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**Adverse drug reactions and targets for
deprescribing in high risk older adults**

Volume 1 of 1

Thesis presented by
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January 2018

Dedicated to my husband, Mick

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Declaration

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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LIST OF ABBREVIATIONS

ACE inhibitor	Angiotensin converting enzyme inhibitor
ADE	Adverse drug event
ADLs	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
Biomed	Biomedical Scientist
Bpm	Beats per minute
Ca ⁺⁺	Calcium
CCB	Calcium channel blocker
CIRS	Cumulative illness rating scale
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CUH	Cork University Hospital
DI	Drug interaction
DILI	Drug induced liver injury
DM	Diabetes mellitus
DOAC	Drug-acting oral anticoagulants
Dr.	Doctor
DSM-V	Diagnostic & Statistical Manual of Mental Disorders
ECG	Electrocardiogram
ED	Emergency department
eGFR	estimated Glomerular Filtration Rate
GORD	Gastro-oesophageal reflux disease
GP	General Practitioner
GS	Gold standard
HF	Heart failure

HRB-CRF	Health Research Board – Clinical Research Facility
HSE	Health Service Executive
IHD	Ischaemic heart disease
IP	Inappropriate prescribing
IRR	Inter-rater reliability
K ⁺	Potassium
Kg	Kilogram
LLE	Limited life expectancy
LO	Liaison officer
MAI	Medication appropriateness index
MBT	Months backward test
MDRD	Modification of Diet in Renal Disease
Mg	Milligram
MMSE	Mini-Mental State Examination
MOCA	Montreal Cognitive Assessment
MUH	Mercy University Hospital
Na ⁺	Sodium
NASSa	Noradrenergic and selective serotonergic anti-depressants
NCPOP	National Clinical Program for Older Persons
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OH	Orthostatic hypotension
OncPal	Oncological palliative care deprescribing guideline
Pharm	Pharmacists
PI	Principal Investigator
PIM	Potentially inappropriate medication
PIP	Potentially inappropriate prescribing
Phys	Physicians
PPI	Proton pump inhibitor

PPO	Potential prescribing omission
PR	Primary researcher
Prof.	Professor
RCPI	Royal College of Physicians Ireland
RCT	Randomized control trial
SHiM	Structured History taking of Medication use
SSRI	Selective serotonin reuptake inhibitor
SENATOR	Software ENGINE for the Assessment & optimisation of drug and non-drug Therapy in Older peRsons
SPC	Summary of product characteristics
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Persons potentially inappropriate Prescriptions
STOPPFrail	<u>S</u> creening <u>T</u> ool of <u>O</u> lder <u>P</u> ersons <u>P</u> rescriptions in <u>F</u> rail adults with limited life expectancy
TCA	Tricyclic antidepressant
TILDA	The Irish Longitudinal stuDY on Ageing
UCC	University College Cork
UK	United Kingdom
UN	United Nations
US	United States
WHO	World Health Organisation
WHO-UMC	World Health Organisation - Uppsala Monitoring Center
↑	Increased
↓	Decreased

STATISTICAL SYMBOLS

CI	Confidence interval
<i>df</i>	Degrees of Freedom
n	Sample size
P	Probability
p-value	Probability value
r	Pearson correlation coefficient
<i>t</i>	Test statistic for independent t-test
<i>U</i>	Test statistic for Mann-Whitney test
χ^2	Chi-squared test statistic

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Thesis Overview

Over the last twenty years, many prescribing tools have been developed and validated to identify inappropriate prescribing (IP) in older adults and assist physicians in medication optimisation. However, these prescribing tools have predominantly focused on identifying IP in the general older adult population, rather than targeting the population cohort that is growing at the fastest rate and that is at the highest risk of IP and adverse drug reactions (ADRs) i.e. older frailer multimorbid patients with a poor survival prognosis.

Extensive research on the prevalence of ADRs has been published. However many different definitions of ADRs and many different ADR causality tools have been employed across different studies, making it difficult to compare the results of studies. To confound this area of investigation further, many ADR causality tools are not appropriate to use in older frail multimorbid adults. In addition, a limited amount of research has occurred identifying the morbidity associated with ADRs in older adults. To date, there is no standardized approach to identifying, assessing and reporting ADRs in older adults.

This doctoral thesis was designed to (i) standardise the identification, assessment and reporting of ADRs in older adults, (ii) assess ADRs using this new methodology in high risk populations, and (iii) develop and validate a new usable set of criteria called STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy) to assist deprescribing in older frail multimorbid adults with a poor survival prognosis i.e. patients where the role of preventative therapy is questionable.

This thesis comprises eleven chapters. The first chapter is an introduction, divided into four sections i.e. (i) demographic changes and the proportional increase in high risk older adults, (ii) prescribing considerations for older adults, (iii) consequences of IP including ADRs and (iv) potential targets for intervention. The second chapter proposes a methodologically robust way of identifying, assigning causality and reporting ADRs and tests this theory on physicians, pharmacists, biomedical scientists and nurses. The third chapter uses this new ADR methodology to identify the prevalence of ADRs in older adults presenting to hospital. The fourth chapter compares older and younger adults with cancer in terms of multimorbidity, medication use and ADRs using the same methodology proposed in Chapter 2. The fifth chapter develops and validates STOPPFrail criteria, an explicit prescribing tool to assist deprescribing in frail older adults with a poor one year survival prognosis. The sixth chapter describes the inter-rater reliability (IRR) of STOPPFrail criteria between physicians. The seventh chapter, applies STOPPFrail criteria to two representative populations i.e. a proportion of older adults deemed suitable for nursing home care and a proportion of older adults presenting for hospitalisation. Chapter eight considers the relevance of the research data developed in this thesis as well as questions any issues arising from these research studies. Chapter nine contains peer-reviewed articles that were published and awards received during the writing of this thesis. Finally, chapters ten and eleven list the references and appendices, respectively.

CHAPTER 1:

Introduction

1.1 AGEING DEMOGRAPHICS & MULTIMORBIDITY

1.1.1 Predicted demographic changes nationally and internationally

The United Nations (UN) defines an older person as ≥ 60 years and the oldest old as ≥ 80 years of age (1). In well-resourced developed countries transition to older age is generally accepted as occurring at the age of retirement. Therefore, older age is often defined as ≥ 65 years. More people are now reaching older age than ever before due to improvements in nutrition, drinking water and sanitation, as well as improvements in the treatment of infectious diseases and overall improvements in healthcare. In addition to increasing life expectancy, fertility rates have dropped which has led to a shift in the population demographics of developed countries where there are now more adults ≥ 65 years than there are children under 10 years.

The National Clinical Program for Older People (NCPOP), a joint initiative by the Health Service Executive (HSE) and the Royal College of Physicians Ireland (RCPI), highlights that, in Ireland, those ≥ 65 years of age are predicted to increase from 11.4% in 2012 to 18% in 2042 (2). In addition, those ≥ 85 years are expected to increase by 150% by 2031 (2). At a European level, Eurostat foresees that those ≥ 65 years will continue to increase in the coming years and that those ≥ 80 years will likely double (3). The World Health Organisation (WHO) predicts that the global population of those aged ≥ 60 years will increase from 11.3% in 2013 to 21.2% in 2050, with those ≥ 80 years expected to quadruple (4). Overall, the absolute increase in those ≥ 65 years is expected to increase by 976 million internationally, between 2010 and 2050, with the largest increase in older adults expected in developing countries.

1.1.2 Multimorbidity in high risk older adults

With ageing comes an increase in the number and severity of medical conditions (5), functional impairment, cognitive impairment (6) and frailty (7). Thus, the evolving demographic changes in the population pyramid will have a very large impact on healthcare delivery. Comorbidity was the original term used to define the occurrence of medical conditions in addition to an index disease (8). Subsequently, in 1976, the term multimorbidity was introduced by Brandlmeier to capture the co-existence of two or more diseases, rather than the focus being on one primary condition (9). However, the most widely used and accepted definition is that of the WHO i.e. the co-occurrence of two or more chronic medical conditions in one person (10).

As a result of different definitions of multimorbidity being employed across different studies, the prevalence of multimorbidity can be difficult to truly ascertain. To date, observational studies and systematic reviews have focused on the prevalence of multimorbidity in community dwelling older adults, with no study to date focusing primarily on hospitalised older adults. In primary care, two systematic reviews by Violan *et al.* and Fortin *et al.* have reported multimorbidity prevalence rates of 12.9 – 95.1% (11) and 13.1 – 71.8% (12), respectively. A United States (US) population-focused systematic review, based on Medicare data, reports a multimorbidity prevalence rate of 67% with this rate increasing with advancing age i.e. 50% for persons under age 65 years, 62% for those aged 65–74 years and 81.5% for those aged ≥ 85 years (13). At age 85 compared to age 70, the prevalence of chronic multimorbidity has been reported to increase 3-fold (14). Older age, female gender and lower socio-economic status are factors known to be independently associated with multimorbidity (5)

Multimorbidity has been linked to increased mortality, with one study reporting a 73% increase in death for adults with 2 conditions or more compared to those without multimorbidity (Odds ratio 1.73 [95%CI: 1.41 - 2.13]) and a 172% increase in the mortality rate for those with 3 conditions or more compared to those without (Odds ratio 2.72 [95%CI: 1.81 - 4.08] (15). Multimorbidity, will certainly increase in prevalence in tandem with the ageing of populations globally.

1.1.3 Specific population changes

Populations at highest risk of multimorbidity are increasing at a very rapid rate i.e. persons aged ≥ 80 years will account for 19% of the total international population in 2050 and 28% in 2100. This means that there will be seven times as many persons ≥ 80 years at the end of the century compared to 2013 (1). For adults aged ≥ 85 years, approximately 1 in every 5 persons has chronic cognitive impairment, 2 in every 5 persons have urinary incontinence and 1 in every 2 persons are dependant in basic and instrumental activities of daily living (14). In such multimorbid patients, the final months of life are commonly characterised by frailty and increased dependency with many patients requiring nursing home care (16, 17). In Ireland, 4.5% of adults' ≥ 65 years reside in nursing homes, increasing to 49% for females' ≥ 95 years and 26% for males' ≥ 95 years (18). In the US, approximately 5% of adults aged ≥ 67 years reside in residential care facilities (19). Therefore, with the predicted demographic shifts, the number of frailer multimorbid older adults will very likely increase, as will the demand for nursing home care.

Another population that will increase substantially over the coming decades is older adults with a diagnosis of cancer. Between 2010 and 2030, the incidence of cancer in older adults is expected to increase from 61% to 70% (20), coinciding with the ageing population (1, 3, 21). Thus, the demand for cancer treatment services in older patients is likely to increase concomitantly. However, as outlined above, multimorbidity increases with age so cancer may be only one of several complex diagnoses in an older individual. A diagnosis of cancer, coupled with co-existing polypharmacy, cognitive impairment and functional impairment can present the treating clinician with challenging pharmacotherapeutic and ethical dilemmas. High risk populations such as multimorbid frailer older adults and multimorbid older adults with cancer will increase in numbers which will inevitably lead to an increase in medication use, presenting many unique challenges for the prescriber.

1.2 PRESCRIBING FOR OLDER ADULTS; CONSIDERATION AND CHALLENGES

1.2.1 Prescribing for older adults: general considerations

Prescribing for the heterogeneous older adult population is challenging, in particular prescribing for frail older adults with multiple medical conditions. Prescribers need to be cognizant of age-related anatomical, biochemical and physiological changes that affect pharmacokinetics and pharmacodynamics. They also must be aware of the potential for important drug-drug interactions as well as drug-disease interactions with concurrently prescribed drugs and co-existing disease states. Prescribers should have an appreciation of the potentially low therapeutic yield in very frail older patients with poor life expectancy where the risk of certain treatments

can exceed the potential clinical benefit. These important tenets of appropriate prescribing for older patients are briefly summarised below.

1.2.2 Pharmacokinetics and pharmacodynamics

The key pharmacokinetic changes commonly associated with ageing are summarized in **Table 1.1**.

Table 1.1: Pharmacokinetics and ageing: important changes associated with old age compared to young adulthood (22)

Absorption	Distribution	Metabolic	Excretion
↓ amount of saliva	↓ cardiac output	↓ microsomal hepatic oxidation	↓ renal perfusion
↓ gastric acid secretion	↑ Peripheral vascular resistance	↓ clearance	↓ renal size
↓ gastric surface area	↓ renal blood flow	↑ steady state levels	↓ glomerular filtration rate
↓ gastrointestinal motility	↓ hepatic blood flow	↑ half lives	↓ tubular secretion
↓ active transport mechanisms	↓ body water	↑ levels of active metabolites	↓ tubular reabsorption
↑ gastric pH	↑ body fat tissue	↓ first pass metabolism due to reduced ↓ blood flow	
↑ gastric emptying	↓ serum albumin levels		
	↑ for lipid soluble and decrease for water soluble drugs		

Legend: ↑ = increased, ↓ = decreased

Older people also experience significantly different pharmacodynamic responses to similar drug concentrations than their younger counterparts. Differences can be caused by a shift in receptor affinity, density, post receptor events at the cellular level, or in adaptive homeostatic response mechanisms. Pathologic organ changes may also affect pharmacodynamic responses, particularly in frail older patients. Prescribers should be aware of commonly encountered age-related pharmacodynamic differences as listed in **Table 1.2**. Generally, it is recommended to

initiate medications at the smallest possible dose and titrate slowly according to response.

Table 1.2: Age associated changes in pharmacodynamic responses to commonly prescribed drugs (22)

Drug type	Specific drug	Pharmacodynamic response in an older person	Potential clinical consequence
Analgesia	Morphine	↑	Excessive sedation, confusion, constipation, respiratory depression
Anticoagulants	Warfarin	↑	Bleeding
	Dabigatran (≥75 years, <50kg)	↑	Bleeding
ACE inhibitor	Enalapril	↑	Hypotension
CCB	Diltiazem	↑	Hypotension
Diuretic	Furosemide,	↓	Reduced diuretic effect at a standard dose
	Bumetanide	↓	
Psychoactive drugs	Diazepam, Temazepam, Triazolam, Midazolam	↑	Excessive sedation, confusion, postural sway, falls
Psychoactive drugs	Haloperidol	↑	Excessive sedation, confusion, postural sway, falls

Legend: ACE = angiotensin converting enzyme, CCB = calcium channel blocker, ↑ = increased pharmacodynamics response, ↓ = decreased pharmacodynamics response, Kg = Kilogram

1.2.3 Medication use and polypharmacy

Over recent decades, the incidence and prevalence of polypharmacy has been increasing steadily due to a rapidly increasing ageing population experiencing multimorbid illness and advances in the treatment of chronic diseases. Various definitions of polypharmacy have been employed in research studies (23). Historically, polypharmacy has been defined in two ways. The first definition is ‘concomitant use of multiple drugs, which is measured by a simple count of

medications', with many using 3-5 medications as a cut-off point (24). The second definition is the daily intake of 6 or more drugs (25). High level polypharmacy has been proposed to encompass the daily consumption of ≥ 11 prescription drugs. It is a characteristic feature of multimorbid older people and is likely to increase markedly in prevalence as a by-product of global ageing in the 21st century. Another definition of polypharmacy is 'the administration of one medication or more that is not clinically indicated' (24).

Recently, a clear distinction has emerged to differentiate between appropriate and inappropriate or problematic polypharmacy (26). Appropriate polypharmacy has been defined as 'prescribing for an individual with complex or multiple conditions in circumstances where medicine use has been optimised and the medicines are prescribed according to best evidence' (26). Maintaining good quality of life, improving life-span and minimising drug related harm are the aims of appropriate polypharmacy (26). Problematic, or inappropriate polypharmacy occurs when 'multiple medications are prescribed inappropriately, or where the intended benefit of the medication is not realised' (26). The causes of inappropriate polypharmacy are several, principally the lack of an evidence base for particular prescriptions and an unfavourable risk/benefit ratio from particular drugs in individual patients. On other occasions, the demands of taking multiple medications compromise adherence. Finally, inappropriate polypharmacy can result from so-called 'prescribing cascades' i.e. the prescribing of additional drugs to counteract symptoms that are not recognised as adverse effects of other drugs taken by the same patient (27).

Currently, the highest rates of polypharmacy are seen in older people (28). In the UK, approximately 20% of the population is aged over 65 years, but receive 45% of all dispensed drugs (29). Similarly in the US, people aged 65 to 79 years proportionately take five times more medication than young adults aged 19 to 25, with those over 80 years remaining the largest per person users of prescription drugs (30). Inappropriate polypharmacy exists to similar degrees in the community and hospital settings. In nursing home residents, approximately 15 – 40% of residents take ≥ 9 medications and approximately 1 in 2 older persons take one or more medications that aren't medically indicated (28).

Prescription of multiple drugs impacts negatively on adherence and compliance. Clinicians are sometimes unaware of their patients complete prescription record, sometimes because of multiple prescribers or under reporting of medication intake by patients at time of consultation. Frank *et al.* reported that almost 40% of patients were taking drugs without the knowledge of their doctors, and approximately 1 out of 20 patients were not taking medications listed on their prescription record (31). Prescribers should make every effort to obtain an accurate medication list and pharmacy reconciliation protocols are useful for this purpose in hospital environments. Tools to facilitate medication reconciliation such as the Structured History of Medications use (SHiM) can also be very useful (32).

1.2.4 Potentially inappropriate prescribing

Inappropriate prescribing (IP) refers to use of medications that may cause more harm than good and, of equal importance, the under-prescription of clinically indicated

medications (33). There is firm evidence of substantially high prevalence rates of IP in older people in a variety of clinical settings (34, 35). Recent data from southern Ireland using STOPP (Screening Tool of Older Persons potentially inappropriate Prescriptions) criteria (36, 37), an explicit prescribing tool, are illustrated in **Table 1.3**. Not surprisingly, identification of potentially inappropriate medications (PIMs) increases steadily from primary care through secondary acute hospital care to long term nursing home care.

Table 1.3: Reported inappropriate prescribing rates according STOPP criteria in Ireland

Cohort	≥ 1 daily STOPP medication
Population based (n = 3454) (38)	14.6%
Population based (n = 121,454) (39)	36%
Population based (n = 539,792) (40)	37.3%
Primary care (n = 1329) (41)	21.4%
Primary care (n = 931) (42)	42%
Community dwelling (n = 2051) (43)	52.7%
Community dwelling (n = 931) (44)	42%
Older adults presenting with acute illness to hospital (n = 715) (45)	35%
Older adults presenting with acute illness to hospital (n = 600) (46)	56.2%
Older adults presenting to ED with a fall (n = 1016) (47)	53.1%
Nursing home residents attending ED (n = 195) (48)	84.8%
Nursing home residents (n = 313) (49)	59.8%
Nursing home residents (n = 514) (50)	70%
Legend: ED = Emergency department	

Clinical judgments of prescribing appropriateness with respect to therapeutic benefit can be difficult to make because of insufficient scientific evidence for the older population. Those with multiple co-morbidities and multiple medications are often poorly represented in clinical trials (51) and physicians often have to extrapolate scientific evidence from the use of medications in younger, unrepresentative patient populations, with fewer illnesses and fewer concurrent medications.

Under-prescribing of essential medication, particularly for preventive benefit, is perhaps an even bigger concern than misuse of medications in older patients (52). The risk of cardio-embolic stroke in those with atrial fibrillation increases with age i.e. 1.2% - 2.5% annual risk in persons aged 60-69 years versus 7.3%-13.7% annual risk in persons aged 80 years and over (53-55). Despite this age-related risk, many do not receive evidence-based preventative anticoagulation (56). The Irish Longitudinal study on Ageing (TILDA) recently reported that 30% of patients had a potential prescribing omission (PPO), most commonly appropriate anti-hypertensive therapy (38). Even greater proportions of hospitalised older patients are reported to have PPOs. Barry *et al.* reported a 57% prevalence of prescribing omissions in one prospective study of 600 hospitalised older adults in Ireland (57).

Prescribing appropriateness must also take into consideration a patient's ability to comply with the prescription as well as their physical ability to take the prescribed medication. In older adults following coronary artery bypass surgery, one study found that in-hospital education was paramount in helping patients adhere to their medication regimens (58). However, almost 25% of patients aged ≥ 80 years will have significant cognitive and memory deficits, which can often contribute to suboptimal medication use (59). Patients may also take multiple doses concurrently, thus placing them at an increased risk of ADRs (60). Physical impairments such as hearing loss, visual loss and impaired manual dexterity can also impact on adherence to prescribed medications, contributing to reduced therapeutic impact and consequently poorer treatment outcomes in some cases.

1.2.5 Current prescribing assessment tools

Prescribing tools have been developed to help prescribers identify inappropriate prescribing and avoid the unintended negative consequences of same. Prescribing tools can be implicit (e.g. Medication Appropriate Index (MAI) (61, 62)), explicit (e.g. Beers criteria (63-67), STOPP/START (Screening Tool of Older Persons Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria (36, 37), FORTA criteria (68, 69)) or a combination of both (Australian prescribing indicators tool (70)).

Explicit criteria are developed from literature reviews, expert opinions and often use consensus techniques for their development. They consist of list of drugs or drug classes with or without doses that are known to cause harm in specific circumstances or in conjunction with specific diseases. They can be applied with limited clinical judgement and are generally time efficient. Limitations of explicit criteria are that they often don't take into consideration patient preferences, they require regular updating with advances in evidence-based medicine and can be country specific. In contrast, implicit criteria rely on expert professional judgement, focus on the patient in question and address the entire medication regimen. However, implicit criteria are generally highly time-consuming and have low inter-rater reliability (IRR) as they are based on the judgement of the clinician in question.

In 2013, Kauffman *et al.*, completed a comprehensive and structured systematic review of existing prescribing tools to assess appropriate prescribing (71). They identified 46 tools, of which 28 (61%) used an explicit approach, 8 (17%) used implicit approach and 10 (22%) used a mixed approach. Thirty six tools (89%) focused

on older adults, 19 (41%) were designed to detect IP in a specific healthcare setting and 6 (13%) were specific to nursing home residents.

The most frequently cited and applied explicit criteria are Beers criteria (62-66), and STOPP/START criteria (36, 37). Potentially inappropriate medications (PIMs) listed in STOPP criteria, have been shown to be significantly associated with avoidable adverse drug events (ADEs) in older people that cause or contribute to hospitalisation (odds ratio 1.8; 95% confidence interval (CI) 1.5–2.3) (46). In addition, the application of STOPP/START criteria has been shown to improve prescribing appropriateness (34, 72) and reduce falls in nursing home residents (73). A recently published randomized control trial (RCT) by O'Connor *et al.*, showed that the application of STOPP/START criteria by an experienced physician within 48 hours of admission reduced ADRs occurring in hospital from 21.0% to 11.7% (74).

Prescribing tools have allowed researchers to identify and report potentially inappropriate prescribing (PIP) in a structured fashion and subsequently complete RCTs to see if their application can improve patients' outcomes.

1.3 CONSEQUENCES OF INAPPROPRIATE PRESCRIBING

1.3.1 Adverse drug reactions

There is an intimate link between polypharmacy, IP and ADR risk. Many different definitions of an ADR and ADEs exist (**Table 1.4**), with clear limitations associated with each definition. The WHO (75) and Laurence *et al.* (76) definitions do not incorporate administration errors (under or over-dosing), withdrawal of medications or reactions to inactive components of drugs. Similarly, minor unwanted reactions

are not included. In the Bates *et al.* definition (77, 78), the word “injury” is ambiguous and leaves ADR assessment open to subjectivity. Despite differences in these definitions, they have been used interchangeably, which has led to difficulty with reporting, interpreting and comparing observational and interventional studies. The definition of an ADR proposed by Edwards and Aronson (79) is the most comprehensive and incorporates what other definitions have lacked. Thus, it is the most all-encompassing and appropriate to use, particularly when assessing ADRs in older adults.

Table 1.4: Definitions of ADRs and ADEs

Author	Year	Definition
WHO (75)	1972	ADR – A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.
Bates <i>et al.</i> (77, 78)	1995	ADE - An injury resulting from medical intervention related to a drug.
Laurence <i>et al.</i> (76)	1998	ADR - A harmful or significantly unpleasant effect caused by a drug at doses intended for therapeutic effect (or prophylaxis or diagnosis) which warrants reduction of dose or withdrawal of the drug and/or foretells hazard from future administration.
Edwards and Aronson (79)	2000	ADR - An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.
Nebeker <i>et al.</i> (80)	2004	ADE - Any physical or mental harm resulting from medication use be it misuse, under-dosing or overdosing

Legend: ADR = adverse drug reaction, ADE = adverse drug event

Furthermore, ADRs were traditionally classified as either “type A” (typically dose related, predictable, and accounting for approximately 80% of ADRs) or “Type B” (non-dose related and unpredictable) (81). This classification has subsequently

broadened into 6 categories defined by Edwards and Aronson i.e. (i) dose related (augmented), (ii) non-dose related (bizarre), (iii) dose related and time related (chronic), (iv) time related (delayed), (v) withdrawal related (end of use) and (vi) failure of therapy (failure) (78). Examples are listed in **Table 1.5**. Edwards and Aronson's classification is also most appropriate to use when assessing older adults.

Table 1.5: Examples of different categories of ADRs per Edwards and Aronson (79)

ADR type	Drug involved	ADR
Dose related (augmented)	Warfarin	Bleeding
Bizarre (non-dose related)	NSAIDs	Interstitial nephritis
Dose related and time related (chronic)	Neuroleptics	Tardive dyskinesia
Time related (delayed)	Immunosuppressant therapy	Lymphoma
Withdrawal (end of use)	Benzodiazepines	Seizure
Failure of therapy (failure)	Warfarin and carbamazepine	↓anti-coagulant effect

Legend: ADR = adverse drug reaction, NSAIDs = non-steroidal anti-inflammatories, ↓ = reduced

1.3.2 Prevalence of ADRs in different populations

ADRs are a common cause of hospitalisation and their incidence increases with ageing (82). A meta-analysis by Kongkaew *et al.* reported that 6.3% (IQR 3.9-9%) of all adult admissions are secondary to ADRs and that this proportion increases to 10.7% (IQR 9.3-13.3%) for older adults (83). A meta-analysis, by Lazarou *et al.* concluded that on average 10.9% (CI 7.9-13.9%) of adults experience an ADR during hospitalisation, with 2.1% reported to be clinically serious (84). A more recent meta-analysis by Alhawassi *et al.* found that ADRs cause hospitalisation in 10% (CI 7.2-12.8%) and occur during hospitalisation in 11.5% (CI 0-27.7%) of adults aged 65 years and older.

Fewer studies have been undertaken on both community dwelling older adults and nursing home residents such that to date there is no systematic review to report same. Hanlon *et al.* reported that 35% of high risk older adults, defined as those on ≥ 5 medications, living in the community experienced an ADR over a 1 year period (85). In addition, Cooper *et al.* reported that 217 out of 332 older people (67.4%) living in nursing homes experienced an ADR over a 2 year period (86).

1.3.3 ADR risk factors in older people

Polypharmacy is strongly predictive of ADRs (87, 88) which is linked to increased frequency of hospitalisation, negative health outcomes and increased healthcare resource utilisation (89-93). The risk of an ADR when taking two concurrent medications is 13%. This risk rises to 38% in patients taking 4 medications and to 82% in those taking ≥ 7 medications (94). This is a cause of concern because the risk of clinically significant ADRs increases in a linear fashion in proportion to the number of daily prescription medicines taken by hospitalised patients (95). The highest rate of polypharmacy occurs in nursing home residents (28), so it is not surprising that ADRs are more prevalent in this group (96).

IP is highly prevalent in older patients. The association between IP and ADRs is well established with Lindley *et al.* showing that 50% of ADRs in older adults are caused by IP (60). A significant association has also been found between IP, ADRs, acute hospitalization, death (97, 98) and higher healthcare costs (99). The association between IP and negative clinical outcomes has been shown in numerous studies in Europe (46, 60, 100) the US (101-103) and Asia (104).

Women have a 1.5 to 1.7 fold increased risk of ADRs compared with men (105). This can be attributed to gender differences in immunological and hormonal physiology which influence pharmacodynamics and pharmacokinetic response, particularly in relation to cardiac and psychotropic medications (106). Genetic factors are thought to play a role in serious ADRs that have been traditionally classified as idiosyncratic, for example drug-induced liver injury, statin-induced myotoxicity and macrolide-induced long QT syndrome (107). Genotyping at an individual level has the potential to optimize drug therapy thereby reducing ADRs (108).

1.3.4 Effects of ADRs

ADRs have major clinical and economic consequences. They prolong hospital stay (109), increase resource utilisation (110), can be fatal (111) and are costly (112). IP and related ADRs represent a major drain on health budgets. One study estimated that 5 - 9% of all hospital costs were related to ADRs (113). In 2004, Pirmohamed *et al.* (114) estimated that ADRs were costing the United Kingdom (UK) National Health Service approximately €700 million per annum. The HARM study in the Netherlands estimated that the average cost of preventable medication related acute hospitalisation was €6009 (115). This figure was calculated by adding the direct medical costs and the productive losses of all preventable admission. The authors extrapolated this average cost to represent approximately 0.5% of the total national Dutch hospital budget (115). The median length of stay of patients hospitalised as a result of medication adversity in the HARM study was the same as that recorded by Pirmohamed *et al.* (114) in the earlier UK study i.e. 8 days. In another recent German

study, Rottenkolber *et al.* (116) calculated that approximately 3.25% of all acute hospital admissions were directly related to ADRs. In that study, the median age of affected patients was 74 years, the median length of stay was once again 8 days and the extrapolated cost to the national exchequer was €434 million i.e. approximately €650 million in 2015 terms. These European studies indicate a consistent level of ADRs resulting directly in acute hospitalisation, affecting older people in the majority and imposing very serious strain on healthcare budgets.

The mortality rate attributable to ADRs in hospitalised patients is reported to be between 0.14% and 4.7% (84, 114). In the US, annual mortality rates of 0.08–0.12/100,000 have been reported, with this rate significantly increasing over the last 7 years (111), with those at greatest risk being aged ≥ 75 years. Mortality associated with ADRs is due to commonly prescribed drugs with predictable side effects such as anticoagulants, opioids and immunosuppressant drugs (111). In the future, the demand for these drugs will increase as the incidence and prevalence of illness requiring these drug treatments increases with age i.e. atrial fibrillation, stroke, cancer and arthritis. In the US, the overall incidence of serious and fatal ADRs are reported as 6.7% and 0.32% respectively during a hospital episode, such that ADRs are now listed as fifth leading cause of death (114). The implication from all these studies is that whilst ADRs are highly prevalent in older sicker patients, they are also predictable and therefore preventable in most cases.

1.3.5 Current difficulties in ADR reporting

Identifying and reporting of ADRs can be challenging in older adults. Older adults are a heterogeneous population, with high levels of multimorbidity and polypharmacy. Therefore, the ADR risk varies considerably between different older patient groups e.g. nursing home patients are at the highest risk. Older adults experiencing ADRs often present with nonspecific symptoms such as cognitive decline, recurrent falls and reduced mobility, such that it can be difficult to discern whether medications have been implicated or not.

Many definitions for ADRs exist (75, 76, 78-80) and variability in ADR definitions means that identification and reporting of ADRs can also vary depending on the definition being employed. Variability in defining ADRs also makes it difficult to compare published studies. Similarly, several standardized methods of assessing ADR causality exist, the advantages and disadvantages of each being summarised in **Table 1.6**. None of the ADR causality tools is universally used or accepted in everyday clinical practice and no method is specifically validated for use in older adults with multimorbidity and polypharmacy.

Table 1.6: Adverse drug reaction (ADR) causality assessment tools (117)

Causality Assessment Tool	Year	Tool Description	Advantages	Disadvantages
1. Expert Judgement / Global Introspection Methods				
Swedish method (Wilholm <i>et al.</i>) (118)	1984	Seven factors for a clinician to assess. Events classified as probably, possible, non-accessible or unlikely.	Quick to use.	There are only a small number of categories into which causality can be placed. Causality can overlap into more than one of these categories and thus ADRs can be wrongly classified.
WHO-UMC criteria (119)		Six different categories for causality: certain, probable, possible, unlikely, conditional, unclassifiable	Clinical and pharmacological aspect of a case and drug-drug interactions taken into consideration.	Knowledge about medical conditions and diseases required.
2. Algorithms				
Dangaumou's French method (120)	1977	Seven criteria for assessment.	Allows certain drugs taken at the same time with the 'suspect' drug to be excluded because each drug is assessed separately.	More time consuming than other algorithms.
Kramer method (121)	1979	Assesses a single clinical manifestation occurring after administration of a single suspect drug.	Transparent method.	Certain levels of expertise, experience required for use. Time consuming to apply. If multiple drugs are involved, each is assessed separately.
Naranjo method (Naranjo <i>et al.</i>) (122)	1981	Can assess causality in a variety of clinical situations using the conventional categories. It comprises ten questions.	Shown to be reliable in prospective studies.	Intended to assess the likelihood of a reaction from one drug not drug-drug interactions. Requires the user to have knowledge of the literature.
Balanced assessment method (Lagier <i>et al.</i>) (123)	1983	It evaluates cases on a series of visual analogue scales.	It considers the possibility of an alternative to causation for each of the factors.	The assessor needs to be knowledgeable for it to be reliable,
Summary time plot (Castle <i>et al.</i>) (124)	1984	Identifies patterns of ADRs in the industry setting.	Time efficient to use. Applicable even with minimal information.	Does not lead to a conclusion on causality. It examines factors that are relevant to the drug-event relationship e.g. time.

Ciba Geigy method (Venulet <i>et al.</i>) (125)	1980	Derived from a number of expert consensus meetings. Causality is assessed by visual analogue scales.	High degree of agreement (62%) between users.	User knowledge and experience required.
Loupi <i>et al.</i> method (126)	1986	Developed to assess teratogenicity of a drug.	Alternative aetiologies considered.	Requires the user to have knowledge about the drug in question.
Roussel Uclaf Causality Assessment Method (RUCAM) (127)	1993	Designed for predetermined diseases and illnesses.	Easy to use.	The range of agreement between users is 37 – 99%. Organ specific and currently not validated for every organ system.
Maria and Victorino (M & V) scale (128)	1997	Scale for diagnosing drug induced liver injury (DILI).	High level of validity and inter-rater reliability.	Specifically for diagnosing DILI. Physicians need to be experienced to use. Where more than one drug is suspected, the scale needs to be computed for individual drugs. Some questions on the scale only apply to immune-allergic hepatitis, making it difficult for scores to be generated.
Drug Interaction Probability Scale (DIPS) (129)	2007	Ten questions scale to evaluated drug interaction cases.	Easy to use.	Requires the user to have accurate knowledge of the drug involved and the interactions.
3. Probabilistic methods (Bayesian approaches)				
Bayesian Adverse Reaction Diagnostic Instrument (BARDI) (130)	1992	Developed to overcome the limitations associated with expert judgements and algorithms. The odds in favour of a particular drug causing an adverse event are compared with an alternative cause.	It can evaluate more than 2 possible causes at a time. Quick to apply,	Requires expertise to operate.

