (2.0)	0.304
TCA in combination with an Opioid or a CCB	2	4	10	16 (1.8)	0.044

Key: PC; Primary Care, SC; Secondary Care, LTC; Long Term Care, PIP; Potential Inappropriate Prescribing, PPI; Proton Pump Inhibitor, LT; Long Term, LA; Long Acting, COPD; Chronic Obstructive Pulmonary Disease, NSAID; Non-Steroidal Anti-Inflammatory, TCA; Tricyclic Antidepressant, CCB; Calcium Channel Blocker. (* Krustal-Wallis test for continuous variables)

Table 5.5 PC, SC and LTC Top 10 Beers PIP instances.

Instances of PIP	PC	SC	LTC	Total (% of Total PIP) (n;%)	p *
Benzodiazepines and a history of falls	0	25	95	120 (20.2)	0.000
Depression and LT benzodiazepine or sympatholytic agents	14	16	39	69 (11.6)	0.000
Constipation and CCBs or anticholinergics or TCAs	2	25	31	58 (9.8)	0.000
Chlordiazepoxide and diazepam	6	13	22	41 (6.9)	0.007
Cognitive impairment and barbiturates, anticholinergics, antispasmodics, muscle relaxants and CNS stimulants	0	6	24	30 (5.1)	0.000
Doxazosin	15	10	5	30 (5.1)	0.076
Bladder outflow obstruction and anticholinergics or antihistamines or GI antispasmodic drugs or muscle relaxants or antidepressants or decongestants.	1	11	15	27 (4.6)	0.011
Stress incontinence and α- blockers, anticholinergics, TCAs and LA benzodiazepines.	1	0	23	24 (4.0)	0.000
GI antispasmodic drugs: dicyclomide, hyoscyamine, propantheline and belladonna alkaloids	0	14	10	24 (4.0)	0.001
Flurazepam	5	7	9	21 (3.5)	0.557
Gastric or duodenal ulcers and NSAIDs or aspirin	8	9	2	19 (3.2)	0.203
Amitriptyline	4	5	10	19 (3.2)	0.189
Daily fluoxetine	8	1	5	14 (2.4)	0.068

Key: PC; Primary Care, SC; Secondary Care, LTC; Long Term Care, PIP; Potential Inappropriate Prescribing, PPI; Proton Pump Inhibitor, LT; Long Term, LA; Long Acting, GI; gastro-intestinal, CNS; Central Nervous System, NSAID; Non-Steroidal Anti-Inflammatory, TCA; Tricyclic Antidepressant, CCB; Calcium Channel Blocker. (* Krustal-Wallis test for continuous variables)

Table 5.6 PC, SC and LTC Top 10 Priscus PIP instances.

Instances of PIP	PC	SC	LTC	Total (% of Total PIP) (n;%)	p *
Digoxin	12	32	22	66 (13.5)	0.007
Alprazolam	11	7	33	51 (10.4)	0.000
Temazepam	7	2	32	41 (8.4)	0.000
Triazolam	9	17	13	39 (8.0)	0.277
Diazepam	5	10	21	36 (7.3)	0.003
Doxazosin	17	12	5	34 (6.9)	0.036
Zolpidem (>5.0 mg/d)	4	7	21	32 (6.5)	0.000
Zopiclone (>3.75 mg/d)	3	9	12	24 (4.9)	0.068
Flurazepam	5	7	9	21 (4.3)	0.557
Amitriptyline	4	5	9	18 (3.7)	0.304
Fluoxetine	8	1	5	14 (2.9)	0.068

Key: PC; Primary Care, SC; Secondary Care, LTC; Long Term Care, PIP; Potential Inappropriate Prescribing. (* Krustal-Wallis test for continuous variables)

5.3.4 Number of PIP criteria deployed by each set of criteria in each care setting

The relevance of any set of PIP criteria is determined by the degree of applicability of the constituent criteria, i.e. the number of the criteria utilised in any PIP prevalence assessment. In the present study, the number of PIP criteria deployed in each care setting according to the Beers, STOPP, Priscus and the combined set of criteria are demonstrated in **Table 5.7**. Observation from the PC to SC, to the LTC settings show that an increasing number of criteria being deployed with each set of criteria. In all three settings more of the combined set of criteria were deployed than any of the individual criteria in isolation.

Table 5.7 Number of PIP criteria deployed in the PC, SC and LTC datasets.

Criteria	PC	SC	LTC
Combined criteria (n=175)	48	64	74
STOPP criteria (n=65)	19	36	41
Beers criteria (n=68)	17	23	25
Priscus criteria (n=83)	27	29	31

Key: PC; Primary Care, SC; Secondary Care, LTC; Long Term Care, STOPP: Screening Tool of Older Person's Prescriptions.

5.3.5 Statistical comparison of PIP between the 3 healthcare settings

Using the Kruskal-Wallis test, we found a statistically significant difference in the number of PIP instances identified in each healthcare setting, when each set of PIP criteria was applied individually and when the combined set of criteria was applied. **Combined PIP instances** H (2, n=900) = 188.432, $p < 0.05$; PC: 308.87, SC: 451.41; LTC: 591.22, **STOPP PIP instances** H (2, n=900) = 189.957, $p < 0.05$; PC: 312.94, SC: 455.52; LTC: 583.04, **Beers PIP instances** H (2, n=900) = 83.179, $p < 0.05$; PC:398.59; SC: 430.95; LTC: 521.96 and **Priscus PIP instances** H (2, n=900) = 47.122, $p < 0.05$; PC:371.98; SC: 443.38; LTC: 536.14.

5.4 Discussion

This is the first study to compare the applicability of the three most commonly used PIP criteria in a European context with each other, while also comparing each with a combined tool made up of all three criteria across a 3 different healthcare settings. Each set of criteria identified an increasing prevalence of PIP from PC to SC to LTC. These findings correlate with the existing evidence, which indicates that as the complexity of care and level of patient frailty increases, from PC to LTC, so too does the number of medications prescribed, the level of co-morbidity and the prevalence of PIP (**Table 5.1 and 5.3**) (379).

Some may question the rationale behind using an amalgamated set of criteria, ideally the most comprehensive PIP review would involve deploying all three sets of criteria consecutively, i.e. applying 65 STOPP criteria, 68 Beers criteria and 83 Priscus criteria. This would result in a total of 216 criteria having to be applied, whereas the amalgamated set of criteria which has the overlapping criteria removed and only contains 175 criteria. Application of 216 or even 175 criteria in routine clinical practice would prove quite challenging; however one possible solution involves the computerisation of the PIP screening process, therefore the number of criteria is theoretically irrelevant.

The overall prevalences of PIP reported in PC in the present study using each set of criteria are consistent with those reported in the literature (43, 95). In the PC datasets the combined criteria identified the highest prevalence of PIP, followed by Priscus criteria, STOPP criteria and Beers criteria. The PIP prevalences reported in the PC dataset is consistent with the prevalences of 31.9% previously reported by Regueiro et al. in a PC population from Spain (381).

The high prevalence of PIP determined by Priscus criteria in the PC dataset was somewhat unexpected, as Priscus criteria identified a higher PIP prevalence than STOPP criteria, which was originally developed for use in Ireland, although since its development, several studies have demonstrated its applicability globally (44, 305, 379, 385-386). However, this high prevalence could in part be attributable to the high level of PIP of digoxin and doxazosin identified in the PC dataset. Although caution is advised when using digoxin and doxazosin in older individuals, in Ireland, prescription of these medications is generally considered reasonable and safe. They may be inappropriate when used under certain circumstances that are (i) use of high dose digoxin in advanced renal impairment and (ii) use of doxazosin as first line mono-therapy for hypertension (12, 38-39, 111, 125).

In the SC dataset the combined criteria identified the highest prevalence of PIP, followed by STOPP criteria, Priscus criteria and then Beers criteria. The PIP prevalences reported in this setting were consistent with the prevalences reported previously both nationally and international for the Beers and the STOPP criteria of 3.7-77.3% (314, 378).

In the LTC setting, once again the combined criteria identified the highest prevalence of PIP, followed by STOPP criteria, Priscus criteria and then Beers criteria, consistent with previously published data (311, 367).

The most common instances of PIP identified in each dataset are outlined in **Table 5.4-5.6**. These PIP instances identified in this paper are consistent with the common instances of PIP reported in other international studies (9, 33-36, 62, 91, 117, 299, 314, 367, 379, 387).

As stated above, the combined criteria identified the highest prevalences of PIP in all three settings of care. STOPP criteria identified the second highest prevalences of PIP in the SC and LTC datasets, while Priscus criteria identified the second highest prevalence of PIP in the PC dataset.

However the controversial PIP instances relating to doxazosin and digoxin are excluded, the adjusted PIP prevalences identified by Beers criteria are 15.3%, 31.3% and 52.3%, adjusted data for Priscus criteria are 23.3%, 26.7% and 52.0% for the PC, SC and LTC datasets respectively.

Disparities between the prevalences observed with the three individual sets of criteria could be explained in part by the fact the STOPP criteria were originally developed in Ireland and are based on medications licensed for use in Ireland, whereas the Beers criteria were developed in North America and are based on medications licensed in the North American market. Similarly the Priscus criteria were developed for use in Germany and are based on medications available in the German pharmaceutical market. Therefore it is not surprisingly that 27 of the medications in Beers criteria and 23 of the medications on the Priscus list are not licensed in Ireland.

A key difference between the STOPP and Priscus criterion are that STOPP criteria mainly assess PIP on the basis of medication classes while Priscus criteria are focus more on specific medicines. Also the lower prevalences of PIP recorded with the Priscus and Beers criteria may reflect differences therapeutic guidelines and/or prescribing practices between the countries of development and Ireland (15-16, 38, 47, 318).

All four sets of criteria identified high prevalences of PIP, but this study shows that using a CDSS which can deploy a combined criteria made up of all three sets of criteria concurrently, will provides the most comprehensive PIP assessment.

Individually, STOPP criteria appear to be the most applicable PIP screening tool for identification of PIP across all healthcare settings in Ireland. However Beers criteria especially Beers ID criteria and Priscus criteria may also have some potential, particularly in the PC setting, where reviewers often have limited access to data, as PIP instances can be identified independent of diagnosis i.e. independent of detailed clinical data. One major advantage of Priscus criteria over the other two sets of criteria, is that apart from highlighting instances of PIP, it also recommends alternatives and provides cautionary advice if a potentially inappropriate medicine (PIM) is intended to be used. However a major limitation of both Beers and Priscus criteria is their lack of comprehensiveness due to a lack of coverage of issues such as drug-drug interactions, and drug class duplication. Another major limitation of Priscus criteria is that it has not yet shown to have impacted on key outcomes such as morbidity and ADR incidence, unlike STOPP and Beers criteria (44, 82, 112, 120, 177, 214, 323, 344).

Some may argue that if two thirds of the combined criteria are not deployed, then they are simply not relevant and therefore they should probably be omitted or ignored when developing a new set of combined criteria. However the criteria which are rarely encountered may in fact be the very instances that result in significant adverse effects. Therefore the authors decided removal of such criteria would be unjustified.

Also there are a number of criteria which relate to PIMs that may not be readily available in an Ireland and therefore it could be argued that these criteria are not relevant in an Irish context. Alternatively there may be a several criteria relating to PIMs that are available in Ireland, but may not be readily available in other countries and therefore it may be argued that such criteria may not be applicable in these other countries. However, in most countries there is the potential for unlicensed use of certain medications, i.e. the prescribing of medications that are not licensed in that particular country, but are available in another country so they can be prescribed. This being the case, there is a potential for these medications to be prescribed. When preparing a set of criteria it is desirable to make them as generalisable, comprehensive and clinically relevant as possible, therefore the set of criteria should be as broad and as inclusive as possible in order to capture the majority of PIP instances. However this may lead to an exhaustive list of PIP criteria, which, if the criteria are being deployed manually may be a major problem, but if the criteria are integrated into a CDSS, the number of criteria is theoretically insignificant, making a very strong case for electronic deployment of the PIP criteria.

5.4.1 Limitations

This work has a number of important limitations. Lack of generalisability is one of the main limitations. The three datasets used in this were compiled from randomly selected samples of patients from larger datasets in the greater Cork region, which had been previous compiled by our research group. Due to the fact that the data collection was confined to a limited jurisdiction, it may be difficult to generalise these findings to all older individuals across the entire Island of Ireland or elsewhere. However, it does give some indication of the prevalence of PIP in older Irish individuals across all healthcare settings.

Another important limitation of this work relates to the fact that the data collection for the three datasets was performed by two different research pharmacists. Using two different pharmacists to collect the data may have introduced some degree of variability in the detail and interpretation of the data.

Another important limitation of this work, relates to the variability in the quality of the data recorded for each of the patients across the three settings. The quality of the data recorded was found to vary considerably from setting to setting and this may have resulted in either under or over estimation of the prevalence of PIP. One possible means of addressing this issue in the future would be to be standardise how the medical data are recorded and stored, by using the same standardised electronic medical record system across all three settings of care. This would allow for standardisation of data, while also facilitating analysis of data for auditing and quality improvement purposes.

5.5 Conclusion

This study highlights high prevalences of PIP among older individuals in all care settings in Ireland, which increased from primary to secondary to long-term care. STOPP criteria appear to be a more applicable screening tool for identification of PIP in older individuals across all settings of care. However the most comprehensive PIP assessment would involve applying all three PIP criteria simultaneously. Therefore an intervention strategy in the form of a CDSS, which facilitates the routine application all three sets of criteria concurrently, would probably be the most effective way of reducing PIP and its associated ADRs in older individuals across all three healthcare settings in Ireland.

Chapter 6

6. Prevention of adverse drug reactions in hospitalised older patients using a software-supported structured pharmacist intervention: a randomised controlled trial.

In this study, I was involved in the drafting of the grant proposal and the development of the study design. I prepared and submitted the ethics application for this study and registered the trial with the United States National Institutes of Health. I built the computerised decision support system (E-Pharma-Assist) to support the structured pharmacist review of medications (SPRM). I undertook the data collection within 48 hours of admission and performed the SPRM intervention. I performed the pharmaceutical care interventions and communicated these to the patient's primary physicians. I also undertook the follow-up review (at 7-10 days or discharge whichever came first) and I undertook the ADR detection using the pre-defined ADR trigger list. I also performed the statistical analysis in this study.

6.1 Introduction

Adverse drug reactions (ADRs) represent a major public health problem in the globally expanding older population (19-20, 186). Multi-morbid illness and associated polypharmacy, coupled with age-related pharmacokinetic and pharmacodynamic changes predispose older people to ADRs (19, 21, 186). In a recent review, Petrovic et al. reported that the average incidence of ADR-related acute hospital admissions was four times higher in older people than in younger people and that up to 88% of these ADRs are preventable; the average incidence of ADRs during hospitalization was 14% (186). In 2005, Passarelli et al. reported a 46% incidence of hospital-acquired ADR, whilst in our centre; we have recently found an in-hospital ADR incidence of 26% (178-179). The higher rates of ADR-related morbidity and mortality in elderly hospitalized patients results in higher investigation and treatment costs and extended length of stay (LOS) (19, 21, 166, 174).

Various interventions have been designed to minimize inappropriate prescribing and curtail hospital-acquired ADRs in older individuals, e.g. Comprehensive Geriatric Assessment, computerized decision support software (CDSS), prescriber education initiatives and structured pharmacist review of medication (SPRM) (19-20, 48, 52, 80, 178, 186). The data on SPRM are encouraging, but limited in scope. In 2006, Spinewine et al. (48) described a SPRM specifically designed for older hospitalized patients. In a subsequent randomised controlled trial (RCT), the SPRM intervention significantly improved medication appropriateness and reduced underutilization of appropriate drug therapy; however, ADRs were not reported as an outcome measure (118). In 2009, Murray et al. reported a 34% reduction in adverse drug events (ADEs) from the application of a SPRM in middle-aged and older hypertensive out-patients with cardiovascular complications, which used a software approach for post-hoc ADE detection (280). These studies suggest that SPRM interventions, supported by appropriate and versatile software, may be an effective means of reducing ADR incidence in older hospitalised patients.

In a recent review, Mueller et al. identified a number of trials which describe interventions designed to attenuate drug-related problems (DRPs) in hospitalized patients (286). The 26 selected studies describe, 15 pharmacist-related, 6 information technology (IT) and 5 miscellaneous interventions. The authors concluded that these interventions consistently reduced medication discrepancies, potential and actual ADEs, but showed inconsistent effects on post-discharge healthcare utilization. With only one of the studies utilised a pharmacist review supported by a computerized medications reconciliation system as a means of reducing potential ADEs (388). However, this study was not exclusive to older patients, did not measure actual

ADEs, showed an inconsistent intervention effect (i.e. the intervention worked in only one of the two participating hospitals), had a complex medication reconciliation design, and involved the use of an IT application that was not fully integrated with the hospital's IT systems until the latter stages of the study. Despite these deficiencies, an intervention based on a SPRM supported by an IT application for medications reconciliation appeared to be potentially effective for minimizing ADRs in older hospitalized patients.

In this study, we aimed to (i) design an SPRM supported by a customized CDSS for reducing ADRs in older hospitalized patients, and (ii) to test this SPRM/CDSS intervention in a prospective RCT in a population of older people admitted to hospital with acute unselected illnesses.

6.2 Methods

6.2.1 Setting and participants

We conducted a RCT in an 810 bed teaching hospital in the Munster region of southern Ireland. All patients aged ≥ 65 years admitted under the care of the medical or surgical services through the emergency department were eligible for inclusion. We excluded patients if they were (i) aged < 65 years, (ii) admitted to psychiatric services, (iii) admitted to the Intensive Care Unit, (iv) admitted to specialist geriatric or clinical pharmacology services or had attended these services in the previous 12 months, (v) terminally ill, (vi) expected to have a LOS < 48 hours, (vii) previously recruited into the study or (viii) admitted electively.

6.2.1.1 Randomisation

We screened and recruited patients into the trial between June 2011 and June 2012. We cluster-randomized the admitting consultants and their teams into two groups prior to study initiation, i.e. intervention or control consultants. We allocated consultants via a random-number table generated from Microsoft Excel software 2010 (Microsoft Office 2010 ®). A consultant from each speciality was represented in each arm of the trial. At admission, based on the consultant assigned primary responsibility for the patient's care, they were allocated to one of two groups, i.e. (i) usual pharmaceutical care (control group) or (ii) SPRM intervention supported by a CDSS designed to optimize geriatric pharmaceutical care (intervention group).

6.2.1.2 Participant recruitment and consent

Within 48 hours of admission, we assessed patients for trial enrolment and obtained written informed consent from patients who fulfilled inclusion criteria; in the case of patients with cognitive impairment, we sought consent from the patients' next-of-kin. The research pharmacist limited recruitment to a maximum of 3 eligible

intervention and 3 control patients from the daily patient admission list, due to the large numbers of older patients being assessed in the emergency department daily.

The regional biomedical ethics committee approved the trial protocol and we subsequently registered the trial with the United States National Institutes of Health (NCT01467128) http://clinicaltrials.gov/show/NCT01467128.

6.2.1.3 Baseline data collection

The research pharmacist undertook an interview with each patient and/or their next-of-kin/carer as well as a detailed review of the medical notes, medication Kardex® and blood laboratory data. The following information was recorded: (i) demographic information, (ii) detailed up-to-date list of medications, (iii) list of current and past medical conditions, (iv) routine laboratory blood results, (v) cognitive function as defined by the abbreviated mental test score (AMTS) (389), and (vi) functional status quantified by the Barthel Index (390).

This information was recorded in a specially developed CDSS (E-Pharma-Assist) (Appendix VI) in order to standardize data entry process and to complement the delivery of the pharmaceutical care by enabling the pharmacist have access to all relevant prescribing information (i.e. drug monographs and current British National Formulary) and clinical information, simultaneously. The patient's co-morbidity was quantified using the Cumulative Illness Rating Scale (CIRS) (391).

All medications at the point of data entry were coded according to the World Health Organisations' (WHO) Anatomical Therapeutic Chemical (ATC) classification system (339), and all medical conditions were coded according to the WHO International Classification of Diseases version 10 (ICD-10).

6.2.1.4 Control group

Control patients received usual care, i.e. routine medical and pharmacist review, depending on their condition. The hospital pharmacists performed pharmaceutical reviews within 24-72 hours of admission for the majority of patients (approximately two-thirds) throughout the study period. The hospital pharmacists undertook these reviews independently of the attending medical team and routinely communicated any identified DRPs in writing or verbally to the medical teams.

6.2.1.5 Pharmacist intervention

Post recruitment the research pharmacist undertook a comprehensive medication reconciliation and appropriateness review. This review was multifaceted, and a number of PIP criteria and reference sources were integrated into the E-Pharma-Assist system to optimise the review process (**Figure 6.1**).

The research pharmacist was present in the hospital 5 days a week, Monday to Friday. Due to the high volume of older patients attending A&E on a daily basis and in order to facilitate a full and comprehensive review and subsequent follow-up, recruitment for each arm of the study was limited to the first three consecutive patients on the bed list / register each day who met the inclusion criteria.

The patients in the intervention group received usual medical and pharmaceutical care in combination with the SPRM/CDSS. The SPRM/CDSS intervention consisted of 4 parts and is outlined in **Figure 6.1**.

The interventions generated by the E-Pharma-Assist system were reviewed by the research pharmacist and a pharmaceutical care plan was generated, which outlined all of the clinically relevant interventions at the point of review. Clinical relevance was assessed by the research pharmacist and was based on the clinical appropriateness/relevance of each intervention at the time of review (i.e. weighing up the risk-benefit ratio for initiation or discontinuation of a certain medication) (**Figure 6.1**). The interventions addressed DRPs (48, 392) i.e. medications reconciliation issues and appropriateness issues relating to both new and long-term medications which were prescribed on both a regular or prn (as-needed) basis.

The interventions were then communicated in writing to the hospital physicians with primary responsibility for the patients care (where possible the recommendations were verbally communicated) (**Figure 6.1**). The research pharmacist was also available to the medical teams to answer queries about specific medications or interventions.