The World Health Organization–Uppsala Monitoring Center (WHO-UMC) criteria (119) (**Table 1.7**) and the Naranjo criteria (122) (**Table 1.8**) are the most frequently cited ADR causality tools in the literature. However, some of the variables required by the Naranjo criteria are difficult to apply to older patients with suspected ADRs. For example, it may be unethical to rechallenge if there is a high index of suspicion of ADR and risk of recurrence or harm is high. In addition, the Naranjo criteria do not allow for drug–drug interactions as a cause of an ADR. Often, many of the required variables cannot be completed, thus making it unlikely for any older patient to score higher than ‘possible or probable’ in this causality system, thereby limiting its utility.

Table 1.7: WHO-UMC causality criteria (119)

Causality	Conditions (All conditions need to be complied with for each causality criteria)
Certain	Event / laboratory test abnormality with plausible time relationship to intake of a drug Cannot be explained by disease or other drugs Response to withdrawal plausible Event definitive pharmacologically or phenomenologically Rechallenge satisfactory, if necessary
Probable	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 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

Table 1.8: The Naranjo ADR causality criteria (122)

	Yes	No	Don't Know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event occur after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or an antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Was the reaction more severe when the drug was increased or less severe when the drug was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0
Legend: Total scores range from -4 to +13; ≥ 9 indicates a definite adverse drug reaction (ADR); a score of 5 to 8 indicates a probable ADR; a score of 1 to 4 indicates a possible ADR; a score of ≤ 0 indicates that an ADR is doubtful			

A standardized method to identify, classify and assess causality of ADRs in older adults is required for future research in order to enhance the accuracy of ADR reporting. Rigorous ADR reporting would greatly improve the accuracy and quality of ADR prevalence and incidence data. In addition, it would allow direct comparisons between studies completed by different research groups and would contribute to interventional studies being more methodologically robust in the future.

1.4 TARGETS FOR INTERVENTION IN POPULATIONS AT HIGH RISK OF ADRS

1.4.1 Deprescribing

Deprescribing is defined as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” (131). It involves (i) reviewing all medications prescribed, (ii) identifying those medications that are inappropriate, (iii) deciding when and how these medications should be reduced or stopped and (iv) arranging adequate monitoring and follow-up (132). Many physicians, healthcare professionals, patients and their relatives all acknowledge the burden of polypharmacy for older frail adults, yet all groups display passivity towards deprescribing (133) with less than half of attending clinicians use a consistent approach to deprescribing (134) and many clinicians avoid it completely.

1.4.2 Need for new deprescribing tools

To date, numerous prescribing tools have been developed to guide physicians with cessation of PIMs in the general older adult population. However, comprehensive tools such as Beers criteria (63-67), STOPP/START criteria (36, 37) and FORTA criteria (68, 69) were not developed to specifically address IP in frail multimorbid older adults with a poor survival prognosis. Prescribing needs for these patients differ from those of the general older population. For instance, patients with limited life expectancy (LLE) would be unlikely to survive long enough to derive benefit from most medications listed in the START criteria. Furthermore, STOPP criteria do not suggest discontinuing major drugs classes that are least likely to have benefits in the last year of life, e.g. statins. Therefore, the population at the highest risk of IP and ADRs that

is growing most rapidly is the one where there is the least clear guidance on prescribing and deprescribing for physicians. To date, no explicit guidelines exist for deprescribing in frailer older people with LLE, other than NORGE-PNH criteria, which are specific to the older nursing home population (135). Therefore, with the accepted need for deprescribing in frailer older persons with LLE, there is a clear associated need for specific explicit deprescribing criteria.

1.4.3 Limited life expectancy

LLE is defined in most studies as a life expectancy of one year or less (136-138). Recognition of a LLE can be challenging for less experienced physicians. However there are some simple mortality predictive tools available that can help guide and support junior physicians in assessing this e.g. Walter Index (139). However, deprescribing in older frailer adults is usually undertaken by patients' General Practitioners (GPs) or senior hospital physicians with high-level prognostic knowledge. The literature to date indicates that co-morbidities and functional impairment are the most consistent predictors of mortality (140).

1.4.4 Frailty

Many older adults with LLE are not clinically frail. Conversely, some older adults who are clinically frail do not have a poor one year survival prognosis. However, in most instances, frailty and poor survival prognosis do co-exist. Frailty in some circumstances can be reversible, but in patients where there is an irreversible, end-stage diagnosis e.g. dementia or disseminated progressive malignancy with

associated severe functional impairment, frailty is implicit and prognosis is usually poor.

Many different frailty assessment tools are available which have been validated across many different healthcare settings and applied to various age groups. In addition, many frailty tools use different criteria. Of 79 frailty instruments recently systematically reviewed by Azzopardi *et al.* (141), 24 included physical characteristic components alone, with all other instruments consisting of two or more components from the following domains: medical, physical, functional and cognitive. Some components were self-reported, others were based on objective measures and in those remaining, a combination of both were employed. Frailty indices are used to assist identification and diagnosis of frailty and are not intended to supersede clinical judgement but rather guide physicians in clinical decision making. The prevalence of frailty in older adults is reported to be 10.7% in the community (7), 14% in hospitals (142) and 52.3% in nursing homes (143).

1.5 CONCLUSIONS

Prescribing for frail multimorbid older patients is often complex and time-consuming, particularly when all of the patients' variables are considered. In addition, older people are a heterogeneous population, with a wide variation in physical, cognitive and functional status. Prescribing appropriately and safely for frail older multimorbid adults with a poor survival prognosis is often highly challenging, particularly when considering the many preventative therapies that may carry greater risk than a clear benefit.

Older frail multimorbid adults surviving with complex clinical conditions contribute to the population that is growing at the fastest rate and will continue to grow for several decades to come. Therefore, research needs to focus on identifying potentially adverse polypharmacy and IP in these multimorbid patients as well as interventions to improve prescribing appropriateness and safety. ADRs need to be identified speedily and accurately, correctly classified and reported in a standardized manner to assist best clinical practice and ensure that research studies are methodologically robust.

Evaluation of the therapeutic goal must take into account the scientific rationale of using a drug as well as the potential benefit to the patient. There is a lack of guidance on deprescribing in older frail multimorbid patients for present day physicians. Explicit deprescribing criteria are required so that the evidence base for deprescribing in this growing population can develop and support physicians in their routine clinical decision making.

1.6 OBJECTIVES OF THIS THESIS

The objectives of this thesis were to:

- (i) Develop a standardized method of assessing, classifying and reporting ADRs in older people.
- (ii) Identify multimorbidity, medication use and IP in older adults with unselected acute illness presenting to hospital for admission.
- (iii) To assess the prevalence of ADRs causing hospitalisation in an acutely ill general older unselected population using this new ADR assessment

methodology and to compare these rates to those reported in the literature to date.

- (iv) Identify multimorbidity, medication use and IP in older adults with cancer using the same ADR methodology in order to determine the prevalence of ADRs causing hospitalisation in this cohort.
- (v) Develop a new explicit prescribing tool to address deprescribing in older frail multimorbid patients with a poor one year survival prognosis.
- (vi) Determine the inter-rater reliability of this newly developed deprescribing tool and apply it to a representative population of frail, multimorbid older people.

CHAPTER 2:

Development and validation of an adverse drug reaction (ADR) trigger list

2.1 INTRODUCTION

Adverse drug reactions (ADRs) are common and their incidence increases with ageing (82). A recent meta-analysis reported that ADRs cause or contribute to hospitalisation in approximately 10% of older adults (83, 144). Furthermore, ADRs occur in approximately 11.5% of older adults during their hospital admission (84, 144). However, it is often difficult to compare individual studies because of considerable heterogeneity in (i) definition of ADRs, (ii) identification of causality and (iii) variations in population cohorts studied.

The economic burden of ADRs in terms of healthcare resource consumption (99, 113-116, 145) and mortality (84, 111, 114) is well established and has been discussed in Chapter 1. However, the clinical nature and severity of ADRs is often poorly described. More specifically, differences in drug-related morbidity between older and younger patients are rarely investigated or compared. Recognition and diagnosis of ADRs can be challenging in everyday clinical practice, particularly in older patients with multiple symptoms that may feasibly be attributed to multiple co-morbid illnesses e.g. falls, cognitive decline, fatigue or constipation. ADRs that require intensive medical input are generally identified and managed accordingly e.g. acute liver injury secondary to a statin or clinically significant bleeding secondary to an anticoagulant. However, in cases where symptomatology is milder, or viewed as non-life threatening e.g. severe constipation, drug causation is often under-recognised. Older adults often experience a large burden of co-morbid illnesses and frequently present with non-specific symptoms such as falls, delirium and dizziness, most of which have several causative factors. A fall may occur in a patient with visual impairment and gait instability attributable to severe osteoarthritis, but that same

patient may also fall because of postural hypotension attributable to a new antihypertensive agent. All factors may have contributed to the fall, thus making it difficult to precisely conclude that the event was caused by a drug.

Ideally, a standardized approach should be employed to accurately identify and classify suspected ADRs, in order to minimise associated morbidity and prevent recurrence. One such approach would be to determine an individual's risk of developing an ADR using a tool such as the GerontoNet ADR risk prediction score (146). This tool considers an individual's risk of developing an ADR according to the presence or absence of variables including increasing numbers of medications, presence of liver dysfunction and renal dysfunction. This approach, though promising, is not universally applicable, with one study (outside of the original research validation exercise) showing poor predictive ability in correctly identifying ADRs, thus limiting the clinical applicability of GerontoNet as a reliable ADR prediction tool (146).

Another approach would be to focus on the most common adverse clinical syndromes attributable to medications in older patients e.g. falls, bleeding, electrolyte disturbance and cognitive dysfunction. The presence of such symptoms in an older person should prompt a medication review to investigate whether or not such symptoms could be caused by a prescribed medication i.e. these symptoms should "trigger" further investigation of the adverse event (AE) in question and determine whether a drug is implicated i.e. an "AE trigger". This would require a standardized definition of an ADR and a robust and valid process of determining whether or not a drug contributed to the clinical event. Accordingly, the aim of this

study was to develop and validate a new **Trigger List** of clinical symptoms and syndromes that may herald the presence of an ADR and to devise a robust, standardized process of assessing these symptoms to determine whether or not a drug is culprit. The specific study objectives are detailed below.

2.1.1 Objectives

The objectives of this study were:

- (i) To develop a **Trigger List** of clinical symptoms or events to identify potential ADRs in older patients.
- (ii) To develop and validate a standardized investigative process for each event on the **Trigger List** in order to ascertain whether or not the event was an ADR.
- (iii) To develop a standardized approach to assessing the morbidity associated with ADRs.
- (iv) To determine the inter-rater reliability (IRR) of this new methodology amongst physicians, pharmacists, nurses and biomedical scientists, all of whom are working as researchers on a multi-centred RCT investigating the role of medication optimisation software on ADRs that occur during hospital stay.

The work in this chapter was undertaken with support and input from the SENATOR (Software **EN**gine for the **Assessment** and optimisation of drug and non-drug Therapies in **Older peR**sons) consortium (147).

2.2 METHODS

This study involved four distinct phases: (i) development of a list of common potential ADRs in older patients i.e. the **AE Trigger List**; (ii) development of a standardized investigative process for each AE on the **Trigger List** in order to ascertain whether or not the event was an ADR, (iii) development of a standardized process for ascertaining ADR-related morbidity i.e. inter-dependent relationships between **AE Trigger List** symptoms deemed ADRs i.e. **Sequence of Events**, and (iv) conduct of a study to test the IRR of the process between doctors, nurses, pharmacists and biomedical scientists using clinical cases. Each of these phases is described in more detail below.

2.2.1 Development of the **AE Trigger List**

Each **AE** on the **Trigger List** should be a clinical symptom or syndrome that may be indicative of an ADR and requires investigation using a standardized process to determine if this is the case. The **Trigger List** must (i) incorporate the most common ADRs reported in older adults and (ii) include clear definitions of all AEs to avoid any ambiguity around whether the event in question occurred or not.

As discussed in Chapter 1, the definition of an ADR proposed by Edwards and Aronson (79) is the most comprehensive definition and incorporates what other definitions lack. Thus, it is the most all-encompassing and appropriate to use, particularly when assessing ADRs in older adults. Therefore it will be the definition used going forward for this thesis i.e. “An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product,

which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

The **AE Trigger List** was composed by incorporating the most common ADRs identified in an earlier observational study at Cork University Hospital (CUH); an observational study in which the clinical manifestations of the most common ADRs were defined in a robust manner (148) (**Table 2.1**). A large study by Budnitz et al looked at national data in America and identified that warfarin, insulin, anti-platelets and oral hypoglycaemic agents were the most common drug classes implicated in ADRs and that bleeding and hypoglycaemia events dominated ADRs in older adults (149). It was decided not to base our trigger list on this study as there was detection bias. Firstly many ADRs that occur in older patients were not listed for coders who inputted data into the hospitals electronic system, therefore this study was not an accurate representation of all ADRs in older adults.

Table 2.1: Most common ADRs identified by O'Connor MN *et al.* (148)

Drug/Drug Class	Adverse Drug Event	Number (%)
Diuretics	AKI/electrolyte disturbance	45 (25%)
Benzodiazepines	Falls	32 (18%)
Opiates	Delirium/falls/sedation/constipation	32 (18%)
Beta blockers	Symptomatic bradycardia/OH	16 (9%)
Anti-hypertensives	OH/AKI/hyperkalaemia	14 (7.8%)
NSAIDs	Gastritis/peptic ulceration/AKI	10 (5.6%)
Warfarin	Haemorrhage	8 (4.5%)
Anti-platelets	Haemorrhage	6 (3.3%)
Neuroleptics	Falls/parkinsonism	3 (1.6%)
SSRIs	Hyponatraemia	3 (1.6%)
Antibiotics	<i>Clostridium difficile</i> colitis	3 (1.6%)

Legend: AKI = Acute kidney injury, OH = Orthostatic hypotension, NSAIDs = Non-steroidal anti-inflammatories, SSRIs = Selective serotonin re-uptake inhibitors

In this prospective observational study, ADRs were defined rigorously according to the World Health Organisation-Uppsala Monitoring Center (WHO-UMC) causality criteria (119), a causality assessment tool that has been discussed in Chapter 1. Two physicians jointly reviewed all ADRs and only included those where there was consensus between them that a probable/certain ADR had occurred. The 10 ADRs most commonly reported were (i) acute kidney injury (AKI), (ii) electrolyte disturbance, (iii) falls, (iv) delirium, (v) constipation, (vi) orthostatic hypotension (OH), (vii) dyspepsia, (viii) bleeding (ix) diarrhoea and (x) symptomatic bradycardia. These ADRs formed the basis of the ***AE Trigger List*** of potential ADRs i.e. AEs requiring further investigation.

The SENATOR consortium (of which I am a member), is a European group comprising of renowned researchers from across Europe that has a strong clinical and research background in Geriatric Pharmacotherapy. Although I was funded by the SENATOR project, this chapter is the only part of my PhD that is linked to the consortium. The SENATOR group discussed this ***AE Trigger List***. On the basis of clinical experience, two additional AEs were proposed for inclusion i.e. gait disturbance and symptomatic hypoglycaemia. Their inclusion was agreed by consensus. The result, a 12 ***AE Trigger List***, to assist in the unbiased reporting of ADRs. It was acknowledged that not all potential ADRs were included on the 12 point ***Trigger List*** e.g. anaphylaxis, but those not included were those that were more likely to have severe symptomatology and consequently less likely to be missed; an “unspecified AE” was added to the ***AE Trigger List*** to capture these.

2.2.2 Development of a standardized investigative process for each AE on the trigger list in order to ascertain whether or not the event was an ADR

As I worked as a primary researcher on the SENATOR feasibility study (150), the first study to employ the ***AE Trigger List***, it became evident that there was huge variability in AE assessments between researchers. This was due to the subjective nature in assessing a drug's role in symptomatology, lack of clarity around the timing of events, lack of clarity around the duration of events and in general the unstandardized approach employed to assessing whether an ADR occurred. This inevitably can lead to the inaccurate reporting of ADRs.

Therefore after developing the ***AE Trigger List***, I set out to develop a robust and valid process, of determining whether or not a drug contributed to clinical AEs that could be used by researchers going forward. The aim was to remove the current subjective nature of this process, thus ensuring accurate capture and reporting of ADRs. This work was undertaken by me under the guidance of Prof. Denis O'Mahony (senior academic consultant/geriatrician, University College Cork), Dr. Paul Gallagher (senior academic consultant/geriatrician, University College Cork) and Prof. Joseph Eustace (senior academic consultant/nephrologist/Director of the Health Research Board Clinical Research Facility (HRB-CRF), University College Cork (UCC)).

This involved (i) each AE on the ***Trigger List*** having a clear definition, (ii) a clear definition around the ***timing and duration*** of each AE, (iii) a clear standardized approach to assessing whether a drug was involved using both direct focused questions and the WHO-UMC causality criteria (119) and ensuring a structured scale

to apply severity was employed if an AE was deemed an ADR i.e. Hartwig & Siegel Scale (151) and lastly (iv) the use of an independent ***adjudication process*** to confirm the presence of an ADR. Each of these phases is described in more detail below.

(i) AE Trigger List definitions

Each of the 12 AEs on the ***AE Trigger List*** were given a clear definition based on what was deemed *clinically significant* e.g. it was proposed that the definition for symptomatic bradycardia be “a heart rate of < 50 beats/minute with symptoms”. Definitions were included to ensure that a drug cause was investigated *only* for *clinically significant* AEs. Older adults can often present to hospital with an acute illness, such as a urinary tract infection, and incidentally be found to have for example bradycardia but are asymptomatic and don’t require intervention. I wanted to ensure that *clinically asymptomatic* AEs were not being investigated inappropriately and consequently ADRs were not being over reported. Each definition was proposed based on clinical experience and subsequently agreed upon by consensus by the SENATOR consortium.

(ii) Timing and duration of AEs

The SENATOR feasibility study also highlighted the inability, in most cases, for researchers to reliably and reproducibly separate prolonged or repeated occurrences of the same ADR into separate discrete events e.g. if a persons had 3 falls (AEs) and it is discovered that there was a drug cause (ADR), this had the potential to be

reported as either 3 ADRs or 1 ADR. Lack of clarity as to what precisely defines an AE leads to subjectivity in ADR reporting and can lead to over-estimation of ADRs. I proposed that AEs and subsequently ADRs should be viewed as **processes** rather than **discrete** events i.e. in the example case above, **falling** occurs secondary to a medication. The only time a second ADR should be declared is if a second drug becomes implicated after the first original drug and is felt to cause re-emergence of the same symptoms or worsening of current symptoms. For example, if a person developed hyponatraemia secondary to a thiazide diuretic, which was subsequently stopped and the hyponatraemia resolved and then the same person was prescribed an selective serotonin reuptake inhibitor (SSRI) and a further substantial drop in Na⁺ (sodium) occurred then this would be classified as two separate ADRs.

In addition, it became apparent that there was confusion around the timing of AEs, which subsequently led to inaccurate reporting of the timing of ADRs. As a result I proposed that ADRs occurring pre-hospital should be distinct from those occurring during hospitalisation i.e. “**prevalent**” ADRs and “**incident**” ADRs. A **prevalent** event is one which commences pre hospital and an **incident** event is one which commences post admission to hospital. This distinction between **prevalent** and **incident** ADRs is paramount to assess ADRs in order to prevent future ADRs.

(iii) Development of a standardized approach to causality and severity

As discussed in detail in Chapter 1, in 2015, I completed a review looking at ADR causality tools (152). I reviewed 13 tools, and concluded that the WHO-UMC causality assessment tool was the most appropriate to apply to older adults (119). As a tool, it

takes into consideration the clinical and pharmacological aspects of a drug, as well as ensuring drug-drug interactions are not overlooked. It offers clear guidance on the likelihood of an AE being an ADR and is easy to apply. It does not require rechallenge with the culprit medication, which can often be unsafe in older adults and in general is very easy to understand and apply. In addition, the Hartwig & Siegel scale robustly categorise ADR severity into seven groups according to clinical consequences, including resultant harm and the intensity of medical intervention required (**Table 2.2**) (151). These tools are most appropriate to use to assess causality and severity of ADRs in older adults.

Table 2.2: Hartwig & Siegel Severity Scale (151)

Severity Grade	
1	An ADR occurred but no change in treatment with suspected drug
2	The ADR required that treatment with the suspected drug be held, discontinued or otherwise changes. No antidote or other treatment required. No increase in length of stay.
3	The ADR required that treatment with the suspected drug be held, discontinued or otherwise changed, or an antidote or other treatment. No increase in length of stay.
4	Any level 3 ADR which increases length of stay by at least one day or the ADR was the reason for admission.
5	Any level 4 ADR which required intensive medical care.
6	Any ADR causing permanent harm to the patient.
7a	The ADR was indirectly linked to the death of the patient.
7b	The ADR was directly linked to the death of the patients

Legend: ADR = adverse drug reaction.

(iv) Development of an independent adjudication process

To avoid unbiased reporting of ADRs, all AEs assessed on the ***AE Trigger List***, should be forwarded to an adjudication committee, regardless of the probability that the AE in question is an ADR. This will ensure that ADRs are not under or over reported. The

evidence for each AE must be presented in a standardized fashion to those involved in the adjudication committee. Evidence that indicates causality (temporal relationship, appropriate time line in resolution or recurrence etc.) must be stated along with additional qualifying explanatory text. To ensure this information was presented in a standardized format, a form for each AE, incorporating all the components as discussed above, was compiled. This standardised AE form is present in Table 2.5, page 80.

2.2.3 Development of a standardized process for ascertaining ADR-related morbidity

It also was apparent from the SENATOR feasibility study that for many patients there was an interrelationship between different types of AEs that were deemed ADRs e.g. a patient could present with diarrhoea secondary to an antibiotic, leading to fluid depletion and subsequently orthostatic hypotension, which subsequently leads to a fall and injury. Data collection processes to date have not captured this associated morbidity, but rather report the starting event or the event causing hospitalisation i.e. in the example given above, diarrhoea or a fall would be reported.

In order to capture the morbidity associated with ADRs, I proposed that the ***Sequence of Events*** surrounding an ADR should be evaluated. AEs that are deemed drug-related, as determined by the WHO-UMC causality tool (119), should have their inter-dependent relationships captured to ensure the associated morbidity is not missed. The use of the ***AE Trigger List*** and determination of the inter-dependant relationships between events will capture this morbidity prospectively i.e. ***Sequence of Events***.

2.2.4 Conduct of a study to test the IRR of the process between doctors, nurses, pharmacists and biomedical scientists using clinical cases

(i) Application of *AE Trigger List* process to clinical cases

The aim was to determine the inter-rater reliability (IRR) of the AE process between healthcare professionals. Eight clinical cases histories were selected from a cohort of 240 consecutive patients, aged ≥ 65 years, who were admitted with an acute medical (i.e. non-surgical) illness to the general medical services at Cork University Hospital, between August 2014 and July 2016. The purpose of this observational study was to determine ADR incidence causing hospitalisation. This study will be discussed in Chapter 3, however for the purpose of this IRR exercise, participants included in this observational study had their medical conditions, concurrent medications, cognitive and functional impairment documented. The eight cases were selected based on case complexity to ensure a variety of clinical scenarios were presented to participants. The details of these 8 clinical cases can be found in **Appendix 1**.

Each clinical case was presented in the same format with an appropriate amount of information to make an ADR assessment i.e. medical diagnoses, concurrent medications, allergies, laboratory tests, electrocardiogram (ECG), functional status and cognitive status. Participants were also given information regarding what occurred during hospitalisation to assist their assessments. Survey Monkey[®] was the platform used to distribute this information to participants. An example of one clinical case is presented in **Figure 2.1** and the questions asked, incorporating the key concepts as discussed above to guide ADR assessment of the AEs, is presented in **Figure 2.2**.

Figure 2.1: Example of a clinical case.

Patient & symptoms: 66 year old male presented with a 3 day history of new painless jaundice.					
HPC: He presented with cellulitis of his right leg to his GP 5 days earlier. At this time he was commenced on Flucloxacillin. After 2 days of treatment a yellow discoloration of his skin occurred which became worse over the following days. After 5 days of treatment he stopped taking the antibiotics and presented to the emergency department. No nausea, no diarrhoea, no constipation, no vomiting, on confusion, no falls.					
Medical History: 1. Varicose veins 2. Gastro-oesophageal reflux disease (GORD) 3. Hiatus hernia – Gastroscopy 6 months ago 4. Hypertension					
Medications (regular):					
	Drug Name	Dose	Route	Frequency	Duration
1	Tramadol	50mg	Oral	Once a day	2 weeks
2	Diclofenac gel	One application	Topical	Three times a day	2 weeks
3	Esomeprazole	40mg	Oral	Once a day	6 months – 1 yr
4	Bisoprolol	5mg	Oral	Once a day	>5 years
5	Ramipril	10mg	Oral	Once a day	>5 years
6	Paracetamol	1g	Oral	As required (last took 6 weeks ago)	>5 years
Recent short courses of treatment:					
	Drug Name	Dose	Route	Frequency	Duration
1	Flucloxacillin	500mg	Oral	Four times a day	5 days
Courses was started 5 days prior to admission					
Allergies: Amoxicillin/clavulanate – history of jaundice					
Social History: Ex-smoker, no alcohol, lives with wife, fully independent of ADLs					
Barthel Index score: 20/20, MMSE score: 30/30, 4AT score: 0					
Blood results (at admission): Serum creatinine 70 $\mu\text{mol/l}$, eGFR 104 ml/min/1.72m ² , Na ⁺ 137, K ⁺ 4.8, Haemoglobin 12.8g/l, WCC 9.8, Neutrophils 5.4, Platelets 304, Albumin 36 g/l, Bilirubin 242 $\mu\text{mol/l}$ $\uparrow$, Ca ⁺⁺ (corrected) 2.30 mmol/l, ALT 40, ALP 753 $\uparrow$, GGT 152					
ECG: Normal sinus rhythm, 65 bpm, no conduction blocks					
Course of events in hospital: - Diagnosis made by attending team: Acute Liver Failure - The patient spent a total of 6 weeks in hospital - His liver function recovered with monitoring. - It took 6 weeks until liver function tests were within normal limits. - During the hospitalisation he had no falls, no nausea, no vomiting, no diarrhoea, no constipation.					
Medication changes during admission: 1. Tramadol stopped 2. Flucloxacillin stopped by the patient the day before admission					
Legend: MMSE = Mini mental state examination, 4AT = Screening test for delirium (≥ 4 possible delirium +/- cognitive impairment, 1-2 possible cognitive impairment, 0 = delirium or severe cognitive impairment)					

Figure 2.2: Questions asked on each clinical case.

Did this patients have any AE: yes or no

If yes:

	Event y/n	Prevalent or incident	Drug implicated y/n	Drug 1	WHO causality	Drug 2	WHO causality
New onset fall							
New unsteady gait							
Acute kidney injury							
Symptomatic orthostatic hypotension							
Severe electrolyte disturbance							
Symptomatic bradycardia							
New major constipation							
Acute bleeding							
Dyspepsia, nausea or vomiting							
Acute diarrhoea							
Delirium							
Symptomatic hypoglycaemia							
Unspecified							

If an ADR occurred, grade severity according to Hartwig and Siegel? 1 – 7 _____

Was there a **Sequence of Events**? If yes list order:

	Order of events		Order of events
New onset fall		New major constipation	
New unsteady gait		Acute bleeding	
Acute kidney injury		Dyspepsia, nausea or vomiting	
Symptomatic orthostatic hypotension		Acute diarrhoea	
Severe electrolyte disturbance		Delirium	
Symptomatic bradycardia		Symptomatic hypoglycaemia	
		Unspecified	

Narrative:

Legend: AE = adverse event

The median age of patients in the 8 clinical cases was 77 (IQR 69 – 24) years. Four of eight patients were male. The median number of active medical conditions was 10 (IQR 7.5 – 11.75) and the median number of prescribed medications was 9 (IQR 6.25 – 10) regular medications. Their median Barthel score was 18/20 (IQR 17.25 – 20) and their median MMSE was 26 (IQR 18.5 – 29.75). Four patients experienced an ADR; there were four **prevalent** ADRs and one of these patients had an **incident** ADR during the acute hospitalisation.

(ii) Participant recruitment and training

Twenty one persons, across 6 European centres, were asked to participate, all of whom accepted. Participants were selected on the basis of their recognised academic credentials, clinical practice, experience and geographical diversity. All participants were researchers, either primary investigators or primary researchers, for an observational study determining ADR incidence during hospitalisation across 6 European sites (SENATOR) (150). Participants consisted of physicians (Consultant Geriatricians, Consultant Clinical Pharmacologists and registrars training in Geriatric Medicine), clinical pharmacists, biomedical scientists and nurses (**Table 2.3**). Participants were invited to attend a training session. This training was offered during one afternoon and encompassed training on ADR identification, classification and their associated morbidity. Following training, 4 cases experiencing AEs, incorporating the key concepts highlighted above, were discussed.

Table 2.3: Participants in the ADR assessment inter-rater reliability exercise

Name	Discipline	Place of practice
Dr. Roy Soiza	Geriatric Medicine (Consultant)	Grampian Health Board (Aberdeen, Scotland)
Prof. Alfonso Cruz-Jentoft	Geriatric Medicine (Consultant)	Hospital Universitario Ramón y Cajal (IRYCIS) (Madrid, Spain)
Prof. Mirko Petrovic	Clinical Pharmacology & Geriatric Medicine (Consultant)	Universiteit Gent (Gent, Belgium)
Dr. Aðalsteinn Guðmundsson	Geriatric Medicine (Consultant)	Landspítali University Hospital (Reykjavik, Iceland)
Prof. Denis O'Mahony	Geriatric Medicine (Consultant)	Cork University Hospital (Cork, Ireland)
Prof. Antonio Cherubini	Geriatric Medicine (Consultant)	Geriatría ed Accettazione Geriatrica d'urgenza, IRCCS-INRCA, (Ancona, Italy)
Dr. Selvarani Subbarayan	Research fellow	Grampian Health Board (Aberdeen, Scotland)
Dr. Denis Curtin	Geriatric Medicine (specialist registrar) and research fellow	Cork University Hospital (Cork, Ireland)
Dr. Anna Cerenzia	Geriatric Medicine (registrar) and research fellow	Geriatría ed Accettazione Geriatrica d'urgenza, IRCCS-INRCA, (Ancona, Italy)
Dr. Marisol Cotourello Ferreiro	Geriatric Medicine (registrar) and research fellow	Geriatría ed Accettazione Geriatrica d'urgenza, IRCCS-INRCA, (Ancona, Italy)
Dr. Ólafur Samúelsson	Geriatric Medicine (Consultant)	Landspítali University Hospital (Reykjavik, Iceland)
Mr. Michael McCarthy	Pharmacist and research fellow	Cork University Hospital (Cork, Ireland)
Mr. Kieran Dalton	Pharmacist and research fellow	Cork University Hospital (Cork, Ireland)
Ms. Andrea Resi	Pharmacist	Hospital Universitario Ramón y Cajal (IRYCIS) (Madrid, Spain)
Ms. Lore Vandaele	Biomedical scientist	Universiteit Gent (Gent, Belgium)
Ms. Eline Meireson	Biomedical scientist	Universiteit Gent (Gent, Belgium)
Ms. Sirjana Devkota	Nurse	Grampian Health Board (Aberdeen, Scotland)
Ms. Sandra Nelson	Nurse	Grampian Health Board (Aberdeen, Scotland)
Ms. Pamela Paton	Nurse	Grampian Health Board (Aberdeen, Scotland)
Ms. Ástrós Sverrisdóttir	Nurse	Landspítali University Hospital (Reykjavik, Iceland)
Ms. Védís Húnbogadóttir	Nurse	Landspítali University Hospital (Reykjavik, Iceland)

(iii) **Expert Gold Standard (GS) Assessment of ADRs according to the *AE Trigger List***

Two trained physicians (Dr. Paul Gallagher and I) assessed each of the 8 clinical cases. It was first ascertained if the patient described was experiencing any AEs on the ***AE Trigger List***. Each of these AEs was then assessed for a possible drug cause using the WHO-UMC casualty tool. Once potential ADRs were identified, their timing, whether ***prevalent*** or ***incident***, was determined. Finally, morbidity was identified by ascertaining the ***Sequence of Events***, and the ADR severity was assessed using the Hartwig & Siegel rating scale (151). Complete agreement, in terms of all ADR assessments, was reached between the two assessors. This combined level of agreement (labelled “rater 1”) was set as the gold standard (GS), against which other participants’ assessments were compared.

2.2.5 Statistical analysis

For the purpose of this study, physician responses were dichotomized into whether each clinical case experienced an ADR or not. The responses of raters were cross-tabulated with those of the GS assessment. Statistical analysis was performed using IBM SPSS® Statistics version 22. Cohen’s Kappa Statistic was used to determine the level of agreement between each rater and the GS. This was also a chance-corrected measure of agreement on how raters classify individual items into the same category, in this instance the presence or absence of an ADR. The calculation of the kappa statistic is detailed in **Figure 2.3**. The kappa statistic was interpreted as poor if ≤ 0.2 ,

fair if 0.21–0.40, moderate if 0.51–0.6, substantial if 0.61–0.8 and good if 0.81–1.00 (153).

Figure 2.3: Calculation of the kappa statistic and proportions of positive and negative agreement between raters 1 and 3

ADR ascertainment		Rater 1 (GS)		Total
		ADR occurred	No ADR	
Rater 3	ADR occurred	4 (50%)	1 (12.5%)	5 (62.5%)
	No ADR	0 (0%)	3 (37.5%)	3 (37.5%)
Total		4 (50%)	4 (50%)	8

Kappa co-efficient = (observed agreement – chance agreement) / (1 – chance agreement)

Observed agreement = $(4 + 3) / 8 = 0.875$

Chance agreement = $(0.625 \times 0.500) + (0.500 \times 0.375) = 0.500$

Kappa = $(0.875 - 0.500) / (1 - 0.500) = 0.750$

Proportion of positive agreement (ppos) = $2 (4) / (8 + 4 - 3) = 0.89$

Proportion of negative agreement (pneg) = $2 (3) / (8 - 4 + 3) = 0.86$

2.3 RESULTS

2.3.1 The AE Trigger List

The 12 **AE Trigger List** and the definitions agreed upon by consensus are displayed in

Table 2.4.

Table 2.4: Adverse event (AE) Trigger List.

Event	Definition
New onset fall/s	New fall
New onset of unsteady gait	New onset of unsteady gait that results in poor mobility and unsteady balance
Acute kidney injury	An increase in serum creatinine by 0.3mg/dl (26.5 µmol/l) within 48 hours or an increase in serum creatinine by 1.5 baseline, which is known or presumed to have occurred within the prior 7 day
Symptomatic orthostatic hypotension	A systolic blood pressure drop ≥ 20 mmHg $\pm$ diastolic blood pressure drop ≥ 10 mmHg within 3 minutes of standing from the lying or sitting posture associated with symptoms
Major serum electrolyte disturbance	A sodium (Na ⁺) of < 130 mmol/l or > 145 mmol/l and/or a potassium (K ⁺) < 3.5 mmol/l or > 5.2 mmol/l and/or a corrected calcium (Ca ⁺⁺) < 2.1 mmol/l or > 2.7 mmol/l
Symptomatic bradycardia	Heart rate of < 50 beats/minute with symptoms
New major constipation	Subjective symptoms of hard stools and/or less than 3 bowel movements per week and/or supported by nursing records
Acute bleeding	Melaena or haematuria or haematemesis or haemoptysis with or without a drop in haemoglobin level >2g/dl (not due to rehydration) or associated symptoms (hypotension, tachycardia, pallor) or secondary renal failure
Acute dyspepsia/nausea/vomiting	Subjective symptoms of acute 'indigestion'/'upset stomach' or acute abdominal pain or acute refusal to eat or acute heartburn/acid reflux or acute nausea/vomiting
Acute diarrhoea	New liquid stools reported by the patient or the nursing staff or new liquid stools detected by medical staff on physical examination or new liquid (non-solid) stools occurring more than 3 times in 24 hours
Acute delirium	Confirmed by a reliable witness and the DSM-V criteria. Supported by a 4AT ≥ 4 and/or MMSE < 23/30
Symptomatic hypoglycaemia	Symptoms with a blood glucose of < 3.5 mmol/L or < 63 mg/dl

Legend: MMSE = Mini mental state examination, 4AT = Screening test for delirium

2.3.2 A standardized investigative process for each AE on the *Trigger List* to ascertain whether an ADR occurred and assessment of the associated morbidity.

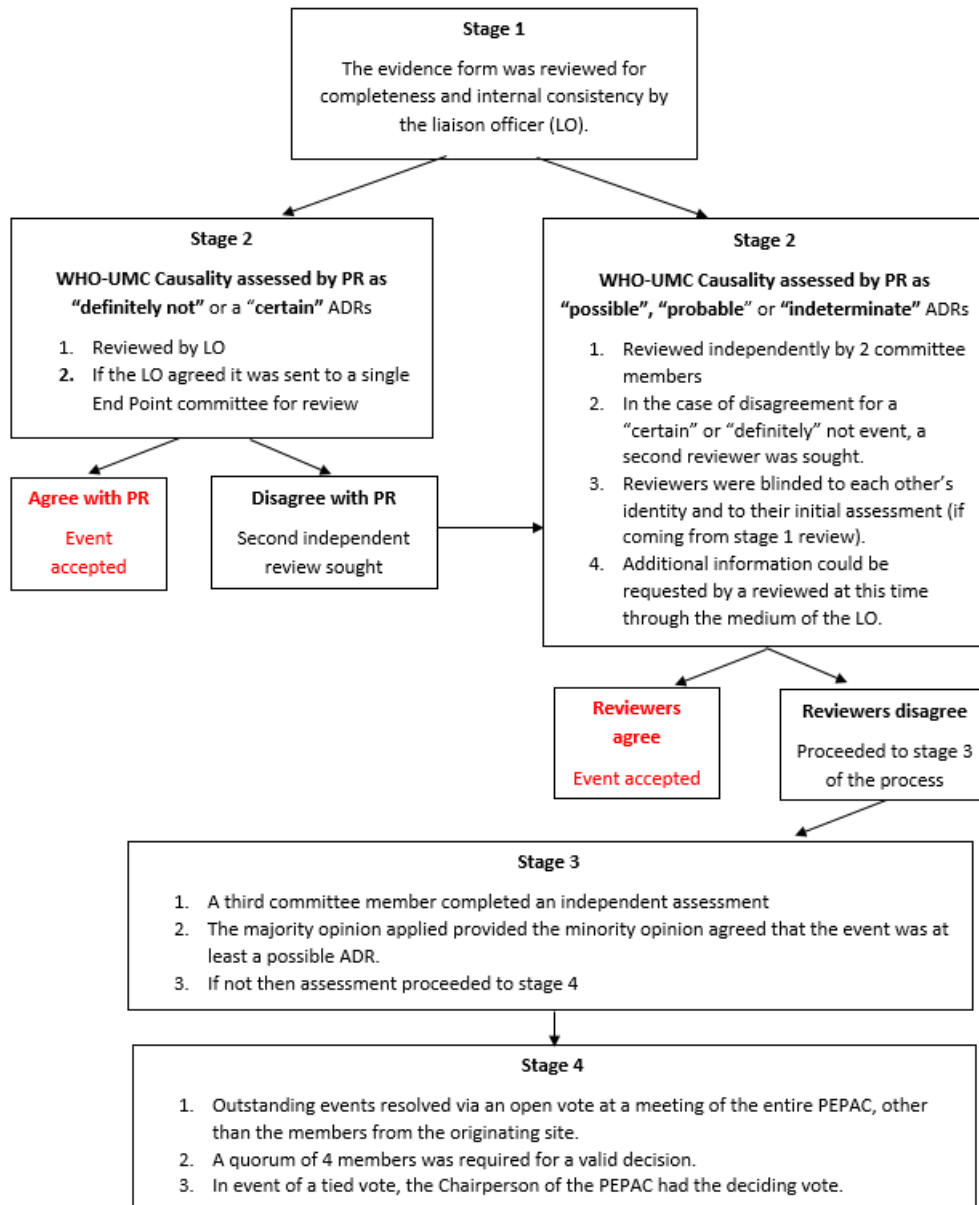
A standardized AE assessment form was developed to incorporate all the key concepts that were discussed above (**Table 2.5**). This standardized form includes asking questions about the timing of the AE, the duration of the AE and key questions to guide the likelihood of a drug being involved e.g. “is the event a known reaction to the drug in question?”. If an AE is found to be an ADR then the Hartwig & Siegel scale must be completed. Every AE should be assessed in the same robust manner. If an ADR occurs, the ***Sequence of Events*** should be recorded to robustly assess morbidity.

Once an AE is recorded and the below form completed, this form should then be sent to an adjudication committee for assessment. The structured process put forward to assist this robust process portrayed in **Figure 2.4**. An ADR is confirmed if two persons agreed that a probable or certain ADR, as per the WHO-UMC causality assessment has occurred.

Table 2.5: Standardized AE assessment form

Event = [name event type]										
Did the event occur:										
1. Pre hospital (prevalent)										
2. Occurred in hospital (incident)										
Approximate duration of the process:										
1. Discrete event										
2. < 1 day										
3. 1 – 3 days										
4. 4 – 7 days										
5. 8 – 10 days										
6. ≥ 11 days										
Were drug(s) the exclusive/predominant cause of the event?								Y/N		
If no possible culprit drug implicated in the process, tick here and skip the below questions and process to narrative box at the end of the form										
Name drug implicated: (a list of drugs commonly implicated in the above event is listed here)										
Regarding drug named:										
Is the event a known reaction/adverse effect to the drug in questions?										
Did this reaction/event previously occur in this patient secondary to this drug?										
Was the medication changed in a potentially deleterious fashion (↑, ↓ or abruptly stopped) prior to event?										
Was the medication changed in a potentially corrective fashion post event?										
Was the corrective change in medication post event associated with resolution?										
Is there an additional medication involved? If yes answer the above questions for this drug?										
Did any of the following conditions contribute to the event? (a list of conditions commonly implicated in the above event is listed here)										
Did the environment contributed to the event? Specify: _____										
Evidence for event/process (tick all that apply)										
Physician narrative										
Nursing narrative										
Radiology evidence										
Laboratory/blood evidence										
Other: _____										
Did the team implicate a medication in the event								Y or N		
Drug (name)	Causality (WHO-UMC)		Severity (Hartwig & Siegel)							
	Certain		0	1	2	3	4	5	6	7
	Probable									
	Possible									
	Unlikely									
Did process/event occur as part of a sequel?										
										Y or N
If yes, list sequel order Example: A patient began VOMITING because of clarithromycin which subsequently caused an ACUTE KIDNEY INJURY which then led to a FALL . [Vomiting = 1, AKI = 2, Fall = 3]										
Narrative										

Figure 2.4: Adjudication Process



2.3.3 The IRR of this new ADR process

(i) Participants and training

The 21 participants included 11 physicians, 5 nurses, 3 pharmacists, and 2 biomedical scientists, of whom 12 attended the training session i.e. 4 of 11 physicians, 2 of 3 pharmacists, 2 of 2 biomedical scientists and 4 of 5 nurses. There was no significant

difference in the numbers attending training from each group, $\chi^2 (3) = 4.617$, $p = 0.062$, however there was a trend towards more physicians not attending training than all other groups, $\chi^2 (1) = 4.073$, $p = 0.056$.

(v) GS assessment of ADR occurrence in the eight clinical cases

All 8 clinical cases experienced AEs, with four experiencing ADRs (**Table 2.6**). Eight of the twelve AEs listed on the **Trigger List** occurred and required assessment. One patient had an ADR that was not listed on the **AE Trigger List** i.e. drug-induced liver injury (DILI). Excluding the DILI, 16 AEs were identified of which 8 AEs were identified as ADRs with inter-dependent relationships identified between events.

Table 2.6: Answers to the eight clinical cases in the inter-rater reliability exercise

Case	Name and Number of prevalent AEs		Prevalent ADRs		Name and Number of incident AEs		Incident ADRs	
1	DILI	1	DILI	1		0		0
2	Constipation Nausea/vomiting	2	Constipation Nausea/vomiting	2		0		0
3	AKI Elect disturbance	2		0		0		0
4	Delirium	1	Delirium	1	AKI Diarrhoea	2	AKI Diarrhoea	2
5	Constipation Nausea/vomiting	2		0		0		0
6	Fall Elect disturbance Delirium	3		0		0		0
7	Fall OH	2	Fall OH	2	Constipation	1		0
8	Acute kidney injury Elect disturbance	2		0		0		0

Legend: AEs = adverse events, ADRs = adverse drug reactions, DILI = drug induced liver injury, AKI = acute kidney injury, elect = electrolyte, OH = orthostatic hypotension

(i) Inter-rater reliability (IRR)

Table 2.7 displays the kappa co-efficient for all raters compared to the GS for determining the presence or absence of ADRs. Columns A, B, C and D indicate the status of agreement between raters and the GS. For example, rater 1 (GS) and rater 2 agreed that ADRs were not identified in 4 clinical cases (column A). There were no instances in which rater 1 did not identify an ADR but rater 2 did so (column B). Similarly, there were no instances where rater 2 identified an ADR that rater 1 did not (column C). In 4 instances, both rater 1 and rater 3 identified an ADR (column D).

The overall median IRR was 0.750 (IQR 0.750 – 0.875); for physicians, the IRR was 0.75 (IQR 0.500 – 1.000), for pharmacists, the IRR was 0.750 (IQR 0.750 – 1.000), for biomedical scientists, the IRR was 0.750 (SD 0.750 – 0.750) and for nurses, the IRR was 0.750 (SD 0.750 – 0.750). The IRR of those who attended training was 0.750 (IQR 0.562 – 0.750), whilst among those that did not attend training, the IRR was 0.750 (IQR 0.750 – 1.00), with no significant difference identified between these two groups, $U = 42$, $p = 0.422$. Four physicians and 1 pharmacist obtained a perfect kappa score of 1.

Table 2.7: Inter-rater reliability (IRR) of the presence of ADRs

Kappa Co-efficient	Level of agreement to gold standard identifying out of 8 patients how many had ADRs				
Rater	A	B	C	D	Kappa
Gold standard * Rater 2 – physician	4	0	0	4	1.000
Gold standard * Rater 3 – physician	3	1	0	4	0.750
Gold standard * Rater 4 – physician	4	0	0	4	1.000
Gold standard * Rater 5 – physician	3	1	0	4	0.750
Gold standard * Rater 6 – physician	3	1	0	4	0.750
Gold standard * Rater 7 – physician	4	0	0	4	1.000
Gold standard * Rater 8 – physician	2	2	1	3	0.250
Gold standard * Rater 9 – physician	4	0	0	4	1.000
Gold standard * Rater 10 – physician	4	0	2	2	0.500
Gold standard * Rater 11 – physician	4	0	2	2	0.500
Gold standard * Rater 12 - physician	1	3	0	4	0.250
Gold standard * Rater 13 - pharmacist	4	0	0	4	1.000
Gold standard * Rater 14 - pharmacist	4	0	1	3	0.750
Gold standard * Rater 15 - pharmacist	4	0	1	3	0.750
Gold standard * Rater 16 – Biomedical scientist	4	0	1	3	0.750
Gold standard * Rater 17 - Biomedical scientist	4	0	1	3	0.750
Gold standard * Rater 18 – nurse	4	0	1	3	0.750
Gold standard * Rater 19 – nurse	4	0	1	3	0.750
Gold standard * Rater 20 - nurse	4	0	1	3	0.750
Gold standard * Rater 21 – nurse	3	1	0	4	0.750
Gold standard * Rater 22 – nurse	4	0	1	3	0.750
Median Kappa					0.750 (IQR0.750 – 0.875)
A – Both the gold standard and rater in question agreed no ADR occurred B – Gold standard concluded an ADR did not occur / rater in question concluded an ADR did occur C – Gold standard concluded an ADR occur / rater in question concluded an ADR did not occur D – Both the gold standard and rater in question agreed an ADR occurred					

Table 2.8 displays the kappa co-efficient for all raters compared to the GS for determining whether a patient had a **prevalent** or an **incident** ADR. For each case, a prevalent ADR could or could not occur and similarly an incident ADR could or could not occur. Columns A, B, C and D indicate the status of agreement between raters and the GS. For example, rater 1 (GS) and rater 2 agreed that no prevalent or incident ADR occurred in 11 instances (column A). In 0 instances, rater 1 did not identify a prevalent or incident ADR but rater 2 did so (column B). There was one instance where rater 2 identified a prevalent or an incident ADR that rater 1 did not (column C). In 4 instances, both rater 1 and rater 2 identified prevalent or incident ADR correctly in 4 cases an ADR (column D).

The median kappa was 0.673 (IQR 0.478 – 0.846); for physicians 0.625 (0.478 – 0.846), for pharmacists 0.673 (IQR 0.204 – 0.846), for biomedical scientists 0.846 (0.846 – 0.846) and for nurses 0.586 (IQR 0.412 – 0.673). The IRR of those who attended training was 0.673 (IQR 0.478 – 0.846), compared to 0.625 (IQR 0.466 – 0.750) among those who did not, i.e. no significant difference identified between the two groups, $U = 49$, $p = 0.754$. One physician scored a perfect kappa score of 1.

Table 2.8: Inter-rater reliability of whether prevalent or incident events occurred

Kappa Co-efficient	Agreement with prevalent and incident ADRs				
Rater	A	B	C	D	Kappa
Gold standard * Rater 2 – physician	11	0	1	4	0.846
Gold standard * Rater 3 – physician	10	1	0	5	0.862
Gold standard * Rater 4 – physician	11	0	1	4	0.846
Gold standard * Rater 5 – physician	9	2	1	4	0.586
Gold standard * Rater 6 – physician	9	2	1	4	0.586
Gold standard * Rater 7 – physician	11	0	1	4	0.846
Gold standard * Rater 8 – physician	8	3	2	3	0.310
Gold standard * Rater 9 – physician	11	0	0	5	1.000
Gold standard * Rater 10 – physician	11	0	3	2	0.478
Gold standard * Rater 11 – physician	11	0	3	2	0.478
Gold standard * Rater 12 - physician	8	3	0	5	0.625
Gold standard * Rater 13 - pharmacist	11	0	1	4	0.846
Gold standard * Rater 14 - pharmacist	11	0	2	3	0.204
Gold standard * Rater 15 - pharmacist	11	0	2	3	0.673
Gold standard * Rater 16 – Biomedical scientist	11	0	1	4	0.846
Gold standard * Rater 17 - Biomedical scientist	11	0	1	4	0.846
Gold standard * Rater 18 – nurse	11	0	2	3	0.673
Gold standard * Rater 19 – nurse	11	0	2	3	0.673
Gold standard * Rater 20 - nurse	11	0	3	2	0.478
Gold standard * Rater 21 – nurse	9	2	1	4	0.586
Gold standard * Rater 22 – nurse	10	1	3	2	0.347
Median Kappa					0.673 (IQR0.478 – 0.846)
A – Both the gold standard and rater in question agreed no prevalent or incident ADR occurred B – Gold standard concluded a prevalent or incident ADR did not occur / rater in question concluded a prevalent or incident ADR did occur C – Gold standard concluded a prevalent or incident ADR occur / rater in question concluded a prevalent or incident ADR did not occur D – Both the gold standard and rater in question agreed a prevalent or incident ADR occurred					

(ii) Variability between raters

The level of agreement between raters and the GS for each individual case with regards to causality, severity and ***Sequence of Events*** are displayed in **Table 2.9**.

Variability was identified between the various raters and the GS assessment when assigning severity scores to ADRs as per Hartwig & Siegel severity scale; agreement rates varying between 9.5% and 52.4% were identified.

Additionally, raters' responses varied when determining whether events were inter-dependent or completely independent ADRs. Three cases contained a recognizable ***Sequence of Events*** i.e. case 2, case 4 and case 7. For case 2, 17 of the 21 raters identified that constipation occurred secondary to a drug in case 2, however, just 5 raters identified nausea and vomiting as a drug-related event. For case 4, 15 of the 21 raters identified that diarrhoea occurred secondary to a medication, however just 3 raters correctly determined that this led to acute kidney injury. Lastly for case 7, 7 of the 21 raters identified a fall occurred secondary to a drug, however 6 identified a fall as a sequence to orthostatic hypotension (OH).

Table 2.9: Percentage of agreement for each case with the gold standard i.e. correct answer.

Variable		Gold standard	PIs (n=6)	PR (phys) (n=5)	PR (pharm) (n=3)	PR (biomed) (n=2)	PR (nurses) (n=5)	Total (n=21)
Case 1								
ADR type	N (%)	Liver failure	6 (100%)	5 (100%)	3 (100%)	2 (100%)	5 (100%)	21 (100%)
Prevalent or incident	N (%)	Prevalent	6 (100%)	5 (100%)	3 (100%)	2 (100%)	5 (100%)	21 (100%)
Causative Drug (probable/certain)	N (%)	Flucloxacillin	6 (100%)	5 (100%)	3 (100%)	2 (100%)	5 (100%)	21 (100%)
Extra drug (tramadol)	N (%)	No	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.76%)
Extra drug (paracetamol)	N (%)	No	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (4.76%)
H and S	N (%)	5	0 (0%)	1 (20%)	1 (33.3%)	0 (0%)	0 (0%)	2 (9.5%)
Case 2								
ADR type 1	N (%)	Constipation	6 (100%)	3 (60%)	3 (100%)	2 (100%)	3 (60%)	17 (81%)
ADR sequence 2	N (%)	Dyspepsia / nausea / vomiting	2 (33.3%)	0 (0%)	2 (66.66%)	0 (0%)	1 (20%)	5 (23.8%)
Prevalent or incident	N (%)	Prevalent	6 (100%)	3 (60%)	3 (100%)	2 (100%)	3 (60%)	17 (81%)
Causative drug 1 (probable/certain)	N (%)	Oxycodone	6 (100%)	3 (60%)	3 (100%)	2 (100%)	3 (60%)	17 (81%)
H and S	N (%)	4	4 (66.7%)	3 (60%)	2 (66.66%)	0 (0%)	2 (40%)	11 (52.4%)
Case 3								
ADR type	N (%)	No ADR	5 (83.3%)	3 (60%)	3 (100%)	2 (100%)	1 (20%)	17 (81%)
Case 4								
ADR type 1	N (%)	Delirium	4 (66.7%)	3 (60%)	2 (66.7%)	2 (100%)	2 (40%)	13 (61.9%)
Prevalent or incident	N (%)	Prevalent	4 (66.7%)	3 (60%)	2 (66.7%)	2 (100%)	2 (40%)	13 (61.9%)
Causative drug (probable/certain)	N (%)	oxycodone	4 (66.7%)	3 (60%)	2 (66.7%)	2 (100%)	2 (40%)	13 (61.9%)
Extra drug (tramadol)	N (%)	No	3 (50%)	2 (40%)	2 (66.7%)	2 (100%)	1 (20%)	10 (47.6%)

H and S	N (%)	4	3 (50%)	2 (40%)	2 (66.7%)	1 (50%)	1 (20%)	9 (42.9%)
ADR type 2	N (%)	Diarrhoea	5 (83.3%)	4 (80%)	0 (0%)	2 (100%)	4 (80%)	15 (71.4%)
ADR type 3	N (%)	AKI	2 (33.3%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	3 (14.3%)
Prevalent or incident	N (%)	Incident	5 (83.3%)	4 (80%)	0 (0%)	2 (100%)	4 (80%)	15 (71.4%)
Causative drug (probable/certain)	N (%)	Piperacillin / tazobactam	4 (66.7%)	4 (80%)	0 (0%)	2 (100%)	3 (60%)	13 (61.9%)
Extra drug (cefuroxime)	N (%)	No	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	2 (9.5%)
H and S	N (%)	4	3 (50%)	3 (60%)	0 (0%)	1 (50%)	4 (80%)	11 (52.4%)
Case 5								
ADR type	N (%)	No ADR	6 (100%)	4 (80%)	3 (100%)	2 (100%)	5 (100%)	20 (85.2%)
Case 6								
ADR type	N (%)	No ADR	5 (83.3%)	4 (80%)	3 (100%)	2 (100%)	5 (100%)	19 (90.5%)
Case 7								
ADR type 1	N (%)	OH	1 (16.7%)	1 (20%)	2 (66.6%)	0 (0%)	0 (0%)	6 (28.6%)
ADR type 2	N (%)	Fall	3 (50%)	2 (40%)	2 (66.6%)	0 (0%)	0 (0%)	7 (33.3%)
Prevalent or incident	N (%)	Prevalent	4 (66.7%)	2 (40%)	2 (66.6%)	0 (0%)	0 (0%)	7 (33.3%)
Causative drug (probable/certain)	N (%)	furosemide	4 (66.7%)	1 (20%)	2 (66.6%)	0 (0%)	0 (0%)	7 (33.3%)
Extra drug (Dosulepin)	N (%)	No	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)
Extra drug (Diltiazem)	N (%)	No	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)
H and S	N (%)		2 (33.3%)	2 (40%)	1 (33.3%)	0 (0%)	0 (0%)	5 (23.8%)
Case 8								
ADR type	N (%)	No ADR	6 (100%)	4 (80%)	3 (100%)	2 (100%)	5 (100%)	20 (95.2%)

Legend: PI = principal investigator, PR = primary researcher, phys = physicians, pharm = pharmacists, biomed = biomedical scientist

2.4 DISCUSSION

An ***AE Trigger List***, based on the 12 most common ADRs that occur in older adults, was developed and validated for application in older adults. Each AE on the ***Trigger List*** was given a clear definition to ensure accurate capture of *clinically significant* AEs and thus *clinically significant* ADRs. ADRs should be clearly classified as occurring prehospital, ***prevalent ADRs***, or during hospitalisation, ***incident ADRs***. To avoid over-reporting of ADRs, all AEs and ADRs should be viewed as ***processes*** rather than ***discrete events***. To capture the morbidity associated with ADRs, the inter-dependent relationship between AEs on the ***Trigger list***, if deemed drug related, should be recorded i.e. ***Sequence of Events***. Lastly to further strengthened ADR assessments, all AEs assessed for a drug cause should be sent to an adjudication committee to ensure 2 people agree on the final causality per the WHO-UMC causality criteria.

The above proposed approach to ADR assessments has the potential to standardise the identification, classification and reporting of ADRs. ADR assessments approached in this manner has the potential to allow comparisons between future observational studies. In addition, where ADRs are the primary endpoints in interventional studies, it will ensure ADRs are captured in a clear and robust manner and thus, interventions to reduce same are appropriately assessed. Using this approach may also mean that more ADRs are identified and therefore the offending drug is stopped earlier and the associated morbidity and mortality avoided. To date, economic consequences and mortality associated with ADRs has been captured but the true morbidity associated has not. The role of ***Sequence of Events*** will be paramount going forward.

The IRR of ascertaining ADRs using this 12 point AE **Trigger List** and the IRR of ascertaining the of the timing of ADRs (**prevalent vs incident**) was found to be substantial with median values of 0.750 (IQR 0.750 – 0.875) and 0.673 (IQR 0.478 – 0.846) respectively. Disagreements were identified regarding the grading of ADR severity using the standardized Hartwig & Siegel scale (151). In addition, variations were identified when identifying the **Sequence of Events**. Overall, the kappa co-efficient indicate that the common reading and interpretation of the above proposed methodology was good.

However, there were limitations identified for the IRR exercise. Firstly, not all participants attended the training session, notably fewer physicians attended, presumably because they considered themselves already proficient in ADR ascertainment. Furthermore, for those that did attend the ADR ascertainment training, there was no pre-training exercise with which to compare their post training answers i.e. to determine if the training exercise improved their ADR ascertainment capabilities. It is speculative whether improvements in kappa co-efficient would have been observed if all participants had attended the training exercise and all participants completed this assessment pre- and post-training. This study could have benefited from participants applying the methodology to more than 8 clinical cases. Kappa coefficient results for physicians for ADR identifications were skewed, with two physicians scoring 0.250 and two others scoring 0.500. This may relate to the fact that English was not the first language among the first pair of physicians. This fact may have resulted in limited value for them from the training exercise.

This research was completed as part of the SENATOR (Development and clinical trials of a new Software Engine for the Assessment and optimization of drug and non-drug Therapy in Older peRsons) clinical trial feasibility study (150), which examined the prevalent rates of **incident** ADRs in older hospitalised adults. This study highlighted many challenges with assessing ADRs as discussed through the chapter and instigated the proposed methodology for the SENATOR RCT. The SENATOR RCT is looking at a software intervention advising on medication optimisation at reducing in hospital ADRs and will be using the methodology proposed in this chapter.

Since this research, two further ADR trigger lists have been developed (154, 155). Both differ from the trigger list proposed in this chapter. The trigger list by Silva *et al.* does not incorporate clinical symptoms of ADRs but rather looks at triggers such as abrupt medication withdrawal or the prescription of specific drug classes (154). This trigger list has been tested and has been found to identify ADRs in only 53.3% of patients. The later, by Guzmán *et al.* comprises a much larger 51 point trigger list. Triggers here are based on medications and their concentrations, antidotes and abnormal lab values. This trigger list has yet to be tested in an observational study.

The ADR ascertainment methodology described in this study, along with the ADR adjudication process could be used to standardize the reporting of ADRs in future ADR studies. This would greatly help with assessment and comparison of ADR attenuating interventions. The next two chapters will report on (i) *prevalent* ADRs in the acute unselected older hospitalised patients and (ii) *prevalent* ADRs in hospitalised adults with cancer, using the above methodology.

CHAPTER 3:

Prevalence of adverse drug reactions (ADRs) in an acute unselected hospital
population as determined by new ADR ascertainment methodology

3.1 INTRODUCTION

The lack of studies examining the prevalence of multimorbidity in hospitalised older adults was discussed in Chapter 1. The subjective nature of ADR identification, classification and reporting was discussed in Chapter 2, in which a novel approach to ADR ascertainment was described and validated. ADRs are reported to cause hospitalisation in approximately 10% of older adults by two large meta-analyses (83, 144), however more recent observational studies report higher *prevalent* ADR rates of 21% to 26.3% (46, 74).

3.1.1 Objectives

The objectives of this study were:

- (i) To investigate and describe the burden of multimorbidity in unselected older (≥ 65 years) adults presenting to hospital with an acute illness.
- (ii) To use the newly developed ***AE Trigger List*** to determine the prevalence of ADRs causing or contributing significantly to hospital admission in an acute unselected older (≥ 65 years) adult population.
- (iii) To classify the identified ADRs according to type, causality, associated morbidity, severity, predictability and preventability.
- (iv) To identify risk factors for ADRs in this patient cohort.

The work undertaken in this chapter, including study design, data collection and statistical analysis, is entirely my own.

3.2 METHODS

3.2.1 Study setting and design

This prospective observational study was conducted at Cork University Hospital (CUH), an academic teaching hospitals in southern Ireland, over 107 days between August 2014 and March 2017. CUH is a major university teaching hospital with 850 inpatient beds and over 25,000 emergency admissions per year. In 2016, there were approximately 65,000 emergency department presentations, approximately 210,000 outpatient attendances and just over 45,000 inpatient discharges.

3.2.2 Patient eligibility and consent

All patients' aged ≥ 65 years admitted as emergency cases under the care of any medical or surgical speciality were eligible for inclusion. Exclusion criteria were as follows: (i) patients who had already enrolled in the study on a previous hospital admission, (ii) patients deemed to be actively dying by the attending physician, at the point of admission, and (iii) patients who declined to participate.

The study's objectives were explained to patients. If they agreed to participate, patients provided written informed consent. In circumstances where patients were unable to give consent due to reduced decision making ability e.g. delirium or advanced dementia, consent was obtained from their legal representative. Inclusion in the study was documented in patients' medical records. The study protocol was assessed and approved by the local research ethics committees at University College Cork (**Appendix 2**).

3.2.3 Study population and sample size calculation

Using an estimated ADR prevalence rate of 20%, with a margin of error of 5% and a 95% confidence limit, a minimum sample of 251 patients was required for this study. This power calculation was based on the formula outlined in **Figure 3.1** and adjusted using admission data from 2015 i.e. the total number of patients admitted to Cork University Hospital (CUH) ≥65 years old between January 1st and December 31st 2015.

Table 3.1: Sample size calculation

Hospital admission rates between January and December 2015 (excluding repeat admissions)		Sample Size calculation
Cardiology	1656	Formula $n = \frac{Z^2 \times P (1 - P)}{D^2}$ n = sample size Z = Z statistic for the level of confidence (1.96) P = Expected prevalence (20% or 0.20) D = margin of error (5% or 0.05) $n = \frac{(1.96)^2 \times (0.20) (1 - 0.2)}{0.05^2} = 246$ Adjusted for population available: Formula $\frac{n_0 \times N}{N_0 + (N - 1)}$ n₀ = population available to recruit from N = sample size calculation $\frac{8945 \times 246}{8945 + (246 - 1)} = 239 (+ 5\%) + 12 = 251$
Endocrinology	61	
Diabetes Mellitus	70	
Gastroenterology	85	
Geriatric Medicine	1035	
Haematology	123	
Neurology	109	
Neurosurgery	152	
Orthopaedics	834	
Plastic surgery	120	
Maxillary facial	8	
Renal Medicine	257	
Respiratory Medicine	450	
Rheumatology	109	
General Surgery	480	
Hepato-biliary Surgery	1	
Vascular Surgery	60	
Breast Surgery	5	
Infectious Diseases	116	
General Medicine	2970	
Cardiothoracic Surgery	168	
Urology	76	
Total	8945	

3.2.4 Data collection

All participants and patients' medical notes were reviewed within 24 hours of admission. Each morning, a list of admissions from the previous 24 hours was compiled. To avoid any bias, patients were enrolled according to the time of presentation to the hospital.

The following data were extracted and transferred onto a standardized proforma (**Appendix 3**): (i) demographic details, (ii) medical co-morbidities (in order to calculate Cumulative Illness Rating Scale (CIRS) scores) (156), (iii) concurrent medications, (iv) functional ability (Barthel Index) (157), (v) cognitive ability (Mini-mental state examination – MMSE), in those ≥ 65 years (158), 4-At (159) and the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) to assess for delirium (160), (vi) laboratory values, and (vii) electrocardiogram (ECG) data. Medication reconciliation was completed using the Structured History taking of Medication use (SHiM) (32). These validated tools are described in brief below.

(i) Cumulative Illness Rating Scale (CIRS)

The CIRS (156) is a scoring system that measures the burden of chronic medical illnesses by considering the severity of each illness (**Figure 3.1**). It does this by ranking the severity of each disease on a scale of 0 to 4; 14 categories of illness are represented according to various physiological systems. A score of 0 represents no active illness, whereas 4 represents an extremely severe problem. The higher a patient's score, the higher the morbidity burden; CIRS scores range from 0 to 56. CIRS was developed to assist physicians in quantifying medical problems and allowing meaningful comparison of medical burden between patients. CIRS is applicable to patients of all ages.

A comprehensive medical history, and relevant laboratory values are required to apply the CIRS tool. CIRS was chosen for this study instead of the more commonly used Charlson Comorbidity Index (161) because the disease weighting system in the

Charlson Comorbidity Index was felt to be outdated e.g. metastatic disease is weighted with a maximum score of 6. This does not reflect the many advances that have occurred in the treatment of metastatic cancer since the original Charlson Index was published in 1987.

Figure 3.1: Cumulative illness rating scale (CIRS) scoring system

Body system	Score
Cardiac	0 – 1 – 2 – 3 – 4
Vascular	0 – 1 – 2 – 3 – 4
Haemopoetic	0 – 1 – 2 – 3 – 4
Respiratory	0 – 1 – 2 – 3 – 4
ENT (eye, ear, throat, larynx)	0 – 1 – 2 – 3 – 4
Upper GI	0 – 1 – 2 – 3 – 4
Lower GI	0 – 1 – 2 – 3 – 4
Hepatic	0 – 1 – 2 – 3 – 4
Renal	0 – 1 – 2 – 3 – 4
Other GU	0 – 1 – 2 – 3 – 4
Musculoskeletal	0 – 1 – 2 – 3 – 4
Neurological	0 – 1 – 2 – 3 – 4
Endocrine-metabolic	0 – 1 – 2 – 3 – 4
Psychiatric/Behavioural	0 – 1 – 2 – 3 – 4
Score (range 0 – 56)	
Scoring	
0 = no problem	
1= current mild problem/past significant problem	
2 = moderate disability or morbidity and/or requires first line treatment	
3 = Severe problem and/or constant and significant disability and/or difficult to control chronic problems	
4 = Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment	
If scoring malignancy	
0 = no cancer	
1 = cancer diagnosed in the remote past without evidence of recurrence or sequelae in the past 10 years	
2 = cancer diagnosed in the past without evidence of recurrence or sequelae in the past five years	
3 = required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past five years	
4 = Recurrent malignancy of life threatening potential/failed containment of the primary malignancy/palliative treatment stage	

Legend: GI = Gastrointestinal; GU = genitourinary

(ii) Barthel Index

The Barthel Index (157) (**Appendix 4**) classifies functional status by measuring activities of daily living (ADLs). It consists of 10 parameters describing ADLs and

mobility. Each parameter can be scored a 0 or 1 and for some parameters a score 2 can be given. The maximum score is 20 i.e. fully independent in personal activities of daily living. The lower the score, the more dependent a person is. To apply the Barthel Index, patients or caregivers need to be able to answer questions on functional ability.

(iii) Mini Mental State Examination (MMSE)

The MMSE is a validated tool designed to assess cognitive status in patients aged ≥ 65 years old (**Appendix 5**) (158). This 30 item questionnaire is widely used to identify cognitive impairment in both the clinical and research settings. It is a poor discriminator of mild cognitive impairment from dementia, in which case the Montreal Cognitive Assessment (MOCA) is more frequently deployed instead (162).

(iv) 4-AT Test

The 4-AT test is a validated tool to assess for the prevalence of delirium (159). It assesses 4 components (**Figure 3.2**): alertness, orientation, attention and fluctuating consciousness. It incorporates the Months Backwards Test (MBT). It is quick and easy to use. The maximum score on the 4-AT is 14. A score of ≥ 4 suggests a possible delirium with or without an underlying cognitive impairment, a score of 1 or 2 suggested possible cognitive impairment and a score of 0 indicates that delirium or severe cognitive impairment is unlikely.