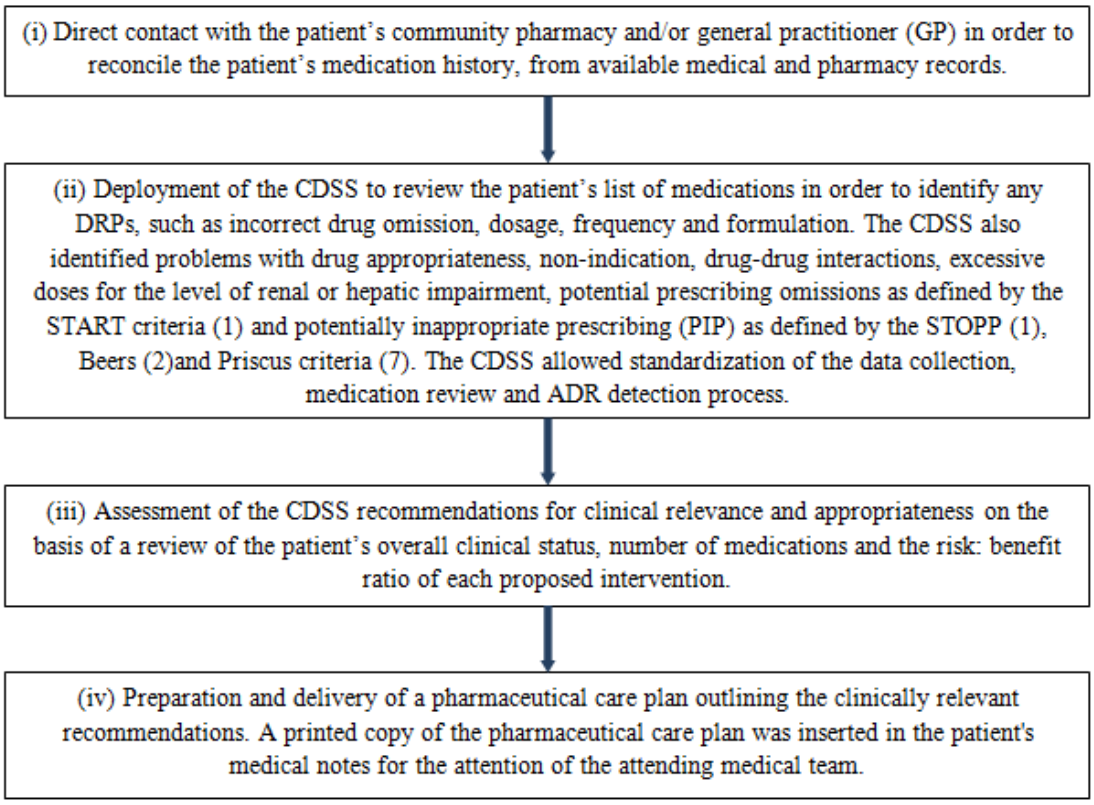


Figure 6.1 Description of pharmacist intervention

6.2.2 Outcome measures

The primary outcome for this study was the proportion of patients in either group who experienced a non-trivial ADR during their hospital stay. For this study, 'non-trivial' ADRs were those that required immediate dose adjustment or drug discontinuation, reversal of drug effect with appropriate treatment or antidote, resulted in severe physiological instability requiring intensive therapy, or caused death.

The secondary outcomes were:

(i) Median hospital LOS (in days).

(ii) Hospital mortality rate.

6.2.2.1 ADR detection

In this study, we used the WHO ADR definition, i.e. "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function" (393).

The research pharmacist performed ADR ascertainment, facilitated by the use of a pre-defined ADR trigger list consisting of the most common clinical manifestations of proven ADRs, derived from a combined database of two recent studies of 600 (120) and 513 (178) of elderly hospitalized patients. The trigger list is illustrated in **Table 6.1**.

Table 6.1 Trigger List of Adverse Drug Reactions.

Trigger Symptom/Clinical Phenomenon	Medicines commonly associated with ADRs as defined by the Trigger List
Falls (i.e. one or more falls following randomization)**/New onset movement disorder**	Benzodiazepines, hypnotics, neuroleptics, opioids
AKI (i.e. estimated GFR reduced by 50% and/or a twofold increase in serum creatinine concentration and/or urine output ≤ 0.5mls/kg/hr for 12 hours).	Non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors, angiotensin receptor blockers.
Significant electrolyte derangement (i.e. serum sodium <130 mmol/l or > 150 mmol/l; serum potassium < 3.0 mmol/l or > 5.5 mmol/l; corrected serum calcium > 2.6 mmol/l).	Non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors, angiotensin receptor blockers.
Orthostatic hypotension symptomatic or not (i.e. reduction in systolic blood pressure ≥20 mmHg and/or diastolic blood pressure ≥10 mmHg from supine to erect posture).	Vasodilators, antihypertensives
Bradycardia (i.e. heart rate = 40 beats per minute symptomatic or not or heart rate <60 beats per minute with symptoms of lightheadness, dizziness, fatigue and/or dyspnoea).	Beta-blockers, digoxin, verapamil, diltiazem
Major constipation (i.e. No bowel motion for ≥72 hours or requiring daily laxatives).	Opioids, Tricyclic antidepressants, verapamil, anticholinergic antispasmodics
Bleeding (i.e. causing a drop in haemoglobin concentration > 2 g/dl or requiring blood transfusion or cessation of antiplatelet or anticoagulant therapy or prescription of an antidote (e.g. vitamin K for warfarin reversal).	Anti-platelet agents, anti-coagulants
Dyspepsia (i.e. early satiation or epigastric pain or epigastric burning or postprandial fullness).	Non-steroidal anti-inflammatory drugs, Anti-platelets, corticosteroids
Diarrhoea (i.e. ≥3 loose stools in 24 hours or a score of ≥6 in the Bristol Stool Chart)	Antibiotics, metformin, acetylcholinesterase inhibitors, colchicine
Acute Cognitive Deterioration (i.e. reduction in AMTS ≥2 points from admission AMTS).	Benzodiazepines, hypnotics, neuroleptics, opioids
Other	• Recognised adverse effect of the drug or • Requires discontinuation of the drug or • Requires medical intervention to reverse, alleviate or attenuate the adverse effect of the drug (e.g. antidote, dialysis, non-invasive or invasive ventilation).

Key AKI; Acute Kidney Injury, GFR: Glomerular Filtration Rate; kg; Kilogram, g; gram, dl; Decilitres, ACE; Angiotensin Converting Enzyme, ADR; Adverse Drug Reaction

For each suspected ADR, the primary researcher recorded details of the suspect medication(s), i.e. dose, formulation and duration, as well as a description of the putative ADR and any actions taken to resolve it. A clinically-trained physician (MO'C) reviewed and verified all putative ADRs identified by the primary researcher. Only ADRs verified by the physician rater were included in the analysis. Subsequently, two experienced pharmacists who independently assessed the verified ADRs using WHO-UMC ADR causality criteria (198), Hallas ADR preventability criteria (203) and Hartwig ADR severity criteria (211). The purpose of this additional pharmacist assessment was to establish whether or not there was a high level of inter-rater agreement on ADR causality, preventability and severity between pharmacists.

At 7-10 days post-admission or at discharge (whichever came first), the primary researcher conducted a follow-up review of each patient's medical notes, nursing notes and medication Kardex®. This allowed (i) ascertainment of any ADRs that had occurred since admission and (ii) evaluation of up-take of recommended interventions. In cases of uncertainty regarding any adverse clinical event that might/might not represent an ADR, the primary researcher contacted a member of the attending medical team or nursing staff in order to clarify the nature of these adverse clinical events.

6.2.3 Statistical Analysis

We calculated median and inter-quartile range (IQR) for the non-parametric data. We used chi-square statistics to compare categorical variables between the groups and used the Mann-Whitney U-test to compare continuous variables between the groups.

We calculated absolute and relative ADR risk reduction statistics, in the event of a lower ADR incidence in the intervention group compared to controls. We used the PASW® statistics software package for all statistical analyses, taking a p-value of < 0.05 as significant.

6.2.4 Sample Size

We used an ADR incidence estimate of 26%, based on recent data from our research group (120, 178). We calculated that an absolute reduction of 7% in hospital-acquired ADRs resulting from the SPRM/CDSS intervention would have clinical relevance. Using a one tailed test design with an 80% power of detection of a significant difference between the intervention and control groups at the 95% confidence limit, we calculated that 356 patients were required in each arm of the study. However when a two tailed test design is used using the same 80% power of detection and a 95% confidence limit, 420 patients are required per arm of the study.

The one tailed test design was chosen because it was hypothesized that the intervention would result in a unidirectional positive impact on the ADR incidence. This assumption was made based on previous intervention studies undertaken by our research group, which had used similar types of interventions focused at optimizing pharmacotherapy in older individuals. All of these studies had produced positive

unidirectional impacts on the patient related outcomes of interest i.e. PIP prevalence and ADR incidence.

However in hindsight this assumption was probably somewhat optimistic and a two tailed test design would have been more appropriate, as in reality the intervention could have led to a bi-directional impact (i.e. resulting in a positive or negative impact) on the ADR incidence in this patient population.

6.2.5 Role of funding source

The funding body (Health Research Board of Ireland) had no role in the design or conduct of this study. Neither had it any influence on the study data analysis, interpretation or in the writing of this report.

6.3 Results

6.3.1 Participant flow

Over the 12 month study period, we screened 1833 patients for inclusion in the trial. Four hundred and forty nine patients did not fulfil the inclusion criteria and 647 patients were not recruited due to time constraints (**Figure 6.2**). We randomized 361 patients to receive the SPRM/CDSS intervention and 376 patients to receive usual hospital pharmaceutical care (control arm). Thirty four patients (17 intervention and 17 control patients) died during their index hospital stay; these patients were included in the final analysis on the basis of intention to treat.

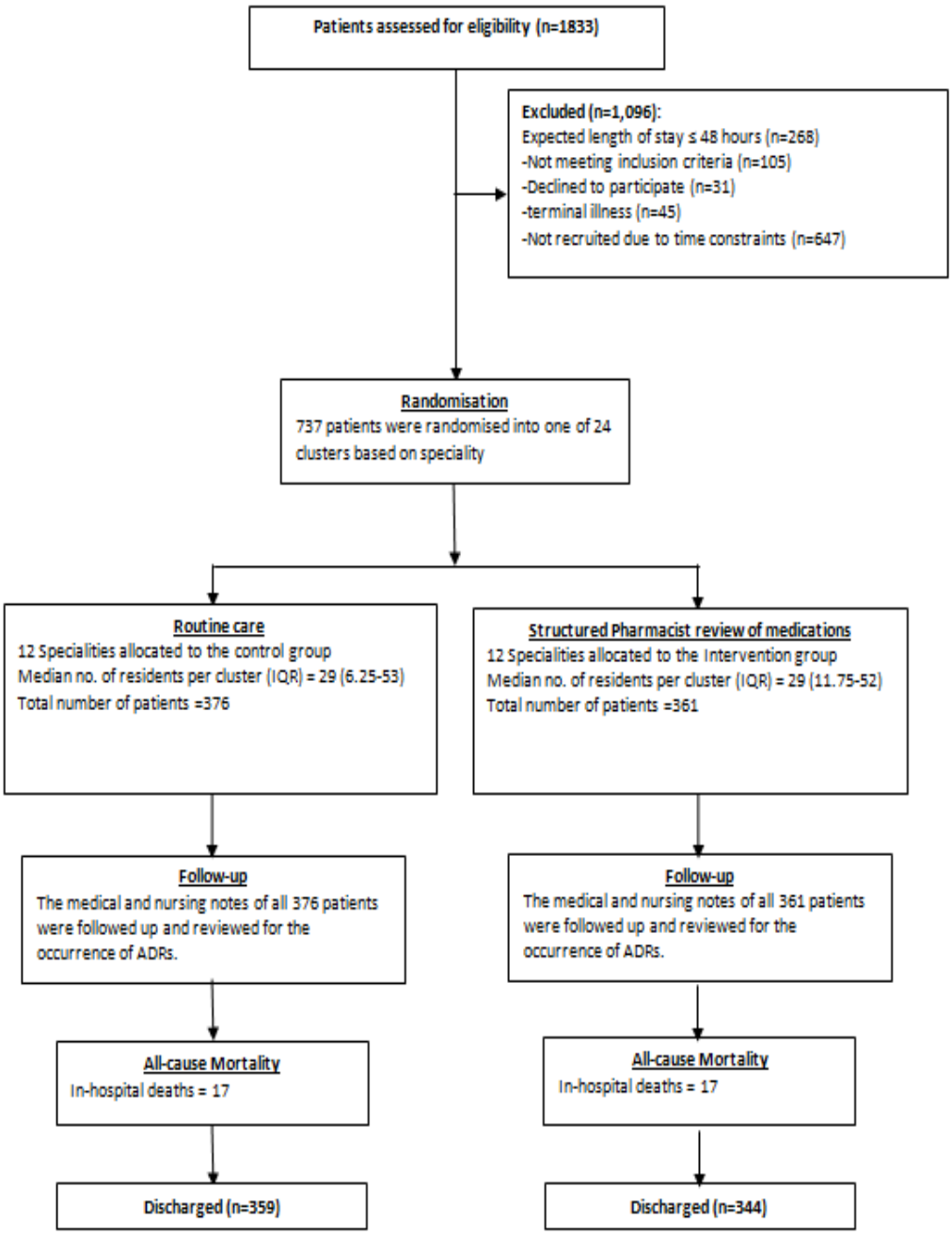


Figure 6.2 Trial Profile

6.3.2 Baseline characteristics

We found no significant differences between the groups in terms of age, gender, functional status, cognitive function or number of medications at entry to the study (**Table 6.2**).

Table 6.2 Baseline and Follow-up Characteristics of Study Population.

Variable		Control (n=376)	Intervention (n=361)	p*
Age	Median (IQR)	78 (72-84)	77(71-83)	0.057
Male	n (%)	190 (50.5%)	180 (49.9%)	0.914
Female	n (%)	186 (49.5%)	181 (50.1%)	0.914
AMTS*	Median (IQR)	10 (9-10)	10 (9-10)	0.681
Cumulative Illness Rating Scale (CIRS)	Median (IQR)	4 (3-6)	5 (3-6)	0.899
Barthel Index	Median (IQR)	19 (16.25-20)	19 (18-20)	0.224
Living independently	n (%)	345 (91.8%)	338 (93.6%)	0.404
Nursing Home resident	n (%)	31 (8.2%)	23 (6.4%)	0.404
Medications (total) at admission	n	3255	3163	0.421
Medications per patient at admission	Median (IQR)	8 (6-11)	9 (6-12)	0.421
Polypharmacy (≥ 5 medications)	n (%)	321 (85.4%)	305 (84.5%)	0.816
Medications (total) at follow-up	n	3747	4192	<0.000
Medications per patient at follow-up	Median (IQR)	9 (7-12)	12 (8-15)	<0.000
Polypharmacy at follow-up (≥ 5 medications)	n (%)	346 (92.0%)	346 (95.8%)	0.44

Key: AMTS; Abbreviated mini mental test score. (* Mann-Whitney U test for categorical variables and chi-square test for categorical variables).

The two populations had similar prevalence of underlying chronic medical conditions, except for atrial fibrillation and osteoporosis (**Table 6.3**).

Table 6.3 Breakdown of the 10 Most Common Underlying Conditions per Population.

Variable		Control (n=376)	Intervention (n=361)	p*
Hypertension	n (%)	229 (60.9%)	201 (55.7%)	0.150
Ischaemic heart disease	n (%)	108 (28.7%)	123 (34.1%)	0.137
Hypercholesterolaemia	n (%)	116 (30.9%)	122 (33.8%)	0.438
Atrial fibrillation	n (%)	86 (22.9%)	114 (31.6%)	0.010
Osteoarthritis	n (%)	75 (19.9%)	75 (20.8%)	0.851
Heart failure	n (%)	61 (16.2%)	68 (18.8%)	0.403
Diabetes	n (%)	69 (18.4%)	71 (19.7%)	0.718
COPD	n (%)	62 (16.5%)	57 (15.8%)	0.874
Osteoporosis	n (%)	59 (15.7%)	35 (9.7%)	0.020
Hypothyroidism	n (%)	43 (11.4%)	36 (10.0%)	0.601

Key: COPD; chronic obstructive pulmonary disease. (* Chi-square test)

6.3.3 Intervention recommendations

All 361 intervention patients received the SPRM, however a pharmaceutical care intervention was generated in only 296 (82.0%) of the patients. The SPRM/CDSS intervention generated 1000 recommendations which were communicated as a printed report to the attending medical teams. Five hundred and seventy seven recommendations (57.7%) related to medication appropriateness, whilst 423 (42.3%) recommendations dealt with reconciliation issues. The physicians in the intervention group implemented a total of 548 recommendations (54.8%), the details of which are shown in **Table 6.4**.

Table 6.4 Breakdown of SPRM/CDSS Clinically Relevant Interventions

Type of Recommendations	Number. of Recommendations	Recommendations accepted n (%)
Appropriateness Issues:	577	222 (38.5%)
• Indication	47	18 (38.3%)
• Interactions	73	29 (39.7%)
• Renal Adjustment	25	13 (52%)
• Appropriateness Tools (STOPP, Beers, PRISCUS, START criteria)	341	135 (39.6%)
• Miscellaneous Appropriateness Issues	91	27 (29.7%)
Reconciliation Issues:	423	326 (77.1%)
• Dosage	95	69 (72.6%)
• Missing Medications	322	252 (78.3%)
• Miscellaneous Reconciliation Issues	6	5 (83.3%)

Key: STOPP; Screening Tool of Older Person's Prescriptions; START; Screening Tool to Alert doctors to Right Therapy.

6.3.4 Outcome Measures

6.3.4.1 Primary outcome measure

In the 361 intervention patients, 61 ADRs occurred in 50 patients (13.9%). We defined 33 ADRs as 'probable' and 28 ADRs as 'possible' according to WHO-UMC ADR causality criteria. Ten patients (2.8%) experienced more than one ADR. Eighteen of the 61 ADRs were classified as mild, 36 were moderate and 7 were severe. The most common ADRs in the intervention group are illustrated in **Table 6.5**. Of the 61 ADRs detected in the intervention patients, 31 were classified as definitely avoidable (50.8%), 23 as possibly avoidable (37.7%) and 7 as unavoidable (11.5%) by the Hallas criteria (203). Fifteen of the 61 ADRs in the intervention group could have been avoided through application of the SPRM/CDSS; in 11 of these 15 ADRs, the primary researcher communicated SPRM/CDSS-derived advice to the attending medical team (**Table 6.6**). Four of these 15 ADRs related to drugs commenced post-intervention. None of the ADRs in the intervention group was attributable to medications initiated as part of the SPRM/CDSS intervention.

In the 376 control patients, 91 ADRs were recorded in 78 patients (20.7%). Of the 91 ADRs, one was defined as certain, 65 were deemed probable and 25 were deemed possible. Fifteen control patients experienced more than one ADR. Fifteen ADRs were classified as mild, 59 as moderate and 17 as severe. Sixty two of the ADRs were classified as definitely avoidable (68.1%), 20 possibly avoidable (32.3%) and 9 unavoidable (14.5%) according to Hallas criteria (203). The most commonly encountered ADRs in the control group are outlined in **Table 6.5**. Thirty eight of the 91 ADRs in the control group (41.8%) related to medications that could have detected by the SPRM/CDSS intervention (**Table 6.6**).

Table 6.5 ADR Details in Control and SPRM/CDSS Intervention Groups.

Drug	Adverse Drug Reaction	Control (n=91)	Intervention (n-=61)
Opioids	Delirium/falls/constipation	29	31
Diuretics	Acute kidney Injury/ Electrolyte disturbance	14	7
Anti-hypertensives (excluding ACEi*/ARB)**	Symptomatic orthostatic hypotension/ Symptomatic bradycardia	13	3
Benzodiazepines	Falls/sedation/cognitive decline	6	1
ACE inhibitor/ARB	Acute kidney injury/hyperkalaemia	4	6
Antibiotic therapy	*Clostridium difficile* diarrhoea	5	2
Anti-coagulants	Bleeding requiring transfusion +/- Intervention	3	1
Others	Miscellaneous	17	10

Key: ACEi; Angiotensin Converting Enzyme inhibitor, ARB; Angiotensin Receptor Blocker

Table 6.6 The Relationship between ADRS and the Interventions outlined by the Structured Pharmacist Intervention.

Study Arm	Number (%) of patients with ≥ 1 DRP	Number of ADRs related to medications implicated in DRPs post-intervention	Number of ADRs *not* related to medications implicated in DRPs post-intervention	Total number of ADRs
Control (n = 376)	318 (84.6%)	38	53	91
Intervention (n = 361)	296 (82.0%)	15*	46	61$^{\delta}$

Key: DRPs; Drug Related Problems, ADR; Adverse Drug Reactions; (Mann-Whitney U Test; * p< 0.05, $^{\delta}$ p< 0.05)

Inter-rater reliability was high for application of the WHO-UMC ADR causality criteria and Hallas criteria, with κ-coefficients of 0.81 and 0.87 respectively. Inter-rater reliability was moderate for application of Hartwig ADR severity criteria (κ = 0.56).

There was a statistically significant difference in ADR incidence between the two groups, i.e.13.9% in the intervention group and 20.7% in the control group (p< 0.001), giving an ADR absolute risk reduction (ARR) of 6.8 % (95% CI, 1.5%-12.3%) and a relative ADR risk reduction of 33.3% (95% CI, 7.7-51.7). The number of patients needed to screen with the SPRM/CDSS intervention to avoid one non-trivial ADR was 15 (95% CI, 8-68).

6.3.4.2 Secondary outcome measures

(i) Median length of hospital stay (LOS)

The median (IQR) LOS in the control group was the 9 days (5-16); in the intervention group it was 8 days (5-13.5); p=0.444. The median LOS in patients from either group who experienced an ADR was 11 days (7-18), significantly longer than that in patients who did not experience an ADR i.e. 8 days (5-13); $p < 0.001$.

(ii) Hospital mortality rate

There was no significant difference found in all-cause mortality rate between the two groups; with 17 patients from both the intervention (4.7%) and control (4.5%) groups dying during their index hospital stay.

6.4 Discussion

The principal findings of this study are: (i) intervention with a SPRM/CDSS significantly reduces hospital-acquired ADRs in older people with acute unselected illness; (ii) the SPRM/CDSS intervention reduces the median hospital LOS slightly, but not significantly; (iii) all-cause hospital mortality was unaffected by the intervention.

This is the first prospective RCT to demonstrate that a SPRM, supported by appropriate software significantly reduces ADRs in older acutely ill hospitalised patients. The ARR of 6.8%, with the number of patients needed to screen at 15 to prevent one non-trivial ADR represents a clinically significant intervention. A previous RCT by Hanlon et al. (180) using a sustained clinical pharmacist intervention that was not supported by a CDSS showed a non-significant reduction in ADEs in an elderly outpatient population. The difference in ADE rate was not significantly different between control and intervention groups, although there was a trend towards fewer ADEs in the intervention group. Schmader et al. (253) subsequently showed that when pharmacists performed regular medication reviews as part of a multidisciplinary geriatric evaluation, frail elderly patients experienced a 35% relative risk reduction in serious ADRs compared to the control patients who received standard medical care. However, the pharmacist intervention was not delivered in a structured format as in the present study. Also, the significant benefit was only observed in the outpatients, not in hospitalized inpatients.