Figure 3.2: 4-AT delirium screening test

	Score
Alertness	
Normal (fully alert, but not agitated, throughout assessment)	0
Mild sleepiness for <10 seconds after waking, then normal	0
Clearly abnormal	4
AMT4	
Age, date of birth, place, current year	
No mistakes	0
1 or more mistakes	1
2 or more mistakes	2
Attention	
“Please tell me the months backwards, starting at December?”	
Achieves 7 or more correctly	0
Starts and scores <7/ refuses to start	1
Untestable (cannot start because unwell, drowsy, inattentive)	2
Acute Change of fluctuating course	
Evidence of significant change/fluctuation in: alertness, cognition, other mental function (e.g. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs	0
No or yes	4
Total Score	

(v) Structured History of Medications (SHiM)

The SHiM (**Appendix 6**) is a structured method that aims to assist physicians with verifying all medications a patient is taking and thus aid with medication reconciliation (32). It comprises 16 questions which ensures, as much as possible, that an accurate account of all medication use, including over the counter medications (OTC) and recent short course treatments, occurs. It also defines adherence to medications, previous side effects and ADRs, as well as patients’ concerns regarding their medications.

(vi) Rockwood's Clinical Frailty Scale (CFS)

The Rockwood Clinical Frailty Scale (**Appendix 7**) is a 9 point scale that was developed to help classify patients according to their level of frailty (163). A score of 1 implies a patient is very fit, whereas a score of 8 indicates high level dependency and impending end-of-life status. Persons receive a score of 9 if they have a terminal diagnosis with a known life expectancy of ≤ 6 months. This tool, although primarily developed for use in classifying frailty in patients with dementia, is now used to identify and classify frailty in all patients. It usually takes less than 30 seconds to apply.

3.2.5 Potentially inappropriate prescribing

Potentially inappropriate prescribing was assessed using STOPP/START criteria (37) (**Appendix 8**). STOPP/START criteria were originally developed and validated through Delphi technique in 2008 (36) and further updated in 2014 (37). STOPP/START is an explicit prescribing tool that aims to highlight common instances of potentially inappropriate prescribing and potentially prescribing omissions (PPOs) in adults 65 years and older. It consists of 80 potentially inappropriate prescriptions (PIPs) and 34 PPOs and is divided according to physiological system. For their application, a physician requires an up to date list of all medical diagnoses, concurrent medications, baseline laboratory values and an ECG. STOPP/START criteria have been used to identify potentially inappropriate medication (PIM) use in multiple studies of older adults, both in Ireland (41, 45, 50) and Europe (34, 164) and elsewhere. PIMs listed in STOPP/START criteria are significantly associated with ADRs (46). The application

of STOPP/START criteria has been shown by way of RCTs to result in sustained improvement in various domains of medication appropriateness (72, 165), and reductions in incident ADRs in hospitalised older patients (74) as well as fewer incident falls in nursing home residents (73). The presence or absence of a PIM, according to STOPP/START criteria, was categorised as a dichotomous variable. Where there was uncertainty regarding appropriateness of a prescription this was treated conservatively i.e. the prescription was deemed appropriate.

3.2.6 Adverse drug reactions

The proportion of patients experiencing one or more non-trivial, probable or certain, ADR causing or contributing significantly to hospital admission was also recorded. For this study, Edwards and Aronson's definition of an ADR was applied i.e. "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (79).

To limit potential bias from selective ADR reporting and to ensure ADRs were not missed, the validated ***AE Trigger List*** of the 12 most common ADRs, as discussed in Chapter 2, was used. Data on any ADR not listed in the ***AE Trigger List*** was also collected e.g. acute liver injury. All AEs representing potential ADRs were recorded prospectively and subsequently reviewed to assess the causative role of current medications. The morbidity associated with ADRs was captured using the ***Sequence of Events***.

3.2.7 ADR causality, severity, predictability and preventability

Causality was assessed using the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) criteria (119). ADR severity was assessed using the Hartwig & Siegel scale, as discussed in Chapter 2 (151). ADR preventability was assessed using Hallas criteria i.e. definitely avoidable, possibly avoidable, unavoidable and unclassifiable (166). ADR predictability was assessed using the summary of product characteristics (SPC) (**Table 3.2**). ADRs were deemed predictable if they commonly ($\geq 1/100$ and $< 1/10$) or very commonly ($\geq 1/10$) occurred in patients prescribed the medication in question.

Table 3.2: ADR predictability

Incident rate	Incident description	Predictability
$\geq 1/10$	Very common	Predictable
$\geq 1/100$ and $< 1/10$	Common	Predictable
$\geq 1/1000$ and $< 1/100$	Uncommon	Unpredictable
$\geq 1/10,000$ and $< 1/1000$	Rare	Unpredictable
$< 1/10,000$	Very rare	Unpredictable

3.2.8 Statistical analysis

Statistical analysis was performed using SPSS® version 22 for windows. Descriptive data were reported using the mean and standard deviation (SD) for variables that were normally distributed and median and interquartile range (IQR) for non-parametric variables. Differences in the distribution of categorical variables were compared using Pearson's Chi-square (χ^2) test and continuous variables using the independent t test. The Mann Whitney U and Kruskal-Wallis tests were used to determine independence of two or more non-parametric variables respectively.

Pearson's kappa coefficient was used to assess correlation between variables. Multivariable logistic regression was used to examine the influence of gender, age, number of medications and burden of co-morbidity on potentially inappropriate prescribing practices. One-way ANOVA was used to determine the difference in the mean of a dependent variable when there were 3 or more categories to the independent variable. The Hosmer & Lemeshow statistic was used to test the goodness-of-fit of the regression model. A probability value of less than 0.05 was considered statistically significant.

3.3 RESULTS

3.3.1 Screening

Between August 2014 and March 2017, a total of 274 emergency admissions were screened for study inclusion. Of these, 240 patients agreed to participate, 81.7% (n=196) of whom were medical patients and 18.3% (n=44) were surgical patients. These data are summarised in **Figure 3.3** together with reasons for study exclusion. The distribution of admissions according to specialty are summarised in **Figure 3.4**.

Figure 3.3: Participant screening, exclusion and enrolment

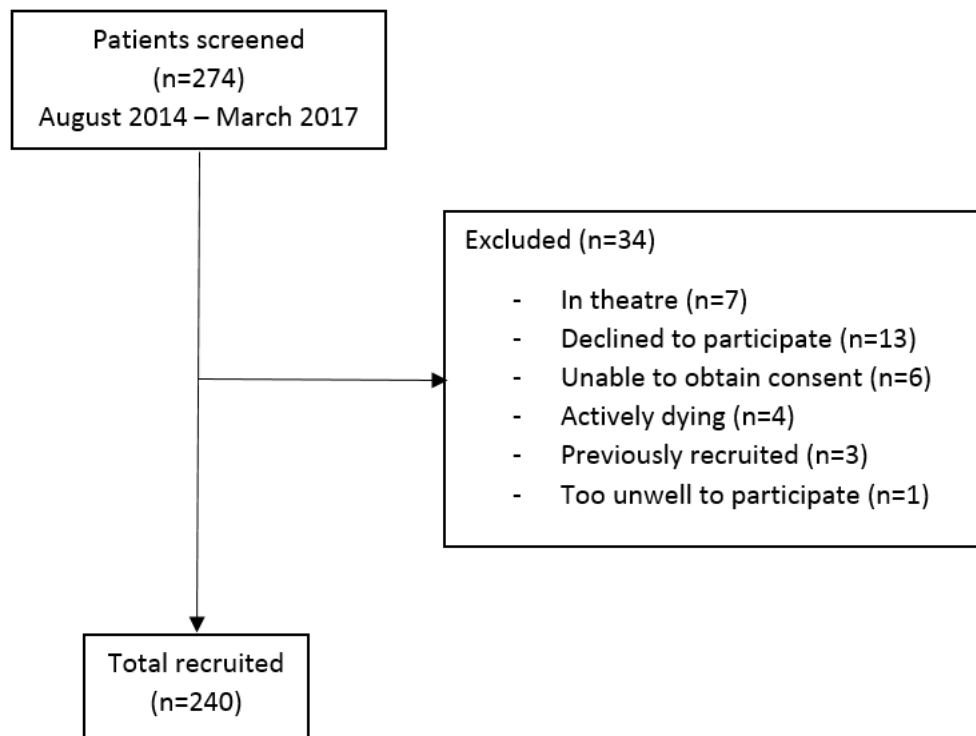
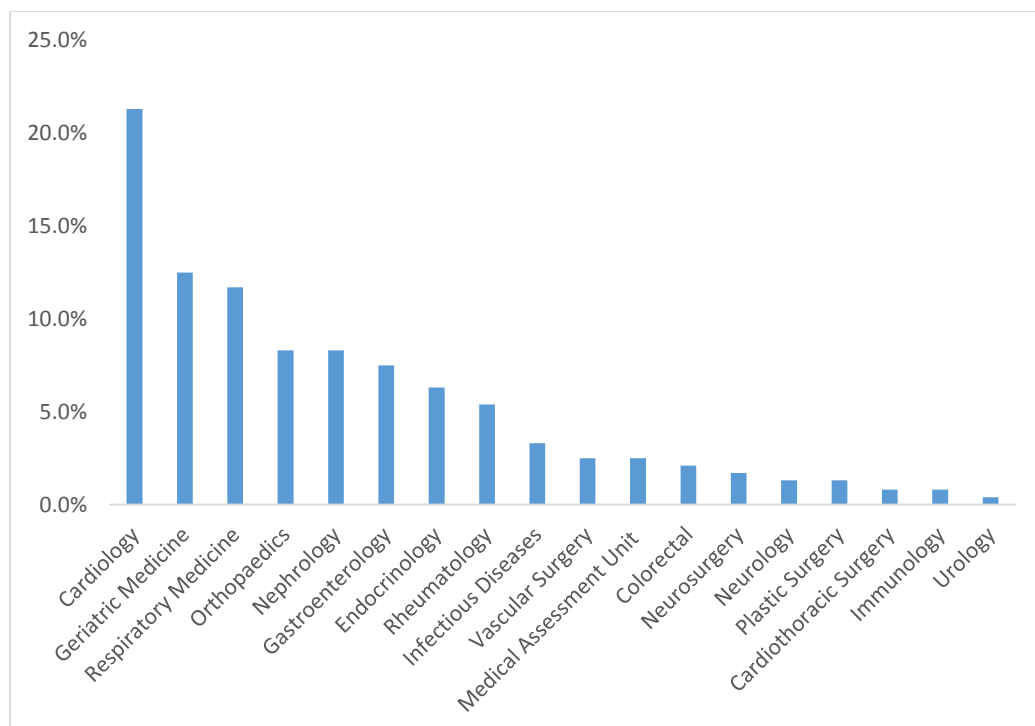


Figure 3.4: Distribution of admissions according to specialty



3.3.2 Population characteristics

Baseline characteristics are displayed in **Table 3.3**. Similar numbers of males and females participated in this study (50.4% vs 49.6%). The mean age was 78.0 (SD 7.6) years. Almost half of the patients (44.2%) were ≥ 80 years old and approximately 1 in 5 (22.5%) were ≥ 85 years old. Most patients were functionally independent, with 71.4% (n=171) being categorised as independent or low level dependency (Barthel Index scores ≥ 16). Eighty three percent of patients (n=199) completed the MMSE. From these scores, normal cognition and mild cognitive impairment were identified in 57.9% and 15% respectively. Approximately 1 in every 5 patients had moderate or severe cognitive impairment. It must be mentioned that acutely ill patients can underperform on a MMSE due to delirium and thus mild cognitive impairment and dementia may be over-estimated. Delirium was identified in 19.6% (n=47) using the 4-AT test and DSM-5 criteria. Collateral history was taken to confirm the presence of delirium. No differences in Rockwood Clinical Frailty Scale scores were identified between genders ($\chi^2(8) = 12.018$, $p = 0.150$). Differences in the level of frailty were identified between age groups ($\chi^2(16) = 37.662$, $p = 0.002$) (**Figure 3.5**).

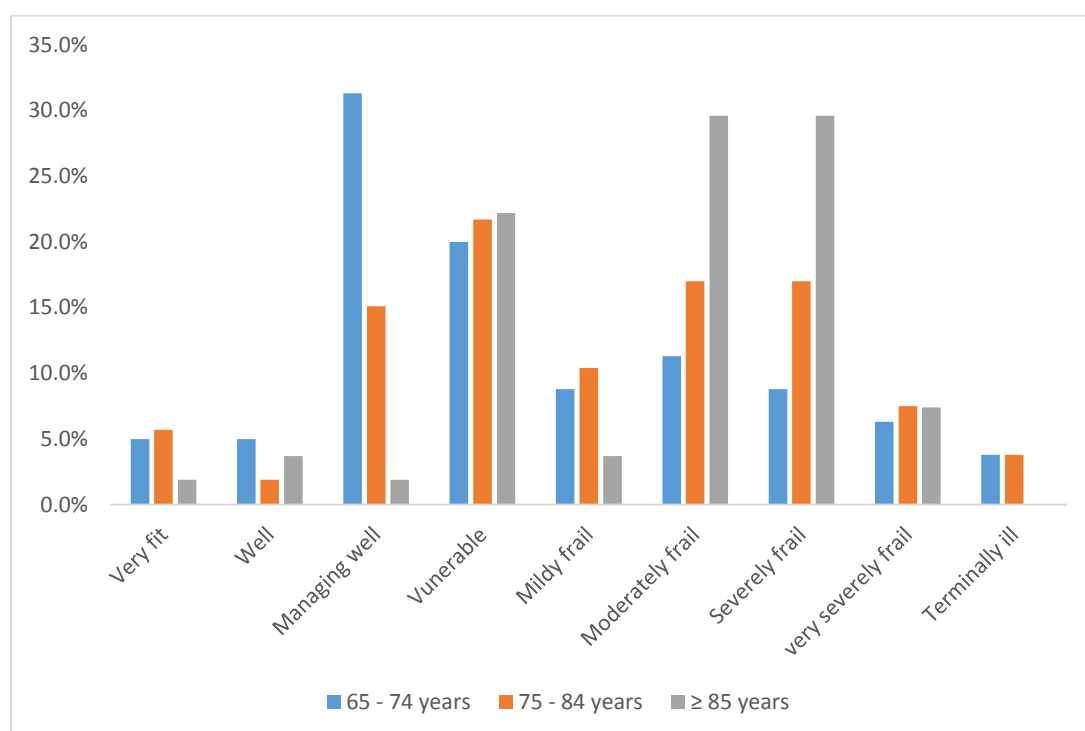
One in four (25.4%) participants consumed alcohol on a weekly basis. Men were significantly more likely to do so (33.9% vs 16.8%, $\chi^2(1) = 9.034$, $p = 0.003$) and significantly more likely to drink more than the recommended weekly allowance (10.7% vs 1.7%, $\chi^2(1) = 3.416$, $p = 0.004$). Eight (3.3%) older adults drank more than 25 units per week. Collateral history was obtained to confirm alcohol intake. One hundred and nineteen (49.6%) patients had a history of smoking and 10.4% (n=25) were current smokers.

Table 3.3: Characteristics of study population according to gender (n = 240)

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
Age distribution				
Mean (SD)	75.6 (7.6)	78.6 (7.7)	78 (7.6)	0.986
65 – 74	42 (34.7%)	38 (31.9%)	80 (33.3%)	0.648
75 – 84	52 (43%)	54 (45.4%)	106 (44.2%)	0.708
≥ 85	27 (22.3%)	27 (22.7%)	54 (22.5%)	0.945
Functional ability (Barthel Index)				
Median (IQR)	20 (14 – 20)	19 (15 – 20)	19 (15 – 20)	0.655
Range	2 – 20	6 – 20	2 – 20	
Independent (≥ 20)	63 (52.1%)	54 (45.4%)	117 (48.9)	0.300
Low dependency (16 – 19)	24 (19.8%)	30 (25.2%)	54 (22.5%)	0.319
Moderate dependency (11 – 15)	20 (16.5%)	22 (18.5%)	42 (17.5%)	0.690
High dependency (6 – 10)	9 (7.4%)	13 (10.9%)	22 (9.2%)	0.349
Maximum dependency (0 – 5)	5 (4.1%)	0 (0%)	5 (2.1%)	0.025*
Cognitive ability (MMSE)				
Number that completed MMSE	98 (81%)	101 (84.9%)	199 (83%)	0.424
Median (IQR)	26.5 (23 – 28)	26 (22 – 28)	26 (22–28)	0.439
Range	9 – 30	8 – 30	8 – 30	
MMSE score 25 – 30	70 (57.9%)	69 (58%)	139 (57.9%)	0.632
MMSE score 20 – 24 suggesting MCI	17 (14%)	19 (16%)	36 (15%)	0.788
MMSE score 11 – 19 suggesting moderate cognitive impairment	10 (8.3%)	11 (9.2%)	21 (8.8%)	0.875
MMSE score 0 – 10 suggesting Severe cognitive impairment	1 (0.8%)	2 (1.7%)	3 (1.3%)	0.579
Severe cognitive impairment (unable to complete MMSE)	11 (9.1%)	4 (3.4%)	15 (6.25%)	
Clinical Frailty Scale				
Mean (SD)	5 (2.1)	5 (1.9)	5 (2)	0.751
Alcohol and Smoking				
Consumes alcohol weekly	41 (33.9%)	20 (16.8%)	61 (25.4%)	0.003*
Consume ≥ recommended weekly limit**	13 (10.7%)	2 (1.7%)	15 (6.3%)	0.004*
History of smoking	79 (65.3%)	40 (33.6%)	119 (49.6%)	<0.001*
Current smokers	17 (14%)	8 (6.7%)	25 (10.4%)	0.063

Legend: SD = standard deviation, IQR = inter-quartile range, MMSE = mini-metal state examination, MCI = mild cognitive impairment** ≥ 11 units for females, ≥ 17 units for males

Figure 3.5: Frailty according to age category



Key Findings 1:

- Approximately 1 in 3 had a moderate to high level of functional dependency.
- Approximately 1 in 5 had a moderate to severe dementia.
- Approximately 1 in 5 experienced delirium.
- Approximately 1 in 4 were very fit, well or managing well per Rockwood's frailty scale
- Approximately 1 in 4 were severely frail, very severely frail or terminally ill per Rockwood's frailty scale

3.3.3 Level of morbidity

The level of morbidity in this population was measured by the total number of chronic conditions, the number of chronic conditions requiring regular medications and the CIRS score. These data are summarised in **Table 3.4**.

Table 3.4: Level of morbidity according to gender

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
Multi-morbidity				
≥2 conditions	120 (99.2%)	117 (99.3%)	237 (98.8%)	0.551
≥3 conditions	117 (96.7%)	114 (95.8%)	231 (96.3%)	0.715
≥4 conditions	106 (87.6%)	111 (93.3%)	217 (90.4%)	0.135
≥5 conditions	103 (85.1%)	100 (84%)	203 (84.6%)	0.815
Conditions				
Mean (SD)	8.8 (4.1)	9 (4.1)	8.9 (4.1)	0.647
range	1 - 20	1 – 19	1 – 20	
Conditions (on regularly medications)				
Mean (SD)	5.6 (2.9)	6 (3.2)	5.8 (3.1)	0.539
range	0 - 12	0 – 17	0 - 17	
CIRS				
Mean (SD)	15.8 (6.3)	14.8 (5.9)	15.3 (6.1)	0.889
range	0 - 30	0 - 30	0 - 30	

Legend: CIRS = Cumulative illness rating scale, SD = standard deviation

Almost all participants (98.8%) were multi-morbid, with 84.6% having ≥ 5 chronic conditions. There was no significant difference between the number of conditions in patients aged 65 – 74 year, 75 – 84 years and those ≥ 85 years, ($F(2, 237) = 2.529$, $p = 0.082$ (**Figure 3.6**). The mean CIRS score was 15.3 (SD 6.1), with no significant difference between genders (15.8 (SD 6.3) vs 14.8 (SD 5.9), $t_{238} = 1.228$, $p = 0.889$). Significant differences in CIRS scores were identified according to patients' age ($F(2, 237) = 3.634$, $p = 0.028$ (**Figure 3.7**). A Tukey post hoc test revealed that the CIRS rating was statistically lower in those aged 65 – 74 years compared to those aged ≥ 85 years i.e. 14.0 (SD 6.3) vs 16.7 (SD 6.1), $p = 0.026$. There was no difference identified between those aged 75 – 84 years and those aged 65 – 74 years (15.6 (SD 5.7) vs 14 (SD 6.3), $p = 0.157$) or between those aged 75 – 84 years those aged ≥ 85 years (15.6 (SD 5.7) vs 16.7 (SD 6.1), $p = 0.506$) (**Figure 3.7**).

Figure 3.6: Number of chronic conditions according to age category

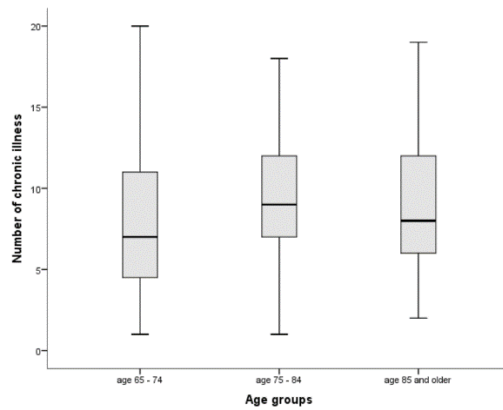


Figure 3.7: Mean (SD) CIRS scores according to age category

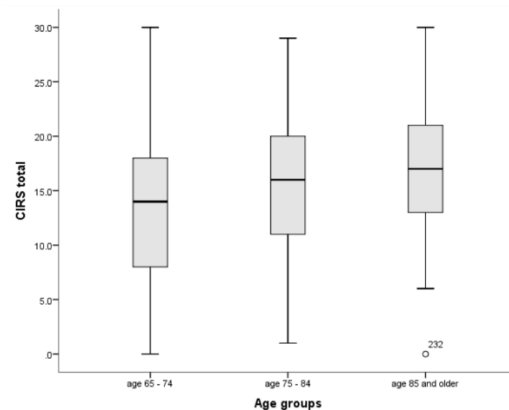
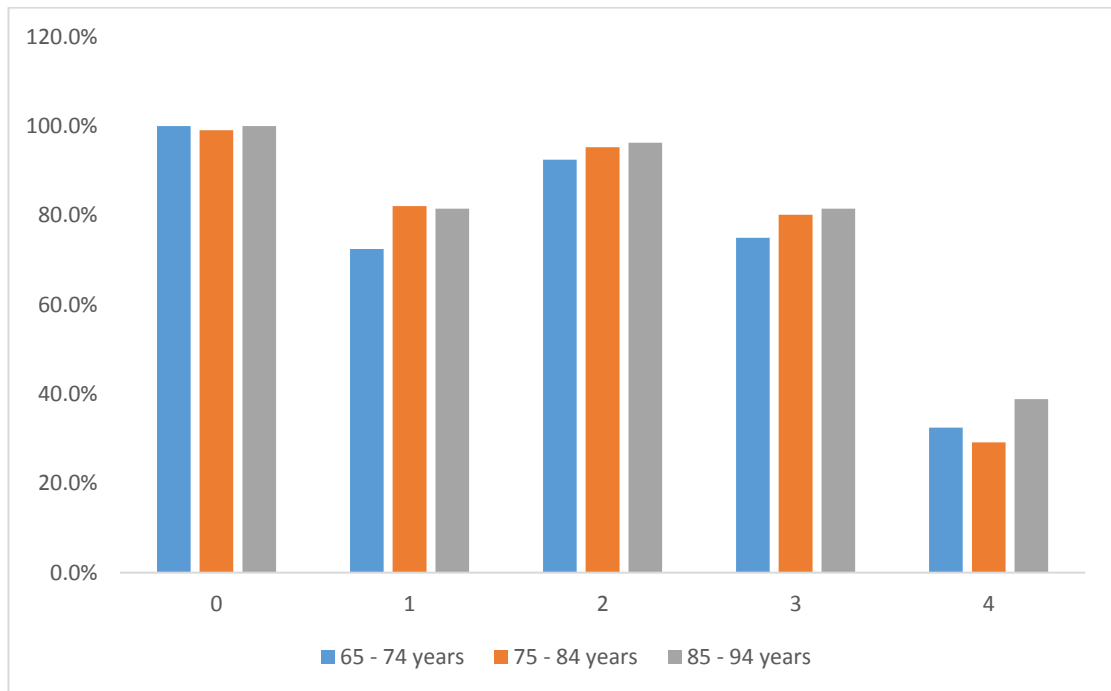


Figure 3.8 illustrates the percentage of participants that rated at least one system with either a 0, 1, 2, 3 or 4 according to age. Approximately 32.5% (n=78) of participants rated at least one illness with a “4” for one physiological system (indicating extremely severe disease requiring immediate treatment or contributing to severe impairment in function), 78.8% (n=189) rated at least one illness with a “3” (indicating a severe condition that is uncontrollable), 94.6% (n=227) at least one “2” (indicating a disease requiring first line treatment or causing moderate disability) and 78.8% (n=189) rated at least at least one “1” (indicating a mild current problem or past significant problem).

Figure 3.8: The number of participants that rated at least one system a 0, 1, 2, 3 or 4 according to age (n=240)



Key Findings 2:

- Multimorbidity was identified in 98.8% of patients.
- More than 8 out of every 10 participants (84.6%) had ≥ 5 conditions.
- Adults' ≥ 85 years had a significantly higher burden of illness compared to those 65 – 74 years as determined by their CIRS score.

3.3.4 Diagnoses

The most common diagnoses identified are displayed in **Table 3.5**. Approximately two thirds of participants had a diagnosis of hypertension and dyslipidaemia. Approximately two fifths of participants had a diagnosis of atrial fibrillation and ischaemic heart disease (IHD). Approximately 1 in 3 participants had a diagnosis of osteoarthritis or constipation. Approximately 1 in 4 patients had a diagnosis of heart failure, diabetes mellitus, chronic obstructive pulmonary disease, anaemia or chronic

kidney disease. Approximately 1 in 5 participants had a diagnosis of osteoporosis, hypothyroidism and urinary incontinence.

Table 3.5: Diagnoses according to gender

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
Diagnoses (in order of frequency)				
1. Hypertension	88 (66.1%)	86 (72.3%)	166 (69.2%)	0.302
2. Dyslipidaemia	64 (52.9%)	80 (67.2%)	144 (60%)	0.023*
3. Atrial fibrillation	50 (41.3%)	45 (37.8%)	95 (39.6%)	0.579
4. IHD	62 (51.2%)	30 (25.2%)	92 (38.3%)	<0.001*
PCI	14 (11.6%)	9 (7.6%)	23 (9.6%)	0.292
MI	23 (19%)	10 (8.4%)	33 (13.8%)	0.017*
CABG	24 (19.8%)	6 (5%)	30 (12.5%)	0.001*
Angina	9 (7.4%)	7 (5.9%)	16 (6.7%)	0.629
5. Osteoarthritis	45 (37.5%)	44 (37%)	89 (37.1%)	0.972
6. Anaemia	48 (39.7%)	32 (26.9%)	80 (33.3%)	0.036*
7. Chronic constipation	36 (29.8%)	37 (31.1%)	73 (30.4%)	0.821
8. Heart Failure	30 (12.5%)	28 (23.5%)	64 (26.7%)	0.276
9. Diabetes Mellitus	31 (25.6%)	29 (24.4%)	60 (25%)	0.823
10. COPD	36 (29.8%)	21 (17.6%)	57 (23.8%)	0.028*
11. GORD	25 (20.7%)	32 (26.9%)	57 (23.8%)	0.257
Previous GI bleed	4 (3.3%)	8 (6.7%)	12 (5%)	0.225
Previous ulcer	4 (3.3%)	5 (4.2%)	9 (3.8%)	0.715
Oesophagitis/gastritis/duodenitis	10 (8.3%)	11 (9.2%)	21 (8.8%)	0.788
12. Chronic kidney disease	30 (24.8%)	26 (21.8%)	56 (23.3%)	0.590
13. Previous fracture	17 (14%)	38 (31.9%)	55 (22.9%)	0.001*
14. Depression with/without Anxiety	21 (17.4%)	32 (26.9%)	53 (22.1%)	0.075
15. Osteoporosis	12 (9.9%)	36 (30.3%)	48 (20%)	<0.001*
16. Hypothyroidism	17 (14%)	30 (25.2%)	47 (19.6%)	0.029*
17. Urinary incontinence	17 (14%)	30 (25.2%)	47 (19.6%)	0.029*
18. Stroke	14 (11.6%)	25 (21%)	39 (16.3%)	0.048*
19. Benign prostatic hypertrophy	37 (30.6%)	0 (0%)	37 (15.4%)	<0.001*
20. Dementia	18 (14.9%)	18 (15.1%)	36 (15%)	0.957
21. Insomnia	16 (13.2%)	20 (16.8%)	36 (15%)	0.437
22. Falls	17 (14%)	16 (13.4%)	33 (13.8%)	0.892
23. Diverticular disease	17 (14%)	15 (12.6%)	32 (13.3%)	0.742
24. Peripheral vascular disease	23 (19%)	7 (5.9%)	30 (12.5%)	0.002*
25. Gout	13 (10.7%)	17 (14.3%)	30 (12.5%)	0.407
26. History of cancer	15 (12.4%)	6 (5%)	28 (11.7%)	0.044*
27. Current active cancer	13 (10.7%)	15 (12.6%)	21 (8.8%)	0.653

Legend: GORD = gastro-oesophageal reflux disease, IHD = Ischaemic heart disease, PCI = percutaneous coronary intervention (Stents), MI = myocardial infarction, CABG = coronary artery bypass graft, HF = heart failure, COPD = chronic obstructive pulmonary disease

Women were significantly more likely to have osteoporosis ($\chi^2 (1) = 15.505$, $p < 0.001$), urinary incontinence ($\chi^2 (1) = 4.745$, $p = 0.029$), a history of fractures ($\chi^2 (1) = 10.862$, $p = 0.001$), hypothyroidism ($\chi^2 (1) = 4.745$, $p = 0.029$), dyslipidaemia ($\chi^2 (1) = 5.136$, $p = 0.023$) and a history of stroke ($\chi^2 (1) = 3.927$, $p = 0.048$). Men were significantly more likely to have IHD ($\chi^2 (1) = 17.196$, $p < 0.001$), peripheral vascular disease ($\chi^2 (1) = 9.451$, $p = 0.002$) and COPD ($\chi^2 (1) = 4.855$, $p = 0.028$).

3.3.5 Prescription medications

A total of 2,110 medications were prescribed regularly to this cohort of 240 patients, with a mean of 8.7 (SD 4.6), range of 0 - 23. Approximately 98% of all participants were prescribed ≥ 1 medication (**Table 3.6**). Polypharmacy (≥ 6 daily medications) and high level polypharmacy (≥ 11 daily medications) were identified in 76.7% and 32.5% respectively. There was no significant difference between the mean number of medications prescribed to men and women, i.e. 8.3 (4.4) and 9.1 (4.7) respectively, $t_{238} = 1.484$, $p = 0.037$. As expected, the number of medications prescribed significantly increased with the level of comorbidity (CIRS), r-statistic 0.582, $p < 0.001$.

Table 3.6: Prescribing according to gender (n=240)

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
Patients taking at least 1 medication	120 (99.2%)	116 (97.5%)	236 (98.3%)	0.305
Medications (regular)				
Mean (SD)	8.3 (4.4)	9.1 (4.7)	8.7 (4.6)	0.637
Range	0 - 23	0 - 23	0 - 23	
1 – 5 medications	32 (26.4%)	21 (17.6%)	53 (22.1%)	0.100
6 – 10 medications	53 (43.8%)	52 (43.7%)	105 (43.8%)	0.987
≥ 11 medications	35 (28.9%)	43 (36.1%)	78 (32.5%)	0.233
≥ 6 medications	88 (72.7%)	96 (80.7%)	184 (76.7%)	0.146

Legend: SD = standard deviation

3.3.6 Medication use according to age

There was no significant difference between the numbers of medications prescribed to patients age 65 – 74 years, 75 – 84 years and those ≥ 85 years, ($\chi^2 (4) = 6.914$, $p = 0.141$) (**Figure 3.9**). There was no significant difference between the proportions of patients that experienced polypharmacy, ($\chi^2 (2) = 1.318$, $p = 0.517$) and high level polypharmacy, ($\chi^2 (2) = 5.149$, $p = 0.076$) according to age groups (**Figure 3.10**).

Figure 3.9: Medication use according to age group

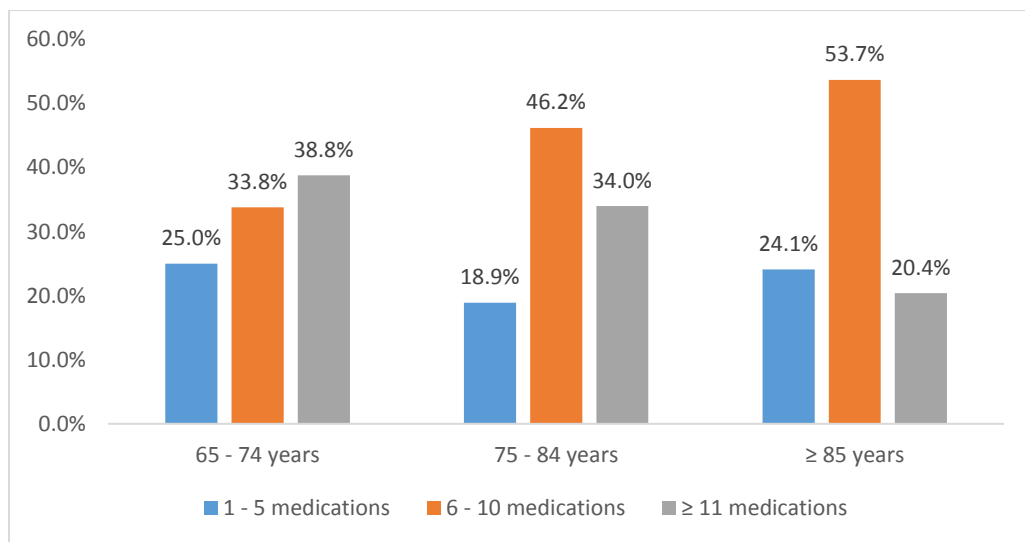
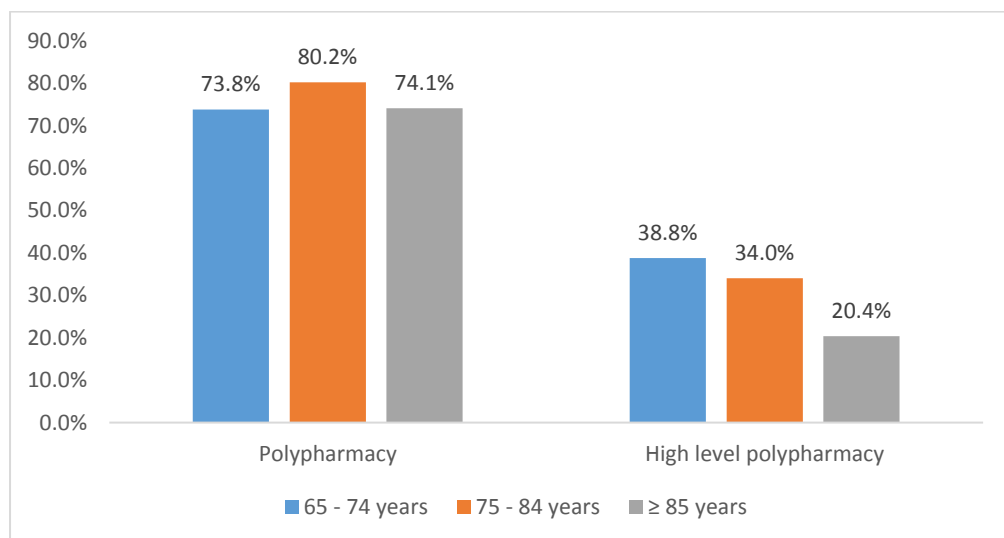


Figure 3.10: Prevalence of polypharmacy and high level polypharmacy according to age



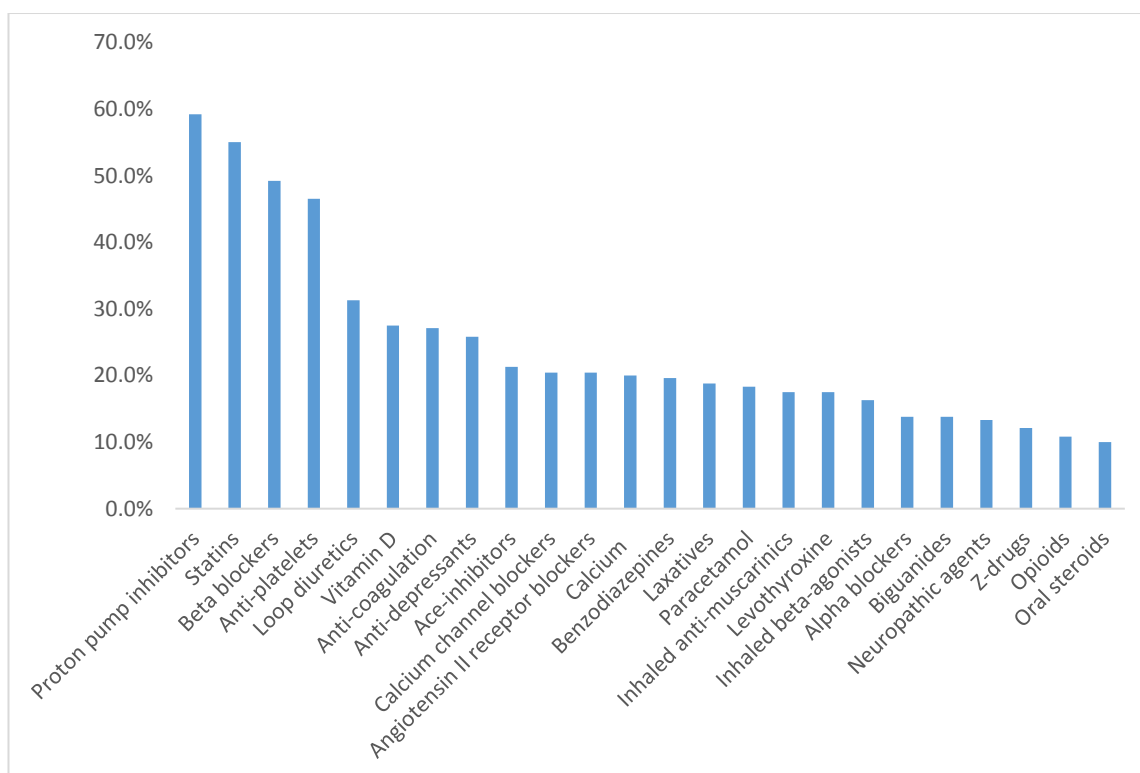
Key Findings 3:

- Approximately 3 of every 4 (76.7%) patients experienced polypharmacy.
- Approximately 1 of every 3 (32.5%) patients experienced high level polypharmacy.

3.3.7 Medication use according to drug class

The most common medications prescribed are displayed in **Figure 3.11**. Approximately 1 in 2 participants were prescribed proton pump inhibitors (PPIs), statins, beta blockers and anti-platelets. Approximately 1 in 3 were prescribed loop diuretics. Approximately 1 in 4 were prescribed vitamin d, anti-coagulation and anti-depressants. Approximately 1 in 5 were prescribed ace inhibitors, calcium channel blockers, angiotensin receptor blockers (ARBs), calcium and benzodiazepines.

Figure 3.11 Drug classes most commonly prescribed (n=240)



3.3.8 Drug class use according to gender

Differences in drug class prescriptions between genders are displayed in **Table 3.7**.

Table 3.7: Most common prescription medications (n=240)

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
Regular prescriptions (in order of frequency)				
1. Proton pump inhibitors	87 (55.4%)	75 (63%)	142 (59.2%)	0.228
2. Statins	89 (57%)	63 (52.9%)	132 (55%)	0.525
3. Beta blockers	58 (47.9%)	66 (50.4%)	118 (49.2%)	0.700
4. Anti-platelets	63 (52.1%)	44 (37%)	107 (44.6%)	0.019*
5. Loop diuretics	39 (32.2%)	36 (30.3%)	75 (31.3%)	0.741
6. Vitamin D	19 (15.7%)	47 (39.5%)	66 (27.5%)	<0.001*
7. Anticoagulants	30 (24.8%)	35 (29.4%)	65 (27.1%)	0.421
Warfarin	13 (10.7%)	21 (17.6%)	34 (14.2%)	0.125
Direct oral anti-coagulants	17 (14%)	14 (11.1%)	31 (12.9%)	0.598
8. Anti-depressants	26 (21.5%)	36 (30.3%)	62 (25.8%)	0.121
SSRIs	17 (14%)	18 (15.1%)	35 (14.6%)	0.813
Tricyclic anti-depressants	6 (5%)	14 (11.8%)	20 (8.3%)	0.056
NASSAs	3 (2.5%)	14 (11.8%)	17 (7.1%)	0.005*
9. ACE inhibitors	32 (26.4%)	19 (16%)	51 (21.3%)	0.047*
10. Calcium channel blockers	20 (16.5%)	29 (24.4%)	49 (20.4%)	0.132
11. Angiotensin receptor blockers	20 (16.5%)	29 (24.4%)	49 (20.4%)	0.132
12. Calcium supplements	14 (11.6%)	34 (28.6%)	48 (20%)	0.001*
13. Benzodiazepines	17 (14%)	30 (25.2%)	47 (19.6%)	0.029*
14. Laxatives	21 (17.4%)	24 (20.2%)	45 (18.8%)	0.577
Osmotic	7 (5.8%)	5 (4.2%)	36 (15%)	0.255
Stimulant	15 (12.4%)	21 (17.6%)	12 (5%)	0.574
Bulk forming	1 (0.8%)	1 (0.8%)	2 (0.8%)	0.991
15. Paracetamol	16 (13.2%)	28 (23.5%)	44 (18.3%)	0.039*
16. Inhaled anti-muscarinics	26 (21.5%)	16 (13.4%)	42 (17.5%)	0.101
17. levothyroxine	15 (12.4%)	27 (22.7%)	42 (17.5%)	0.036*
18. inhaled beta agonists	10 (8.3%)	10 (8.4%)	39 (16.3%)	0.969
19. Alpha blockers	29 (24%)	4 (3.4%)	33 (13.8%)	<0.001*
20. Neuropathic agents	18 (14.9%)	14 (11.8%)	32 (13.3%)	0.478
21. Metformin	15 (12.4%)	18 (15.1%)	33 (13.8%)	0.538
22. Hypnotic Z drugs	13 (10.7%)	16 (13.4%)	29 (12.1%)	0.521
23. Opioids	10 (8.3%)	16 (13.4%)	26 (10.8%)	0.197
Weak opioid	21 (17.4%)	21 (17.6%)	26 (10.8%)	0.953
Strong opioid	12 (9.9%)	7 (5.9%)	19 (7.9%)	0.247
24. Oral corticosteroids	8 (6.6%)	16 (13.4%)	24 (10%)	0.079

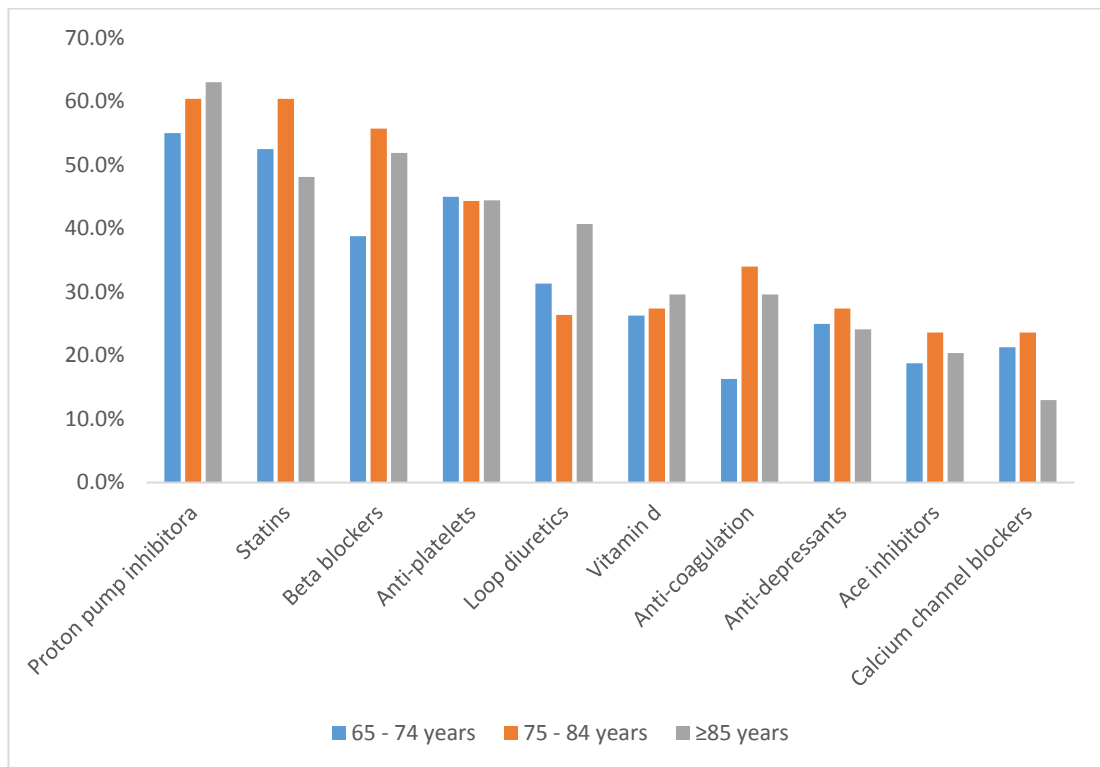
Legend: SSRIs = selective serotonin reuptake inhibitors; NASSAs = Noradrenergic and specific serotonergic anti-depressants;

Men were prescribed significantly more angiotensin converting enzymes (ACE) inhibitors (26.4% vs 16%, $\chi^2 (1) = 3.938$, $p = 0.047$), angiotensin receptor blockers (ARBs) (24.0% vs 3.4%, $\chi^2 (1) = 2.270$, $p < 0.001$) and anti-platelets (52.1% vs 37.0%, $\chi^2 (1) = 5.530$, $p = 0.019$). Women were more commonly prescribed levothyroxine (22.7% vs 12.4%, $\chi^2 (1) = 4.402$, $p = 0.036$), benzodiazepines (25.2% vs 14.0%, $\chi^2 (1) = 4.745$, $p = 0.029$), paracetamol (23.5%) vs 13.2%, $\chi^2 (1) = 4.256$, $p = 0.039$), calcium (28.6% vs 11.6%, $\chi^2 (1) = 10.838$, $p = 0.001$), vitamin d (39.5% vs 15.7%, $\chi^2 (1) = 17.036$, $p < 0.001$) and NASSa (11.8% vs 2.5%, $\chi^2 (1) = 7.859$, $p = 0.005$).

3.3.9 Drug class use according to age category

Differences identified in drug class prescriptions between the different age categories are displayed in **Figure 3.12**. The only drug class in which a significant difference in prescribing rate was shown between the 3 age groups was anti-coagulants, (i.e. 16.3% vs 34% vs 29.6%, $\chi^2 (2) = 7.471$, $p = 0.024$), reflecting significantly higher prevalence of atrial fibrillation in the older age groups compared to patients aged 65 to 74 years.

Figure 3.12 Drug classes most commonly prescribed according to age (n=240)



3.3.10 Medication adherence

Sixty nine percent of patients managed their medications alone, with 46.3% using a blister pack. Nine percent participants admitted to problems of various kinds taking their daily medications, with approximately 15.4% forgetting to take some or all of their medications at least once in the preceding month.

3.3.11 Potentially inappropriate prescriptions as determined by STOPP criteria

STOPP criteria for potentially inappropriate medication (PIM) use were applied to all 240 patients. Four hundred and five prescriptions (19.2%) out of the total of 2,110 prescriptions were potentially inappropriate according to STOPP criteria. These were

distributed amongst 67.5% (n=162) of the study population with 53 patients (22.1%) receiving 1 PIM, 43 patients (17.9%) receiving 2 PIMs and 66 patients (27.5%) receiving ≥ 3 PIMs. An increasing number of daily medications number was significantly associated with increasing PIM number ($R = 0.644$, $p < 0.001$).

The most frequently encountered PIMs identified by STOPP criteria are listed in order of descending frequency in **Table 3.8**. More than 1 in 3 participants (41.3%) were prescribed a drug beyond the recommended duration. Approximately 1 in 4 (24.8%) participants were prescribed a PPI for uncomplicated PUD/erosive oesophagitis at full therapeutic dosage for more than 8 weeks. One in five (20%) participants were prescribed a drug without an evidence-based clinical indication. Over 1 in 6 participants (17.6%) were prescribed a benzodiazepine for ≥ 4 weeks. A similar proportion of patients who were at risk of falls were prescribed a benzodiazepine (15.4%). **Table 3.8** displays the most prevalent PIMs in the patient as a whole and also according to gender. Females were more likely than males to be inappropriately prescribed anti-cholinergic drugs in the context of delirium or dementia i.e. 6.7% vs 1.7%, $\chi^2(1) = 3.862$, $p = 0.049$. Criteria STOPP A2 (Any drug prescribed beyond the recommended duration) was based on BNF indications and up to date clinical guidelines.

Table 3.8: Most common potentially inappropriate medications (PIMs) according to STOPP criteria according to gender

STOPP criteria (code & descriptor)	Male n = 121	Female n = 119	Total n = 240	P-value
A2: Any drug prescribed beyond recommended duration	50 (41.3%)	49 (41.2%)	99 (41.3%)	0.982
F2: PPI for uncomplicated PUD/erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	33 (27.3%)	26 (21.8%)	59 (24.6%)	0.329
A1: Any drug prescribed without an evidence-based clinical indication	24 (19.8%)	24 (20.2%)	48 (20%)	0.949
D5: Benzodiazepines for ≥ 4 weeks	16 (13.2%)	27 (22.7%)	43 (17.9%)	0.056
K1: Benzodiazepines (those at $\uparrow$ risk of falls)	15 (12.4%)	22 (18.5%)	37 (15.4%)	0.191
L2: Use of regular opioids without concomitant laxative	12 (9.9%)	15 (12.6%)	27 (11.3%)	0.510
K4: Hypnotic Z-drugs (those at $\uparrow$ risk of falls)	13 (10.7%)	13 (10.9%)	26 (11.3%)	0.964
A3: Any duplicate drug prescription	11 (9.1%)	14 (11.8%)	25 (10.4%)	0.498
F3: Drugs likely to cause constipation in patients with chronic constipation	10 (8.3%)	7 (5.9%)	17 (7.1%)	0.472
B6: Loop diuretic as first-line treatment for HTN	5 (4.1%)	8 (6.7%)	13 (5.4%)	0.375
D2: Initiation of TCAs as first-line antidepressant treatment	6 (5%)	10 (8.4%)	16 (6.7%)	0.285
D14: First generation anti-histamines	7 (5.8%)	7 (5.9%)	14 (5.8%)	0.974
D10: Neuroleptics as hypnotics	8 (6.6%)	4 (3.4%)	12 (5%)	0.248
K2: Neuroleptic drugs (those at $\uparrow$ risk of falls)	6 (5%)	5 (4.2%)	11 (4.6%)	0.779
D8: Anti-cholinergic drugs in patients with delirium or dementia	2 (1.7%)	8 (6.7%)	10 (4.2%)	0.049*
K3: Vasodilator drugs (with persistent postural hypotension)	7 (5.8%)	3 (2.5%)	10 (4.2%)	0.206

3.3.12 Risk Factors for receiving a potentially inappropriate medication according to STOPP criteria.

Differences were identified between participants who were prescribed PIMs and those who were not prescribed PIMs (**Table 3.9**). Males and females were equally likely to be prescribed a PIM ($\chi^2 (1) = 0.544$, $p = 0.461$), as were all age groups ($\chi^2 (2) = 1.373$, $p = 0.503$). Patients prescribed PIMs had more chronic conditions (median 9.5 (IQR7-12) vs median 6 (IQR3.75-9), $U = 3987$, $p < 0.001$), a higher median CIRS score (17 (13-21) vs 11 (8 – 17), $U = 3638.5$, $p < 0.001$) and were prescribed a high median number of daily medications (10 (IQR7-13) vs 5 (IQR2-7), $U = 2254$, $p < 0.001$). As expected, the number of PIMs significantly increased with the number of treated conditions ($R = 0.455$, $p < 0.001$), the number of daily prescription medications ($R = 0.644$, $p < 0.001$) and with the CIRS score ($R = 0.318$ $p < 0.001$).

Table 3.9: Comparison between older adults prescribed at least 1 potentially inappropriate medication (PIM) and older adults prescribed no PIM

Variable	PIMs (n=162)	No PIMs (n=78)	Total n = 240	P-value
Gender (female)	85 (51.8%)	36 (46.2%)	119 (49.6%)	0.461
Age, median (IQR)	78 (73-84)	76 (70-84)	78 (72-80)	0.270
Range	65 - 99	65 - 93	65 - 99	
Chronic conditions, median (IQR)	9.5 (7-12)	6 (3.75-9)	8 (6-12)	<0.001*
Range	1 - 20	1 - 18	1 - 20	
Treated chronic conditions, median (IQR)	6 (5-8)	4 (2-6)	6 (4-8)	<0.001*
Range	1 - 17	0 - 12	0 - 17	
CIRS score, median (IQR)	17 (13-21)	11 (8-17)	16 (11 – 19.75)	<0.001*
Range	0 - 30	0 - 28	0 - 30	
Medications, median (IQR)	10 (7-13)	5 (2-7)	8.5 (9-12)	<0.001*
Range	1 - 23	0 - 15	0 - 23	

Legend: IQR = Inter quartile range, CIRS = Cumulative Illness rating scale

Logistic regression was used to determine the influence of age, gender, chronic conditions, burden of co-morbidities as defined by CIRS score and number of medications on the likelihood of receiving a STOPP-defined PIM; the results are detailed in **Table 3.10**.

Table 3.10: Risk factors for receiving a PIM according to STOPP criteria

Variable	B (SE)	Wald	df	p-value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Female	.101 (.350)	.083	1	0.773	1.106	0.557	2.196
Age	.033 (.023)	2.112	1	0.146	1.034	0.988	1.081
Meds	.347 (.069)	25.536	1	<0.001*	1.415	1.237	1.619
Cond	.065 (.077)	.707	1	0.400	1.067	0.917	1.242
CIRS	-.023 (.051)	.206	1	0.650	0.977	0.885	1.079
Constant	-4.784 (1.872)	6.528	1	0.011	0.008		

Legend: Hosmer and Lemeshow, $\chi^2(8) \geq 9.918$, $p=0.552$; B = beta value; Snell $R^2=0.285$; Nagelkerke $R^2 = 0.398$; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio; meds = number of daily prescription medications; cond = conditions, CIRS = cumulative index rating scale.

The only factor associated with a significantly increased risk of receiving a PIM was the number of daily prescribed medications, when all other variables are kept at a constant. For every additional medication prescribed, the odds of receiving a PIM increased by 41.5% (Odds ratio 1.415, 95% CI 1.237 – 1.619, $p < 0.001$).

Key Findings 4:

- Two out of every three (67.5%) adults' ≥ 65 years were prescribed at least one PIM according to STOPP criteria.
- Adults' receiving at least 1 PIM had a significantly higher number of conditions, had a significantly higher burden of co-morbidities and were prescribed a higher number of medications.
- For every one medication prescribed, the odds of receiving a PIM increased by 41.5%.

3.3.13 Potentially prescribing omissions as determined by START criteria

START criteria were applicable to 170 of the 240 participants (70.8%). For the remaining 80 participants, a more palliative approach to pharmacotherapy was appropriate i.e. starting medications would have been inappropriate. Over 1 in 2 (52.9%) of participants were identified as having a potentially prescribing omissions (PPO), with 53 patients (31.2%) having 1 PPO, 24 patients (14.1%) having 2 PPOs and 13 patients (7.6%) having ≥ 3 PPOs. There was no significant difference identified between the numbers of PPOs according to gender ($\chi^2(3) = 3.435$, $p = 0.329$). The most frequently encountered PPOs identified by START criteria are listed in **Table 3.11**.

Approximately 1 in 8 patients (12.4%) were not prescribed ACE inhibitors with systolic heart failure and/or coronary artery disease. Approximately 1 in 12 (8.4%) were not prescribed bone anti-resorptive or anabolic therapy with known osteoporosis. Approximately 1 in 13 patients (7.6%) were not prescribed vitamin D and calcium with known osteoporosis or vitamin D when housebound or experiencing falls. Approximately 1 in 16 (6.5%) were not prescribed beta blockers with known ischaemic heart disease.

Table 3.11: Most common PPOs according to START criteria

START criterion	Male n = 80	Female n = 90	Total n = 170	P-value
A6: ACE inhibitor with systolic heart failure and/or coronary artery disease	13 (16.3%)	8 (8.9%)	21 (12.4%)	0.145
E4: Bone anti-resorptive or anabolic therapy in patients with osteoporosis	6 (7.5%)	8 (8.9%)	14 (8.2%)	0.742
E3: Vitamin D and calcium in patients with known osteoporosis	5 (6.3%)	8 (8.9%)	13 (7.6%)	0.518
E5: Vitamin D in older adults who are housebound or experiencing falls	7 (8.8%)	6 (6.7%)	13 (7.6%)	0.610
A7: Beta blocker with ischaemic heart disease	7 (8.8%)	4 (4.4%)	11 (6.5%)	0.255
A1: Vitamin K antagonists or DOACs in the present of atrial fibrillation	5 (6.3%)	5 (5.6%)	10 (5.9%)	0.848
A5: Statin therapy with a history of coronary, cerebral or peripheral vascular disease	6 (7.5%)	2 (2.2%)	8 (4.7%)	0.105
D2: Fibre supplements for diverticulosis with a history of constipation	2 (2.5%)	6 (6.7%)	8 (4.7%)	0.200
F1: ACE inhibitor or Angiotensin Receptor Blocker in diabetes with evidence of renal disease with or without serum biochemical renal impairment	5 (6.3%)	3 (3.3%)	8 (4.7%)	0.370
E6: Xanthine-oxidase inhibitors with a history of recurrent episodes of gout	3 (3.8%)	4 (4.4%)	7 (4.1%)	0.820
A8: Appropriate beta blockade with stable systolic heart failure	3 (3.8%)	3 (3.3%)	6 (3.5%)	0.883
B1: Regular inhaled β_2 agonist or anti-muscarinic bronchodilator for mild to moderate asthma or COPD	3 (3.8%)	3 (3.3%)	6 (3.5%)	0.883
G2: 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy unnecessary	5 (6.3%)	0 (0%)	5 (2.9%)	N/A
H2: Laxatives in patients receiving opioids regularly	1 (1.3%)	4 (4.4%)	5 (2.9%)	0.219

3.3.14 Risk factors for potentially prescribing omissions according to START criteria

No significant differences were identified between participants who had a PPO and those who did not (**Table 3.12**).

Table 3.12: Comparison between older adults experiencing one potential prescribing omission according to START criteria and older adults not

Variable	PPOs (n=90)	No PPO (n=80)	Total n = 170	P- value
Gender (female)	44 (48.9%)	46 (57.5%)	119 (49.6%)	0.725
Age, median (IQR)	76 (70.75-84)	77 (70.25-81.25)	78 (72-84)	0.858
Range	65 - 93	65 – 99	65 - 99	
Chronic conditions, median (IQR)	8 (6-11)	6 (4–9)	8 (6-12)	0.215
Range	1 - 18	1 – 16	1 - 20	
CIRS score, median (IQR)	15 (10-18)	11.5 (9-15)	16 (11-19.75)	0.498
Range	0 - 29	1 – 27	0 - 30	
Medications, median (IQR)	8 (4.75-11)	7 (5-11)	8.5 (8-12)	0.228
Range	0 - 19	0 – 18	0 - 23	

Key findings 5:

- Approximately 1 of every 2 (52.9%) adults' ≥ 65 years were identified as having one PPO as determined by START criteria.
- No significant differences were identified between adults having a PPO and those not.

3.3.15 Adverse drug reactions (ADR) prevalence rates

A total of 284 adverse events (AEs) were identified in 161 (67.1%) of the 240 patients. One hundred and two AEs were drug-related in 53 (22.1%) of the 240 patients enrolled (**Table 3.13**). ADRs directly caused hospitalisation in 17.1% (n=41) and contributed significantly for 5% (n=12) of all patients enrolled. The **AE Trigger List**

identified 79.3% (n = 43) of all ADRs. The remaining 11 ADRs are shown in **Table 3.14**.

As discussed in Chapter 2, all ADRs were viewed as processes rather than discrete events e.g. a person who fell more than once as a result of adverse medication was classified as having had one ADR only.

Table 3.13: Adverse event (AE) conversion to adverse drug reaction (ADR)

AE description	AE incidence (% of total)	Number of ADRs represented by AE
New onset fall/s	55 (19/4%)	16 (5.6%)
New onset unsteady gait	1 (0.4%)	1 (0.4%)
Acute kidney injury	32 (11.3%)	12 (4.2%)
Symptomatic orthostatic hypotension	7 (2.5%)	6 (2.1%)
Major serum electrolyte disturbance	44 (15.5%)	14 (5%)
Symptomatic bradycardia	2 (0.7%)	1 (0.4%)
New major constipation	11 (3/9%)	2 (0.7%)
Acute bleeding	20 (7%)	10 (3.5%)
Acute dyspepsia / nausea / vomiting	33 (11.6%)	11 (3.9%)
Acute diarrhoea	16 (5.6%)	2 (0.8%)
Acute delirium	48 (16.9%)	15 (5.3%)
Symptomatic hypoglycaemia	2 (0.7%)	1 (0.4%)
Other (unspecified)	13 (4.6%)	11 (3.9%)
Total Number	284	102
Number of patients involved	161	53

Table 3.14: ADRs not identified by the 12 point *AE Trigger List*

ADRs not identified by the <i>Trigger List</i> (n=11)	
Seizure following withdrawal of anti-epileptic drugs (carbamazepine and levetiracetam)	2
Parkinsonism following recently introduced haloperidol	1
Diabetic ketoacidosis secondary to cessation of long acting insulin (levemir)	1
Anaphylaxis following moxifloxacin	1
Exacerbation of cardiac failure following withdrawal of furosemide	1
Chest pain and atrial fibrillation following ingestion of supra-therapeutic daily dose of pseudoephedrine for 3 days	1
Extreme pain following abrupt withdrawal of fentanyl	1
Urinary retention following withdrawal of tamsulosin	1
Type two respiratory failure and pneumonia following commencement of daily alprazolam that caused drowsiness	1
Relapse of unstable angina following aspirin cessation	1

Key Findings 6:

- Approximately 1 in 5 (22.1%) adults' ≥ 65 years are admitted secondary to an ADR.
- For approximately 1 in 6 (17.1%) an ADR directly causes admission.
- For approximately 1 in 20 (5%) an ADR contributes significantly to admission.
- The 12 point **AE Trigger List** identified 79.3% (4 in every 5) ADRs.

3.3.16 Type of adverse drug reactions

The primary ADRs, as defined by the **AE Trigger List**, are displayed in **Table 3.15**.

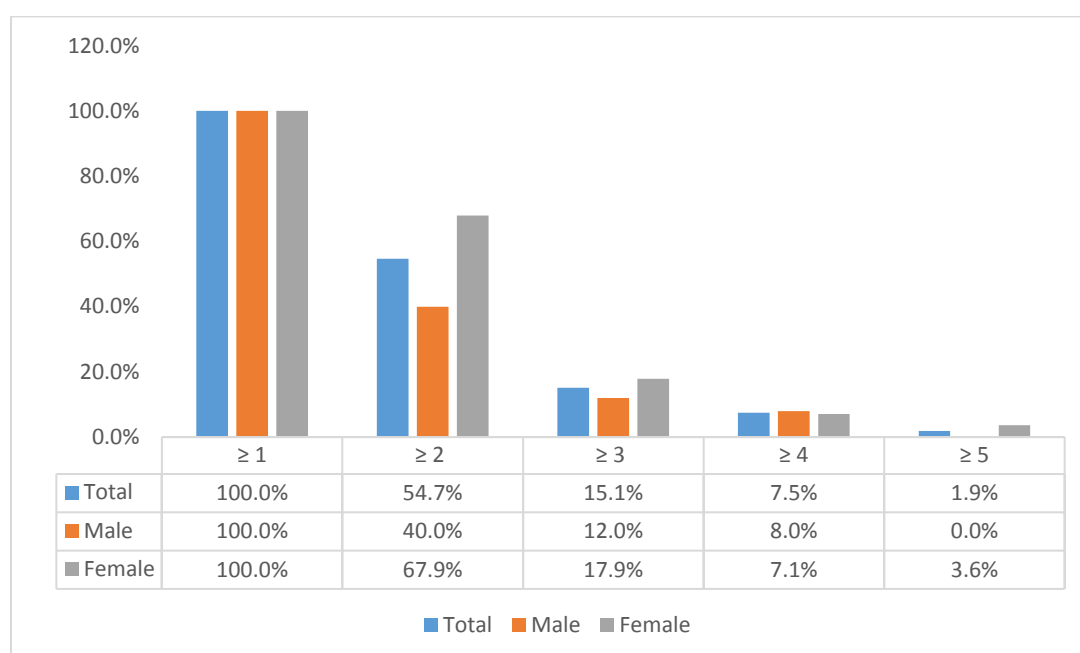
Table 3.15: Types of primary ADR *in order of frequency*.

Variable	Male n = 121	Female n = 119	Total n = 240	P-value
1. Unspecified	7 (5.9%)	4 (3.4%)	11 (4.6%)	0.266
2. Bleeding	4 (3.3%)	4 (3.4%)	8 ((3.3%)	
3. New onset fall/s	5 (4.1%)	1 (0.8%)	6 (2.5%)	
4. Severe electrolyte disturbance	2 (1.7%)	4 (3.4%)	6 (2.5%)	
5. Delirium	2 (1.7%)	4 (3.4%)	6 (2.5%)	
6. Dyspepsia/nausea/vomiting	1 (0.8%)	4 (3.4%)	5 (2.1%)	
7. Symptomatic orthostatic hypotension	1 (0.8%)	4 (3.4%)	5 (2.1%)	
8. Severe constipation	1 (0.8%)	1 (0.8%)	2 (0.8%)	
9. Acute kidney injury	2 (1.7%)	0 (0%)	2 (0.8%)	
10. Diarrhoea	0 (0%)	1 (0.8%)	1 (0.4%)	
11. Symptomatic bradycardia	0 (0%)	1 (0.8%)	1 (0.4%)	

Twenty nine of the 53 participants (54.7%) who experienced an ADR experienced a **Sequence of Events** e.g. severe vomiting leading to an acute kidney injury and severe electrolyte disturbance. The number of patients who experienced **Sequence of Events** can be seen in **Figure 3.13**. Women were significantly more likely to experience **Sequence of Events** as a consequence of a medications, (67.9% vs 40%, $X^2(1) = 4.137$, $p = 0.042$). Men and women were equally likely to experience the same

type of ADRs ($\chi^2(10) = 12.288$, $p = 0.266$). There was no significant difference in the prevalence rate of ADRs experienced across the 3 age groups of 65 – 74 years, 75 – 84 years and 85 years and older, ($\chi^2(20) = 20.809$, $p = 0.408$).

Figure 3.13: Percentage of patients who experienced ADRs who had a sequence of one or more adverse events (n=53).



Key findings 7:

- The three most common ADRs experienced were bleeding, falls and electrolyte disturbances.
- Approximately 1 in 2 participants (54.7%) who experienced an ADR had a Sequence of Events.
- Women were significantly more likely to experience a Sequence of Events

3.3.17 Adverse drug reaction causality

As per the WHO-UMC causality criteria, medication probably/certainly caused or contributed significantly to admission in 53 (22.1%) cases. The medications implicated are listed, in order of frequency, in table 3.16.

Table 3.16: Drug classes involved in ADRs

	Drug class	Total (n=53)
1	Opioids	7 (13.2%)
2	Direct oral anti-coagulants (DOACs)	6 (11.3%)
3	Benzodiazepines	4 (7.5%)
4	Aldosterone antagonists	3 (5.7%)
5	Antibiotics	3 (5.7%)
6	Neuroleptics	3 (5.7%)
7	Loop diuretics	3 (5.7%)
8	Anti-epileptic drugs	3 (5.7%)
9	Selective α_1 - alpha blockers	2 (3.8%)
10	Thiazide diuretic	2 (3.8%)
11	Anti-platelets	2 (3.8%)
12	Non-adrenergic and specific serotonergic anti-depressants	2 (3.8%)
13	Z-drug (hypnotics)	1 (1.9%)
14	Anti-cholinergic	1 (1.9%)
15	Selective serotonin reuptake inhibitors	1 (1.9%)
16	Anti-coagulants (warfarin)	1 (1.9%)
17	Corticosteroids	1 (1.9%)
18	Insulin	1 (1.9%)
19	Non-steroidal anti-inflammatories	1 (1.9%)
20	Metformin	1 (1.9%)
21	Beta blocker	1 (1.9%)
22	Angiotensin converting enzyme-inhibitors	1 (1.9%)
23	Anti-histamines	1 (1.9%)
24	Decongestant (pseudoephedrine)	1 (1.9%)
25	Laxatives	1 (1.9%)

3.3.18 Adverse drug reaction severity, predictability and preventability

Of the 53 ADRs causing or contributing significantly to acute index admission, 6 ADRs (11.3%) were grade 5 on the Hartwig & Siegel scale of severity i.e. they required intensive medical treatment. The remaining 47 ADRs (88.7%) were Hartwig & Siegel graded 4 i.e. for the direct cause of the admission or increased length of stay by ≥ 1 day. Forty-five (84.9%) of the ADRs were predictable according to the SPC guidelines of the individual medications in question. Using Hallas ADR avoidability criteria, 24

ADRs (45.3%) were definitely avoidable, 24 ADRs (45.3%) possibly avoidable and 5 ADRs (9.4%) unavoidable.

3.3.19 Adverse drug reaction risk factors and outcomes

A comparison of patients who did and did not experience ADRs is shown in **Table 3.17**. Adults who experienced ADRs had a higher burden of co-morbid illness as defined by their CIRS scores ($U = 4069.5$, $p = 0.047$), were prescribed a higher number of medications ($U = 3751$, $p = 0.007$) and were more likely to die during the index admission ($\chi^2 (1) = 6.05$, $p = 0.014$).