The use of a trigger list to detect ADRs in the present study was considered justified for several reasons. Firstly, the trigger list provides a standardized method of ADR detection. Secondly, the trigger list allowed for comprehensive ADR ascertainment,

whilst minimizing subjectivity and overestimation/underestimation of ADRs in the two patient groups. Thirdly, potential ADRs identified from the trigger list were validated by a clinically trained observer (MNO'C). The trigger list in this study closely resembles the list of common ADRs described in a similar RCT by Schmader et al. (253).

The 6.8% ARR in the present study is a conservative indicator of the potential impact of the SPRM/CDSS intervention, given that only 54.8% of the recommendations were implemented. The reasons for this suboptimal recommendation uptake are unclear. A higher rate of uptake (84%) has been found when recommendations are given by a physician rather than a pharmacist (394). The timing and location of the pharmacist intervention may also be important. In the present study, the intervention took place in the emergency department at a single time point within 48 hours of admission. There is evidence that pharmacist-generated medication recommendations are more likely to be implemented when the pharmacist is part of a geriatric inter-disciplinary team (19-20, 52, 80).

The intervention in the present study is also likely to be cost-effective, since the median LOS in patients who experienced ADRs was significantly longer than the median LOS in the patients who did not.

6.4.1 Limitations

There are some limitations to our study. Firstly, this was a single centre RCT, carried out in a population of hundreds rather than thousands. Secondly, primary outcome assessment was not blinded, but was instead undertaken by the primary researcher using an ADR trigger list, with putative ADRs corroborated by a trained physician. The primary researcher recorded all documented new symptoms and clinical phenomena from every patient's medical records electronically and these were cross-referenced with the trigger list, thereby minimizing (but not abolishing) potential observer bias. Thirdly, the single time point nature of the SPRM/CDSS review may have underestimated the full potential value of this intervention. It is likely that deployment of the intervention at further time points during older patients' hospitalizations will further reduce ADR incidence.

Another major limitation pertaining to this study relates to the sample size and the power calculation methodology used. In this study the original power calculation was based on statistical advice provided by external statistical consultancy group. Upon their advice a sample size of 356 patients was calculated per arm, with 712 patients required in total. The sample size of 712 patients was calculated based on the premise that the study was a controlled trial with randomisation occurring at the individual level and an estimated ADR incidence of 26% for the control group (based on recent data from our research group) (120, 178) and a projected absolute reduction of 7% in hospital-acquired ADRs in the intervention group, with an 80% power of detection and a 95% confidence limit.

There are a number of issues relating to the calculation that was used, one relates to the fact that this power calculation was a one tailed test design, as opposed to a two tailed test design. The one tailed test design was chosen because it was hypothesized that the intervention would result in a unidirectional positive impact on the ADR incidence. This assumption was made based on previous intervention studies undertaken by our research group (120). All of these studies had produced positive unidirectional impacts on the patient related outcomes of interest i.e. PIP prevalence and ADR incidence. However this assumption was somewhat optimistic and a two tailed test design would have been more appropriate, as in reality the intervention could have led to a bi-directional impact (i.e. resulting in a positive or negative impact) on the ADR incidence in this patient population. A retrospective calculation of the sample size using a two tailed test design, which uses the same alpha of 0.05 and the same 80% power of detection, estimates that 420 patients are required per arm with 840 patients being required in total. Aside from the fact that a one tailed design was used instead of a two tailed design, of greater consideration is the actual type of power calculation methodology that was used in this study and how the use of the incorrect power calculation type may have contributed to an underestimation of the true sample size required for this study.

As indicated above, the sample size calculation was based on the premise that this RCT was an individualized randomized trial, when in fact this study was designed as a cluster randomized controlled trial and therefore one needs to adjust for the effect of the clustering i.e. the sample size needs to be increased by the design effect, otherwise it may result in the study being significantly underpowered.

The design effect is calculated based on the cluster size i.e. number of units per cluster and the intra-cluster correlation coefficient (EQ1).

Design effect = $1 + (m- 1) \rho$ **Equation 1**

Where ρ is the intra-cluster correlation coefficient and m is the mean cluster sample size. This intra-cluster correlation coefficient is usually a value between 0 and 1 and for outcome variables, it is usually 0.05 or lower (395).

Therefore we retrospectively calculated the sample size required for this study and we have included an appendix that indicates the different sample sizes at differing mean cluster sizes that would be required to observe a statistical significant reduction of 30% (Appendix VII). From the data reported in this study, the mean cluster size was approximately 30 patients per cluster, using an intra-cluster correlation coefficient of 0.05 based on the coefficient outlined by Campbell et al. for outcome variables, the required sample size required for this study would be 1029 per arm (Appendix VII, Table 10.1). From this inflated estimated of the sample size, it appears that the study outlined above may in fact be underpowered.

Another important consideration with cluster RCTs is the type of statistical analysis used to analyze the data and the level of analysis, i.e. whether it is analyzed at a cluster or individuals level. When analyzing a cluster RCTs at an individual level it is important to ensure that the correct statistical approach is used. If standard approaches to statistical analysis are used this may result in spurious statistical significance findings with bias of the p-values downwards.

Standard statistical approaches assume independence (i.e. each patient is independent) and this is the true in individualized RCTs, however in clustered randomized trial, the patients are clustered together and this can leads to a degree of correlations/similarities between the individuals within each cluster, therefore the individuals become non-independent. This co-variance results in the downwards tendency of the p-values. Failure to factor the design effect in the analysis, will not affect the ADR incidence and in this study the intervention still will produce a reduction in ADRs between the control and the intervention group, however the issue relates to the confidence in the p value and the significant level.

The analysis of cluster RCTs at an individual level, must take into account the clustered nature of the data. Standard statistical techniques may not be appropriate for individual level outcomes, however when analysis is performed at the cluster levels, standard statistical methods are acceptable. However if the outcomes are at an individual basis it may be more appropriate to undertake the analysis at an individual level. When analyzing at an individual level, failure to consider the clustering effect may result in loss of statistical power and lead to p-values that are artificially extreme and confidence intervals may be overly narrower, thereby increasing the chance of significant significance being concluded spuriously.

Although the randomization of patients at a cluster level often comes at a price, resulting in lack of independence among the individuals in the same clusters, i.e. between cluster variations creates a number of specialized methodological challenges in both the design and the analysis of these studies. However in certain instance it is often necessary to randomize in this fashion and in this study we used a

cluster RCT design was to try and avoid treatment contamination between the patients under the same consultants. However in this study although the randomization was done at a cluster level, inference of outcomes was at an individual level.

Research in Context

Systematic review

We searched PubMed, Medline, and Scopus databases for articles published in English with the terms “adverse drug reactions”, “hospital” and “elderly” up to August, 2013, without publication date restrictions. We also searched the reference lists of relevant articles and non-randomised studies that examined adverse drug reactions (ARDs) in elderly hospitalised patients. We did not identify any previous randomised trials that examined the impact of a structured pharmacist intervention supported by a CDSS on the incidence of ADRs in older hospitalised patients.

Interpretation

Serious adverse drug reactions (ADRs) in hospitalized elderly patients are increasing in incidence in tandem with rising levels of multi-morbid illness and polypharmacy. To date, no pharmacist-driven intervention has been shown to significantly reduce ADRs in this growing patient group. This is the first randomized controlled trial to show that a structured pharmacist review of medication supported by customized dedicated software significantly reduces the incidence of hospital-acquired ADRs in older patients with acute illness.

In summary, this study indicates that a carefully-designed structured pharmacist intervention, supported by dedicated CDSS is an effective means of identifying and counteracting hospital-acquired ADRs in older people.

Chapter 7

7. The Impact of a Structured Pharmacist Intervention on the appropriateness of prescribing in Older Hospitalised Patients.

This study is a sub-study of the larger cluster RCT outlined in Chapter 6. This study focuses on the intervention arm of the larger study. As stated above, I was involved in the drafting of the grant proposal, the development and registration of the study design, application for ethical approval and the building of the CDSS to support the structured pharmacist review of medications (SPRM). I also undertook the data collection and delivery of the SPRM intervention at admission. I prepared the pharmaceutical care interventions and communicated these pharmaceutical care recommendations to the patient's primary physicians. I applied the different PIP criteria to the patient profiles of the 361 intervention patients at both admission and follow-up (i.e. 7-10 days or discharge, whichever came first). At follow-up, I undertook a follow-up review, to evaluate the impact that the SPRM/CDSS intervention had on the appropriateness of prescribing and examine the acceptance rates of the pharmaceutical care recommendations. To evaluate the appropriateness of prescribing, I applied the MAI and the modified ACOVE criteria to the profile of each patient. I also performed all of the statistical analysis of the data in this study.

7.1 Introduction

Older individuals aged ≥65 years constitute approximately 12% of the Irish population, with this figure expected to almost double by 2045 (1, 396). During the same period the proportion of individuals ≥85 years expected to almost triple (1, 396). Although older individuals constitute just in excess of 10% of the population they consume approximately 50% of all prescription medications (7-8).

Drug related problems (DRPs) (48, 118), such as poor compliance, medicines reconciliation issues, potentially inappropriate prescribing (PIP) and adverse drug reactions (ADRs) are prevalent in older hospitalised patients (397). Older individuals may be especially vulnerable to DRPs (118, 223, 232) at the interface of care, particularly on admission to hospital. It is estimated that unintentional medication omissions and errors i.e. medicines reconciliation issues, may be present in up to 70% of medication histories taken at this time (223, 225, 232, 286, 398) and that PIP prevalence may be as high as 96% (18, 20, 23, 44, 308, 314, 367, 379, 386). Medicines reconciliation issues and PIP have both been highlighted repeatedly as major contributory factors in ADEs, increased morbidity, mortality and increased healthcare utilisation in older individuals (14, 20-21, 76, 177, 399).

The medication reconciliation process is designed to ensure that the most accurate and comprehensive list of medications are maintained throughout the continuum of care (83, 223, 232). Medication reconciliation has been described as "the process of identifying the most accurate list of patient's current medications- including names, dosage, frequency and route and comparing them to the current list in use, recognising any discrepancies and documenting any changes thus resulting in a complete list of medications" (228-230). In 2007, the World Health Organisation (WHO) expanded the scope of this definition by indicating that the medication reconciliation process should be accompanied by a review of appropriateness "the medication reconciliation process provides an opportunity to reconsider the appropriateness of a patients medications" (227). In order to ensure that medications are prescribed appropriately and to minimise the risk of ADEs during the entire time

in hospital, it is important that an up-to-date and accurate medication history is recorded at the point of admission (223, 400-401).

In older individuals, one approach to assessing appropriateness of prescribing is to use a set of validated PIP criteria, these may either be implicit (judgement based) criteria i.e. medication appropriateness index (MAI) (126) and Assessment of Care of Vulnerable Elders (ACOVE) (134, 402) or explicit (criterion-based) criteria i.e. Beers criteria (12, 111, 124-125), Screening Tool of Older Person's Prescriptions (STOPP) (38), Screening Tool to Alert doctors to Right Treatment (START) (38) and Priscus criteria (39).

Involvement of pharmacists in the prescription review and monitoring process is an efficient means of optimising prescribing and improving patient outcomes (14, 20, 52). Clinical pharmacy services are intended to (i) be patient centred, (ii) be focused on optimisation of pharmacotherapies and (iii) try to minimise costs (48). Pharmacists are well positioned to perform a medication reconciliation and appropriateness review (19-20, 57, 230, 286, 403). Structured pharmacist review of medications (SPRM) interventions focused on medication optimisation and counselling patients, have the potential to identify and reduce DRPs (14, 76, 399).

Studies investigating the use of computerised decision support systems (CDSS), have reported that CDSS can significantly reduce DRPs and can have a positive effect on ADE occurrence (19, 57, 286, 403).

To date, the authors are aware of no study which has examined the impact of SPRM interventions using CDSS on overall medication appropriateness in older Irish hospitalised patients.

The objective of this study was to evaluate the impact of a SPRM care intervention using CDSS on the appropriateness of prescribing in older Irish hospitalised inpatients.

7.2 Methods

7.2.1 Study population and setting

The data presented in this study are a sub-study of a larger cluster randomised controlled trial, with the data reported here relating to the intervention patients of this trial. In this study we prospectively studied 361 patients, aged ≥65 years who were admitted to an Irish University Teaching Hospital over a 13 month period. Full details of the study population and setting are outlined in Chapter 6, section 6.2.1.

7.2.2 Intervention

The pharmacist intervention is outlined in detail in Chapter 6, Section 6.2.1.5 and in Figure 6.1. As outlined, the pharmacist intervention involved the pharmacist undertaking a comprehensive medication reconciliation and appropriateness review of the patients' medical records and medication Kardex post admission and any clinical relevant pharmaceutical care issues that were identified were then communicated in writing to the medical teams with primary responsibility for the patients' care.

These patients were then followed-up at day 7-10 or discharge whichever came first, to establish (i) the up-take of intervention and (ii) impact that the intervention had on prescribing appropriateness as defined by the MAI and ACOVE. The research pharmacist was a postgraduate pharmacist with previous experience in geriatrics care.

7.2.3 Assessment of Prescribing Appropriateness

PIP was assessed in this study using the STOPP (38), Beers (2003) (111) and Priscus (39) criteria. For the purpose of this study the 2003 Beers criteria were used as the 2012 version had not been published prior to the initiation of this study. The Screening Tool to Alert doctors to Right Treatment (START) (38) was used to assess potential underprescribing. Potential drug-drug interactions were assessed using the British National Formulary (BNF) 61st edition (404). PIP in individuals with renal impairment and hepatic impairment was assessed using the BNF 61st edition (404).

7.2.4 Outcome measures

The primary outcome for this study was the appropriateness of prescribing as defined by the medication appropriateness index (MAI) (126) and a modified subset of the ACOVE criteria (118) at follow-up i.e. 7-10 days or discharge, whichever came first.

The secondary outcome measures were:

(i) Uptake and acceptance of interventions by the hospital physicians with primary responsibility for the patients care.

(ii) The prevalence of PIP as defined by STOPP, Beers 2003 and Priscus criteria, and the combined PIP at admission and follow-up.

7.2.5 Data Analysis

Statistical analysis was performed using PASW (Predictive Analytics SoftWare) version 19 for Windows (SPSS^{TM}, Inc Chicago, IL, USA). Descriptive statistics included median and inter-quartile range (IQR) for non-parametric data; for normally distributed data, mean and standard deviation were calculated.

The Wilcoxon Signed Rank test was used to examine the difference in the median summated MAI score, the ACOVE frequency, the PIP frequency (as defined by the STOPP, Beers Independent of Diagnosis (ID), Beers Considering Diagnosis (CD)

and Priscus criteria), PPO frequency (as defined by the START criteria), drug-drug interactions frequency and the frequency of medications that required renal dosage adjustment at admission and follow-up.

A Mann-Whitney U test was used to examine the differences between each individual element of the MAI criteria between admission and follow-up. A probability value of <0.05 was considered statistically significant.

7.3 Results

7.3.1 Demographics

Three hundred and sixty one patients were consecutively recruited; 50.1% were female, 93.6% of the sample lived independently (**Table 7.1**). Median (IQR) age was 77 (71-83) years. The median (IQR) number of prescribed medications at admission was 9 (6-12) and at follow-up was 12 (8-15) (**Table 7.2**). Median (IQR) length of stay was 8 (5-13.5) days. Seventeen patients (4.7%) died during the hospital stay.

Table 7.1 Baseline characteristics of study population.

Variables		
Age	Median (IQR)	77 (71-83)
Male	n (%)	180 (49.9%)
Female	n (%)	181 (50.1%)
AMTS	Median (IQR)	10 (9-10)
CIRS	Median (IQR)	5 (3-6)
Barthel Index	Median (IQR)	19 (18-20)
Living Independently	n (%)	338 (93.6%)
Nursing Home residents	n (%)	23 (6.4%)

Key: AMTS; Abbreviated mental test score, CIRS; Cumulative Illness Rating Score.

Table 7.2 Breakdown of medications usage at admission and follow-up.

Variables	Admission	Follow-up
Number of medications	3,163	4,192
Median number of medications (IQR)	9 (6-12)	12 (8-15)
Polypharmacy (≥ 5 medications) n (%)	305 (84.5%)	346 (95.8%)
Major Polypharmacy (≥ 10 medications) n (%)	157 (43.5%)	241 (66.8%)

Key: IQR; Inter Quartile Range.

7.3.2 Characteristics of Interventions

On review of these DRPs clinical relevance, one thousand interventions were made by the research pharmacist in 296 (82.0%) patients. Two hundred and sixty seven patients (74%) had ≥1 appropriateness issue, while one hundred and sixty one patients (44.6%) had ≥1 reconciliation issue. A median of 2 (IQR: 1-4) interventions were made per patient. Five hundred and seventy seven (57.7%) of these recommendations related to appropriateness issues, while 423 (42.3%) of the recommendations related to reconciliation issues. The physicians with primary responsibility for the patients care accepted 548 (54.8%) of the overall interventions. The SPRM highlighted one thousand nine hundred and five potential DRPs, but on review of the clinical relevance of each DRP instance, 1,000 of these DRPs were intervened on. **Table 7.3** summarizes the main characteristics of all interventions made.

Table 7.3 Breakdown of the interventions relating to the clinically relevant drug related problems.

Type of Recommendations	No. of Recommendations	Recommendations accepted N (%)
Appropriateness Issues:	**577**	**222 (38.5%)**
• **Indication**	47	18 (38.3%)
• **Interactions**	73	29 (39.7%)
• **Renal adjustment**	25	13 (52%)
• **Appropriateness tools (STOPP, Beers, PRISCUS)**	297	135 (45.5%)
• **Underprescribing assessment tool (START criteria)**	44	13 (29.5%)
• **Miscellaneous appropriateness issues**	91	27 (29.7%)
Reconciliation Issues:	**423**	**326 (77.1%)**
• **Dosage**	95	69 (72.6%)
• **Missing medications**	322	252 (78.3%)
• **Miscellaneous reconciliation issues**	6	5 (83.3%)

Key: STOPP; Screening Tool of Older Person's Prescriptions, START; Screening Tool to Alert doctors to Right Treatment

7.3.3 Potentially inappropriate prescribing

At admission the STOPP criteria identified 449 instances of PIP relating to 232 (64.2%) patients, the Beers ID criteria identified 90 instances of PIP in 76 (21.0%) patients, the Beers CD criteria identified 188 instances of PIP in 115 (31.8%) of patients and the PRISCUS criteria identified 197 instances of PIP in 153 (42.4%) of patients. When the criteria were combined and overlapping criteria were removed 712 instances of PIP were identified in 275 (76.3%) patients.

At follow-up, 362 instances of PIP were identified in 200 (55.5%) patients using the STOPP criteria, 103 instances of PIP were identified in 66 (18.3%) patients using the

Beers ID criteria, 179 PIP instance in 114 (31.6%) patients using the Beers CD criteria and 190 instances of PIP were identified in 147 (40.6%) patients using the PRISCUS criteria. When the criteria were combined and overlapping criteria were removed 633 instances of PIP were identified in 257 (71.2%) patients.

A Wilcoxon Signed Rank Test revealed a statistically significant reduction in PIP as defined by the combined criteria (median at admission (M-Adm): 1, median at follow-up (M-Fol): 1; z=-4.001, p < 0.001), STOPP criteria (M-Adm: 1, M-Fol: 1; z=-5.492, p < 0.001). A reduction in PIP as defined by the Beers CD and Priscus criteria was also reported but this was not found to be statistically significant (Beers CD; M-Adm: 0, M-Fol: 0; z=-1.075, p=0.282, Priscus; M-Adm: 0, M-Fol: 0; z=-0.804, p=0.421). While a statistically significant increase in PIP as defined by the Beers ID criteria was reported (M-Adm: 0, M-Fol: 0; z=-2.197, p < 0.001).

7.3.4 Potential prescribing omissions

At admission the START criteria identified 155 instances of PPO in 112 (31.0%) patients, and at follow-up 150 instances of PPO were identified in 114 (31.5%) patients using the START criteria. A Wilcoxon Signed Rank Test reported a reduction in the PPO, but this was not found to be statistically significant (M-Adm: 0, M-Fol: 0; z=-0.656, p=0.512).

7.3.5 Drug-drug interactions and renal impairment dosage adjustment

At admission, the E-Pharm-assist system identified 405 potentially major drug-drug interactions in 208 (57.7%) patients and identified 61 potentially inappropriate dosages in 35 (9.7%) patients with renal impatient.

At follow-up the E-Pharm-Assist system identified 439 potentially major drug-drug interactions in 231 (63.9%) of patients and identified 43 potentially inappropriate dosages in 26 (7.2%) patients with renal impatient.

A Wilcoxon Signed Rank Test found a statistically significant increase in the number of drug-drug interactions from admission to follow-up (M-Adm: 1, M-Fol: 1; z=-1.964, p=0.05) and statistically significant reduction in the number of medications requiring renal dosage adjustment (M-Adm: 0, M-Fol: 0; z=-2.170, $p < 0.05$).

7.3.6 Medication appropriateness index (MAI)

A Wilcoxon Signed Rank Test revealed a statistically significant difference between the summated MAI measurements at admission and follow-up, M-Adm (IQR): 15 (7-21), M-Fol (IQR): 12 (6-18); z=-7.486, $p < 0.001$. In total 214 (59.3%) patients had a lower MAI score at follow-up, 107 (29.6%) had a higher MAI score and 40 (11.1%) patients had no change in their MAI score.

At admission almost 65% of the medications and at follow-up just over 55% of the medications had at least one inappropriate rating. The SPRM intervention resulted in improvements in all of the MAI criteria outlined in **Table 7.4**. There was a slight reduction in the number of patients with ≥1 inappropriately rated MAI criteria, with 357 (99.0%) patients at admission and 354 (98.1%) at follow-up, this reduction was not found to be significant (p=0.543).

Table 7.4 Percentage of medications with an inappropriate rating on admission and at follow-up as defined by the Medication Appropriateness Index (MAI).

MAI Criterion	Admission n (%)	Follow-up n (%)	p*
Indication	343 (9.8%)	275 (6.5%)	0.000
Dose	16 (0.5%)	6 (0.1%)	0.011
Directions	57 (1.6%)	64 (1.5%)	0.741
Duration	177 (5.0%)	102 (2.4%)	0.000
Practicality of directions	34 (1.0%)	33 (0.8%)	0.398
Drug-drug interaction	361 (10.3%)	386 (9.2%)	0.118
Drug-disease interaction	211 (6.0%)	187 (4.5%)	0.002
Duplication	39 (1.1%)	32 (0.8%)	0.114
Cost	1762 (50.1%)	2085 (49.7%)	0.752
Effectiveness of therapy	421 (12.0%)	377 (9.0%)	0.000

Key: MAI; Medication appropriateness index. (* Mann-Whitney U test)

7.3.7 Assessing Care of Older Vulnerable Elders (ACOVE)

At admission and follow-up, 28.3% and 26.9% of the patients respectively had at least one inappropriately rated ACOVE criteria. Between admission and follow-up there was a slight improvement but this was not found to be clinically significant (p=0.739) (**Table 7.5**).