Table 3.17: Comparison between older patients experiencing ADRs and patients not experiencing ADRs

Variable	ADRs (n=53)	No ADRs (n=187)	Total n = 240	P-value
Gender (female)	28 (52.8%)	91 (48.7%)	119 (49.6)	0.592
Age, median (IQR)	81 (72.5-84.5)	77 (72.84)	78 (72-84)	0.329
Range	65 - 94	65 - 99	65 – 99	
Chronic conditions, median (IQR)	10 (7-12)	8 (6-12)	8 (6-12)	0.107
Range	3 - 18	1 - 20	1 – 20	
CIRS score, median (IQR)	18 (12 – 21)	15 (10-18)	16 (11-19.75)	0.047*
Range	3 - 30	0 - 30	0 - 30	
Medications, median (IQR)	10 (7-13)	8 (5-11)	8.5 (6-12)	0.007*
Range	2 - 30	0 – 23	0 – 23	
Length of stay, median (IQR)	8 (4.5-14.5)	7 (3-14)	8 (3-13.75)	0.279
Range	1 - 43	0 – 101	0 – 101	
Death during index hospital admission	5 (12.2%)	4 (2.8%)	9 (4.9%)	0.014*

Logistic regression analysis was used to determine the influence of age, gender, number of conditions, burden of co-morbid illness and number of medications on the risk of experiencing an ADR. The results are detailed in **Table 3.18**.

Table 3.18: Risk factors for experiencing an ADR

Variable	B (SE)	Wald	df	p-value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Female	-.091 (.325)	.078	1	0.780	.913	.913	1.726
Age	.023 (.022)	1.155	1	0.282	1.024	.981	1.068
Meds	.098 (.047)	4.399	1	0.036*	1.103	1.006	1.210
Cond	-.037 (.065)	.326	1	0.568	.964	.849	1.094
CIRS	.018 (.041)	.197	1	0.657	1.018	.936	1.104
Constant	-3.893 (1.755)	4.921	1	0.027			

Legend: Hosmer and Lemeshow, $\chi^2(5) \geq 9.704$, $p=0.271$; B = beta value; Snell $R^2=0.034$; Nagelkerke $R^2 = 0.053$; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio; Meds = medications; Cond = number of conditions; CIRS = cumulative index rating scale

The only factor significantly and independently associated with an increased risk of ADRs was the number of medications a patient was prescribed, when all other variables are kept at a constant. For every extra medication prescribed, the odds of experiencing an ADR increased by 10.3% (Odds ratio 1.103, 95% CI 1.006 – 1.210, $p < 0.001$).

3.4 DISCUSSION

The present study is one of the first to use this novel standardized approach to identifying, classifying and reporting ADRs in older people. This study has also characterized the current older adult population presenting with acute unselected illness to hospital in terms of multimorbidity, medication use and potentially inappropriate prescribing.

Almost half (44.2%) of these older adults presenting to hospital were ≥ 80 years old and more than 1 in 5 (22.5%) were aged ≥ 85 years old. Approximately 1 in 3 older adults had a moderate to high level functional dependency. In addition,

approximately 1 in 5 had moderate to severe dementia and in a further 1 in 5 patients, delirium was evident at the time of presentation to hospital. Applying the Rockwood Clinical Frailty Scale, approximately 1 in 4 patients were severely frail, very severely frail or terminally ill.

Multimorbidity was identified in almost all patients (98.8%), with 84% of patients having ≥ 5 chronic medical conditions. Two in five older adults had atrial fibrillation and IHD, 1 in 3 had symptomatic osteoarthritis and constipation, 1 in 4 had heart failure, diabetes mellitus, COPD or chronic kidney disease and 1 in 5 had osteoporosis, hypothyroidism or urinary incontinence. These results illustrate the higher rates of multimorbidity encountered in hospitalised older adults compared to clinically stable older adults living in the community.

Approximately 3 out of 4 (76.7%) patients experienced polypharmacy (≥ 6 medications) and 1 in 3 (32.5%) experienced high level polypharmacy (≥ 11 medications). Further analysis shows that approximately 1 in 2 patients were prescribed a PPI, statin, beta blocker or loop diuretic. One in four were prescribed vitamin D, anti-coagulants and anti-depressants. Lastly, 1 in 5 were prescribed an ACE-inhibitor, ARB, calcium channel blocker or benzodiazepine. One in 10 (9%) patients had problems taking their daily medications and 1 in 3 required another person to oversee the management of same. 1 in 6 (15.4%) had forgotten to take some or all of their daily medications in the month preceding admission. Considering the extent of multimorbidity generally and cognitive impairment specifically in this patient cohort, these findings of problematic or impaired medication adherence are not surprising.

Potentially inappropriate prescribing was evident in two-thirds (67.5%) of the patients studied. Less than half (41.3%) of the patients were taking at least one drug beyond the recommended duration, 24.8% of patients were on a potentially inappropriate high dose of PPI drug for 8 weeks or more with uncomplicated disease and 20% of patients were prescribed a drug without any clear clinical indication. In addition, 17.6% of patients were prescribed a benzodiazepine for ≥ 4 weeks and 15.4% of patients were prescribed a benzodiazepines whilst simultaneously being at risk of falls. Those who were prescribed at least 1 PIM had a higher burden of co-morbid illness and were prescribed a higher number of medications than patients who were not prescribed PIMs. For every extra medication prescribed, the odds of receiving a PIM increased by 41.5%.

Approximately 1 in every 2 (52.9%) patients were prescribed ≥ 1 PPO. One in eight (12.4%) patients were not prescribed an ACE inhibitor with a known diagnosis of heart failure of coronary heart disease and 1 in 12 (8.4%) were not prescribed anti-resorptive medication with known osteoporosis, where no contraindications to these medications existed.

ADRs caused or contributed to acute admission in approximately 1 in 5 (22.1%) older adults. The ***AE Trigger List*** identified 79.3% of all verified ADRs. The most common ADRs reported were bleeding, falls and electrolyte disturbances. Approximately 1 in 2 (54.7%) patients who experienced an ADR had a ***Sequence of Events***, with women significantly more likely to experience this adverse sequence than their male counterparts (67.9% vs 40%). This is the first time this ***AE Trigger List*** approach has been used to classify ADR morbidity.

The three drugs most commonly implicated in ADRs were opioids (13.2%), direct oral anti-coagulants (11.7%) and benzodiazepines (7.5%). Forty-five (84.9%) of ADRs were predictable, with 45.3% (n = 24) ADRs definitely avoidable and 45.3% (n = 24) possibly avoidable. Those who experienced ADRs had a higher burden of co-morbid illness, were prescribed more medications and more likely to die during the index admission than patients who did not experience ADRs. For every extra medication prescribed, the odds of experiencing an ADR increased by 10.3%.

These results demonstrate that a significant proportion of older adults presenting with acute unselected illness to hospital for admission are over 80 years and are often highly frail and multimorbid with cognitive and functional impairment, consistent with the changing population demographic profile, as predicted by the NCPOP (2), Eurostat (3) and WHO (4). Importantly, despite most of these older adults being multimorbid and having significant complex care needs, just 1 in 8 (12.5%) were admitted to the specialist Geriatric Medicine service. This emphasizes the need for all doctors practising in all specialties who care for acutely ill older patients to have continued postgraduate education in managing the pharmacotherapy of older adults. This education need is likely to grow as the general population in Ireland and elsewhere expands.

This study confirms what has already been reported in other studies in Ireland (45-47, 167) i.e. that many older adults presenting to hospital are prescribed at least one PIM and thus at risk of ADRs. Hospitalisation is an opportune time to optimise prescribing in a high risk population, through comprehensive geriatric assessment (CGA) and IP screening tools. However, there are currently no explicit IP criteria

designed to guide prescribing in frail multimorbid adults with a poor one year survival prognosis.

The ability of patients to adhere to prescribed medications is a key consideration in medication review of frailer, multimorbid older people. The present study identified that at least 1 in 10 older adults experience serious problems taking their medications according to SHiM assessment and are therefore likely to have reduced medication benefit. This is not a new finding, but it is consistent with previous studies of medication adherence in the multimorbid older patient population (168, 169).

The ADR prevalence rate at admission to hospital reported here (22.1%) is consistent with the most recent observational studies on ADRs causing hospitalisation conducted at CUH, in which the reported prevalence rate ranges from 21.0% to 26.3% (46, 74). The ADR prevalence in multimorbid acutely ill older people reported in the CUH studies is significantly higher than in most other studies. A recent systematic review by Alhawassi *et al.* (144) of the prevalence and risk factors for ADRs in older people in the acute care setting indicated a median ADR prevalence of 10%. Using the **AE Trigger List** in the present study, as well as rigorous approach to ADR assessment, resulted in detection of approximately twice as many prevalent ADRs as reported by Alhawassi *et al.* Serious under detection of ADRs in acutely ill frailer multimorbid older people has serious clinical ramifications and supports the case for routine scrutiny of **AE Trigger List** events as possible ADRs and follow-up rigorous structured medication review by appropriately trained medical and pharmacist staff in the hospital setting.

The ***AE Trigger List*** highlighted 4 in 5 verified ADRs in the present study. The ***AE Trigger List*** also allowed capture of sequential morbidity associated with ADRs i.e. one ***Trigger List*** ADR leading to further ***Trigger List*** ADRs. The present study shows that in more than half (54.7%) of the patients who experience a primary ADR, there were ≥ 1 further ADR that was directly related to the primary ADR. For 1 in 7 patients (15.1%), there was a sequence of 3 events and for 1 in 13 (7.5%), this progressed to 4 sequential, related ADRs. Women are more prone to this sequence phenomenon than men, highlighting the importance of early detection of ADRs early to prevent further ADR-related problems.

There were some limitations with this study. Firstly, patients were only recruited to the study on one admission, and thus it is possible that ADRs causing readmission were missed. Secondly, only one person assessed patients, their case records and laboratory data for evidence of ADR occurrence. Ideally, all putative ADRs would be corroborated by a second trained assessor in an unbiased manner as suggested in Chapter 2. Thirdly, prevalent ADR assessment took place in one clinical setting only. Evaluation of older frailer multimorbid patients in other settings, such as ambulatory assessment units, primary care and nursing home care would be important for comparison with similar older patients in the acute hospital setting.

CHAPTER 4:

Prevalence of multimorbidity, potentially inappropriate prescribing and
adverse drug reactions (ADRs) in patients with cancer

4.1 INTRODUCTION

Between 2010 and 2030, the incidence of cancer in older adults is expected to increase from 61% to 70% (20), coinciding with an ageing population (2-4). The demand for cancer treatment services in older patients is also likely to increase concomitantly. However, cancer may be only one of several complex diagnoses in an older individual. These, coupled with co-existing polypharmacy, cognitive and functional impairments can present the treating clinician with challenging therapeutic and ethical dilemmas.

4.1.1 Multimorbidity in patients with cancer

Multimorbidity, defined as the co-occurrence of two or more chronic medication conditions in one person (10), is highly prevalent in the general (non-cancer) older population; prevalence rates of 50% in those aged ≤ 65 years and 80% in those ≥ 80 years have been reported (13). To date, there has been a relative paucity of research into the burden of co-morbid illnesses in patients with cancer. Wedding *et al.* reported multimorbidity rates of 51% in patients with cancer aged < 65 years and 76% in patients with cancer aged ≥ 65 years (170).

Data from insurance company databases identifies multimorbidity in two thirds of patients with cancer, with older adults with cancer having a higher rate of co-morbid illness than their age-matched controls (171-173). However, the reliability of these data is likely to be limited by the accuracy of patient recall and precision of data input. Studies of medication use in patients with cancer have identified a high

prevalence of co-morbid illnesses (see **Table 4.1**). However, specific prospective studies investigating the burden of multimorbidity in older patients are lacking.

Table 4.1: Multimorbidity in patients with cancer

Author	Year	Country	n	Age (years)	Clinical conditions
Riechelmann RP <i>et al</i> (174)	2007	Canada	405	Median 58 (IQR 21-88)	Median 1 (IQR 0-5)
Sokol KC <i>et al</i> (175)	2007	US	100	Mean 78 (r 70-90)	Mean 3
Puts MT <i>et al</i> (176)	2009	Canada	112	Mean 74.2 (SD6)	48.2% 1 or 2 31.2% ≥ 3
Prithviraj GK <i>et al</i> (177)	2012	Canada	117	Mean 74.6 (SD6.9)	0 – 4 (55%) ≥ 5 (45%)
Saarelainen LK <i>et al</i> (178)	2014	Australia	385	Mean 76.7 (SD4.8) All ≥ 70 years	CCI 0 -2 (66.5%) CCI ≥ 3 (33.5%)
Nightingale G <i>et al</i> (179)	2015	US	234	Mean 80	Mean 7.69
Alkan A <i>et al</i> (180)	2017	Turkey	445	Mean 75 (SD60-89) All ≥ 65 years	76.6% multi-morbid

Legend: IQR = Interquartile range; SD = Standard deviation; CCI = Charlson Co-morbidity Index.

4.1.2 Medication use in patients with cancer

It is well established that increasing levels of co-morbid illness correlates with increasing numbers of prescribed medications (181). Unsurprisingly, polypharmacy, commonly defined as ≥ 5 or (23) ≥ 6 medications (25), is reported to be as frequent in patients with cancer as those without (182), though robust data on the prevalence and impact of polypharmacy in older patients with cancer are limited. **Table 4.2** highlights studies of medication use, including the prevalence of potentially inappropriate medications (PIMs) in older patients with cancer. The prevalence of polypharmacy in patients with cancer is reported to range from 35% to 80%. The proportions of patients prescribed at least one PIM is reported to be between 21% and 41%, Beers criteria being used most commonly to identify PIMs (65, 66).

Table 4.2: Medication use and prevalence of PIMs in patients with cancer

Author	Year	Country	n	Age (years)	Medications	PIMs
Riechelmann RP <i>et al.</i> (174)	2007	Canada	405	Median 58 (IQR 21-88)	Median 5 (r 0 -23)	-
Sokol KC <i>et al.</i> (175)	2007	US	100	Mean 78 (r 70-90)	Mean 9	-
Puts MT <i>et al.</i> (176)	2009	Canada	112	Mean 74.2 (SD6)	Median 5 (IQR 3-9)	47.6% moderate or severe DIs
Flood KL <i>et al.</i> (173)	2009	US	47	Mean 73.5	-	21% ≥ 1 PIM (Beers) (64)
Cashman <i>et al.</i> (184)	2010	UK	100	Median 73.5 (IQR65-88)	Median 7 (IQR 1-17)	-
Jorgensen TL <i>et al.</i> (185)	2012	Denmark	24,808	47% ≥ 70	≥ 5 meds 35% ≥ 70 , 39% ≥ 80 41% ≥ 90	-
Prithviraj GK <i>et al.</i> (177)	2012	Canada	117	Mean 74.6 (SD6.9)	Mean 7 (r 0 -17) 80% ≥ 5 meds	41% ≥ 1 PIM (Beers) (64)
Saarelainen LK <i>et al.</i> (178)	2014	Australia	385	Mean 76.7 (SD4.8)	Mean 5.7 (SD3.7)	26.5% ≥ 1 PIM (Beers) (182)
Kotlinska-Lemieszek A <i>et al.</i> (186)	2014	Europe	2282	Mean 62.3 (SD12.3)	Mean 7.8 (SD3.2) 25% ≥ 10 meds	-
Maggiore RJ <i>et al.</i> (187)	2014	US	500	Mean 73 All ≥ 65 years	Mean 5 (SD4)	29% ≥ 1 PIM (Beers) (182)
Nightingale G <i>et al.</i> (179)	2015	US	234	Mean 80	Mean 9.23 (SD4.29) 41% ≥ 5 meds 43% ≥ 10 meds	40% ≥ 1 PIM (Beers) (182) 38% ≥ 1 PIM (STOPP) (35)
Samuelsson <i>et al.</i> (188)	2016	Sweden	7279	All ≥ 75 years	No PIMs Mean 3.5 (SD2.7) ≥ 1 PIM Mean 6.5 (SD 3.3)	22.5% ≥ 1 PIM (National Board of Health & Welfare) (186)
Leger DY <i>et al.</i> (189)	2017	France	122	Mean 81.5 All ≥ 75 years	Mean 6.6 75.4% ≥ 5 meds	34.4% ≥ 1 PIM
Alkan A <i>et al.</i> (180)	2017	Turkey	445	Mean 75 (SD60-89)	Median 3 (0-14) 30.8% ≥ 5 meds	26.6 % ≥ 1 PIM (Beers) (182)

Legend: PIM = potentially inappropriate medication, DI = drug interaction, r = range

4.1.3 Adverse drug reactions in patients with cancer

Polypharmacy (144) and IP (35) contribute to ADRs. ADRs are common, the prevalence in the general older adult population at time of hospital admission being as high as 20% depending on the definitions and methodologies used to identify ADRs. ADRs associated specifically with chemotherapy have been well studied. Indeed, potential toxicities are well documented in medications' summary of product characteristics (SPCs) e.g. neutropenia can occur in 30% of patients receiving chemotherapy (190). In addition, multiple online educational resources exist e.g. [http\\:www.chemocare.com](http://www.chemocare.com) and [http\\:www.MacMillan.com](http://www.MacMillan.com). These clearly list, classify and risk stratify potential ADRs of chemotherapy so that patients, and clinical practitioners can be aware of, and vigilant for ADRs prior to and during treatment. However, little is known about the prevalence rates of non-chemotherapy related ADRs in patients with cancer and whether or not older patients with cancer are more vulnerable to ADRs than their younger counterparts.

Lau *et al.* investigated the potential for cancer specific treatments as well non-cancer specific treatments to cause ADRs *during* hospitalisation in patients with cancer and reported that the following ADRs were most commonly experienced by patients: (i) constipation, (ii) nausea/vomiting, (iii) fatigue, (iv) alopecia, (v) drowsiness, (vi) myelosuppression, (vii) skin reactions, (viii) anorexia, (ix) mucositis and (x) diarrhoea, with 74.3% of patients experiencing at least 1 ADR during hospitalisation (191). This study population had a mean age of 59 years (range 20 – 92), however no comparisons were made between the prevalence and nature of ADRs in younger versus older patients.

There is relative paucity of research on the prevalence and impact of multimorbidity, IP and ADRs in older patients with cancer. Studies to date that report on this weren't all designed to capture multimorbidity, IP and ADRs in older patient with cancer and for some data is from large databases where the precision of data input may not accurate. Medical and radiation oncologists are managing and treating cancer in a heterogeneous group of older patients, many of whom have age-related physiological change, complex co-morbidities, complex polypharmacy as well as functional and cognitive impairments. The burden of multimorbidity, prevalence of medication use and related ADRs has not been studied in older patients with cancer in Ireland, nor has there been an investigation into the differences between older and younger patients with cancer in Ireland. With a rapidly changing demographic distribution, more older patients are expected to be diagnosed with cancer in the coming decades. This will require more complex and multidisciplinary clinical and social care. More robust data are required about this patient group in order to effectively design and administer appropriate interventions.

4.1.4 Objectives

The specific objectives of this study were:

- (i) To investigate and describe the burden of multimorbidity in patients attending a tertiary specialist oncology unit, comparing younger and older adults.
- (ii) To assess the pattern of prescription drug use in these patients, both oncological and non-oncological.

- (iii) To determine the prevalence of polypharmacy (≥ 6 medications) and high level polypharmacy (≥ 11 medications) in patients attending a specialist oncology unit.
- (iv) To determine the prevalence of potentially inappropriate prescribing, where applicable, using STOPP (Screening Tool of Older Person's potentially inappropriate Prescriptions) criteria (**Appendix 8**) (36) and OncPal (Oncological palliative care deprescribing guideline) (**Appendix 9**) (190).
- (v) To determine the incidence of ADRs causing or contributing significantly to hospital admission in patients with cancer.
- (vi) To classify ADRs according to type, causality, associated morbidity, severity, predictability and preventability.
- (vii) To identify risk factors for ADRs in older and younger patients with cancer.
- (viii) To analyse the outcomes for patients who experience ADRs.

The work undertaken in this chapter, including study design, data collection and statistical analysis, is entirely my own.

4.2 METHODS

4.2.1 Study setting and design

This prospective observational study was conducted in two academic teaching hospitals in the Republic of Ireland; Cork University Hospital (CUH) and Mercy University Hospital (MUH). It was conducted over a 12 month period (January 1st 2016 – December 31st 2016), following a one month pilot in which study procedures and logistics were refined and finalised.

CUH is a level 4 University Teaching Hospital with 850 inpatients beds and over 25,000 emergency admissions per year. It caters for approximately 5300 medical oncology admissions per year comprising 4500 day cases, 500 emergency inpatient admissions and 300 elective inpatient admissions. In addition, there are approximately 30,000 day unit radiation oncology admissions per year. MUH is a 300 bed level 3 University Teaching Hospital, with a smaller medical oncology service catering for 4400 admissions per year. This comprises 4000 day cases, 300 emergency inpatient admissions and 100 elective inpatient admissions. MUH has no radiation oncology service. Both hospitals serve a population of over 800,000 people and together form one of the eight regional cancer centres in the Republic of Ireland.

4.2.2 Patient eligibility and consent

All patients' aged 16 years and older, admitted under the medical oncology or radiation oncology services in CUH and MUH, were eligible for inclusion in this prospective study. For the purpose of this study older adults were defined as being

aged ≥ 70 years. Participants were enrolled from three different admission pathways; emergency, elective and medical oncology day unit admissions. Radiation oncology day unit admissions were excluded due to logistical difficulties noted during the 1 month pilot phase, principally due to rapid treatment turnover times and lack of appropriate office space to conduct patient interviews in the radiation oncology centre.

Emergency and elective admissions to the medical oncology service were recruited within 72 hours of presentation to hospital. Chemotherapy day unit admissions i.e. patients attending for daily treatment on a regular basis, were reviewed over a two week period (March 28th to April 8th 2016); one week being allocated to each hospital. Day unit admissions encompass patients undergoing regular cycles of cancer treatment and therefore the same patients attend weekly for a defined period of time. Exclusion criteria were as follows: (i) patients already enrolled in the study on a previous hospital admission and (ii) patients deemed to be actively dying by the attending physician, at the point of admission.

The study's objectives were explained to patients. If agreeable, patients provided written consent to participate. In circumstances where patients were unable to give consent due to reduced decision making ability e.g. delirium or advanced dementia, consent was obtained from their legal representative. Inclusion in the study was voluntary and was clearly documented in patients' medical records. The study protocol was assessed and approved by the local Clinical Research Ethics Committees at University College Cork (**Appendix 2**).

4.2.3 Study population and sample size calculation

(i) Sample size required to determine the prevalence of potentially inappropriate prescribing

Using an estimated prevalence of potentially inappropriate prescribing (PIP) of 20%, a margin of error of 4% and 95% level of confidence, a minimum sample of 322 patients was required for this study. This power calculation was based on the formula outlined in **Table 4.3** and adjusted using oncology service admissions data from 2015.

(ii) Sample size required to determine the prevalence of adverse drug reactions

In the acute unselected population of all ages, the reported ADR rate is approximately 7%, therefore this study was powered to record an ADR rate of 7% with a margin of error of 2% with 95% confidence. This determined that a minimum sample of 333 patients was required (**Table 4.3**).

Table 4.3: Sample size calculation

Hospital admission rates: January to December 2015					Sample size calculation Potentially Inappropriate Prescribing	Sample size calculation Adverse Drug Reactions
All admission episodes (including multiple/repeat admissions)					Formula $n = \frac{Z^2 \times P (1 - P)}{D^2}$	Formula $n = \frac{Z^2 \times P (1 - P)}{D^2}$
	Emergency	Elective	Day unit	Total	n = sample size Z = Z statistic for the level of confidence (1.96) P = Expected prevalence (20% or 0.20) D = margin of error (4% or 0.04) $n = \frac{(1.96)^2 \times (0.20) (1 - 0.2)}{0.04^2} = 384$ Adjusted for population available:	n = sample size Z = Z statistic for the level of confidence (1.96) P = Expected prevalence (7% or 0.07) D = margin of error (2% or 0.02) $n = \frac{(1.96) \times (0.07) (1 - 0.07)}{0.02^2} = 625$ Adjusted for population available
CUH (MO)	482	313	4538	5333		
MUH (MO)	235	109	3956	4300		
CUH (RO)	117	126		243		
Total	834	548	8494	9633		
Numbers of individual patients admitted at least once in 2015					Formula $\frac{n_0 \times N}{N_0 + (N - 1)}$	Formula $\frac{n_0 \times N}{N_0 + (N - 1)}$
	Emergency	Elective	Day unit	Total	$\frac{1538 \times 384}{1538 + (384 - 1)} = 307 (+ 5\%) + 15 = \mathbf{322}$	$\frac{644 \times 625}{644 + (625 - 1)} = 317 (+ 5\%) + 16 = \mathbf{333}$
CUH (MO)	237	101	457	795		
MUH (MO)	107	32	437	576		
CUH (RO)	83	84		167		
	427	217	894	1538		

Legend: MO = medical oncology; RO = radiation oncology; CUH = Cork University Hospital; MUH = Mercy University Hospital

4.2.4 Data collection

All participants were reviewed within 72 hours of admission. Each morning, a list of admissions from the previous 72 hours was compiled. To avoid any bias, patients were enrolled in chronological order of admission i.e. those in hospital the longest were recruited first.

The following data were abstracted onto a standardized proforma (**Appendix 3**): (i) demographic details, (ii) medical co-morbidities using the Cumulative Illness Rating Scale – CIRS (156), (iii) concurrent medications, (iv) functional ability using the Barthel Index (157), (v) cognitive status using a standardized Mini-mental state examination – MMSE, in those ≥ 65 years (158), the 4-AT (159) and the Diagnostic and Statistical Manual of Mental Disorders V - DSM-V to assess for delirium (160), (vi) laboratory values, and (vii) electrocardiogram (ECG). Medication reconciliation was completed using the Structured History taking of Medication use (SHiM) (32). These tools have been described in detail in Chapter 3.

Potentially inappropriate prescribing (PIP) was assessed using STOPP criteria (**Appendix 8**) (37) and OncPal (**Appendix 9**) (192). A brief description of STOPP criteria has been presented in chapter 3. A brief description of the development and validity of OncPal follows. OncPal (192) is an explicit prescribing tool, developed and validated in Australia, to assist physicians with deprescribing for patients with cancer and a poor survival prognosis. It aims to highlight medications that are of limited benefit in this patient group. Similar to STOPP criteria it is divided into physiological systems. It focuses primarily on preventative therapy e.g. aspirin for primary prevention and anti-hypertensives. To date, only one study has been published that

used OncPal (192). This prospective study of 61 patients (mean age 66 (range 23 - 93) showed that 70% of patients with cancer and a limited life expectancy were prescribed at least one potentially inappropriate medication (PIM) and that 21.4% of all medications prescribed to this population were potentially inappropriate (192).

4.2.5 Potentially inappropriate prescribing

STOPP criteria (**Appendix 8**) (37) were applied to the abstracted data of all patients ≥ 65 years. OncPal criteria (**Appendix 9**) (192) were applied to the abstracted data on participants who died within 6 months of enrolment. The presence or absence of a PIM, according to STOPP and OncPal criteria, was categorised as a dichotomous variable. Where there was uncertainty regarding appropriateness of a prescription this was treated conservatively i.e. the medication was deemed appropriate.

4.2.6 Adverse drug reactions (ADRs)

The proportion of patients experiencing one or more non-trivial, probable or certain, ADR causing or contributing significantly to hospital admission was determined using Edwards and Aronson's definition of an ADR i.e. "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (79).

To limit potential bias from selective ADR reporting and to ensure ADRs were not missed, the ***AE Trigger List*** of the 12 most common adverse events (AEs) linked to ADRs was used, as previously discussed in Chapter 2, data on any ADR not listed in the ***AE Trigger List*** were also collected e.g. drug anaphylaxis. All AEs including potential ADRs were recorded and subsequently reviewed to assess the causative role of prescribed medications. ADRs were assessed prospectively at the time of enrolment.

4.2.7 ADR causality, severity, predictability and preventability

Causality was assessed using the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) criteria whereby the likelihood of a drug causing the adverse event is classified as either certain, probable, possible, unlikely or unrelated (119). ADR severity was assessed using the Hartwig & Siegel scale. This grades ADR severity according to clinical consequence on a scale of 1 to 7 with a grade 1 ADR being trivial and requiring no medical intervention and a grade 7 ADR representing a fatal event (151). Preventability of the ADR was assessed using Hallas criteria i.e. definitely avoidable, possibly avoidable, unavoidable and unclassifiable (166). Predictability was assessed using the summary of product characteristics (SPC) (**Table 4.4**). ADRs were deemed predictable if they were listed in the relevant SPC as occurring commonly ($\geq 1/100$ and $< 1/10$) or very commonly ($\geq 1/10$).

Table 4.4: Adverse drug reaction predictability

Incident rate	Incident description	Predictability
$\geq 1/10$	Very common	Predictable
$\geq 1/100$ and $< 1/10$	Common	Predictable
$\geq 1/1000$ and $< 1/100$	Uncommon	Unpredictable
$\geq 1/10,000$ and $< 1/1000$	Rare	Unpredictable
$< 1/10,000$	Very rare	Unpredictable

4.2.8 Statistical analysis

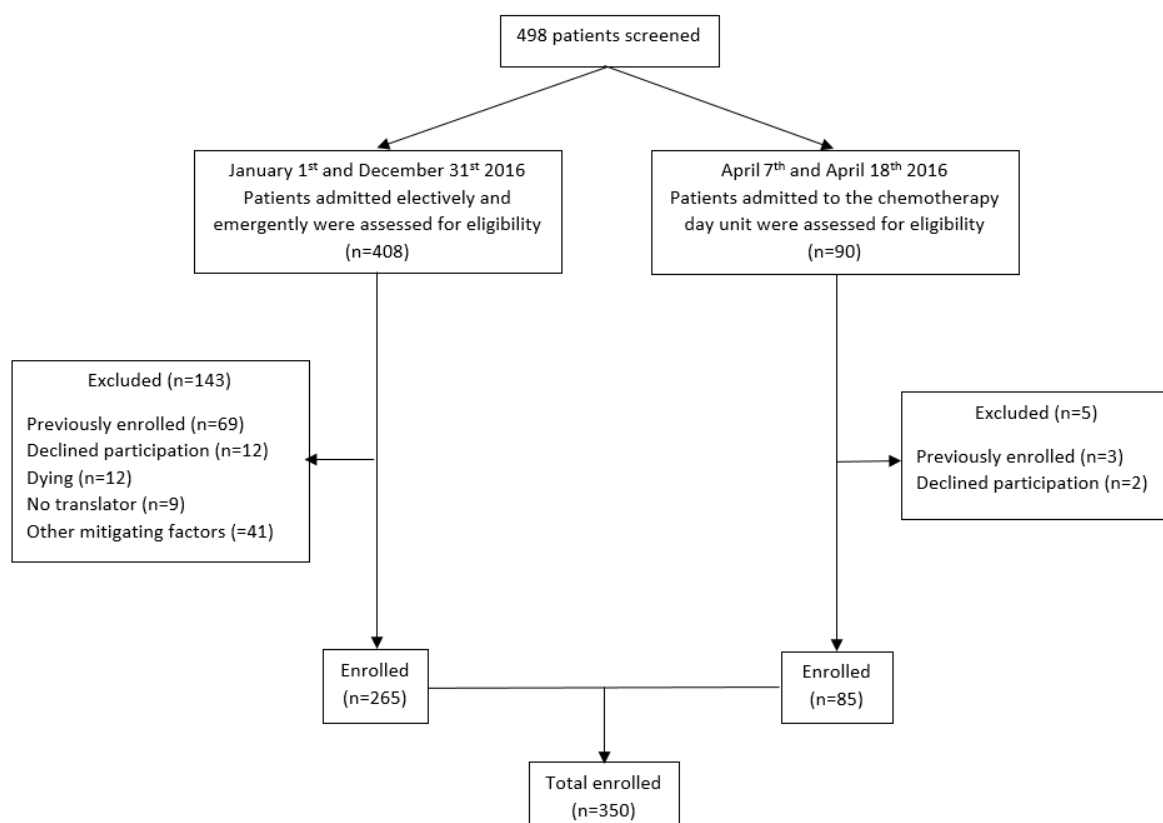
Statistical analysis was performed using IBM SPSS® Statistics version 22 for windows. Descriptive data were reported using the mean and standard deviation (SD) for variables that were normally distributed and median and interquartile range (IQR) for non-parametric variables. Differences in the distribution of categorical variables were compared using the Pearsons Chi-square (X^2) test and continuous variables using the independent t-test. The Mann Whitney U and Kruskal-Wallis tests were used to determine independence of two or more non-parametric variables respectively. Pearson's kappa coefficient was used to assess correlation between variables. Logistic regression was used to examine the influence of gender, age, number of medications and burden of co-morbidity on PIP practices. The Hosmer and Lemeshow statistic was used to test the goodness of fit of the regression model. A probability value of less than 0.05 was considered statistically significant.

4.3 RESULTS

4.3.1 Screening

A total of 408 emergency and elective admissions to the medical and radiation oncology services in CUH and MUH were screened for study inclusion between the 1st of January 2016 and the 31st December 2016. Of these, 265 patients agreed to participate of whom 201 were admitted emergently (57.4% of total study sample) and 64 were admitted electively (18.3% of total study sample). Ninety patients attending the Oncology Chemotherapy Day Unit treatment were screened for eligibility, of whom 85 agreed to participate (24.3% of total study sample). These data are summarised in **Figure 4.1**, together with reasons for study exclusion. Overall, 350 patients attending the oncology services were enrolled in this study.

Figure 4.1: Participant screening, exclusion and enrolment



4.3.2 Population characteristics

Baseline characteristics are displayed in **Table 4.5**. The mean age was 63.6 (SD12.1) years, range 16 – 90. Males were significantly older than females (65.4 (SD10.7) vs 61.9 (SD13) years, $t_{345.954} = 2.731$, $p = 0.005$). Accordingly, 37.1% of males and 32.2% of females were ≥ 70 years ($\chi^2(1) = 0.921$, $p = 0.198$). Most patients were functionally independent with 95.5% (n=334) being categorised as independent or being of low dependency using the Barthel Index (scores ≥ 16). The MMSE was applied to participants ≥ 65 years to assess cognitive ability, 88.3% (n=165) of whom completed this assessment. In participants who completed the MMSE, normal cognition and mild cognitive impairment were identified in 87.3% and 8.5% respectively. Delirium was identified in 6.3% (n=22) at the point of admission using the 4-AT and DSM-V.

One in four (25.4%) participants consumed alcohol on a weekly basis with 6.9% drinking more than the recommended weekly allowance. One hundred and ninety five (65.7%) patients had a history of smoking and 10% (n=35) continued to smoke. Differences identified between older and younger adults are displayed in **Table 4.6**. The key findings with regard to population demographics are presented in **Key findings box 1**.

Key Findings 1:

- One in three (34.5%) patients attending a regional oncology unit were ≥ 70 years.
- One in twenty (6.5%) patients were aged ≥ 80 years.
- Functional independence was identified in 95.5%.
- The majority of patients with cancer aged ≥ 65 years had normal (87.3%) or mild cognitive impairment (8.5%) as determined by the MMSE.

Table 4.5: Characteristics of study population according to gender (n = 350)

Variable	Male n = 167	Female n = 183	Total n = 350	P-value
Age distribution (years)				
Mean (SD)	65.4 (10.7)	61.9 (13)	63.6 (12.1)	0.005*
≤ 64	67 (40%)	97 (53%)	164 (46.9%)	0.016*
65 – 74	73 (43.7%)	59 (32.2%)	132 (37.7%)	0.027*
75 – 84	23 (13.9%)	24 (13%)	47 (13.4%)	0.857
≥ 85	4 (2.4%)	3 (1.6%)	7 (2%)	0.614
Functional ability (Barthel Index)				
Median (IQR)	20 (20 – 20)	20 (20 – 20)	20 (20 – 20)	0.006*
Range	11 - 20	7 - 20	7 - 20	
Independent (≥ 20)	141 (84.4%)	130 (71%)	271 (77.4%)	0.003*
Low dependency (16 – 19)	21 (12.7%)	42 (22.7%)	63 (18%)	0.012*
Moderate dependency (11 – 15)	6 (3.6%)	8 (4.3%)	14 (4%)	0.710
High dependency (6 – 10)	0 (0%)	3 (1.6%)	3 (0.9%)	0.097
Maximum dependency (0 – 5)	0 (0%)	0 (0%)	0 (0%)	NA
Driving				
Ability to drive	150 (90.4%)	129 (71.7%)	279 (80.6%)	<0.001*
Actively still driving	111 (66.9%)	87 (47.5%)	198 (57.2%)	<0.001*
Cognitive ability (MMSE)				
Number of patients ≥65 years	101 (60.5%)	86 (47%)	187 (53.5%)	0.012*
Number ≥65 that completed MMSE	88 (87.2%)	77 (89.5%)	165 (88.3%)	0.742
Median (IQR)	28 (26 – 29)	28 (26 -29)	28 (26 – 29)	0.610
Range	14 - 30	12 - 30	12 - 30	
Normal MMSE score (24 – 30)	81 (92%)	63 (81.8%)	144 (87.3%)	0.049*
Mild cognitive impairment (19 - 23)	5 (3%)	9 (11.7%)	14 (8.5%)	0.167
Moderate cognitive impairment (10 – 18)	2 (1.2%)	5 (6.5%)	7 (4.2%)	0.180
Severe cognitive impairment (0 – 9)	0 (0%)	0 (0%)	0 (0%)	NA
Alcohol and Smoking				
Consumes alcohol weekly	54 (32.7%)	35 (19.4%)	89 (25.4%)	0.005*
Consume ≥ recommended weekly limit	14 (8.4%)	10 (5.5%)	24 (6.9%)	0.285
History of smoking	105 (63.9%)	90 (49.2%)	195 (55.7%)	0.010*
Current smokers	18 (10.8%)	17 (9.3%)	35 (10%)	0.643

Legend: SD = standard deviation; IQR = inter-quartile range; MMSE = mini-metal state examination,

** ≥11 units for females, ≥17 units for male

Table 4.6: Characteristics of study population according to age category (*n* = 350)

Variable		< 70 years n=229 (65.5%)	≥ 70 years n=121 (34.5%)	p-value	< 80 years n=327 (93.5%)	≥ 80 years n=23 (6.5%)	p-value
Functional ability							
Barthel Index	Med (IQR)	20 (20-20)	20 (18-20)	<0.001*	20 (20-20)	19 (17-20)	<0.001*
Independent (≥ 20)	n (%)	191 (83.4%)	80 (66.1%)	<0.001*	262 (80.1%)	9 (39.1%)	<0.001*
Low dependency (16 – 19)	n (%)	32 (14%)	31 (25.6%)	0.007*	52 (15.9%)	11 (47.8%)	<0.001*
Moderate dependency (11 – 15)	n (%)	6 (2.6%)	8 (6.6%)	0.070	13 (4%)	1 (4.3%)	0.930
High dependency (6 – 10)	n (%)	0 (0%)	0 (0%)	0.017	1 (0.3%)	2 (8.7%)	<0.001*
Maximum dependency (0 – 5)	n (%)	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
Driving							
History of driving	n (%)	187 (82.4%)	92 (77.3%)	0.257	264 (81.7%)	15 (65.2%)	0.053
Current driving	n (%)	130 (57.3%)	68 (57.1%)	0.982	190 (58.8%)	8 (34.8%)	0.024*
Cognitive ability							
MMSE	Med (IQR)	28 (26-30)	27 (25-29)	0.029*	28 (26-29)	26 (21.75-27)	<0.001*
Number of patients completed MMSE (≥65years)	n (%)	56 (86.2%)	109 (90.1%)	0.420	143 (87.7%)	22 (95.7%)	0.261
Normal cognition (25 – 30)	n (%)	49 (87.5%)	89 (81.7%)	0.336	126 (88.1%)	12 (54.5%)	<0.001*
Mild cognitive impairment (20 – 24)	n (%)	4 (7.1%)	15 (13.8%)	0.207	12 (8.4%)	7 (31.8%)	<0.001*
Moderate cognitive impairment (10 – 19)	n (%)	3 (5.4%)	5 (4.6%)	0.827	5 (3.5%)	3 (13.6%)	0.039*
Severe cognitive impairment (0 – 10)	n (%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Alcohol and smoking							
Consumes alcohol weekly	n (%)	62 (27.7%)	27 (22.3%)	0.277	86 (26.7%)	3 (13%)	0.148
Consume ≥ recommended weekly limit	n (%)	14 (6.3%)	10 (8.3%)	0.483	24 (7.5%)	0 (0%)	0.175
History of smoking	n (%)	129 (56.3%)	66 (54.5%)	0.749	186 (56.9%)	9 (39.1%)	0.098
Current smokers	n (%)	30 (13.1%)	5 (4.1%)	0.008*	33 (10.1%)	2 (8.7%)	0.829

Legend: IQR = Inter-quartile range; MMSE = Mini mental state examination.

4.3.3 Level of morbidity

The level of morbidity in this population was measured by the total number of chronic conditions, the number of chronic conditions requiring regular drug treatment and the CIRS score. These data are summarised in **Table 4.7**.

Most participants (96.9%) were multimorbid, with almost 7 out of every 10 patients (68%) having 5 or more chronic conditions. Older adults (≥ 70 years) were significantly more likely to be multimorbid than younger adults, 100% vs 95.2%, $\chi^2(1) = 6.001$, $p = 0.014$ (**Figure 4.2**). Older adults (≥ 70 years) were also significantly more likely to have 5 or more chronic conditions than younger adults, 81.1% vs 60.7%, $\chi^2(1) = 16.228$, $p < 0.001$.

Participants had a median of 6 (IQR 4-8) clinical conditions, with a median of 3 (IQR 2-5) requiring regular medication use. Older adults (≥ 70 years) had a significantly higher number of conditions compared to younger adults, median of 7 (IQR 5-10) vs 5 (IQR 3-7) $U = 8168.5$, $p < 0.001$ (**Figure 4.3**). Additionally they had a significantly higher number of conditions requiring regular medication use, 4 (IQR 3-6) vs 3 (IQR 2-4) $U = 8827$, $p < 0.001$.

Table 4.7: Level and severity of co-morbid illnesses according to age category

Variable	< 70 years n=229 (65.5%)	≥ 70 years n=121 (34.5%)	p-value	< 80 years n=327 (93.5%)	≥ 80 years n=23 (6.5%)	p-value	Total N = 350
Multi-morbidity							
≥2 conditions	218 (95.2%)	121 (100%)	0.014*	316 (96.6%)	23 (100%)	0.371	339 (96.9%)
≥3 conditions	201 (87.8%)	119 (98.3%)	0.001*	297 (90.8%)	23 (100%)	0.129	320 (91.4%)
≥4 conditions	171 (74.4%)	110 (90.9%)	<0.001*	260 (79.5%)	21 (91.3%)	0.169	281 (80.3%)
≥5 conditions	139 (60.7%)	99 (81.1%)	<0.001*	219 (67%)	19 (82.6%)	0.120	238 (68%)
Total conditions							
Median (IQR)	5 (3-7)	7 (5-10)	<0.001*	6 (4-8)	8 (5-9)	0.018*	6 (4-8)
Range	1-17)	2-18		1-18	3-15		1-18
Conditions (requiring regular meds)							
Median (IQR)	3 (2-4)	4 (3-6)	<0.001*	3 (2-5)	4 (3-8)	0.030*	3 (2-5)
Range	1-12	0-14		0-14	1-12		0-14
CIRS							
Median (IQR)	11 (9-14.5)	15 (11-19)	<0.001*	12 (9-16)	16(13-19)	0.004*	13 (9-16)
Range	2-26	6-30		2-30	6-29		2-30

Legend: CIRS = Cumulative illness rating scale, IQR = inter-quartile range, meds = medications, SD = standard deviation

Figure 4.2: Prevalence of multimorbidity according to age category

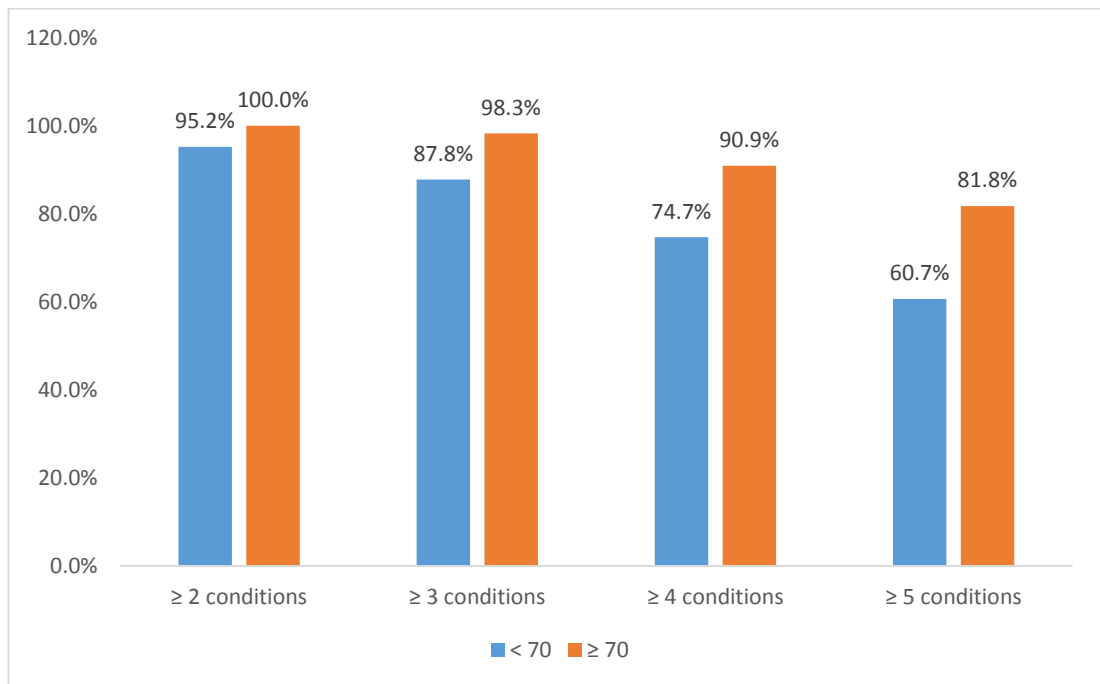
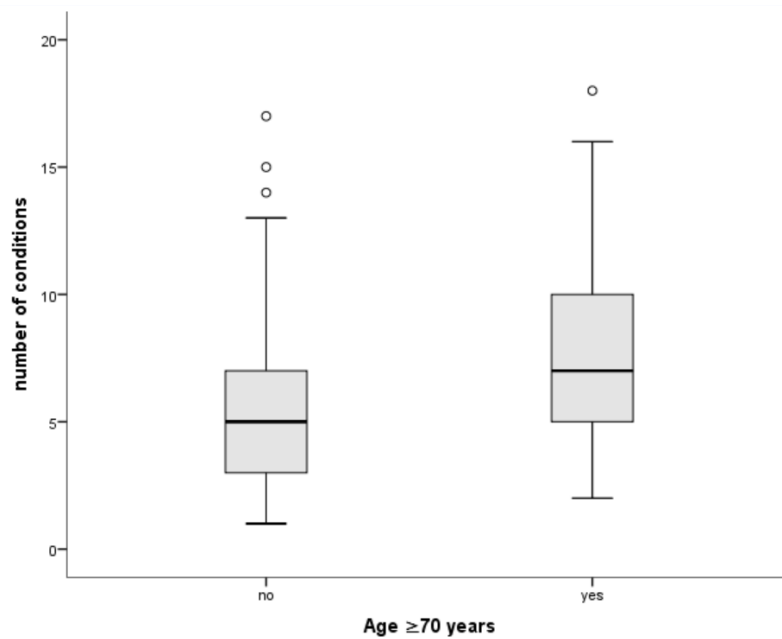


Figure 4.3: Number of chronic conditions according to age category



4.3.4 Cumulative Illness Rating Scale (CIRS) scores

The median CIRS score was 13 (IQR 9-16), with adults 70 years and older having a significantly higher CIRS score than those < 70 years (15 (IQR 11-19) vs 11 (IQR 9-14.5), $U = 8511.5$, $p < 0.001$). Adults aged 80 years and older also had a significantly higher CIRS score than those aged < 80 years (16 (IQR 13-19) vs 12 (IQR 9-16), $U = 2416$, $p = 0.004$ (**Figure 4.4**).

Figure 4.4: CIRS score according to age category

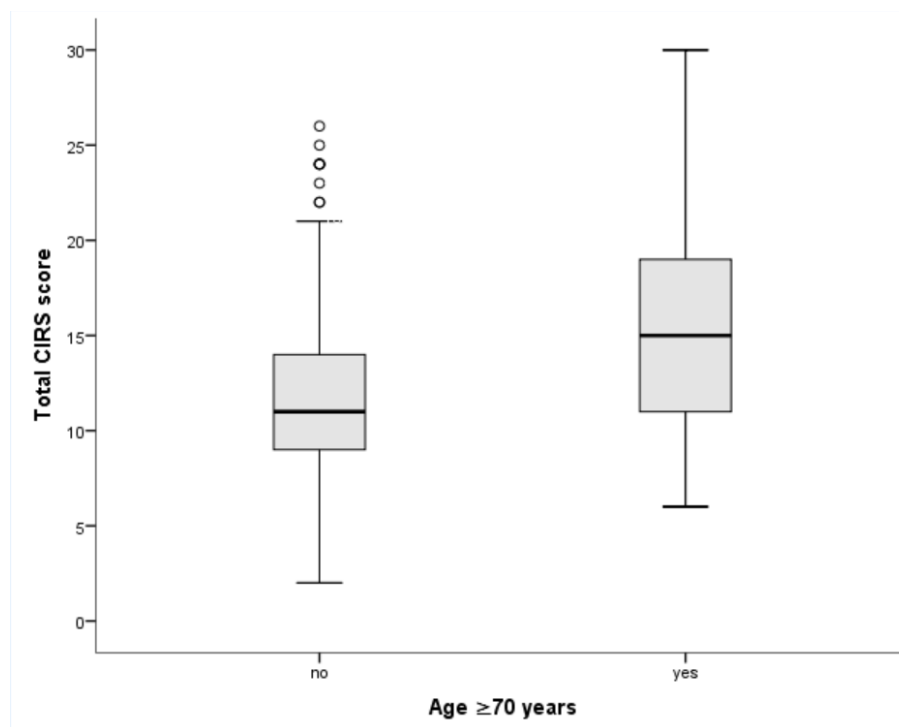
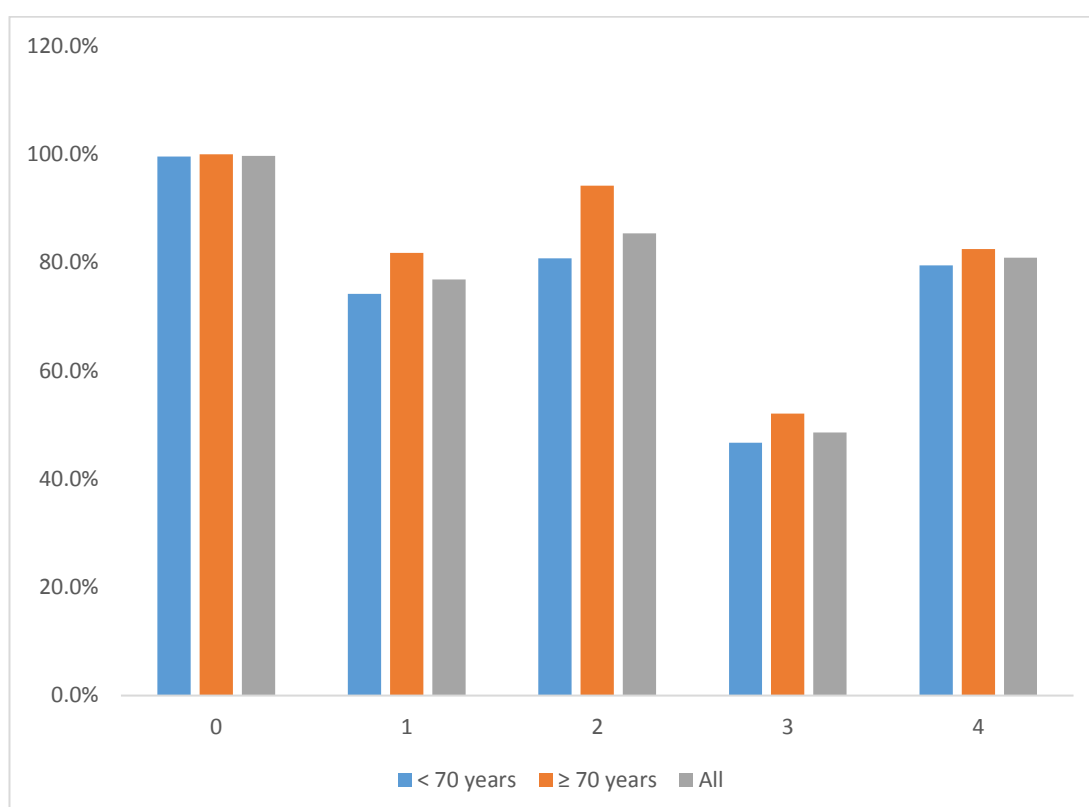


Figure 4.5 illustrates the CIRS ratings of system-based illnesses. Approximately 81% (n=283) of participants rated at least one illness with a “4” for one physiological system (indicating extremely severe disease requiring immediate treatment or contributing to severe impairment in function), 48.6% (n=170) rated at least one illness with a “3” (indicating a severe condition that is uncontrollable), 85.4% (n=299) at least one “2” (indicating a disease requiring first line treatment or causing

moderate disability) and 76.9% rated at least (n=269) at least one “1” (indicating a mild current problem or past significant problem).

Figure 4.5: The number of participants according to age that rated at least one system with a score of 0, 1, 2, 3 or 4 (n = 350)



Key Findings 2:

- Older adults (≥ 70 years) had a higher cumulative index rating score (CIRS) than younger comparators, 15 (IQR 11-19) vs 11 (IQR 9-14.5).

4.3.5 Cancer diagnoses

The most common primary cancer sites in this population were (i) breast, (li) lung and (iii) colorectal (see **Table 4.8**). Older adults (≥ 70 years) were significantly more likely to have a primary lung cancer diagnosis (22.3% vs 13.5%, $X^2(1) = 4.411$, $p = 0.036$), whereas younger adults (< 70 years) were significantly more likely to have a

primary breast cancer diagnosis (21.4% vs 12.4%, $\chi^2 (1) = 4.292$, $p = 0.038$). Additionally, adults ≥ 80 years were significantly more likely to have a primary lung cancer diagnosis than their younger counterparts (100% vs 17.7%, $\chi^2 (1) = 4.411$, $p = 0.027$). There was no significant difference according to age for all other primary cancer diagnoses. Approximately 17% ($n=28$) men had a history of another cancer or a concurrent cancer diagnosis compared to 9.9% ($n=18$) of females ($\chi^2 (1) = 4.988$, $p = 0.026$).

Table 4.8: Primary cancer diagnoses

Variable	Male n = 167	Female n = 183	Total	P-value
Primary cancer diagnosis (in order of frequency)				
1. Breast	4 (2.4%)	60 (32.4%)	64 (18.3%)	<0.001*
2. Lung	35 (21%)	23 (12.6%)	58 (16.6%)	0.035*
3. Colorectal	31 (18.6%)	15 (8.2%)	46 (13.1%)	0.004*
4. Lymphoma	15 (9%)	15 (8.2%)	30 (8.6%)	0.793
5. Ovarian	0 (0%)	15 (8.2%)	15 (4.3%)	<0.001*
6. Pancreatic	7 (4.2%)	8 (4.4%)	15 (4.3%)	0.934
7. Prostate	14 (8.4%)	0 (0%)	14 (4%)	<0.001*
8. Oesophageal	10 (6%)	4 (2.2%)	14 (4%)	0.070
9. Melanoma	7 (4.2%)	6 (3.3%)	13 (3.7%)	0.652
10. Gastric	4 (2.4%)	7 (3.8%)	11 (3.1%)	0.444

4.3.6 Non-cancer diagnoses

The most common non-cancer diagnosis in this population were (i) hypertension (ii) dyslipidaemia and (iii) gastro-oesophageal reflux disease (GORD) (see **Table 4.9**). Females were significantly more likely to have hypothyroidism ($\chi^2 (1) = 8.034$, $p = 0.038$), and thromboembolic disease ($\chi^2 (1) = 6.696$, $p = 0.010$). Men were significantly more likely to have ischaemic heart disease ($\chi^2 (1) = 9.398$, $p = 0.002$).

and diabetes mellitus ($X^2 (1) = 4.258$, $p = 0.039$). The key findings with regard to diagnoses are presented in **Key Findings 4**.

Table 4.9: Non-cancer diagnoses

Variable	Male n = 167	Female n = 183	Total	P-value
Non-cancer diagnosis (in order of frequency)				
1. Hypertension	75 (44.9%)	64 (35%)	139 (39.7%)	0.058
2. Dyslipidaemia	68 (40.7%)	65 (35.5%)	133 (38%)	0.317
3. Gastro-oesophageal reflux disease	45 (26.9%)	50 (27.3%)	95 (27.1%)	0.937
4. Depression/Anxiety	35 (21%)	46 (25.1%)	81 (23.1%)	0.355
Depression	26 (15.6%)	32 (17.5%)	58 (16.6%)	0.630
Anxiety	14 (8.4%)	25 (13.7%)	39 (11.1%)	0.117
5. Osteoarthritis	25 (15%)	32 (17%)	57 (16.3%)	0.524
6. Ischaemic heart disease	35 (21%)	17 (9.3%)	52 (14.9%)	0.002*
Percutaneous coronary intervention	17 (10.2%)	3 (1.6%)	20 (5.7%)	0.001*
Myocardial Infarction	16 (9.6%)	6 (3.3%)	22 (6.3%)	0.015*
Coronary artery bypass graft	10 (6%)	2 (1.1%)	12 (3.4%)	0.012*
Heart Failure	5 (3%)	3 (1.6%)	8 (2.3%)	0.397
7. Diabetes Mellitus	29 (17.4%)	18 (9.8%)	47 (13.4%)	0.039*
8. Hypothyroidism	13 (7.8%)	33 (18%)	46 (13.1%)	0.005*
9. Chronic obstructive pulmonary disease	22 (13.2%)	21 (11.5%)	43 (12.3%)	0.629
10. Thromboembolic disease	11 (6.6%)	28 (15.3%)	39 (11.1%)	0.010*
11. Atrial fibrillation	21 (12.6%)	17 (9.3%)	38 (10.9%)	0.324

Older adults (≥ 70 years) were significantly more likely to have a diagnosis of hypertension (62.8% vs 27.5%, $X^2 (1) = 41.202$, $p < 0.001$), dyslipidaemia (51.2% vs 31%, $X^2 (1) = 13.769$, $p < 0.001$), osteoarthritis (24% vs 12.2%, $X^2 (1) = 8.003$, $p = 0.005$), ischaemic heart disease (26.4% vs 8.7%, $X^2 (1) = 19.635$, $p < 0.001$), heart failure (5.1% vs 0.9%, $X^2 (1) = 5.916$, $p = 0.015$), diabetes mellitus (19.8% vs 10%, $X^2 (1) = 6.528$, $p = 0.011$), hypothyroidism (18.2% vs 10.5%, $X^2 (1) = 4.113$, $p = 0.043$) and atrial fibrillation (22.3% vs 4.8%, $X^2 (1) = 25.081$, $p < 0.001$) than their younger counterparts (see **Table 4.10**). Adults aged 80 years and older were significantly more likely to have a diagnosis of hypertension (78.3% vs 37%, $X^2 (1) = 15.278$, $p < 0.001$) and osteoarthritis (34.6% vs 15%, $X^2 (1) = 6.178$, $p = 0.013$) than those aged < 80 years.

Table 4.10: Non-cancer diagnoses according to age

Variable		< 70 n=229 (65.5%)	≥ 70 n=121 (34.5%)	p- value	< 80 n=327 (93.5%)	≥ 80 n=23 (6.5%)	p-value
Non-cancer diagnosis							
Hypertension	n (%)	63 (27.5%)	76 (62.8%)	<0.001	121 (37%)	18 (78.3%)	<0.001*
Dyslipidaemia	n (%)	71 (31%)	65 (51.2%)	<0.001	122 (37.3%)	11 (47.8%)	0.315
GORD	n (%)	62 (27.1%)	33 (27.3%)	0.968	90 (27.5%)	5 (21.7%)	0.547
Depression/Anxiety	n (%)	51 (22.3%)	30 (24.8%)	0.595	77 (23.5%)	5 (17.4%)	0.499
Depression	n (%)	35 (15.3%)	23 (19%)	0.373	55 (16.8%)	3 (13%)	0.638
Anxiety	n (%)	27 (11.9%)	12 (9.9%)	0.596	37 (11.3%)	2 (8.7%)	0.700
Osteoarthritis	n (%)	28 (12.2%)	29 (24%)	0.005	49 (15%)	8 (34.6%)	0.013
IHD	n (%)	20 (8.7%)	32 (26.4%)	<0.001	46 (14.1%)	6 (26.1%)	0.117
PCI	n (%)	10 (4.4%)	10 (8.3%)	0.135	19 (5.8%)	1 (4.3%)	0.770
MI	n (%)	11 (4.8%)	11 (9.1%)	0.116	19 (5.8%)	3 (13%)	0.180
CABG	n (%)	6 (2/6%)	6 (5%)	0.253	11 (3.4%)	1 (4.3%)	0.807
HF	n (%)	2 (0.9%)	6 (5%)	0.015	7 (2.1%)	1 (4.3%)	0.499
Diabetes Mellitus	n (%)	23 (10%)	24 (19.8%)	0.011	43 (13.1%)	4 (17.4%)	0.564
Hypothyroidism	n (%)	24 (10.5%)	22 (18.2%)	0.043	42 (12.8%)	4 (17.4%)	0.533
COPD	n (%)	23 (10%)	20 (16.5%)	0.079	43 (13.1%)	0 (0%)	0.063
Thromboembolic dx	n (%)	25 (10.9%)	14 (11.6%)	0.853	38 (11.6%)	1 (4.3%)	0.284
Atrial fibrillation	n (%)	11 (4.8%)	27 (22.3%)	<0.001	34 (10.4%)	4 (17.4%)	0.297

Legend: GORD = gastro-oesophageal reflux disease, IHD = ischaemic heart disease, PCI = percutaneous coronary intervention (stents), MI = myocardial infarction, CABG = coronary artery bypass graft, HF = heart failure, COPD = chronic obstructive pulmonary disease, dx = disease

Key Findings 3:

- The three most common cancer sites were breast, lung and colorectal.
- The three most common non-cancer diagnoses were hypertension (HTN), dyslipidaemia and gastro-oesophageal reflux disease (GORD).

4.3.7 Prescription medications

A total of 2,575 medications were prescribed regularly to 326 (93.1%) patients, 6.9% (n=24) were not prescribed medications. Additionally, 491 medications were prescribed “as required” to 280 (80%) patients. The median number of medications prescribed per patient was 5 (IQR 3-8), range 0 - 24, with 47.1% (almost 1 in 2 patients) experiencing polypharmacy and 11.4% (almost 1 in 9 patients) experiencing high level polypharmacy (**table 4.11**). There was no significant difference between the numbers of medications prescribed to males and females ($\chi^2 (3) = 3.619$, $p = 0.306$).

Table 4.11: Prescribing according to gender (n=350)

Variable	Male n = 167	Female n = 183	Total n = 350	P-value
Medications (regular)				
Median (IQR)	5 (3-8)	5 (3-8)	5 (3-8)	0.658
Range	0 - 24	0 - 17	0 - 24	
Medications (as required)				
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.012*
Range	0 - 6	0 - 12	0 - 12	
Patients taking at least 1 medication	152 (91%)	174 (95.1%)	326 (93.1%)	0.133
1 – 5 medications	72 (43.1%)	89 (48.6%)	161 (46%)	0.301
6 – 10 medications	58 (34.7%)	67 (36.6%)	125 (35.7%)	0.714
≥ 11 medications	22 (13.2%)	18 (9.8%)	40 (11.4%)	0.327
≥ 6 medications	80 (47.9%)	85 (46.4%)	165 (47.1%)	0.785

Legend: IQR = inter quartile range

4.3.8 Medication use according to age category

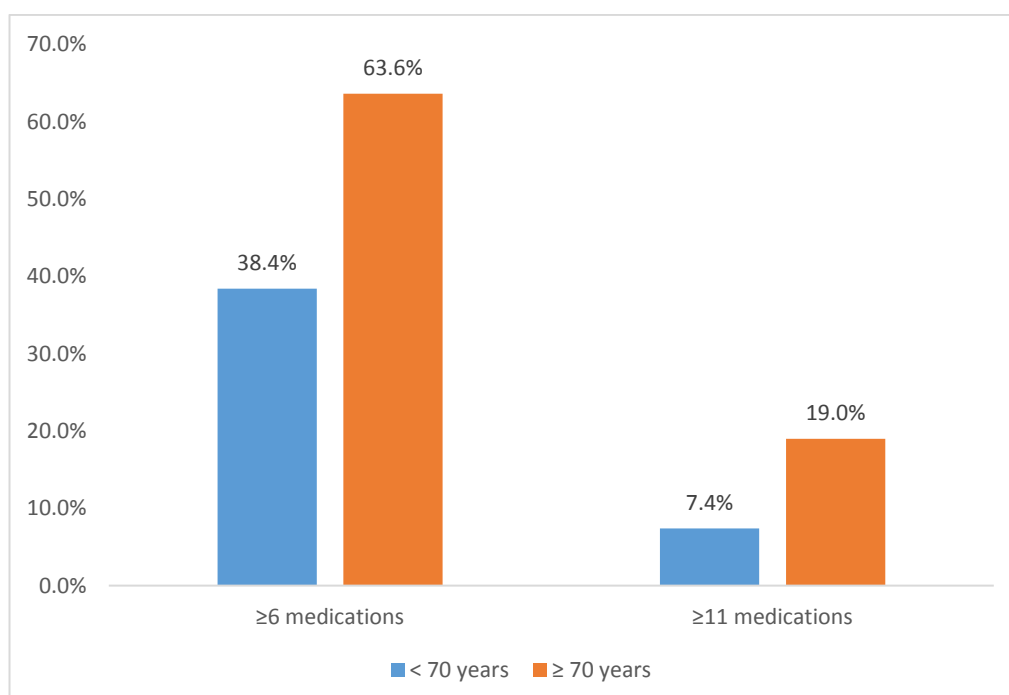
Adults aged ≥ 70 years were prescribed more medications than those aged < 70 years (median 7 (IQR4-9) vs 4(IQR2-7), $U = 9379.5$, $p < 0.001$) (**Table 4.12**) with polypharmacy and high level polypharmacy significantly higher in those ≥ 70 years, $\chi^2 (1) = 20.189$, $p < 0.001$ and $\chi^2 (1) = 10.496$, $p = 0.001$ respectively (**Figure 4.6**).

Table 4.12: Distribution of prescription medications according to age category
(n=350)

Variable	< 70 years n=229 (65.5%)	≥ 70 years n=121 (34.5%)	p-value	< 80 years n=327 (93.5%)	≥ 80 years n=23 (6.5%)	p-value
Medications (regular)						
Median (IQR)	4 (2-7)	7 (4-9)	<0.001*	5 (3-8)	7 (4-9)	0.063
Range	0-24	0-18		0-24	0-16	
Medications (as required)						
Median (IQR)	1 (0-2)	1 (0-2)	0.744	1 (0-2)	1 (0-2)	0.669
Range	0-6	0-12		0-8	0-12	
Patients taking at least 1 med	208 (90.8%)	118 (97.5%)	0.018*	304 (93%)	22 (95.7%)	0.622
1 – 5 medications	120 (52.4%)	41 (33.9%)	0.001*	153 (46.8%)	8 (34.8%)	0.264
6 – 10 medications	71 (31%)	54 (44.6%)	0.010*	114 (34.9%)	11 (47.8%)	0.210
≥ 11 medications	17 (7.4%)	23 (19%)	0.001*	37 (11.3%)	3 (13%)	0.801
≥ 6 medications	88 (38.4%)	77 (63.6%)	<0.001*	151 (46.2%)	14 (60.9%)	0.172

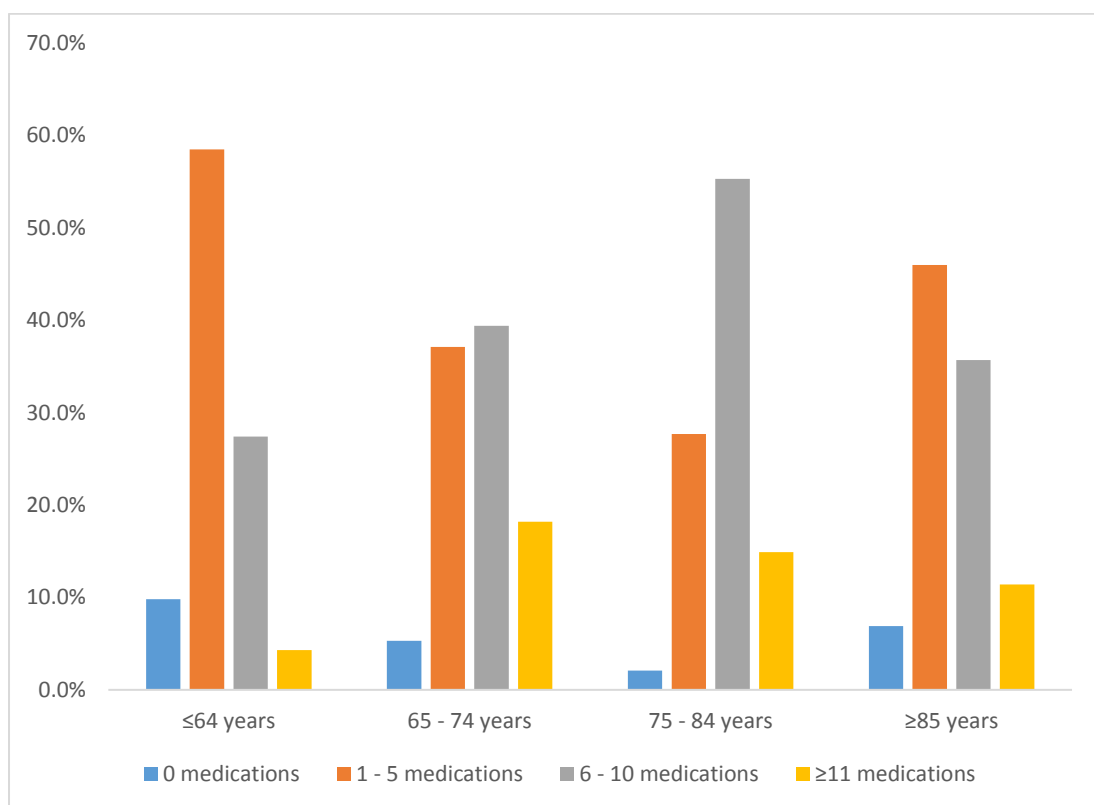
*Statistically significant difference (higher proportions of patients aged >70 prescribed medications in these categories)

Figure 4.6: Polypharmacy and high level polypharmacy according to age (n=350)



There was a significant difference between the numbers of medications prescribed to patients from different age groups ($\chi^2(9) = 39.527$, $p < 0.001$) (**Figure 4.7**). All age groups were equally likely to be prescribed no medications ($\chi^2(3) = 4.818$, $p = 0.186$), however significant differences were seen for the other 3 medication categories 1-5 medications ($\chi^2(3) = 20.958$, $p < 0.001$), 6-10 medications ($\chi^2(3) = 13.694$, $p = 0.003$) and ≥ 11 medications ($\chi^2(3) = 16.843$, $p < 0.001$) (**Figure 4.7**).