Table 7.5 Percentage of patients with at least one breach of an Assessing Care of Vulnerable Elders (ACOVE) Underuse Criteria at admission and follow-up.

ACOVE underuse criteria	Patients with inappropriate rating on admission; n (%)	Patients with inappropriate rating at follow-up; n (%)	p*
Antiplatelet/ anticoagulant in Atrial Fibrillation	17 (4.7)	11 (3.0)	0.134
Antiplatelet in Diabetes mellitus	17 (4.7)	16 (4.4)	0.655
Angiotensin-converting enzyme inhibitor in Heart Failure	29 (8.0)	31 (8.6)	0.564
Beta-blocker in Heart Failure	21 (5.8)	21 (5.8)	1
Antiplatelet in Ischemic heart disease	17 (4.7)	17 (4.7)	1
Beta-blocker in Myocardial infarction	17 (4.7)	16 (4.4)	0.564
Bisphosphonate/calcium, and/or vitamin D in Osteoporosis/Fracture	28 (7.8)	27 (7.5)	0.705

Key: ACOVE; Assessing care of vulnerable elders. (*Wilcoxon Signed Rank test)

7.4 Discussion

This study shows that a SPRM intervention using a CDSS can produce significant improvements in appropriateness of prescribing as defined by the MAI. This is the first Irish study to use a SPRM intervention supported by a CDSS to improve appropriateness of prescribing in older hospitalised individuals. The reasons for the success of this intervention is potentially due to the structured approach taken to the medication history/reconciliation process, and the comprehensive review of appropriateness undertaken using the E-Pharma-Assist system. A number of other studies have reported similar improvements in the prescribing appropriateness using pharmaceutical care interventions (118, 180, 253, 258, 260, 262, 271, 280, 405-406) and using CDSS (225, 298-299, 301, 407-410). The intervention produced an improvement in all aspects of the MAI.

In this study it was found that the intervention produced only a slight improvement in the number of patients who were under-prescribed clinical beneficial medications according to the modified ACOVE criteria. This finding may reflect the poor uptake of recommendations relating to the START criteria, which may relate to the high rate of prescribing already present in this population. A number of studies have reported that polypharmacy can result in the underprescribing of clinically beneficial medications; this may be due to doctors having reservations about initiating additional medications, to already potentially complex regimes (100, 115, 411-415).

The intervention produced improvements in both PIP and PPO as defined by all of the screening criteria except for the Beers CD criteria. Similar findings have been reported in other intervention studies (46, 118, 271, 309, 314).

In our study population 82% of the patients had ≥1 DRP, with 44.6% of the patients having ≥1 medication reconciliation issues. Similar prevalence of medication reconciliation issues have been reported in the literature (223-225, 229). The high prevalence of DRPs identified in this study further supports the importance of carrying out a medications reconciliation and review of appropriateness within 48 hours of admission. These findings illustrate that the first and foremost step in any medication reconciliation and appropriateness review should be the ascertainment of an up-to-date and accurate medication history, a finding which has been echoed in a number of other studies (225, 400, 416).

CDSS have been reported to be useful tools which can support the delivery of pharmaceutical care (229, 286, 388), improve prescribing appropriateness (20, 57, 262, 298, 388) and minimise the occurrence of ADRs (19, 388). In this study the E-Pharma-Assist system proved to be an effective data collection system, while also allowing the research pharmacist access to clinically relevant information at the point of review in order to perform comprehensive medication reconciliation and appropriateness reviews. Although CDSS allow the user to perform a detailed review in a time efficient fashion, they are only as good as the information that is entered into them and they are designed to complement/supplement clinical judgement not to replace it (15, 20, 46, 366). This is reflected in the fact that the CDSS highlighted 1,905 potential interventions in this study, but on review of the clinical relevance of these interventions, only 1000 of these were actually intervened upon. An intervention was considered not clinically relevant based on a review by the research pharmacist.

A number of the interventions that were highlighted by the system but not intervened on related to drug-drug interactions, e.g. angiotensin conversion enzyme inhibitors in combination with potassium sparing diuretics, in these patients their potassium was been regularly monitored. Also there were a number of instances where a PIP instances was flagged by the system, but on review it was deemed that they were not clinically relevant, i.e. PIP of digoxin or doxazosin, although caution is advised when using these medications they are not contra-indicated in older patients and all the patients that were prescribed these medications had been on these medications long term and they were well tolerated.

In this study the most common DRPs intervened on related to instances of PIP or PPO. Three sets of PIP criteria; STOPP, Beers 2003 and Priscus criteria were utilised for this study as the authors felt each set of criteria had their own unique merits. The high rate of PIP observed by each set of criteria individually or in combination was similar to PIP prevalences in older hospitalised patients nationally and internationally (44, 117, 177, 367, 379, 382, 386-387). Similarly the PPO prevalence reported in this study was similar to that reported in other studies in this setting (44-45, 120, 338, 367, 417), however the low rate of acceptance of the recommendations relating to PIP and PPO is an area of some concern.

In this study the second most common DRP identified and intervened on during the medications reconciliation review related to medication omissions (n=322) i.e. the inadvertent/undocumented omission of at least one scheduled medication from a patient medications regimen. A number of other studies have reported similar

findings (223, 225, 232, 416, 418). Over three quarter of the discrepancies relating to omissions were rectified, post intervention.

In this study 54.8% of the interventions were accepted by the prescribing physicians, this acceptance rate is almost identical to the rate of 54% that was reported recently in another Irish study by Galvin et al. (223). The acceptance rate reported in this study may reflect the means by which the recommendations were communicated. A number of studies have reported on the acceptance rates of pharmaceutical care interventions and have found that between 40-90% of these are accepted (84, 416, 418-419). The majority of the studies that have reported high acceptance rates involved a scenario in which the pharmacist worked closely with the doctor and other healthcare professionals as part of a multidisciplinary team or participated in ward rounds (14). However, studies that used primarily written recommendations have reported lower rates of acceptance, similar to those reported in this study (416). Written recommendations were chosen as the means of communication in this study, as it was felt that this reflected how the majority of clinical pharmacy interventions are traditionally communicated in practice. Also the patients involved in this study were also under the care of a number of different specialities, who worked throughout the hospital and logistically it was felt that it would not be feasible to verbally communicate all interventions for each patient.

A high prevalence of DRPs was reported in this patient population. Clinical pharmacists working in A&E are in a prime location to perform both a medication reconciliation and appropriateness review (231, 418). Although studies have shown that clinical pharmacists can reduce DRPs and improve appropriateness of

prescribing (14, 118, 278), these services are often underutilised possibly because of issues relating to limited workforce or reimbursement (19-20, 57, 83, 287-288, 328, 420).

In this study the medication reconciliation review included a patient interview and patient counselling on their medications. A number of studies have shown that including this counselling step in the medication reconciliation process can enhance patient satisfaction, improve compliance and increase identification and corrections of DRPs (14, 118, 231, 421).

A number of papers have proposed that these types of structured pharmaceutical care interventions should possibly be targeted at the most vulnerable/high risk patients, with categorisation of high risk often based upon a patient's level of co-morbidity or their number of medications (143, 153, 177, 180, 225, 259, 294, 421). Adopting such an approach is probably due to the fact that a number of papers have reported that an increased number of medications and/or high level of co-morbidity are associated with increased risk of medication discrepancies and PIP (14-15, 24-25, 100, 416, 419). Although narrowing the scope of such interventions to specific patients may result in reduction in the work load for the pharmacy service, it may however not always be appropriate to prioritise specific patient groups, especially since this study demonstrated a high level of discrepancies and DRPs occur across the entire older hospitalised population. Also prioritising patients based on number of medications may have inherent flaws, as this study has shown that the number of medications transcribed at admission may not always truly reflect all the medications that the patient is actually on.

A number of studies have reported on the importance of performing an accurate medication reconciliation review at admission. Some studies have shown that failure to correctly reconcile a patient's list of medications at admission may perpetuate throughout the patients entire stay from admission to discharge and beyond (232, 418). It is reported that over 50% of the medication discrepancies at discharge may originate at admission. Pharmacists are ideally positioned and have the knowledge and expertise to deliver such services.

This study demonstrates that a pharmacist using a CDSS to supplement their knowledge and to standardise the medication reconciliation and appropriateness review process can significantly improve prescribing appropriateness in older hospitalised patients.

7.4.1 Limitations

This study has a number of important limitations. Our study was undertaken by a single pharmacist working in a single hospital, using a specially developed CDSS, so generalisability may not be possible.

As the study participants were under the care of teams that looked after many patients throughout the hospital it was often difficult to verbally communicate all of the interventions to the doctors with primary responsibility for study participants.

A number of studies have reported on the importance of a medication reconciliation review not only at admission but also at discharge (232, 418-419, 421). Due to limited resources and time consuming nature of the intervention and follow-up review coupled with the disjointed nature in which patients are discharged, the authors felt it would not be possible for a single research pharmacist to perform a detailed medications reconciliation and appropriateness review at both admission and discharge.

Due to the unblinded nature of the intervention process and the fact that the medical teams were aware of the purpose of the study, it is not possible to rule out the presence of the Hawthorne effect i.e. the doctors may have acted/performed differently than they would normally because they were aware that they were part of a study.

Whether or not the intervention impacted on additional outcomes such as compliance and quality of life is outside the scope of this study.

7.5 Conclusion

This study illustrates that DRPs are a problem in older Irish hospitalised individuals. A SPRM intervention supported by a CDSS can substantially improve the appropriateness and accuracy of the medication regimens of older hospitalised patients. This sort of intervention may be a feasible method of reducing DRPs and improving prescribing appropriateness in this patient population. The allocation of additional resources focused on implementation of similar types of SPRM aimed at older individuals at the point of hospital admission and discharge, may lead to significant improvements in both the safety and appropriateness of prescribing in these individuals in the future.

Chapter 8

8. Discussion

Older individuals make up a large proportion of the Irish population, with this expected to almost double in the next 40 years (1-2, 359). This is not just an Irish phenomenon, but a global one (2, 5-6, 422). Older individuals regularly suffer from several co-morbidities, for which they are routinely prescribed a number of concurrent medications.

Although the prescribing of multiple medications can often be justified, it has been linked with DRPs (i.e. PIP and medications reconciliation issues) (18, 20, 41, 57, 83, 112, 224, 229, 232, 328, 400, 416, 419, 423) and ADRs in the literature (19, 21, 24, 166, 178). Both of which have been shown to be highly prevalent in older Irish individuals (9, 15-16, 23, 46, 62, 91, 100, 120, 223, 232, 318). Early detection and prevention of such instances could prove beneficial for both the patient and healthcare system as a whole.

One of the main aims of this work was to determine the most appropriate method of identifying DRPs in Irish older individuals and to develop an effective intervention strategy which could potentially result in improvements in all facets of prescribing, leading to a reduction in the incidence of ADRs.

Over the last 25 years a number of different methods for assessing PIP/DRPs have been proposed in the literature (12, 15, 20, 39-41, 46, 52, 57, 81, 90, 94, 105, 111, 114, 118-119, 122-141, 144, 147, 153, 233-234, 283, 358, 424-427).

Of these, two sets of criteria have gained international recognition and have been widely cited i.e. the STOPP (38) and Beers criteria (12, 111, 125). Recently another promising set of PIP criteria known as the Priscus criteria were published by a German group (39). To date there is limited data relating to the applicability of this set of criteria outside of Germany and its' impact on key outcomes such as morbidity and ADR incidence have yet to be established, however preliminary studies indicate that it may have some potential as a PIP screening tool, especially in situations where there is only access to limited medical information.

In this discussion, we will focus on the differences/commonalities in the prevalence of PIP and PIMs reported across different healthcare settings in Ireland. The applicability of each of the three tools in terms of an Irish context will be examined. The impact the specially developed structured pharmacist intervention, supported by a CDSS will also be discussed.

8.1 Potentially inappropriate prescribing (PIP)

The PIP prevalences determined in chapters 3-7, are consistent with figures previous reported in the literature (**Chapter 2, Electronic Appendix Table 2.3**) (9, 16, 33-37, 43-44, 62, 81, 91, 95, 117, 299, 302, 311, 314, 338, 367, 378-379, 387, 428-429). Using the three different sets of criteria, either in isolation or in combination, PIP was found to be highly prevalent across all three care settings. PIP prevalence was shown to increase from primary care (PC) to secondary care (SC) to long term care (LTC) i.e. using the STOPP criteria, PIP of 23.3% was reported in primary care, 53.3% in secondary care and 73.0% in LTC (**Chapter 5, Figure 5.1** PIP prevalence determined by the Combined, STOPP, Beers and Priscus criteria across the three care settings. Using the Beers criteria, PIP as high as 19.7% in PC, 34.0% in SC and 53.0% in LTC were reported, while with the Priscus criteria, PIP prevalences as high as 31.0% in PC, 38.3% in SC and 55.3% in LTC were found (**Chapter 5, Figure 5.1** PIP prevalence determined by the Combined, STOPP, Beers and Priscus criteria across the three care settings. This increase in PIP prevalence, correlates with previous published work indicating that as the complexity of care and level of patient frailty increases, so too does (i) the number of medications prescribed, (ii) the level of co-morbidity and (iii) the prevalence of PIP (**Chapters 3-7**) (10, 69, 379).

In chapters 3, 4 and 5, it was found that the STOPP criteria determined a higher prevalence of PIP compared to the Beers criteria in all 3 healthcare settings. Also, in all three healthcare settings more of the STOPP criteria than the Beers criteria were utilised. This finding was expected, due to the fact that (i) the STOPP criteria were originally developed based on Irish prescribing practices (38) and (ii) a number of recent papers have highlighted issues relating to the applicability of the Beers criteria outside of North America (14, 20, 38, 91, 100, 177, 182, 430).

In chapter 5, it was found that the Priscus criteria determined a higher prevalence of PIP in the PC dataset, than either of the other two sets. The fact that the Priscus criteria determined a higher prevalence of PIP than the STOPP criteria in the PC dataset was somewhat surprising to the research team. However, this high PC prevalence could in part be attributable to the high level of digoxin and doxazosin related PIP identified by the Priscus criteria. Although caution is advised when using digoxin and doxazosin in older individuals, in Ireland, prescriptions for such medications are generally considered reasonable and safe, once the patient is monitored for signs and symptoms of digoxin toxicity and once doxazosin is not use as the first line anti-hypertensive agent. In the RCT a number of instances of PIP relating to digoxin and doxazosin were flagged by the CDSS, however upon further evaluation it was found that these patients were well established on their therapy and discontinuation of these medicines would expose the patients to an increased risk.

As stated above, a number of studies have raised concerns relating to the applicability of the Beers criteria in a European context (14, 20, 38, 91, 100, 177, 182, 430). The finding that the Priscus criteria appears to be more pertinent at identifying instances of PIP than the Beers criteria across all three healthcare settings, raises further concerns relating to the applicability of this set of criteria in a European context. A head to head comparison of each of these different criteria, which focuses on health related outcomes i.e. ADRs, hospitalisation, morbidity and mortality, may determine which of the PIP criteria is the most applicable for use in an Irish / European context.

In this work, the majority of PIP instances identified by each set of criteria were attributable to a small number of medications/medication classes i.e. PPIs, benzodiazepines, neuroleptics, NSAIDs, non-benzodiazepine hypnotics, calcium channel blockers, antidepressants (i.e. TCAs and SSRIs), opioids, anticholinergics (i.e. bladder antispasmodics, antihistamines, gastrointestinal antimuscarinics), cardiac glycosides (i.e. digoxin), alpha-blockers (i.e. doxazosin), muscle relaxants and anti-arrhythmics (**Chapter 4, Table 4.4 The 5** most common instance of PIP identified by Beers criteria independent of diagnosis and considering diagnosis, **Table 5.4** PC, SC and LTC Top 10 STOPP PIP instances. **Chapter 5 Table 5.5 PC**, SC and LTC Top 10 Beers PIP instances. **Chapter 5, Table 5.6** PC, SC and LTC Top 10 Priscus PIP instances. Throughout the literature, a number of the studies have identified similar medication/medication classes as the primary causes of PIP instances (9, 16, 33-37, 44, 62, 81, 91, 117, 299, 314, 367, 379, 387, 428-429). The main classes of PIMs identified across all setting will be discussed below.

PIP of benzodiazepines featured prominently across all three healthcare settings. A number of studies have raised concerns relating to the appropriateness of benzodiazepines in older individuals. This class of medicines have been reported to expose older individuals to an increased risk of falls, confusion, as well as psychological and physical dependency (16, 62, 91, 111, 182, 352-354). Despite these documented risks, benzodiazepines continue to be prescribed for older individuals, both nationally and internationally across all settings of healthcare (91, 242, 353).

PIP of PPIs was also found to be quite common in all three of the healthcare settings. This medication class would be considered by many, as a rather benign and therapeutically inert group of medicines, with little potential for ADRs. However, several recent papers in the literature have reported on a number of rare but significant ADRs which are associated with long-term use of PPIs e.g. reduced absorption of calcium, vitamin B12, iron or increased risks of fractures, osteoporosis (348-351). It has also been proposed that long-term use of PPIs may be associated with an increased risk of Clostridium difficile infections (348). PIP of this class of medications can result in significant financial costs. Currently it is estimated that expenditure on PPIs constitutes approximately 10 % of overall drugs budget of the Health Services Executive's (HSE's) annually (100, 346, 431).

Antipsychotic medications were also reported frequently as PIMs in all of the studies (Chapter 2-6). When these medications are prescribed appropriately they provide considerable benefit to the patient. However, the reported adverse effects associated with the long-term use of neuroleptics in the older person has been widely documented in the literature, particularly in relation to gait/balance disorders, sedation/cognitive impairment and increased stroke risk (182, 330, 355-357).

Anticholinergics (i.e. bladder antispasmodics, antihistamines, gastrointestinal antimuscarinics) also featured quite prominently as PIMs in all of the healthcare settings. Anticholinergic medications are indicated for an array of different therapeutic indications. When used appropriately they can prove quite beneficial. However, certain older individuals may be more susceptible to the adverse effects of anticholinergic medications. They have been reported to be associated with a number

of different adverse effects in this population i.e. postural hypotension, arrhythmias, cognitive impairment, sedation, urinary retention and constipation (33-39). These effects may vary in severity from patient to patient, but due to increased vulnerability of older individual caution is advised when using these medications.

Throughout these studies PIP of TCA also featured prominently across all three healthcare settings. TCA are primarily used in older individuals, for depression, but more recently they have been used at lower doses for neuropathic pain (33-35, 37-39, 81, 111, 299). Although well tolerated by a large proportion of older individuals, TCA's are highly anticholinergic and have a similar adverse effect profile to other anticholinergics, i.e. sedation, constipation, urinary retention, orthostatic hypotension and QT prolongation (432-438). At lower doses, such as those used in neuropathic pain, these adverse effects less prevalent.

In all three healthcare setting PIP of non-benzodiazepines hypnotics were frequently identified. Similar to long term use of benzodiazepines, the long term prescribing of non-benzodiazepine hypnotics i.e. zolpidem and zopiclone, is also considered potentially inappropriate. The literature indicates that this class of medications has a more favourable side-effect profile in older individuals, when compared to benzodiazepines however these agents still have a propensity to elicit similar adverse effects to that observed with benzodiazepines (39, 439-441). In a small number of older patients, psychiatric type reactions secondary to this class of medications i.e. irritability, hallucinations and psychosis, have also been reported. Similar to benzodiazepines, the non-benzodiazepine hypnotics expose older individuals to a risk of both physical and psychological dependency however this risk appears to be

lower with non-benzodiazepine hypnotics when compare to their benzodiazepine counterparts (439-440). When prescribing these medications in older individuals the potential for dependency should always be considered.

PIP of opioids also featured quite frequently across all three healthcare settings. Opioids are commonly used in older individuals for a multitude of different indications. When used appropriately opioids can impart substantial benefits/relief to the patient. However caution is advised when using opioids, as they are reported to be associated with an array of different adverse effects e.g. constipation, confusions, delirium, hallucination, sedation, postural hypotension, vertigo and falls (39, 358, 438). Opioids are also reported to expose older individuals to and increased risk of dependency (438, 442). When prescribing opioids in older individuals, it is imperative that the medication are initiated at the lowest most effective dose i.e. sufficient to relieve the pain, while also minimising the risk of adverse effects.

As mentioned above one of the main aims of this work was to establish which set of PIP criteria was the most applicable for the assessment of PIP in older individual across different settings of care in Ireland. Upon review of the applicability of each set of the criteria across the different healthcare settings (Studies 1-3), the STOPP criteria appears to be the most applicable for use in an Irish context. However, this work found that each of the three sets of criteria possess a number of their own unique qualities and therefore in order to ensure that the most accurate/comprehensive PIP assessment is performed, it would be more appropriate to deploy all three sets of criteria concurrently.

8.2 Potential prescribing omission

PPO is another important aspect of PIP that often goes under-reported. Only a few tools have been developed which address the issue of PPO i.e. AOU, Australian criteria, ACOVE and START (38, 132-134, 139). There is limited evidence in the literature relating to the prevalence of PPO in older individuals; with the majority of the literature been published in the last 5 years. However, these studies indicate that PPO is highly prevalent in older individuals, with prevalences of 11.2-74.0% being reported in the literature (44-45, 50, 91, 117, 314, 333, 338, 379, 386, 443-444). Due to the retrospective nature of the data used in studies 1-3, it was not possible to assess the applicability of the different PPO assessment tools in the different care settings.

However, due to the fact that the START criteria were developed in Ireland and are based on Irish prescribing practices, it was felt that this set of criteria were the most appropriate to combine with the amalgamated STOPP, Beers and Priscus criteria. The PPO prevalence of 31.0% that was identified in Study 4 was consistent with the prevalences of PPO previously reported for older hospitalised patients in the literature of 11.2-72.7 (44-45, 117, 314, 333, 338, 386, 431, 443). One possible explanation for this, may relate to the fact that in this study a comprehensive medications reconciliation review was undertaken prior to the PPO assessment. This medication reconciliation review established the most up-to-date list of the patient's scheduled medications prior to their admission to hospital. Other studies which reported on the prevalence of PPO during hospitalisation have not indicated if a detailed medications reconciliation review was conducted prior to the PPO review. If such a review was not undertaken prior to the PPO determination, certain

medications that were inadvertently omitted from a patients medication Kardex, may in fact be flagged as PPO instances, when they may just be prescribing omissions.

8.3 Medications Reconciliation

This work also found that at the point of hospital admission, medication reconciliation issues were quite common in older individuals, with almost 50% of patients admitted to the A&E of a University Teaching Hospital having at least one medication reconciliation discrepancy (**Chapter 7, Table 7.3** Breakdown of the interventions relating to the clinically relevant drug related problems. This is consistent with the prevalences of 20.8-65% which has been reported in the literature. While in an Irish contexts, medication reconciliation issues are reported to occur in 50-91% of hospitalised individuals (223, 232).

Similar to the work presented as part of this thesis, the majority of other studies have reported that the most common medication discrepancy encountered at the point of admission relate to the unintentional omission of at least one of a patient's regularly scheduled medications. Omissions have been reported to make up as much as 93% of the overall medication reconciliation discrepancies. Similar to these other studies our results show that almost 80% of the medication reconciliation issues related to omissions (**Chapter 7, Table 7.3** Breakdown of the interventions relating to the clinically relevant drug related problems. The second most commonly encountered discrepancy flagged at admission related to errors in dosage/frequency (**Chapter 7, Table 7.3** Breakdown of the interventions relating to the clinically relevant drug related problems. A number of other studies have reported similar findings (223, 225, 232, 416, 418).

Both PIP and medication reconciliation discrepancies are reported to be associated with the incidence of ADRs. Timely identification and prevention of these DRPs could potentially result in significant reductions/avoidance in ADRs.

8.4 Adverse drug reactions

ADRs have been reported in the literature to be a considerable healthcare problem, implicated as a major cause of morbidity, mortality and increased healthcare utilisation in older individuals (19, 21, 23, 178). This work has found that the incidence of ADRs in older hospitalised in-patients is approximately 21%, which is consistent with the incidence of ADRs that have been previously published in the literature (21, 23, 120, 164, 167, 174, 178-179, 186). This work found that a large proportion of the ADRs were considered preventable a finding that has been echoed throughout the literature (19, 21, 23, 166, 169, 173).

Similar to previous studies the majority of the ADRs were attributable to a small number of medications; (1) opioids, (2) diuretics, (3) anti-hypertensives, (4) antibiotics and (5) anti-coagulants (**Chapter 6, Table 6.5**). Several other studies have reported similar findings (166-167, 169, 173). The fact that these medications are being repeatedly implicated in ADRs is an area of some concern, but it may reflect the high frequency of prescribing of these medications. It may also indicate that we have not fully learnt from our past mistakes. Future work could focus on developing specific strategies to reduce the incidence of ADRs associated with these particular medications/medication classes.

8.5 Interventions Strategies

A number of different approaches have been proposed to address the issues of PIP and ADRs in older individuals. These include CDSS, structured pharmacist interventions, comprehensive geriatric assessment (CGAs) and educational strategies focused at healthcare professionals (19-20, 57, 445). PIP and ADRs are considered a multi-faceted problem and it has been reported that these types of intervention strategies, either delivered in isolation or in combination may have a positive impact on both PIP and ADR incidence in older individuals (19-20, 23, 52, 57, 178, 186). This work, found that the combination of a structured pharmacist intervention with a CDSS, produced a statistically significant improvement in both the appropriateness of prescribing as measured by the MAI (median MAI score reduced from 15 at admission and 12 at follow-up) and significant reduction in the incidence of ADRs, with an absolute risk reduction of 6.8 (95% CI 1.5% - 12.3%) and the number needed to treat of 15 (95% CI 8 - 68) being reported.

8.5.1 Pharmacist/CDSS intervention strategies

A number of papers have reported that involving a pharmacist in the prescription review and monitoring process is an efficient means of optimising prescribing, reducing ADRs and improving patient outcomes (20, 52, 57, 118). Due to pharmacist's detailed knowledge and understanding of medications, they are ideally positioned to perform medication reconciliations and appropriateness reviews (19-20, 57, 230, 286, 403). Structured pharmacist interventions focused on medication optimisation can potentially result in improved detection and resolution of DRPs (14, 76, 399).

A number of reviews have indicated that structured pharmacist interventions can have a positive impact on medication appropriateness and DRPs (14, 20, 52, 57, 118, 180, 230-231, 270). Based on the structured pharmacist model outlined by Spinewine et al., the authors of the present work developed a structured pharmacist intervention and evaluated the impact of this intervention on (i) the appropriateness of prescribing and (ii) incidence of ADRs in older individuals in secondary care in Ireland.

Although PIP is highly prevalent across all three care settings, it was felt that the secondary care setting was the most appropriate location upon which to trial this new pharmacist intervention. The secondary care setting allowed for patients to be conveniently randomised, recruited and monitored throughout their entire indexed hospital stay. It allowed for patients to be reviewed and their medications regimens to be rectified all under the watchful eye of the pharmacist. Also the medical team with primary responsibility for the care of each patient were located on site and therefore any pharmaceutical care recommendations could be communicated to the

team within 48 hours of the review having taken place. Likewise, the patient's recruited into this study were under continuous supervision by medical and nursing staff. Their medical and nursing notes were updated almost daily and therefore any change to a patient's medications profile, or clinical status or the any ADRs were usually documented and therefore they were easy to detect. Routine clinical pharmacy services are already well established in Irish secondary care and the authors felt there would not be the same level of resistance to pharmaceutical care recommendations in the secondary care setting, that may have been observed had the intervention been deployed in primary care or long term care setting. This is supported by a previous pilot study of pharmacist's recommendations to general practitioners in primary care by our research group (446).

Although the LTC would also appear to be a viable setting in which we could have trialled this intervention strategy, the patients that reside in LTC facilities are often quite frail, exhibit a high level of dependency and often are prescribed large complex medication regimens and we felt that it would be more appropriate to establish the effectiveness of the intervention in the secondary care settings first and then examine the applicability of this intervention in a LTC setting.

Our finding from studies 1 and 2, indicate that the available PIP assessment tools may in fact be too sensitive for use in the patients that reside in the LTC care setting. The development of consensus based modified versions of these criteria may be more appropriate in the future if a similar study was to be deployed in a LTC setting. Additionally, if this intervention had been undertaken in PC or LTC it would have required additional resources, in order to recruit multiple patients across multiple

sites. However one major advantage of such an approach would have been that randomisation could have been performed at a practice or facility level therefore allowing for effective blinding and minimising the risk of cross contamination between our intervention and control groups.

CDSS are a powerful resource that can be used to; support the delivery of pharmaceutical care (229, 286, 388), improve prescribing appropriateness (20, 57, 262, 298, 388) and minimise ADRs (19, 57, 286, 388, 403). The CDSS used in our RCT study was specially developed from the work undertaken in chapters 3-5 (appendix 10.6). This CDSS i.e. E-Pharm-Assist system, standardised the data collection and review process, while also allowing the pharmacists access to additional clinically relevant information at the point review e.g. drug-drug interactions, hepatic and renal dosage adjustment and up to date Special Product Characteristics (SPC) for all medicines. This enabled the research pharmacist to perform comprehensive medication reconciliation and appropriateness reviews at the point of data entry and to make an informed decision about the appropriateness of a patient medication regimen. However it is important to remember that although CDSS enabled the user to perform a detailed review in a time efficient fashion, they are dependent on the quality of the data input. Therefore, CDSS are designed to complement/supplement clinical judgement not to replace it (15, 20, 46, 366).

Written recommendations were chosen as the means of communication in work outlined in chapter 6 and 7, as this reflected how the majority of clinical pharmacy interventions were traditionally communicated in this particular practice setting.

Also, as the patients involved in this study could have been under the care of a number of different specialities, who worked throughout the hospital, logistically it was not feasible to verbally communicate all interventions to each medical team involved for each patient.

The success of any intervention strategy is heavily dependent upon the acceptance of intervention recommendations. In this work there was a surprisingly, lower than expected uptake of recommendations (54.8 %). The low uptake of interventions may in part be attributable to a number of different factors.

Firstly the means by which the recommendations were communicated to the physicians. A number of studies have reported substantially lower rates of acceptance with written recommendation, compared with oral recommendations, however a recent Irish study examining the impact of a pharmacist led medication reconciliation reviews in secondary care, which used both oral and written means of communications reported similarly low rates of recommendation acceptance. This indicates that physicians level of acceptance may be influences by more than just the means of communicated (223).

Secondly the professional barriers between pharmacists and physicians i.e. physicians may be less likely to accept/uptake recommendations made by a pharmacist. This theory is further supported by the fact that in a parallel study by O'Connor et al., in which a physician intervened on PIP issues using the STOPP/START criteria only, there was an 84% acceptance rate reported (445).

Thirdly the low uptake of recommendations, may also relate to the point at which the intervention was actually delivered i.e. this study used a single time-point intervention delivered within 48 hours of admission, which was usually performed in the A&E Department. Although logistically, this was probably the most suitable location to perform the review in order to maximise recruitment, it meant that the research pharmacist was reviewing patients under the care of multiple specialities and had little contact time directly with each team. This point is further reinforced by the fact that a several studies have reported improved rates of acceptance, when the pharmacist participates in ward rounds or worked as part of a multidisciplinary teams rather than working in isolation (14, 19-20, 57, 447).

Another important finding of this work is that PPO was highly prevalent in older individuals in secondary care however the structured pharmacist intervention did not significantly improve the appropriateness of underprescribing as defined by the modified ACOVE (118) (Admission; 28.3% and follow-up; 26.9%). This finding was an unexpected finding, however it may be partially explained by the fact that older patients admitted to hospital are frailer and often these patients are suffering from an acute episode of illness. The focus of the medical team is on the acute illness and therefore initiation of new medications may not be high up their list of priorities. Preliminary findings from qualitative work that our research team are currently undertaking with doctors, indicates that they agreed in principle with a number of the START PPO recommendation, however at that time the doctors primary focus was on the treatment of the acute episode rather than chronic disease management.

Future work should examine the impact of similar intervention strategies which are focused on addressing the issue of underprescribing at discharge or once the initial acute medical problem/s has been resolved. This may led to resolution of more PPO instances.

This work is the first to show that PIP is highly prevalent across all three settings of care in Ireland and that a structured pharmacist intervention supported by a CDSS can significantly improve both the appropriateness and accuracy of the medication regimens of older hospitalised individuals, while also significantly reducing their risk of experiencing an ADR. The main reasons for the success of this intervention was the structured approach taken to the medication history/reconciliation process, and the comprehensive review of appropriateness undertaken using the E-Pharma-Assist system.

8.6 Limitations

Our work has a number of limitations. The main limitations associated with each of the studies have already been discussed in detail in the individual papers. However, some of the main overall limitation of this work will be discussed below.

Lack of generalisability is one of the main limitations associated with the findings of all of these studies. The first study was carried out by a single research pharmacist who compiled the data from the medical notes of 732 residents in fourteen LTC facilities in the greater Cork region of Ireland. The second study was based on a sample of patients from study 1, who were age and gender matched with a comparative group of patients from the Northern Irish Fleetwood study. The third study was based on randomly selected samples of patients from three larger datasets from different care settings from the greater Cork region. The data for the fourth and fifth papers were based on data which was compiled by a single pharmacist at a single secondary care site in the greater Cork region. Due to the fact that the data collection for all of these studies were confined to a limited jurisdiction, it is difficult to conclude that these findings are generalisable to the all older individuals across the entire Island of Ireland. However this work does give some indication that PIP and ADRs are a problem in older Irish individuals in all healthcare settings and that specific intervention in secondary care can result in an improvement in the appropriateness of prescribing.

Another important limitation of this work relates to variability in the quality of the data available for each of the patients. This work found that the quality of the data recorded varied considerably from setting to setting and this may have resulted in either under or over estimation of the prevalence of PIP. In the future this problem

could be addressed by standardising the means by which data are recorded and stored for each patient e.g. electronic prescribing records or standardised data collection forms e.g. standardisation of medical records across all three settings of care.

A major limitation of the fourth and fifth studies, related to the way in which recommendations were communicated to the medical teams i.e. primarily written communication. Due to the reasons indicated above it was not possible to orally communicate all of the recommendations directly to the medical teams. Therefore it was decided that written recommendations would be used as the means of communication rather than verbal recommendations. This may or may not have contributed to the lower than expected uptake of recommendations. This is an area that requires further investigation and if this is found to be the case, strategies to overcome these communication barriers need to be implemented.

As already discuss in the fifth paper, due to the nature of the intervention it was not possible to blind the intervention from the medical teams involved in the study. One possible way of overcoming this would have been to carry out a multi-centered study and randomise at a hospital level, as opposed to team or patient level.

8.7 Future Work

This structured pharmacist intervention has demonstrated that it can improve the appropriateness of older individuals medication regimens while also reducing the incidence of ADRs. However, this work is really only a proof of concept and future work should consider examining what steps can be taken to integrate this sort of intervention strategy into routine clinical practice. This work has also indicated that PIP is a major issue across all settings of care in Ireland and the present intervention only examines the impact of the structured pharmacist intervention in a secondary care setting. Future work should examine the impact of similar intervention strategies in LTC and primary care settings.

This work found that there was just over a 50% uptake of interventions observed, and that the means of communication may have had a major impact on the uptake of the recommendations. Therefore as stated above, future work should consider examining the reasons for this poor uptake of recommendations and develop / implement strategies which may improve communication / relationships between pharmacist and doctors. This improved uptake of recommendations could potentially lead to a reduction in DRPs and ADRs and improvement in patient's overall care.

Chapter 9

9. References

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Chapter 10

10. Appendices

10.1 Appendix I Ethical approval for Nursing Home Studies

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.

Our Ref: ECM 4 (jj) 08/12/09

4th November 2009

Dr Stephen Byrne
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Cavanagh Pharmacy Buidling
University College Cork
Cork

Re: Inappropriate prescribing in the elderly, a review of nursing home prescriptions.

Dear Dr Byrne

Expedited approval is granted to carry out the above study in:

[redacted]

The following documents were approved:

- Application Form
- Data Collection Form.

Waiver of consent is granted.

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

- Mr David O'Sullivan, Dr Denis O'Mahony and Professor Carmel Hughes.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

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.

Our Ref: ECM 3 (III) 11/05/10

15th April 2010

Dr Stephen Byrne
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Cavanagh Pharmacy Buidling
University College Cork
Cork

Re: Inappropriate prescribing in the elderly, a review of nursing home prescriptions.

Dear Dr Byrne

The Chairman approved the following amendment application:

[redacted]

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

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.

Our Ref: ECM 3 (e) 07/09/10

30th July 2010

Dr Stephen Byrne
Senior Lecturer in Clinical Pharmacy
School of Pharmacy
Cavanagh Pharmacy Buidling
University College Cork
Cork

Re: Inappropriate prescribing in the elderly, a review of nursing home prescriptions.

Dear Dr Byrne

The Chairman approved the following amendment application:

[redacted]

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

10.2 Appendix II Ethical approval for Three Setting 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.

Our ref: ECM 4 (tt) 10/01/12

20th December 2011

Dr Stephen Byrne
Senior Lecturer
Cavanagh Pharmacy Building
University College Cork
College Road
Cork

Re: A cross section analysis of inappropriate prescribing in the elderly, in primary, secondary and nursing home settings.

Dear Dr Byrne

Expedited approval is granted to carry out the above study.

The following document was approved:

- Application Form.

Waiver of Consent has been granted.

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

- Mr David O'Sullivan, Dr Denis O'Mahony and Mr Alan Kearney.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

10.3 Appendix III Ethical approval for Intervention Studies

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.

Our ref: ECM 4 (o) 10/08/10

21st July 2010

Dr Denis O'Mahony
Consultant Geriatrician
Department of Geriatric Medicine
Cork University Hospital
Wilton
Cork

Re: Adverse drug event incidence in older patients following hospital admission and use of STOPP/START criteria as an intervention tool for prevention of adverse drug events in older patients in hospital: a randomised, controlled trial.

Dear Dr O'Mahony

Expedited approval is granted to carry out the above study in:

[redacted]

The following documents were approved:

- Application Form
- Consent Form Version 1 dated 16th August 2007
- Research Proposal.

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

- Dr Marie O'Connor.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

CORK UNIVERSITY HOSPITAL
26 JUL 2010
GERIATRIC DEPT.

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.

Our ref: ECM 3 (bbb) 07/12/10

19th November 2010

Dr Denis O'Mahony
Consultant Geriatrician
Department of Geriatric Medicine
Cork University Hospital
Wilton
Cork

Re: Adverse drug event incidence in older patients following hospital admission and use of STOPP/START criteria as an intervention tool for prevention of adverse drug events in older patients in hospital: a randomised, controlled trial.

Dear Dr O'Mahony

The Chairman approved the following

- Amendment 1
- Amendment Application Form
- Revised Study Protocol
- Revised Consent Form dated 12th November 2010 (Prior to use please change version 1 on this document to version 2 as we have already approved a version 1)
- Addition of Dr Stephen Byrne and David O'Sullivan as co-investigators.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

10.4 Appendix IV Patient Information Leaflet

Patient Information Leaflet

Reducing Adverse Drug Events in Patients aged 65 years and over.

Dear_____

You have kindly agreed to participate in this study on reducing the risk of adverse events from medications. This will involve your medication list being reviewed by a pharmacist with training in geriatric pharmacotherapy. In addition to reviewing your medications this doctor will also review your list of diagnoses and blood results on admission to hospital and once more during your hospital stay. Any potential inappropriate medications will be highlighted to the team with primary responsibility for your care in hospital. We will liaise with your Consultant and team about any recommendations with regards to the tablets you are taking.

One in five of the patients recruited to the study will be followed up about three months following discharge from hospital. This 3 month follow up will take the form of a telephone call to you at a time and date of your convenience. These patients for three month follow up will be selected at random.

We are very grateful for your participation in this study. We hope that the information gathered in this study will help improve the health and well being of older people in Ireland. If you have any questions in relation to your participation in this study please do not hesitate to contact us here in the Department of Geriatric Medicine at 021-4922396.

David O'Sullivan
Pharmacist & Clinical Researcher
University College Cork
Cork.

Dr. Denis O'Mahony
Consultant Geriatrician & Primary Investigator
Cork University Hospital
Wilton
Cork.

10.5 Appendix V Patient Consent Form

University College Cork

Clinical Research Ethics Committee of the Cork Teaching Hospitals

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH PROTOCOL

Section A

Protocol Number:_____ Patient Name:_____

Title of Protocol:

Use of STOPP/START criteria and Pharmacist Review as intervention tools for the reduction of Adverse Drug Events in Older Patients in hospital: a randomized, controlled trial.

Doctor(s) Directing Research:	Dr. Denis O'Mahony	Phone: 021 4922317
	Dr. Stephen Byrne	Phone 021 4906518
	Dr. Marie O'Connor	Phone: 021 4920985
	David O Sullivan MPharm	Phone: 021 4920985

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

Section B

I. NATURE AND DURATION OF PROCEDURE(S):

People over the age of 65 years often take many medicines at the same time to treat various illnesses. Some medicines are clearly of benefit to older people, while other medicines may not be suitable because of side effects such as constipation, confusion, tiredness or light-headedness that could cause a fall or injury, and result in a GP or hospital visit. It is important to correctly treat each individual illness in the best way possible. It is also important to choose medications that are suitable for you and least likely to cause side effects. We have developed systematic ways of reviewing your medicines that will highlight to your doctor the medicines that may or may not be suitable for you, in accordance with your illnesses. The aim of this study is to compare the new medication review system with current standard hospital care to see if it improves the quality of prescribing for patients. It also aims to examine if any of the medications you are taking are having an adverse effect on your health during your hospital stay. If this is found to be the case the medical team looking after you in hospital will be informed both verbally and in writing.

Should you choose to participate in this study, a doctor or pharmacist will ask you a few questions about your medical history and the medications that you are currently taking as well as any medications that you have had problems with in the past and check the details of these in your medical notes also. You will be randomly assigned to one of three groups. The first group will receive routine, standard hospital care. The second group will also receive standard hospital care in addition to having their prescription medications reviewed with the medication review system by a medical doctor with speciality training in medicine for the older person. The third group will receive standard hospital care and in addition receive a clinical pharmacist's review of medications on admission through to discharge

All three groups will also be examined for any adverse events arising out of their medications during their hospital stay. The medical team with responsibility for your inpatient care will be informed if any such adverse event is detected. As with all patients admitted to hospital, you and your GP will be informed of any changes that are made to your prescription medications.

One in five patients will be asked to attend an outpatient medication review clinic three months following discharge from hospital. This clinic will be in the Assessment and Treatment Centre in St. Finbarr's Hospital, South Douglas Road, Cork.

II. POTENTIAL RISKS AND BENEFITS:

All patients in this study will receive standard hospital care from doctors, nurses and pharmacists. This new medication review system may improve the quality of prescribing and reduce medication-related problems for older people.

III. POSSIBLE ALTERNATIVES:

Participation in this study is voluntary.

_____

_____

Section C

AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. I have had the opportunity to ask questions concerning any and all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate

or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at the Cork Teaching Hospitals. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the doctor(s) listed above. If I have further queries concerning my rights in connection with the research, I can contact the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Lancaster Hall, 6 Little Hanover Street, Cork.

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

_____ _____

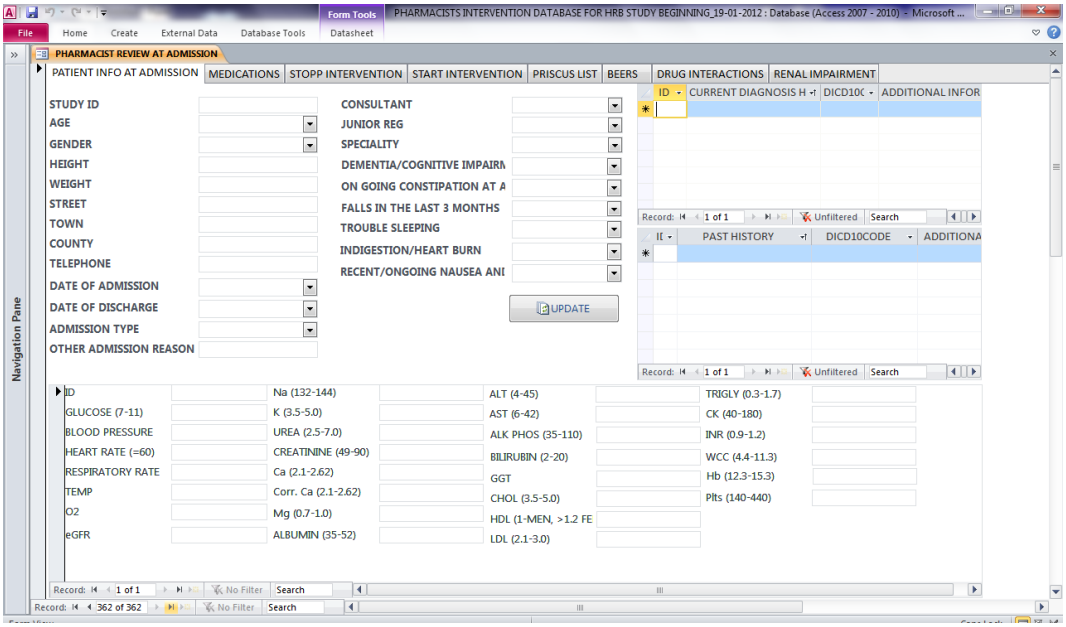
Doctor/Pharmacist: Signature of Patient or Guardian

Date: _____ Time: _____AM/PM

10.6 Appendix VI Description of the E-Pharma-Assist CDSS System.

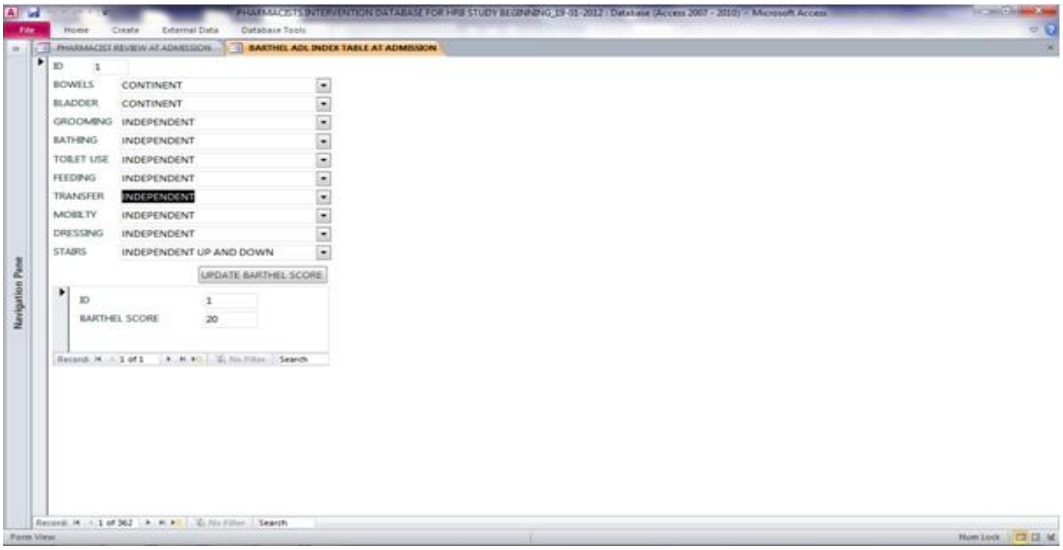
Review at admission:

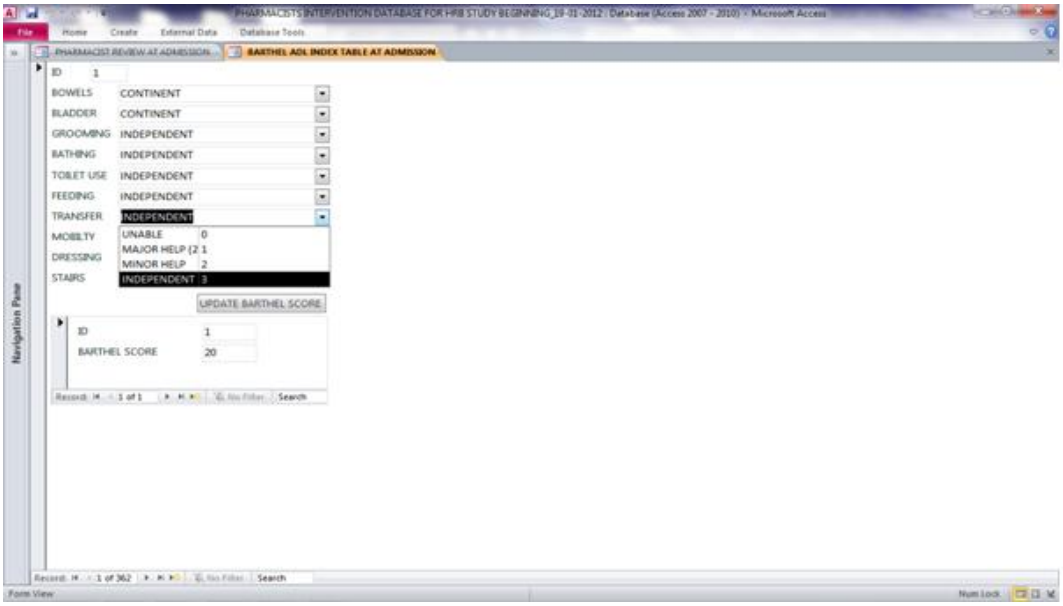
At admission the study patients demographic, current and past medical history and biomedical information were extracted from the patients' medical and nursing notes and entered into the specially developed electronic data collection form. This form was generated from a review of paper data collection forms that our research group had used in previous studies.



Barthel Index:

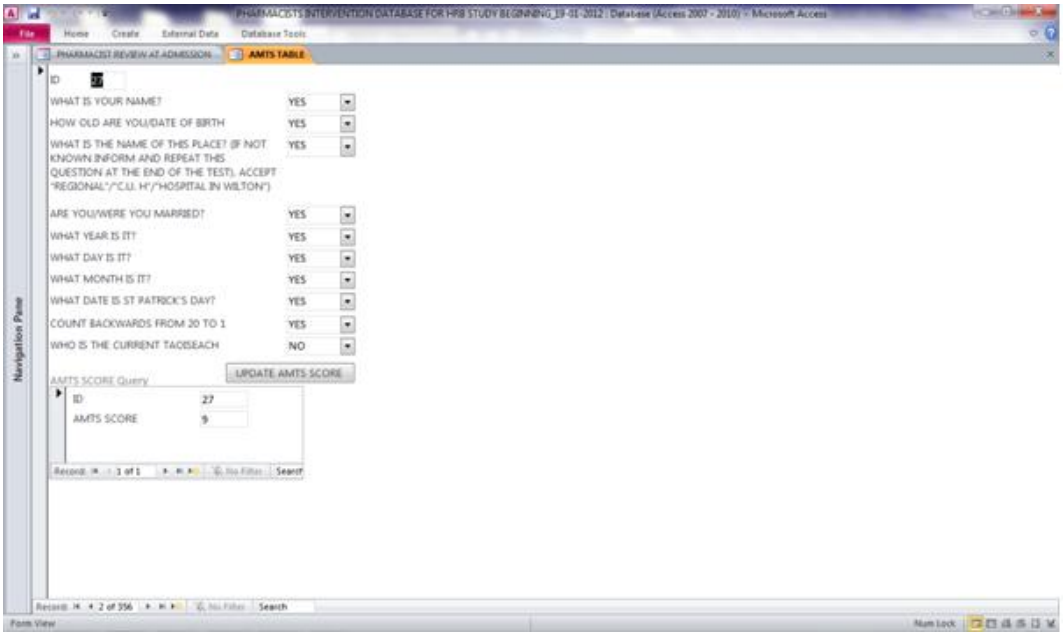
The Barthel Index consists of 10 elements that assess an individual's daily function, specifically their activities of daily living and mobility. The index primarily issues relating to feeding, mobilising, grooming, transfer, toilet use, bathing, going up and down stairs, dressing and level of bowel and bladder continence. The system incorporates a computerised Barthel Index, the user answers the specific questions relating to the Barthel index and the system then calculates and records the corresponding score.

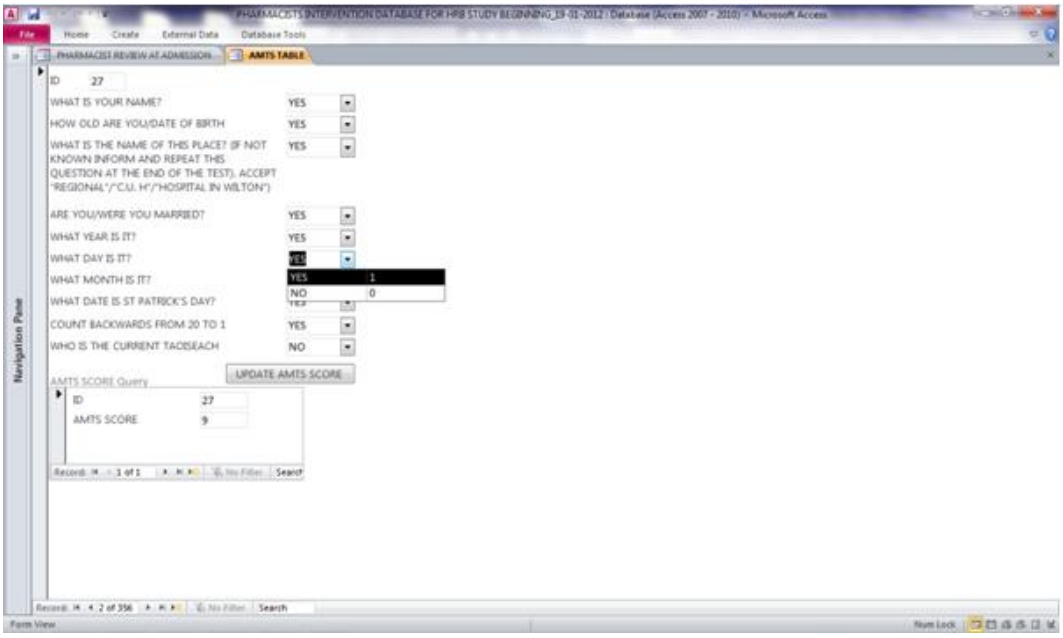




Abbreviated mental test score (AMTS):

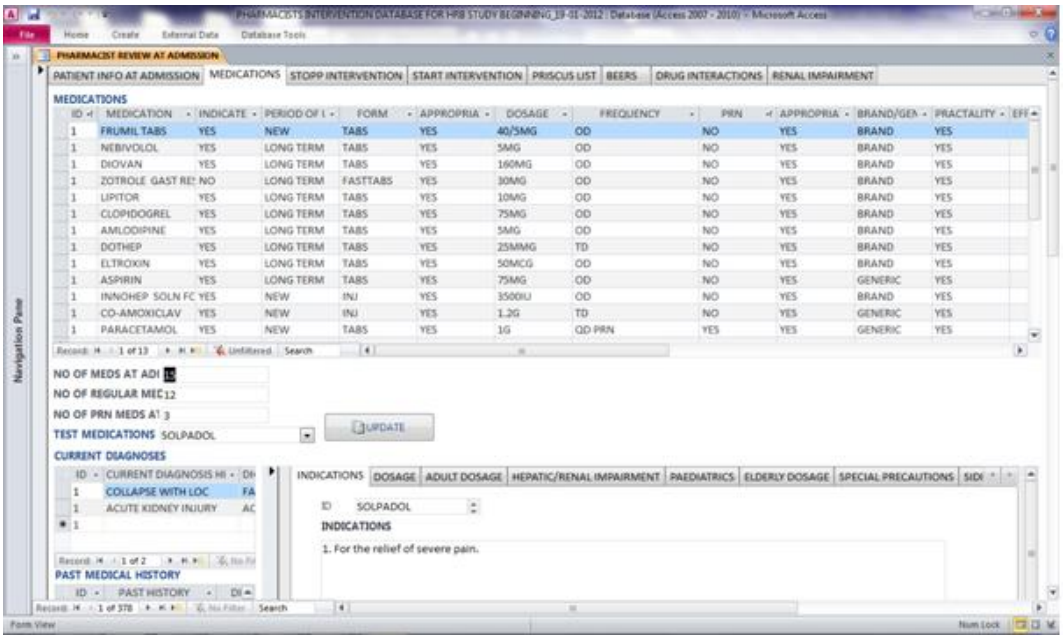
The AMTS is a scoring index for reviewing an individual's level of cognition. The system incorporates a computerised version of the AMTS. The user entered the answers to the specific questions of the AMTS and from these the system calculates and stores the corresponding AMTS score.





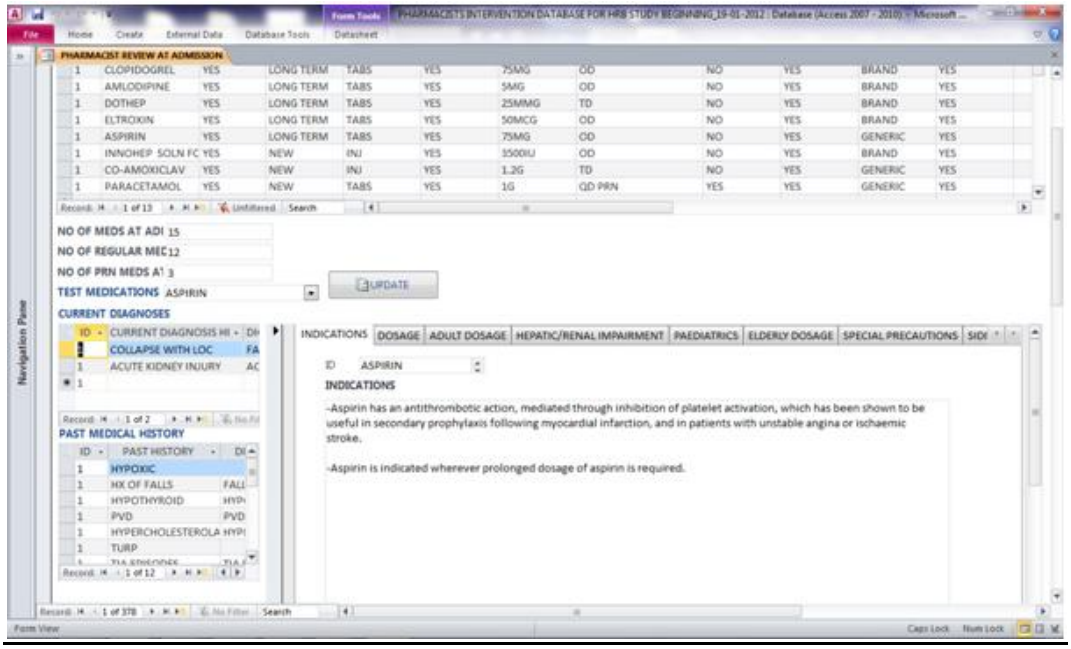
Medication Appropriateness Index (MAI):

The MAI is an index for assessing used for assessing a medication's appropriateness. The user answers the relevant question related to the MAI at the point of data enter while simultaneous checking for the answers in the medication information tab outlined below. When all the relevant fields have been completed the system will calculate and store a MAI score out of 18. The higher the score the less appropriate the medication.



Medication information:

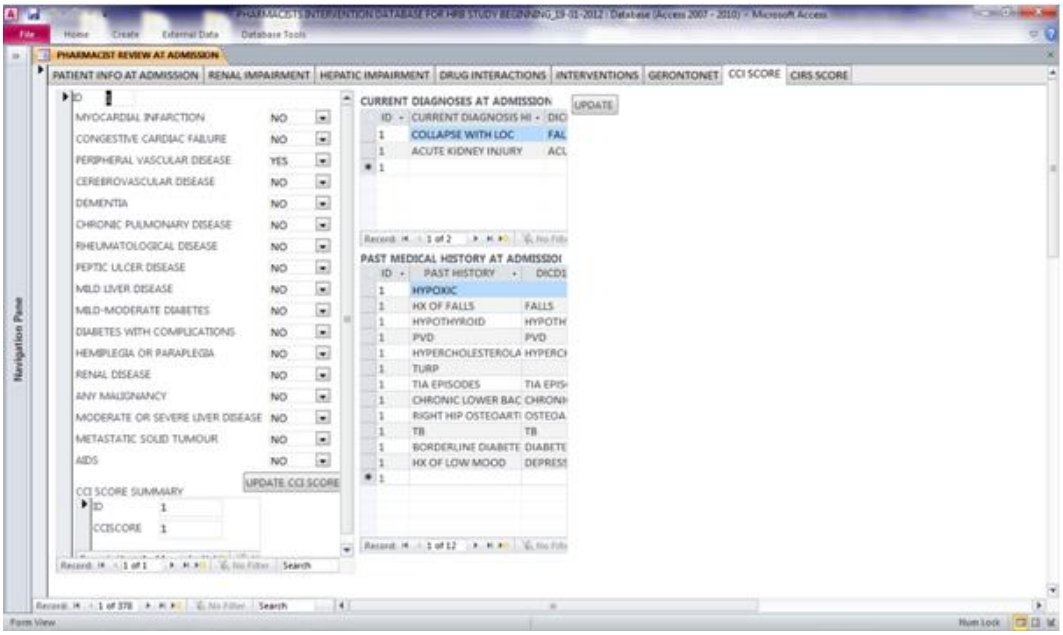
The medications are coded at the point of data entry using a modified version of the ATC codes (D-ATC codes). As the medications are entered, the system is designed to give the user the ability to simultaneously check specific indications, dosages, side effects, cautions and contra-indications etc. in a specially designed drug information tab, which updates based on specific drug selected by the user. The information in this drug information tab was developed from the summary of product characteristics (SPC) for each medication.



The conditions/ disease states are also coded at the point of entry based on a modified version of the ICD-10 codes (D-ICD-10). The medications are entered into an auto/predict- text box and a free text box. The D-ICD-10 codes are based on the ICD-10 codes and the most common described disease descriptions used in practice. On repeat usage new D-ICD-10 codes will be generated based on new descriptions or abbreviated descriptions of diseases and conditions. However eventually this should theoretically reach saturation.

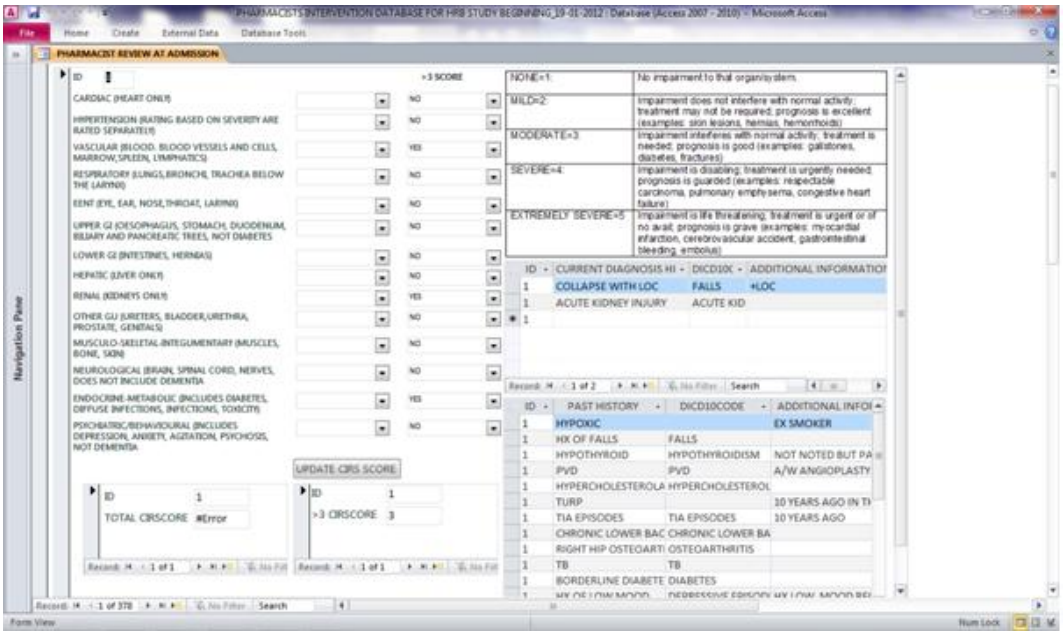
Charlson Co-morbidity Index (CCI):

The Charlson Co-morbidity index (CCI) is an index that quantifies disease burden using a weighted score that address both the number as well as severity of commonly occurring co-morbid conditions. The system incorporates a computerised CCI. The user fills in whether or not a patient has the specific conditions listed in the CCI and the system then calculates and records the corresponding CCI score.



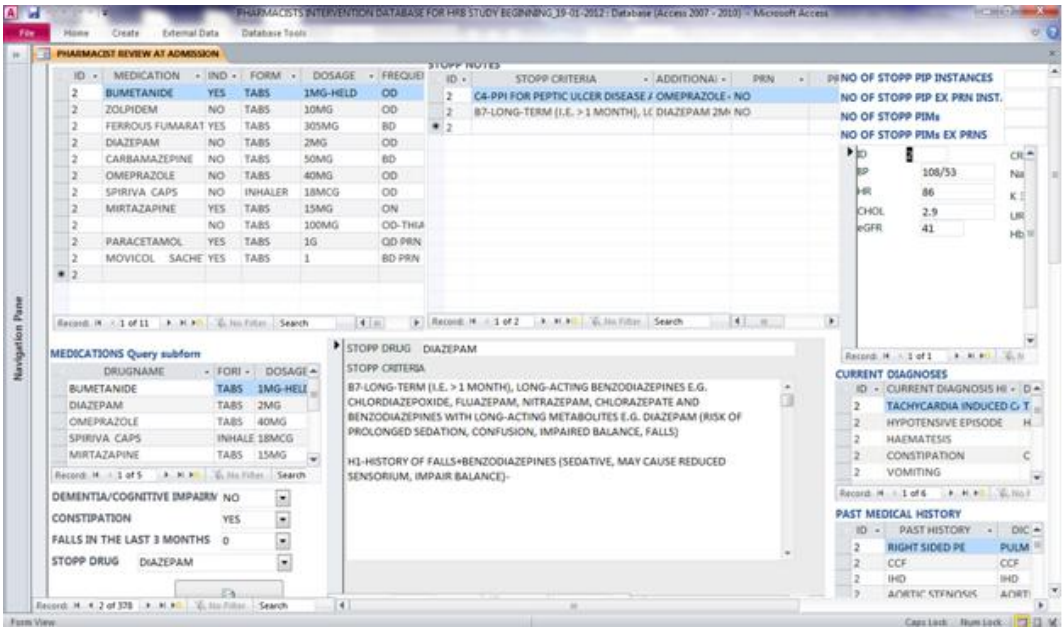
Cumulative Illness Rating Scale (CIRS):

The Cumulative Illness Rating Scale (CIRS) is a rating scale, it allows for the user to calculate disease burden based on the number and the severity of chronic diseases. The system incorporates a computerised CIRS. The user fills in whether or not a patient has the specific conditions listed in the CIRS and the system calculates and records the corresponding CIRS score.



STOPP Intervention 2008:

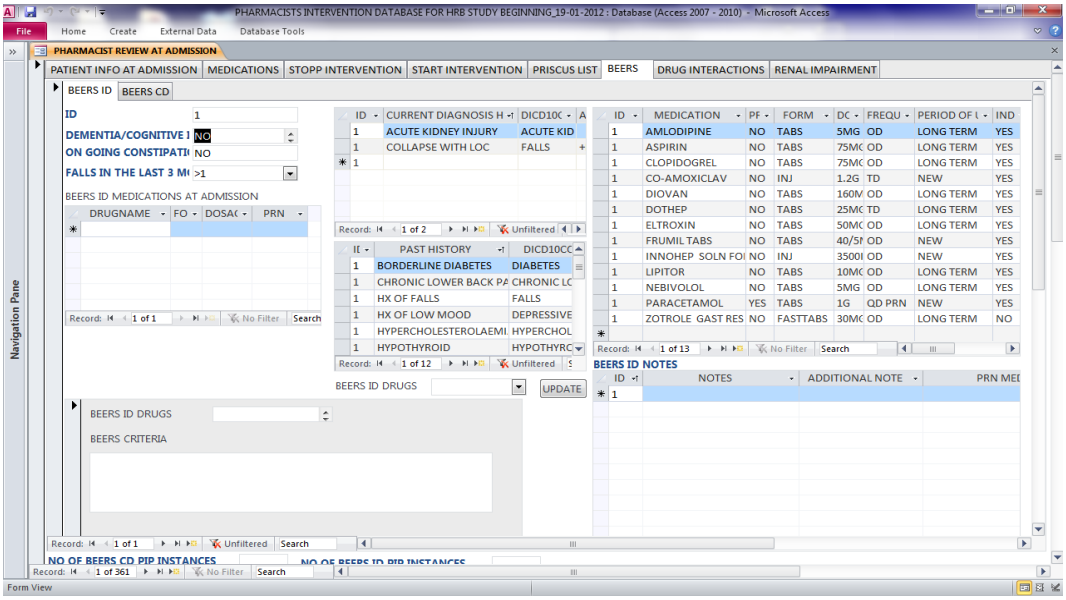
The system is designed to screen for the medications related to the STOPP criteria, based on a subset of STOPP D-ATC filter codes. These medications are filtered out and the user can then select the individual medications to see its corresponding STOPP criteria. The user can then record the relevant instances of potentially inappropriate prescribing (PIP) information in the STOPP recommendations box.

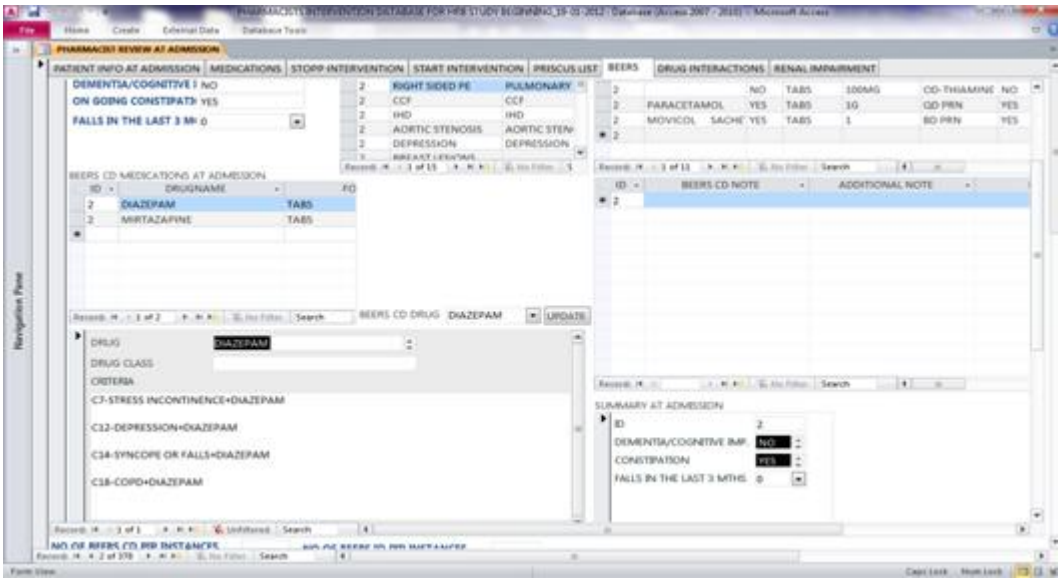


Beers 2003:

Beers Independent of Diagnosis (ID) and Beers Considering Diagnosis (CD)

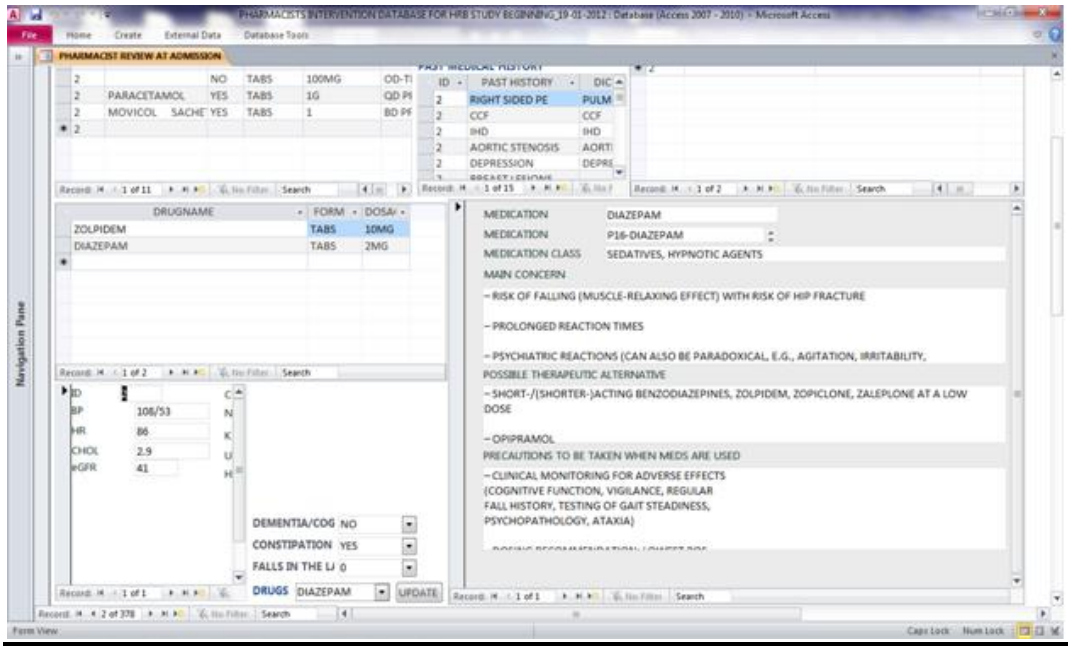
The system is designed to screen for the medications related to both the Beers ID and Beers CD, based on a subset of Beers D-ATC filter codes. The system filters out the relevant medications. The user can then select the specific medications to see Beers ID and Beers CD criteria related to each medication. The user can then record the relevant instances of potentially inappropriate prescribing (PIP) information in the Beer recommendations box.





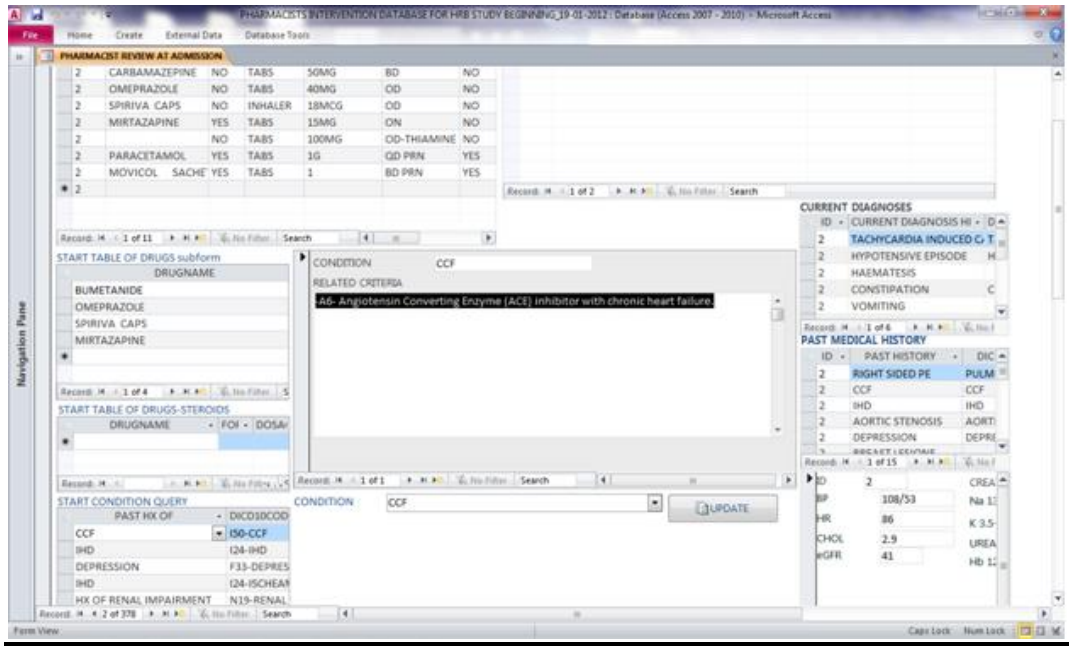
Priscus 2011:

The system is designed to screen for medications relating to the Priscus criteria, based on a subset of Priscus D-ATC filter codes. These medications are filter out and the user can select the specific medications to see the corresponding Priscus criteria, the alternatives and cautionary advice if the medication is to be initiated or continued. The user can then record the relevant instances of potentially inappropriate prescribing (PIP) information in the Priscus recommendations box.



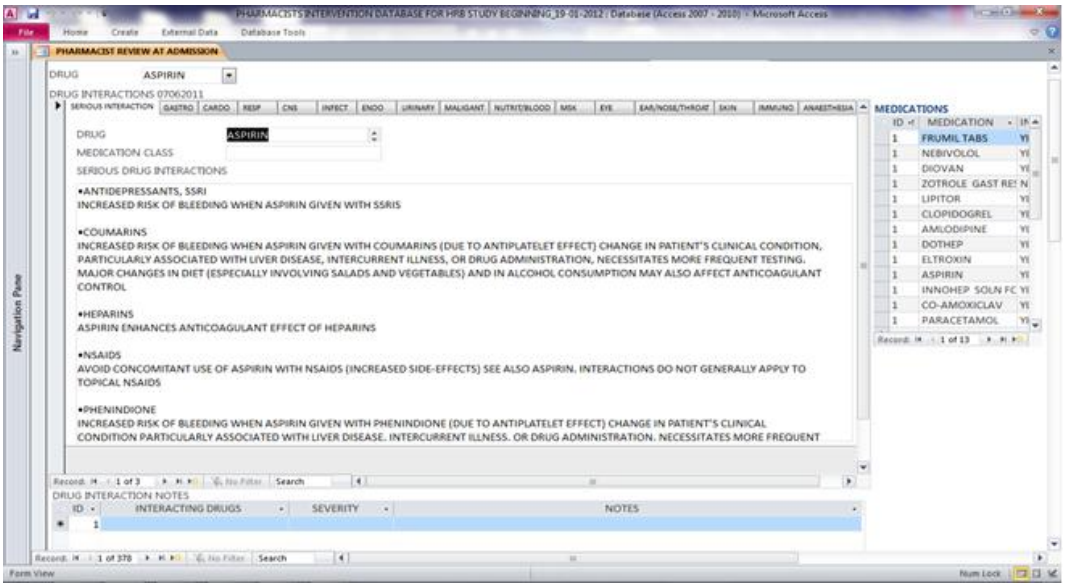
START:

The system is designed to screen for conditions relating to the START criteria, based on a subset of the START D-ICD-10 filter codes and screen for medications relating to the START criteria, based on a subset of the START D-ATC filter codes. These conditions that are filtered out and the user can select the specific conditions to see the corresponding START criteria. The user can then record the relevant instances of potential prescribing omissions (PPOs) information in the START recommendations box.



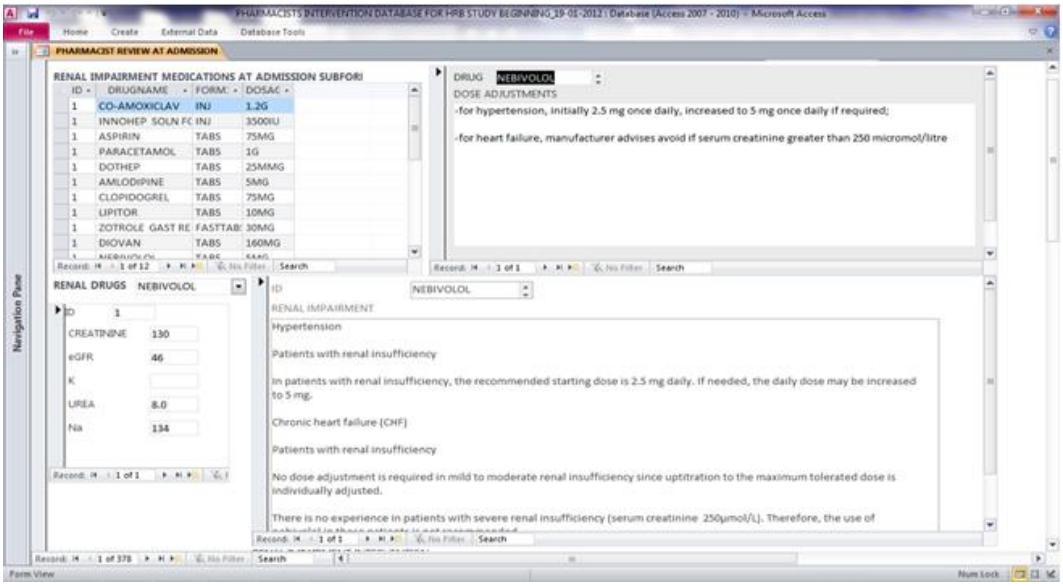
Drug Interaction:

The drug interaction element of the system, works by the user selecting a specific drug and the system then presents all the major interactions and recommendations/courses of action according to the recommendations of the British national formulary (BNF). This element outlines all the major and minor interactions as well as all the interactions subdivided according to the physiological system to which the interacting drugs relate. The user can then record the relevant information in the drug interactions recommendations box.



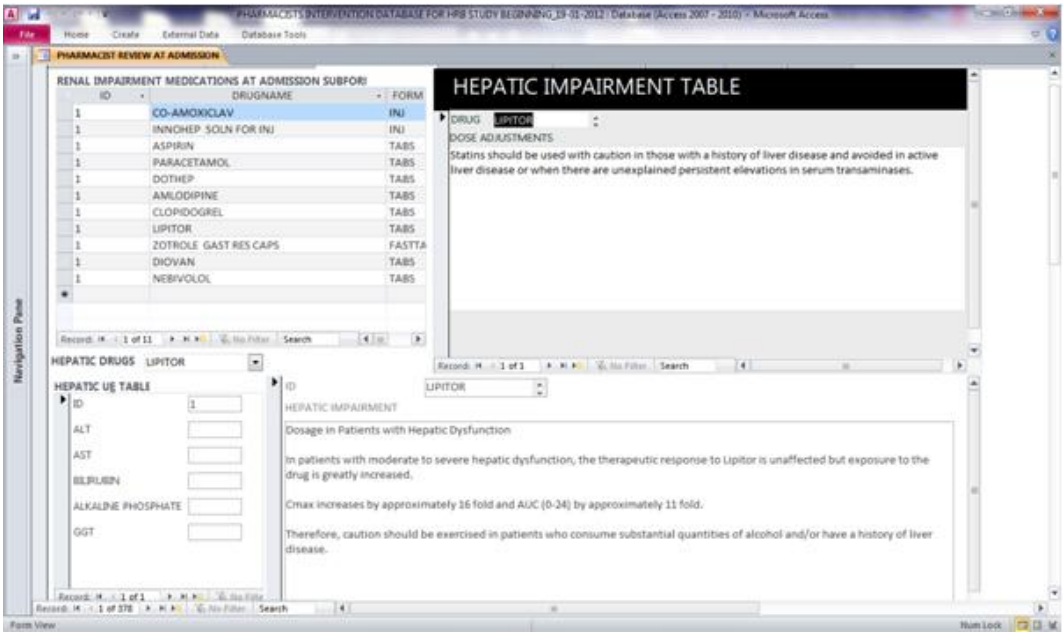
Renal Impairment:

The system screens out all the medications which require dosage adjustments in renal impairment according to the BNF, based on a subset of the D-ATC filter codes. The user can then select the specific medications and the system presents the relevant information/ dosage adjustment/ cautionary recommendations from the BNF and the medications SPC. The user can then record the relevant information in the renal impairment recommendations box.



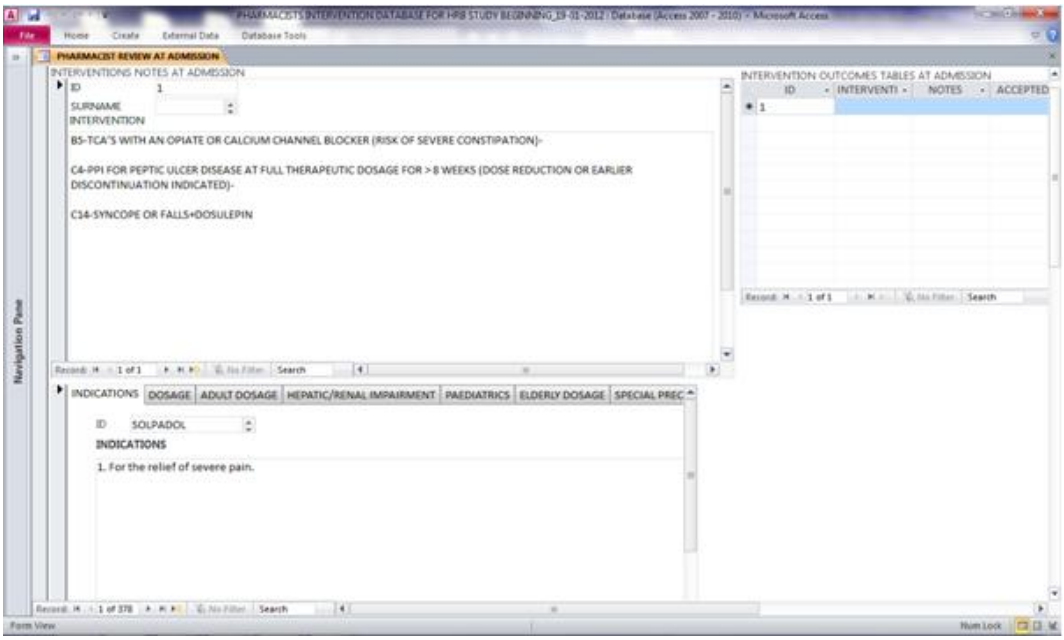
Hepatic Impairment:

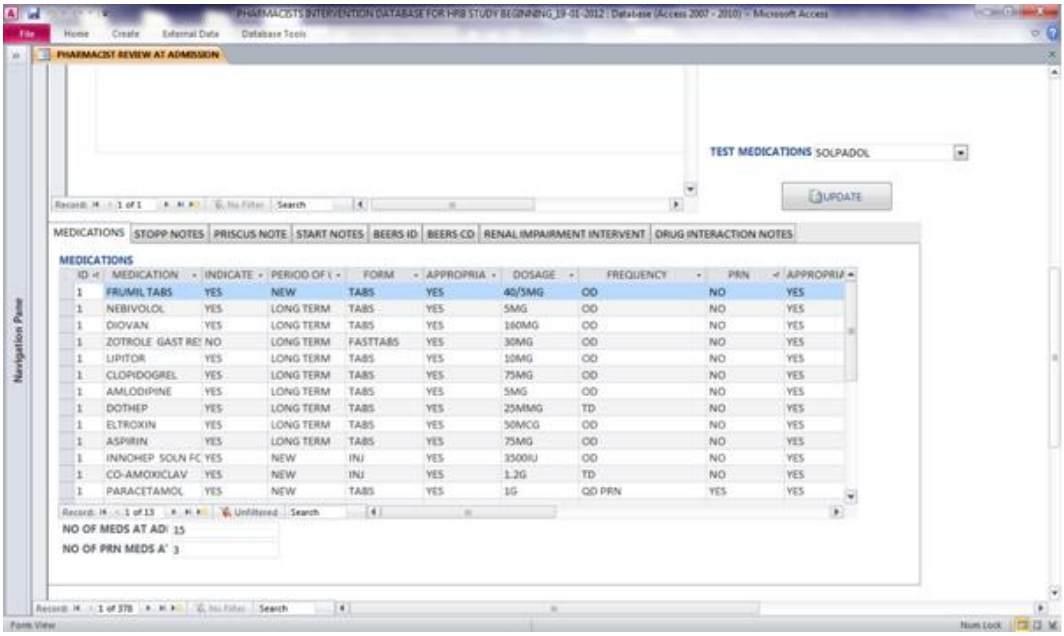
The system screens out all the medications which require dosage adjustments in hepatic impairment according to the BNF, based on a subset of D-ATC filter codes. The user can then select the specific medications and the system will outline any relevant information/dosage adjustments/cautionary recommendations from the medication and medications SPC. The user can then record the relevant information in the hepatic impairment recommendations box.



Recommendations:

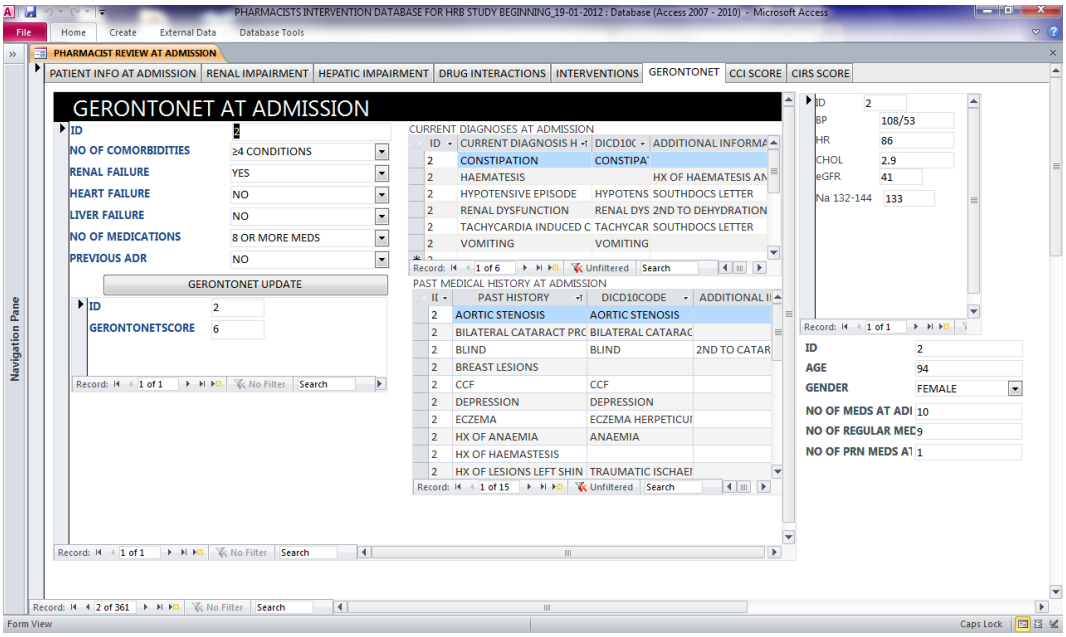
All the relevant recommendations boxes are presented in a separate tab, to allow the user to review the relevant information/recommendations simultaneously and address each of the issues of appropriateness which were highlighted throughout the review.





GerontoNet:

The GerontoNet adverse drug reaction (ADR) risk score is a scoring system designed to quickly and reliably identify older individuals at the highest risk of experiencing an ADR. The system incorporates a computerised version of the GerontoNet tool, the user fills in the relevant questions based on the information presented to them and then the system calculates and records the corresponding GerontoNet score.



Review at 7-10 days:

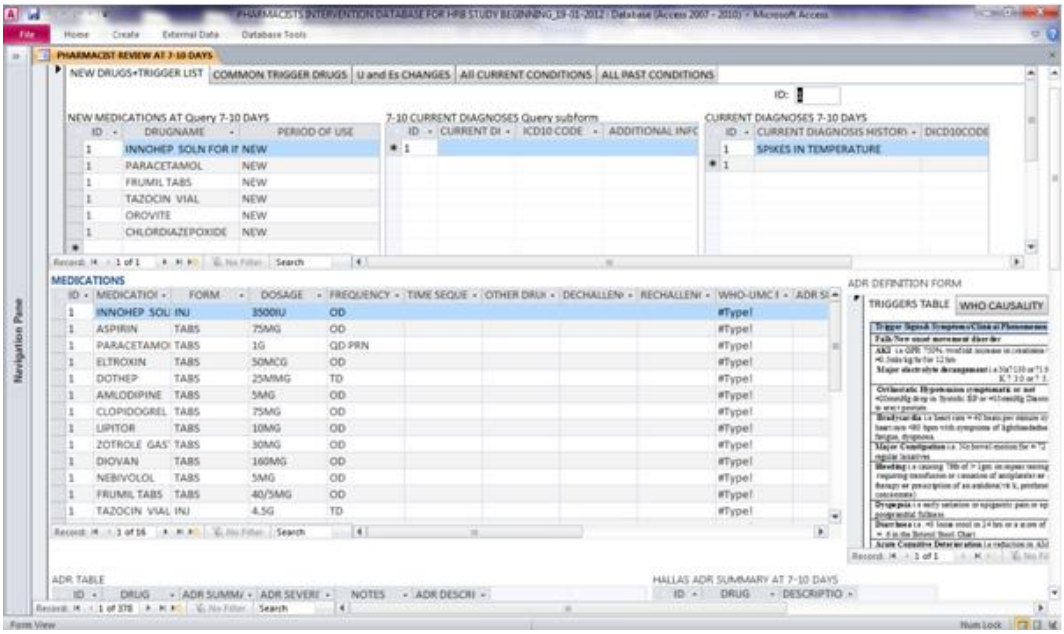
This review tabs incorporates all the tools available in the review at admission element of the system, however it provides the user with all the relevant information from the point of admission, so the user doesn't have to go and re-enter all the information again, they can just copy over the relevant information and then add any additional information where necessary.

The 7-10 day section also includes an additional adverse drug reaction (ADR) assessment tool.

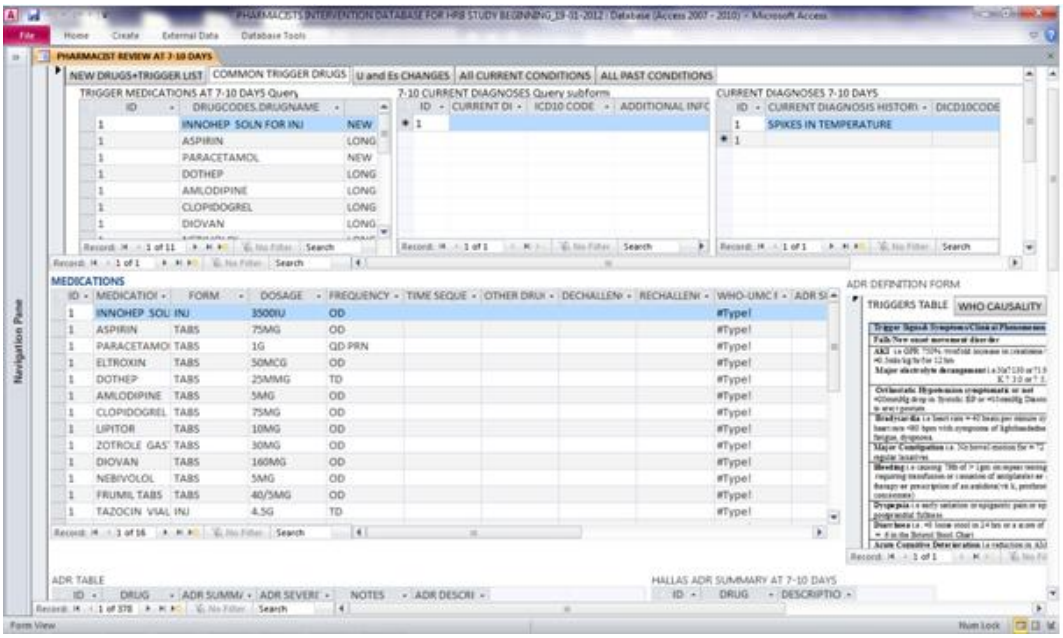
ADR assessment tool:

This tool presents the user with:

(i) A tab which outlines all the new medications started since admission and all the new symptoms, so the user can easily screen for potential ADRs,



(ii) A tab which screens the patient's list of new conditions for commonly occurring ADRs based on a subset of ADR ICD-10 filter codes and also screens the patients list of medications for the most commonly offending ADR related medications based on a subset of the ADR ATC filter codes. These ADR ATC codes and ADR ICD-10 filter codes are based on a specially developed ADR trigger list outlined below.



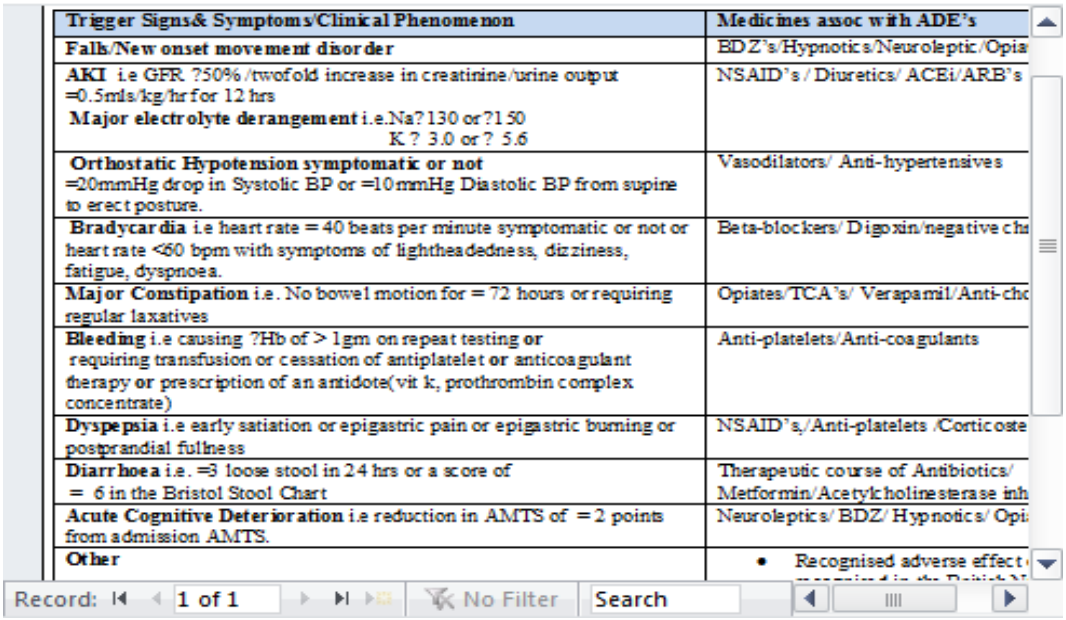
Trigger List

ADR ascertainment was facilitated by the use of a pre-defined ADR trigger list consisting of the most common clinical manifestations of proven ADRs, derived from a combined database of two recent studies of 1113 of elderly hospitalized patients, which was compiled by our research group.

Trigger List of Adverse Drug Reactions.

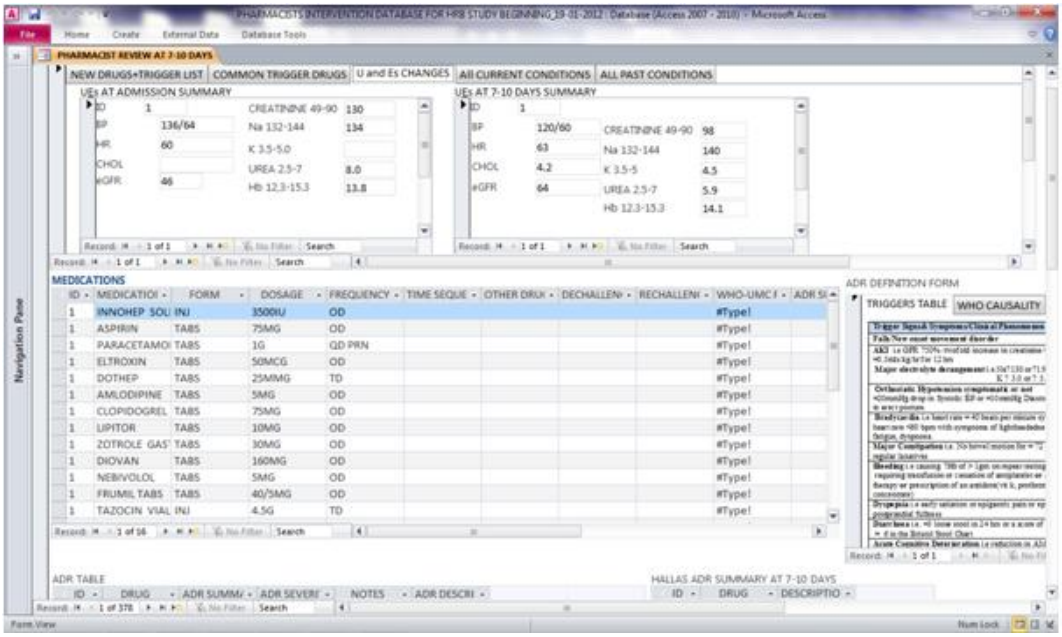
Trigger Symptom/Clinical Phenomenon	Medicines commonly associated with ADRs as defined by the Trigger List
Falls i.e. one or more falls following randomization	Benzodiazepines, hypnotics, neuroleptics, opioids
AKI i.e. estimated GFR reduced by 50% and/or a two fold increase in serum creatinine concentration and/or urine output ≤ 0.5mls/kg/hr for 12 hours	Non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors, angiotensin receptor blockers.
Significant electrolyte derangement i.e. serum sodium <130 mmol/l or > 150 mmol/l; serum potassium < 3.0 mmol/l or > 5.5 mmol/l; corrected serum calcium > 2.6 mmol/l.	Non-steroidal anti-inflammatory drugs, diuretics, ACE inhibitors, angiotensin receptor blockers.
Symptomatic orthostatic hypotension i.e. reduction in systolic blood pressure > 20 mmHg and/or diastolic blood pressure > 10 mmHg from supine to erect posture.	Vasodilators
Presyncope/syncope i.e. transient disturbed level of consciousness and postural tone, of rapid onset, short duration and rapid recovery, due to global cerebral hypoperfusion, usually resulting from hypotension.	Beta-blockers, digoxin, verapamil, diltiazem
Major constipation i.e. requiring daily laxatives	Opioids
Bleeding i.e. causing a drop in haemoglobin concentration > 2 g/dl or cessation of antiplatelet or anticoagulant therapy or requiring blood transfusion or requiring prescription of an antidote (e.g. vitamin K for warfarin reversal)	Anti-platelet agents, anti-coagulants
Dyspepsia	Non-steroidal anti-inflammatory drugs
Diarrhoea i.e. ≥3 loose stools in 24 hours	Antibiotics
Movement Disorders i.e. Parkinsonism/Ataxia/Myoclonus	Benzodiazepines, hypnotics, neuroleptics, opioids
Other	• Recognised adverse effect of the drug or • Requires discontinuation of the drug or • Requires medical intervention

Key AKI; Acute Kidney Injury, GFR: Glomerular Filtration Rate; kg; Kilogram, g; gram, dl; Decilitres, ACE; Angiotensin Converting Enzyme, ADR; Adverse Drug Reaction



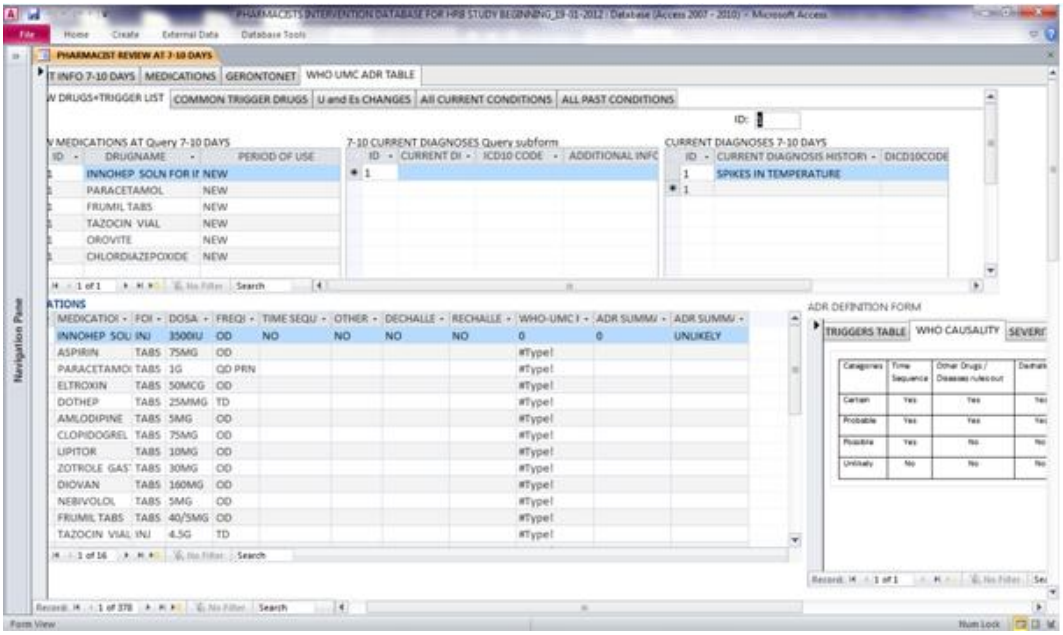
Trigger Signs& Symptoms/Clinical Phenomenon	Medicines assoc with ADE's
Falls/New onset movement disorder	BDZ's/Hypnotics/Neuroleptic/Opia
AKI i.e GFR ?50% /twofold increase in creatinine/urine output =0.5mls/kg/hr for 12 hrs **Major electrolyte derangement** i.e.Na? 130 or ?150 K ? 3.0 or ? 5.6	NSAID's / Diuretics/ ACEi/ARB's
Orthostatic Hypotension symptomatic or not =20mmHg drop in Systolic BP or =10 mmHg Diastolic BP from supine to erect posture.	Vasodilators/ Anti-hypertensives
Bradycardia i.e heart rate = 40 beats per minute symptomatic or not or heart rate <60 bpm with symptoms of lightheadedness, dizziness, fatigue, dyspnoea.	Beta-blockers/ Digoxin/negative chr
Major Constipation i.e. No bowel motion for = 72 hours or requiring regular laxatives	Opiates/TCA's/ Verapamil/Anti-chc
Bleeding i.e causing ?Hb of > 1gm on repeat testing **or** requiring transfusion or cessation of antiplatelet **or** anticoagulant therapy **or** prescription of an antidote(vit k, prothrombin complex concentrate)	Anti-platelets/Anti-coagulants
Dyspepsia i.e early satiation or epigastric pain or epigastric burning or postprandial fullness	NSAID's,/Anti-platelets /Corticoste
Diarrhoea i.e. =3 loose stool in 24 hrs or a score of = 6 in the Bristol Stool Chart	Therapeutic course of Antibiotics/ Metformin/Acetylcholinesterase inh
Acute Cognitive Deterioration i.e reduction in AMTS of = 2 points from admission AMTS.	Neuroleptics/ BDZ/ Hypnotics/ Opi
Other	• Recognised adverse effect

(iii) A tab which lists the patient specific vitals, obs. and biochemistry data at the point of admission and at the follow-up so the user can see if there is any significant changes in these level from the point of admission to follow-up and to check if any of the new medications or a combination of medications may be responsible for these changes. Presenting the information in this fashion allows the user to systematic review each patient for any potential ADRs.



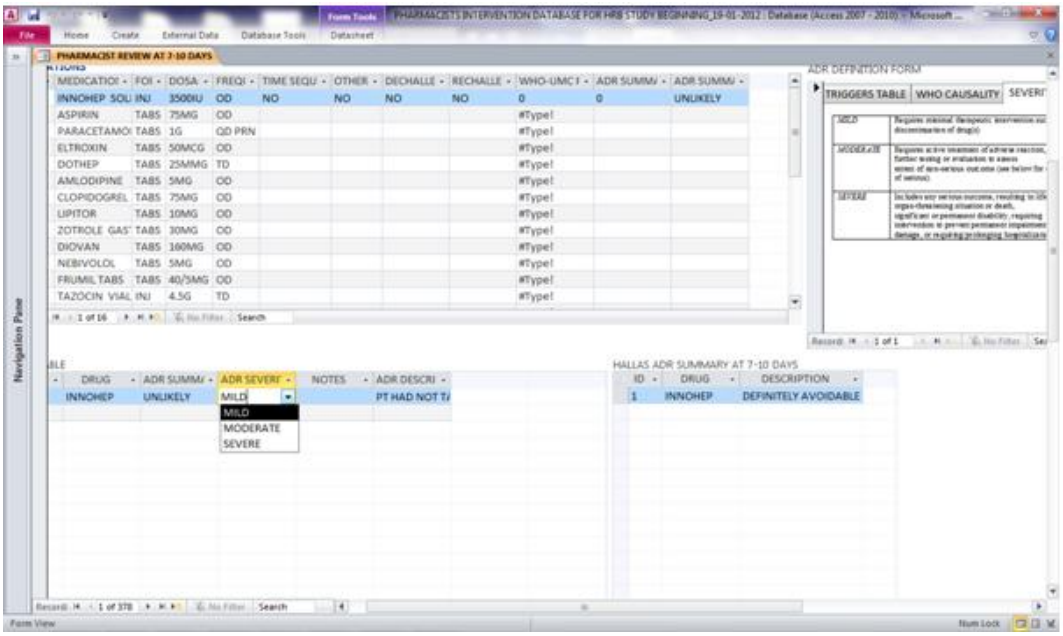
WHO-UMC Causality assessment:

The WHO-UMC causality assessment tool is designed to as a means of assessing ADR. It takes both the clinical aspects of the case history and quality of the documentation into consideration. The system incorporates a computerised WHO-UMC causality index. When the user identifies a medication which could have contributed to an ADR, the user can then complete the causality elements of the tool and the system will generate a causality score i.e. how likely it is that this specific medication is causing the ADR.



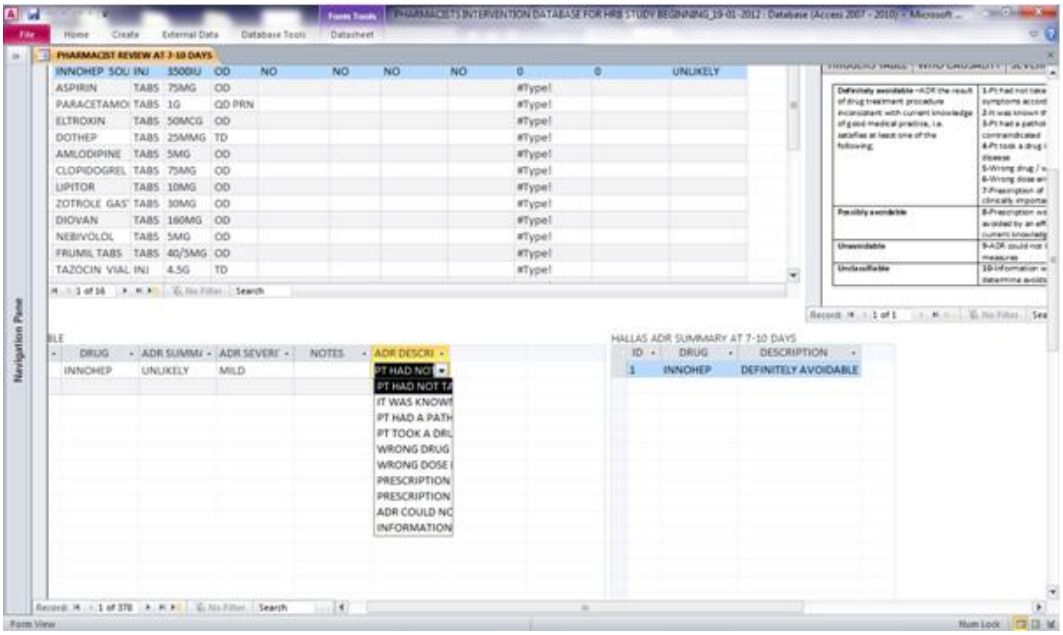
ADR Severity rating:

Once causality has been established the user can then rate the potential severity of the potential ADR based on the Hartwig severity rating scale.



Hallas avoidability criteria:

The Hallas criteria are a set of criteria used to evaluate a ADRs level of avoidability (definitely avoidable, possibly avoidable of unavoidable). The system incorporates a computerised set of Hallas criteria. Once causality has been established and severity been rated the user can then select a reason for the cause of the suspected ADR and the system will generate a level of avoidability



The system then stores all of the corresponding scores and ratings. Assessing ADRs in such a systematic fashion allows for easy assessment of ADRs, while it also allows for quick and easy retrospective reviews of each of the putative ADRs.

10.7 Appendix VII Table for estimation of sample size for Cluster Randomised Controlled Trial

Table 10.1 Sample size calculation for varying cluster sizes 30% decrease at 0.05 (2 sided)

Cluster size	Design effect	Number of patients per arm	Total	10%
50	3.45	1449	2898	3187.8
45	3.2	1344	2688	2956.8
40	2.95	1239	2478	2725.8
35	2.7	1134	2268	2494.8
30	2.45	1029	2058	2263.8
25	2.2	924	1848	2032.8
20	1.95	819	1638	1801.8
15	1.7	714	1428	1570.8
10	1.45	609	1218	1339.8
5	1.2	504	1008	1108.8

Table 10.2 Sample size calculation for varying cluster sizes 30% decrease at 0.05 (1 sided)

Cluster size	Design effect	Number of patients per arm	Total	10%
50	3.45	1228.2	2456.4	2702.0
45	3.2	1139.2	2278.4	2506.2
40	2.95	1050.2	2100.4	2310.4
35	2.7	961.2	1922.4	2114.6
30	2.45	872.2	1744.4	1918.8
25	2.2	783.2	1566.4	1723.0
20	1.95	694.2	1388.4	1527.2
15	1.7	605.2	1210.4	1331.4
10	1.45	516.2	1032.4	1135.6
5	1.2	427.2	854.4	939.8