Figure 4.7: Numbers of prescribed medications according to age groups



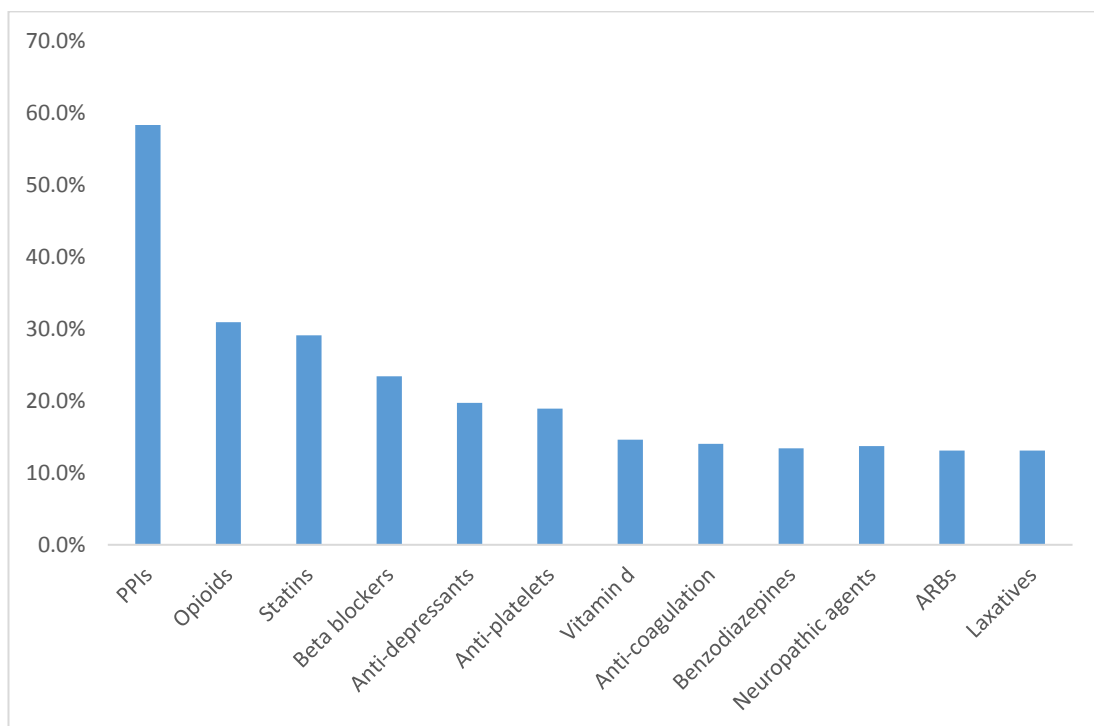
Key Findings 4:

- Seventy seven (63.6%) of older adults (≥ 70 years) and eighty eight (38.4%) younger adults experienced polypharmacy.
- Twenty three (19%) older adults (≥ 70 years) and seventeen (7.4%) younger adults experienced high level polypharmacy.
- Older adults were prescribed a median of 7 regular medications.
- Younger adults are prescribed a median of 4 regular medications.

4.3.9 Medication use according to drug class

The most common non-cancer drug therapies prescribed are displayed in **Figure 4.8**. Almost 6 in 10 (58.3%) were prescribed proton pump inhibitors (PPIs), 1 in 3 (30.9%) were prescribed opioids and 1 in 3 (29.1%) were prescribed statins. Approximately 1 in 5 (19.7%) patients were prescribed anti-depressant medications and 1 in 7 (13.4%) were prescribed regular benzodiazepines. Increasing prevalence of co-morbid illness substantially correlated to increasing medication number with an r-statistic of 0.678, $p < 0.001$.

Figure 4.8 Drug classes most commonly prescribed (n=350)

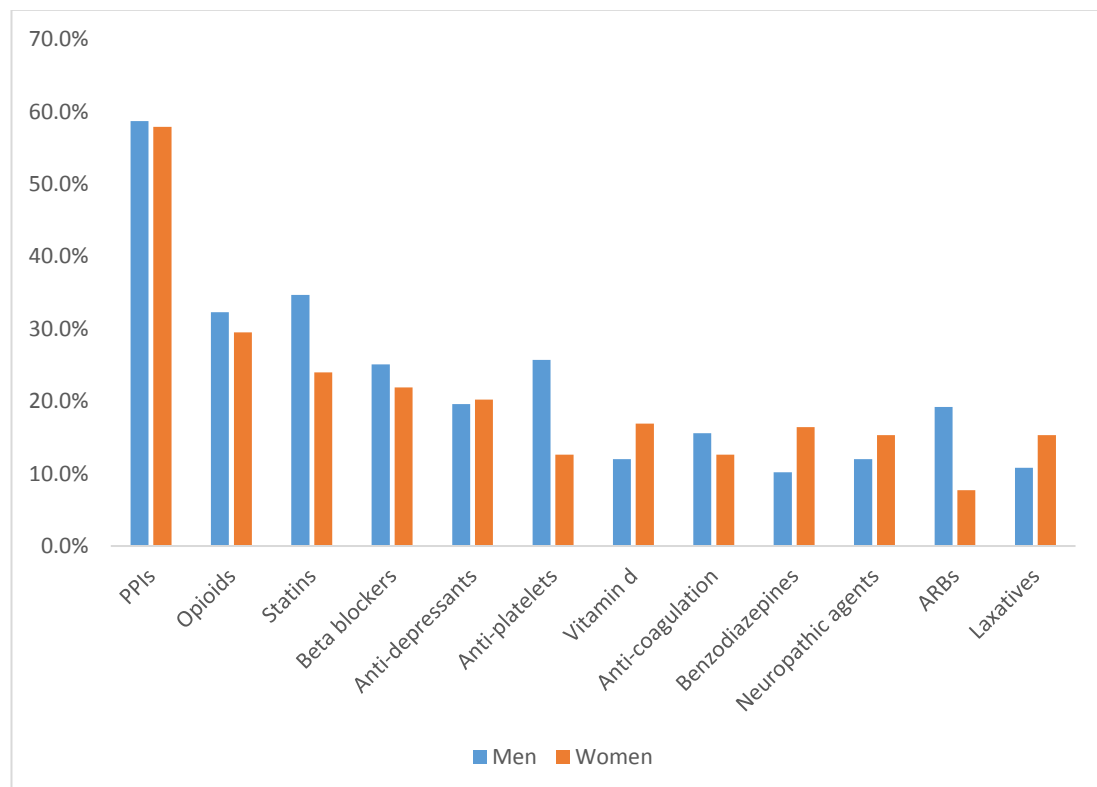


Legend: PPI = proton pump inhibitor, ARBs = angiotensin II receptor blockers

4.3.10 Drug class use according to gender

Differences identified in drug class prescriptions between genders are displayed in **Figure 4.9**. Men were prescribed more angiotensin receptor blockers (ARBs) (19.2% vs 7.7%, $\chi^2(1) = 10.136$, $p = 0.001$), anti-platelets (25.7% vs 12.6%, $\chi^2(1) = 9.913$, $p = 0.002$), statins (34.7% vs 24%, $\chi^2(1) = 4.829$, $p = 0.028$) and alpha-adrenergic blockers (17.4% vs 1.6%, $\chi^2(1) = 25.995$, $p = <0.001$) than women (Figure 4.8). Conversely, women were more commonly prescribed levothyroxine (18% vs 7.2%, $\chi^2(1) = 9.170$, $p = 0.002$). This is in accordance with the differences identified in co-morbid illnesses above. Benign Prostatic Hypertrophy (BPH) was present in one in five men ($n=31$) and accounts for the significantly higher proportion of men on alpha-adrenergic blockade.

Figure 4.9 Drug classes most commonly prescribed according to gender ($n=350$)

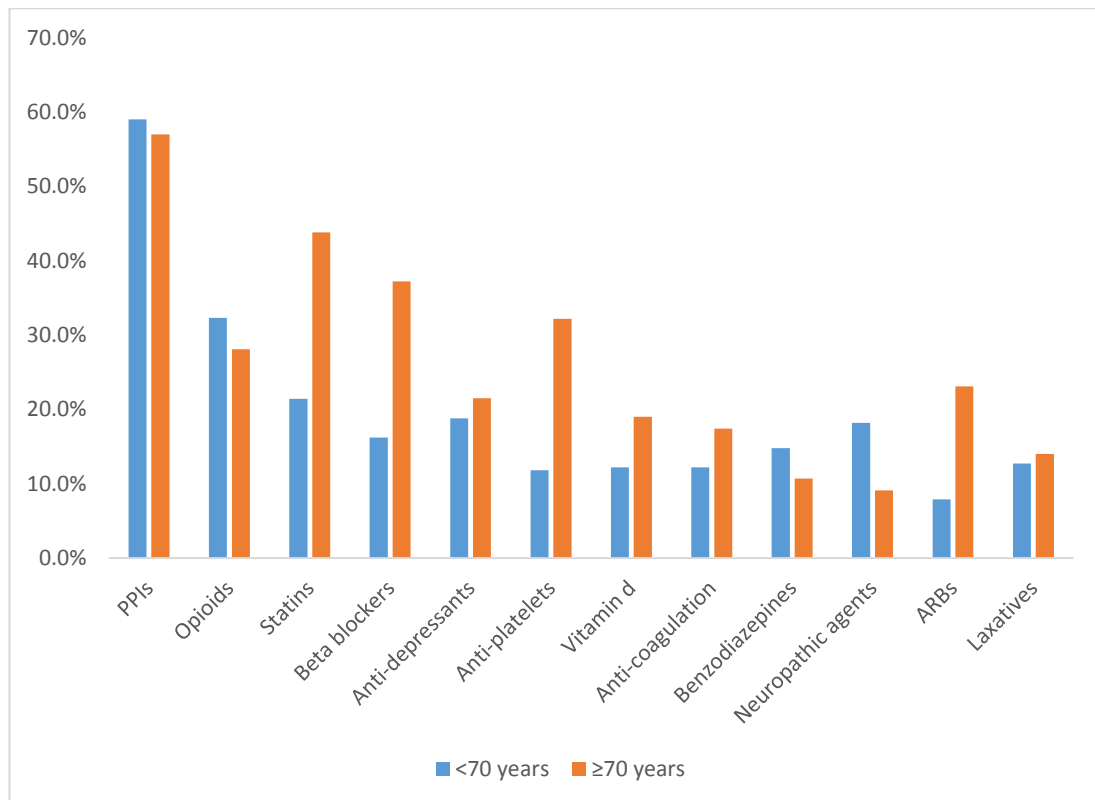


Legend: PPI = proton pump inhibitor, ARBs = angiotensin II receptor blockers

4.3.11 Drug class use according to age

Differences identified in drug class prescriptions between older adults (≥ 70 years) and younger comparators are displayed in **figure 4.10**. Older adults were more commonly prescribed anti-platelet therapy (32.2% vs 11.8%, $\chi^2 (1) = 21.619$, $p < 0.001$), statins (43.8% vs 21.4%, $\chi^2 (1) = 19.244$, $p < 0.001$), ARBs (23.1% vs 7.9%, $\chi^2 (1) = 16.193$, $p < 0.001$) and beta-blockers (37.2% vs 16.2%, $\chi^2 (1) = 19.523$, $p < 0.001$) than younger comparators,

Figure 4.10 Drug classes most commonly prescribed according to age category (n=350)

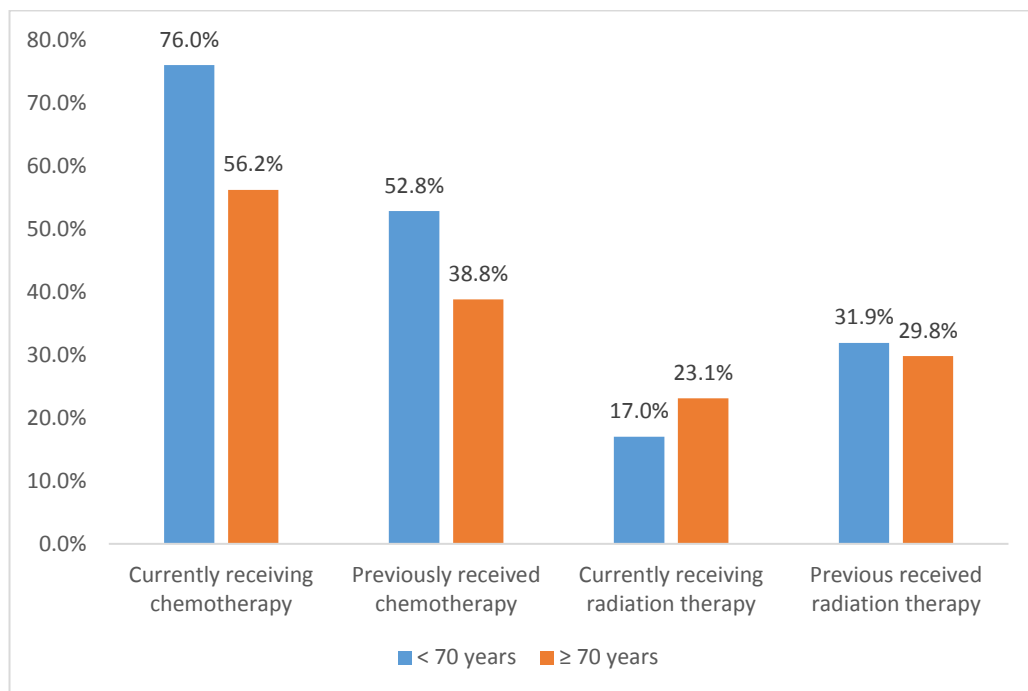


Legend: PPI = proton pump inhibitor, ARBs = angiotensin II receptor blockers

4.3.12 Prescription of chemotherapy and radiation therapy for cancer

Older adults were less likely to be receiving chemotherapy at the time of enrolment (56.2% vs 75%, $\chi^2 (1) = 14.524$, $p < 0.001$). They were also less likely to have received chemotherapy in the past (38.8% vs 52.8%, $\chi^2 (1) = 6.213$, $p = 0.013$). This was not the case for radiation therapy, with both ages equally likely to be receiving radiation therapy (23.1% vs 17%, $\chi^2 (1) = 1.909$, $p = 0.167$) and equally likely to have received same in the past (29.8% vs 31.9%, $\chi^2 (1) = 0.719$, $p = 0.698$) (**Figure 4.11**).

Figure 4.11: Chemotherapy and radiation therapy according to age (n=350)



The most common cancer specific treatments are detailed in **Table 4.13**. In accordance with the most common cancer diagnoses, 5-fluorouracil (18.2%), doxorubicin (12.4%), oxaliplatin (12%) and carboplatin (12%) were the most common chemotherapeutic agents prescribed. The differences in prescriptions rates identified between genders correspond to differences identified in primary cancer

diagnosis. Doxorubicin (12.2% vs 1.7%, $X^2(1) = 11.296$, $p = 0.001$) and oxaliplatin (10.9% vs 3.3%, $X^2(1) = 6.035$, $p = 0.014$) were prescribed significantly more frequently to younger than older adults (**Table 4.14**).

Table 4.13: Most common cancer specific therapies according to gender

Variable	Male n = 167	Female n = 183	Total n = 350	P-value
Number of patients on chemotherapy	114 (68.3%)	128 (69.9%)	242 (69.1%)	0.734
Chemotherapeutic agents				
1. 5-fluorouracil	30 (18%)	14 (7.7%)	44 (18.2%)	0.004*
2. Doxorubicin	11 (6.6%)	19 (10.4%)	30 (12.4%)	0.205
3. Oxaliplatin	21 (12.6%)	8 (4.4%)	29 (12%)	0.005*
4. Cyclophosphamide	9 (5.4%)	20 (10.9%)	29 (12%)	0.060
5. Gemcitabine	9 (5.4%)	14 (7.7%)	23 (9.5%)	0.394
6. Paclitaxel	3 (1.8%)	20 (10.9%)	23 (9.5%)	0.001*
7. Irinotecan	11 (6.6%)	8 (4.4%)	19 (7.9%)	0.361
8. Pemetrexed	7 (4.2%)	7 (3.8%)	14 (5.8%)	0.861
9. Etoposide	12 (7.2%)	2 (1.1%)	14 (5.8%)	0.004*
10. Carboplatin	15 (9%)	14 (7.7%)	14 (5.8%)	0.652

Table 4.14: Most common cancer specific therapies according to age

Variable	< 70 n=229	≥ 70 n=121	Total n = 350	P-value
Number of patients on chemotherapy	174 (76%)	68 (56.2%)	242 (69.1%)	<0.001*
Chemotherapeutic agents				
1. 5-fluorouracil	31 (13.5%)	13 (10.7%)	44 (18.2%)	0.453
2. Doxorubicin	28 (12.2%)	2 (1.7%)	30 (12.4%)	0.001*
3. Oxaliplatin	25 (10.9%)	4 (3.3%)	29 (12%)	0.014*
4. cyclophosphamide	23 (10%)	6 (5%)	29 (12%)	0.101
5. Gemcitabine	18 (7.9%)	5 (4.1%)	23 (9.5%)	0.181
6. Paclitaxel	18 (7.9%)	5 (4.1%)	23 (9.5%)	0.181
7. Irinotecan	14 (6.1%)	5 (4.1%)	19 (7.9%)	0.437
8. Pemetrexed	9 (3.9%)	5 (4.1%)	14 (5.8%)	0.927
9. Etoposide	11 (4.8%)	3 (2.5%)	14 (5.8%)	0.291
10. Carboplatin	18 (7.8%)	11 (9.1%)	14 (5.8%)	0.691

4.3.13 Potentially inappropriate prescribing as determined by STOPP criteria

STOPP criteria for potentially inappropriate medication (PIM) use were applied to 186 patients who were ≥ 65 years (53.1% of study population). PIMs were observed in 136 patients, giving a prevalence rate of 73.1%. Of these, 54 (29%) patients were prescribed 1 PIM, 35 (18.8%) were prescribed 2 PIMs, 26 (14%) were prescribed 3 PIMs, 13 (7%) were prescribed 4 PIMs, 4 (2.2%) patients were prescribed 5 PIMs, 4 (2.2%) patients were prescribed 6 PIMs and 1 (0.5%) patient was prescribed 7 PIMs. Men and women were equally likely to receive 0, 1, 2 or ≥ 3 PIMs ($\chi^2(3) = 6.671$, $p = 0.083$). Increasing medication number, medical conditions and reducing function according to Barthel were substantially correlated to increasing PIM number with r -statistics of 0.622, $p < 0.001$, 0.490, $p < 0.001$ and 0.452, $p < 0.001$ respectively.

The most common PIMs identified are detailed in descending order in **table 4.15**. Almost 1 in 2 (46.8%) participants 65 years and older with a cancer diagnosis were prescribed drugs beyond their recommended duration. Approximately 1 in 3 were prescribed a PPI for uncomplicated PUD/erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks and 1 in 5 were prescribed regular opioids without concomitant laxatives. Both genders were equally likely to be on the above PIMs. One PIM was prescribed more commonly in men i.e. vasodilator drugs with persistent hypotension (10% vs 1.2%, $\chi^2(1) = 6.489$ $p=0.011$).

Table 4.15: Most common PIMs according to STOPP criteria

Variable	Male n = 100	Female n = 86	Total n = 186	P-value
STOPP criteria				
A2: Any drug prescribed beyond recommended duration	45 (45%)	42 (48.8%)	87 (46.8%)	0.601
F2: PPI for uncomplicated PUD/erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks	35 (35%)	30 (34.9%)	65 (34.9%)	0.987
L2: Use of regular opioids without concomitant laxative	21 (21%)	17 (19.8%)	38 (20.4%)	0.835
K4: Hypnotic Z-drugs (↑risk of falls)	16 (16%)	13 (15.1%)	29 (15.6%)	0.868
A1: Any drug prescribed without an evidence-based clinical indication	13 (13%)	15 (17.4%)	28 (15.1%)	0.398
K1: Benzodiazepines (↑risk of falls)	9 (9%)	14 (16.3%)	23 (12.4%)	0.133
D5: Benzodiazepines for ≥ 4 weeks	9 (9%)	12 (14%)	21 (11.3%)	0.287
B6: Loop diuretic as first-line treatment for HTN	8 (8%)	7 (8.1%)	15 (8.1%)	0.972
D2: Initiation of TCAs as first-line antidepressant treatment	6 (6%)	7 (8.1%)	13 (7%)	0.568
L3: Long-acting opioids without short-acting opioids for break-through pain	7 (7%)	5 (5.8%)	12 (6.5%)	0.743
K3: Vasodilator drugs (with persistent postural hypotension)	10 (10%)	1 (1.2%)	11 (5.9%)	0.011*
A3: Any duplicate drug prescription	7 (7%)	4 (4.7%)	11 (5.9%)	0.498

Legend: PPI = Proton pump inhibitor; TCAs = tricyclic anti-depressants, HTN = hypertension

4.3.14 Risk factors for receiving a potentially inappropriate medication according to STOPP criteria

Differences were identified between participants who were prescribed at least 1 PIM and who were not (**Table 4.16**). Patients prescribed at least 1 PIM had more chronic conditions (8.4 (SD3.4) vs 5.2 (SD2.4), $t_{126.266} = 7.13$, $p < 0.001$), a higher CIRS score (18 (12-20) vs 11 (10 - 14), $U = 1724$, $p < 0.001$) and were prescribed a high number of regular medications (8 (IQR6-10) vs 3 (IQR1-4.25), $U = 757.5$, $p < 0.001$).

Table 4.16: Comparison between adults prescribed at least 1 potentially inappropriate medication according to STOPP criteria and adults not

Variable	PIMs (n=136)	No PIMs (n=50)	Total n = 196	P-value
Gender (female)	66 (48.5%)	20 (40%)	86 (43.9%)	0.301
Age, median (IQR)	71 (68 – 76)	71.5 (67.75-75.25)	71 (68-76)	0.833
Range	65 - 90	65 - 90	65 – 90	
Chronic conditions, mean (SD)	8.38 (3.4)	5.22 (2.4)	7.53 (3.4)	<0.001*
Range	2 - 18	2 – 13	2 – 18	
CIRS score, median (IQR)	18 (12-20)	11 (10-14)	14 (11-19)	<0.001*
Range	2 - 30	6 – 21	2 – 30	
Medications, median (IQR)	8 (6-10)	3 (1-4.25)	7 (4 – 9)	<0.001*
Range	0 - 24	0 - 9	0 -24	

Logistic regression was used to determine the influence of age, gender, burden of co-morbidities as defined by CIRS and number of medications on the likelihood of receiving a PIM, as defined by STOPP criteria. The results are detailed in **Table 4.17**. The only factor significantly associated with an increased risk was the number of medications a patient was prescribed, taking into consideration a patient's gender, age and level of morbidity. For every one extra medication prescribed, the odds of receiving a PIM increased by 79.2% (Odds ratio 1.792, 95% CI 1.459 – 2.02, P <0.001).

Table 4.17: Risk factors for receiving a PIM according to STOPP criteria

Variable	B (SE)	Wald	df	p-value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Gender	-.285 (.443)	0.414	1	0.520	0.752	0.216	1.791
Age	-.044 (.038)	1.353	1	0.245	0.957	0.888	1.031
Meds	.584 (.105)	.105	1	<0.001*	1.792	1.459	2.202
CIRS	.025 (.057)	.194	1	0.660	1.026	0.917	1.147
Constan t	.927 (2.695)	.118	1	0.731	2.527		

Legend: Hosmer and Lemeshow χ^2 (8) ≥ 4.185 , $p=0.840$; B = beta value; Snell $R^2=0.356$; Nagelkerke $R^2 = 0.518$; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio; CIRS = cumulative index rating scale

Key Findings 5:

- Three of every four (73.1%) adults' ≥ 65 years were prescribed at least one potentially inappropriate medication (PIM) according to STOPP criteria.
- For every one extra medication prescribed, the odds of receiving a PIM increased by 79.2%.

4.3.15 Potentially inappropriate prescribing as determined by OncPal criteria

Sixteen patients (4.6%) died during their index admission, with a further 111 (31.7%) dying within 6 months of enrolment. In total, 39.1% (n=127) of the total population cohort died. Since these were the patients that preventative therapy was least likely to be of benefit, OncPal criteria were applied to their prescription and clinical data. Both genders were equally likely to die during admission, $\chi^2(1) = 0.035$, $p = 0.831$, but males were more likely to die within 6 months of enrolment, $\chi^2(1) = 5.001$, $p = 0.025$.

PIMs (according to OncPal) were observed in 90 patients, giving a prevalence rate of 70.8%. Of these 90 patients, 32 (25.2%) patients received 1 PIM, 19 (15%) 2 PIMs, 20 (15.7%) 3 PIMs, 11 (8.7%) 4 PIMs, 6 (4.7 %) 5 PIMs, 0 (0%) 6 PIMs and 2 (1.6%) 7 PIMs. Men and women were equally likely to receive 0, 1, 2 or ≥ 3 PIMs ($\chi^2(3) = 3.759$, $p = 0.289$) (see **Figure 4.12**). Similarly, older adults (≥ 70 years) were equally likely to receive 0, 1, 2 or ≥ 3 PIMs ($\chi^2(3) = 3.919$, $p = 0.270$) (see **Figure 4.13**).

The most common PIMs identified by OncPal were intended for treatment of primary or secondary cardiovascular diseases (**Table 4.18**). The three most common drug classes were (i) statins (ii) beta blockers and (iii) PPIs. These were equally

distributed between males and females. One PIM was prescribed more commonly in men i.e. angiotensin receptor blockers (ARBs) (18.6% vs 1.8%, $\chi^2(1) = 9.059$ p=0.003).

Figure 4.12: Percentage of patients with potentially inappropriate medications as determined by OncPal criteria according to gender

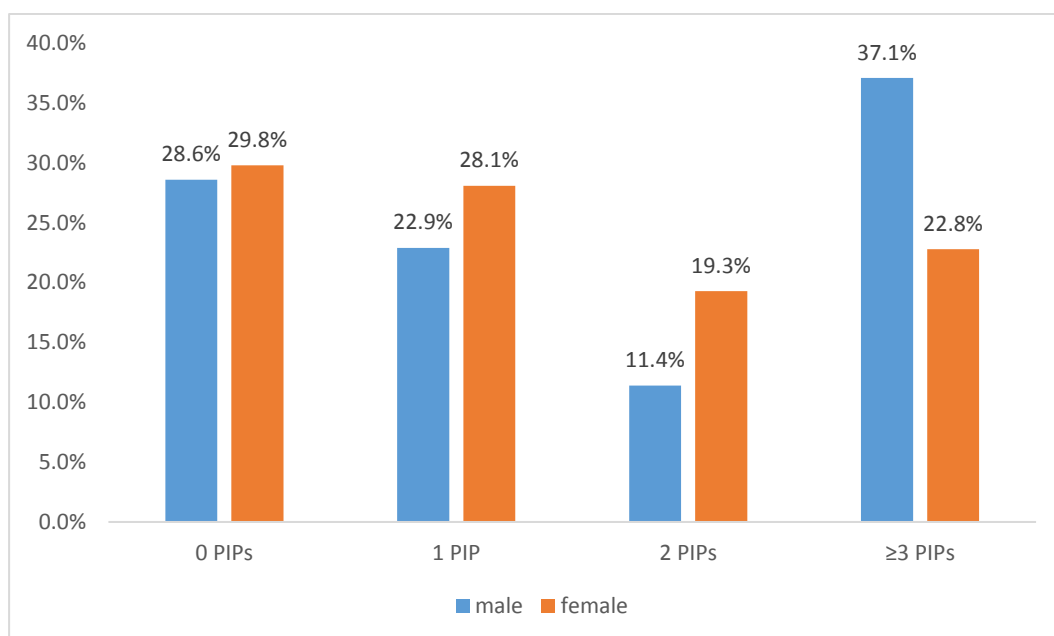


Figure 4.13: Proportions of patients with potentially inappropriate medications as determined by OncPal criteria according to age

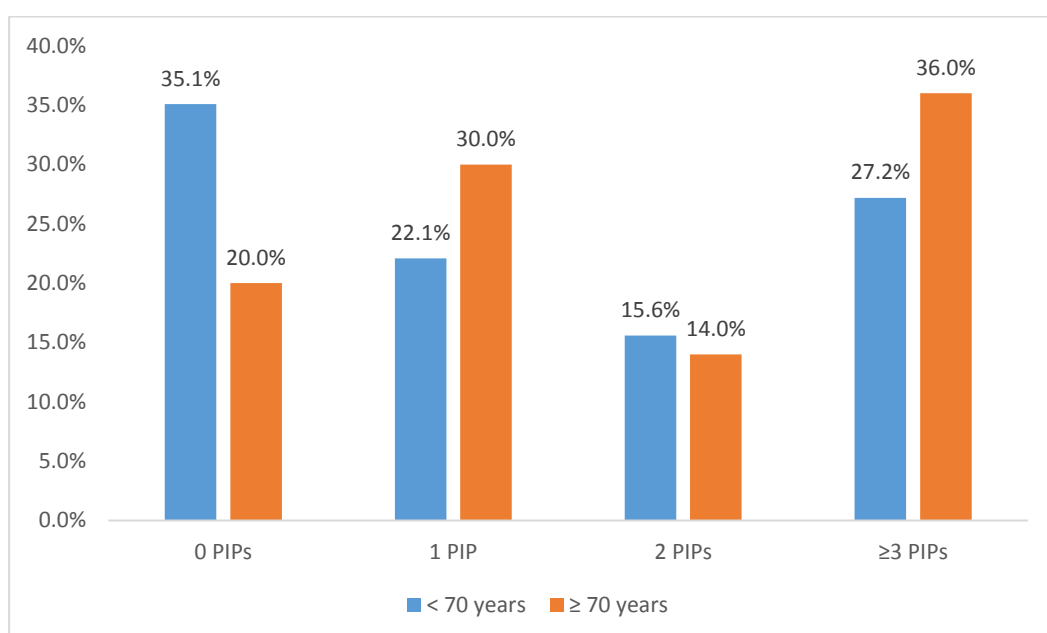


Table 4.18: Most common PIMs according to OncPal criteria in 127 patients

Variable	Male n = 70	Female n = 57	Total n = 127	P-value
OncPal criteria				
Cardiovascular System	37 (52.9%)	22 (38.6%)	59 (46.5%)	0.109
Statins	23 (32.9%)	12 (21.1%)	35 (27.6%)	0.139
Beta blockers	21 (12.6%)	10 (17.5%)	31 (24.4%)	0.104
ARBs	13 (18.6%)	1 (1.8%)	14 (11%)	0.003*
CCB	9 (12.9%)	4 (7%)	13 (10.2%)	0.280
ACE inhibitors	6 (8.6%)	5 (8.8%)	11 (8.7%)	0.968
Thiazides	5 (7.1%)	1 (1.8%)	6 (4.7%)	0.155
Ezetimibe	0 (0%)	2 (3.5%)	2 (1.6%)	0.114
Vitamins (if plasma level not low)	14 (20%)	17 (29.8%)	31 (24.4%)	0.200
Vitamin d	6 (3.6%)	9 (15.8%)	15 (11.8%)	0.210
Folate	7 (4.2%)	6 (10.5%)	13 (10.2%)	0.922
Vitamin b12	2 (2.9%)	4 (7%)	6 (4.7%)	0.272
Multivitamin	1 (1.4%)	2 (3.5%)	3 (3.4%)	0.443
Vitamin c	0 (0%)	2 (3.5%)	2 (1.6%)	0.114
Vitamin b1	1 (1.4%)	0 (0%)	1 (0.8%)	0.365
Alimentary tract and metabolism (prophylaxis of peptic ulcer disease)	19 (27.1%)	10 (17.5%)	29 (22.8%)	0.200
PPIs	19 (27.1%)	10 (17.5%)	29 (22.8%)	0.200
H2 Antagonists	1 (1.4%)	0 (0%)	1 (0.8%)	0.365
Minerals (if plasma level not low)	6 (8.6%)	9 (15.8%)	15 (11.8%)	0.210
Calcium	6 (8.6%)	7 (3.8%)	13 (10.2%)	0.493
Iron	0 (0%)	2 (3.5%)	2 (1.6%)	0.114
Oral Hypoglycaemics	6 (8.6%)	5 (8.8%)	11 (8.7%)	0.968
Sulphonylureas	5 (7.1%)	2 (2.5%)	7 (5.5%)	0.372
Metformin	2 (2.9%)	3 (1.6%)	5 (3.9%)	0.481
DPP4-inhibitors	0 (0%)	2 (2.5%)	2 (1.6%)	0.114
Bloods and blood forming organs (for primary prevention)	2 (2.9%)	3 (5.3%)	5 (3.9%)	0.488
Aspirin	2 (2.9%)	(5.3%)	5 (3.9%)	0.488
Musculoskeletal system (for osteoporosis)	1 (1.4%)	2 (3.5%)	3 (2.4%)	0.443
Bisphosphonates	1 (0.6%)	1 (1.8%)	2 (1.6%)	0.883
Denosumab	0 (0%)	1 (1.8%)	1 (0.8%)	0.266

4.3.16 Risk factors for receiving a potentially inappropriate medication according to OncPal criteria

Differences were identified between participants who were prescribed at least 1 PIM and who were not (**Table 4.19**). Patients prescribed at least 1 PIM according to OncPal criteria were older (69 years vs 57 years, $U = 974$, $p < 0.001$), had more chronic conditions (7.4 (SD3.6) vs 5.8 (SD5.5), $t_{128} = 2.43$, $p = 0.017$), a higher CIRS score (15 (12-19) vs 12 (10 – 15.5), $U = 1106.5$, $p = 0.00s$) and were prescribed a high number of regular medications (6.5 (IQR4.75-10) vs 5 (IQR2.5-7.5), $U = 1002.5$, $p < 0.001$).

Table 4.19: Comparison between adults prescribed at least one PIM according to OncPal criteria and adults without PIMs

Variable	PIMs (n=136)	No PIMs (n=50)	Total n = 196	P-value
Gender (female)	40 (44.4%)	17 (45.9%)	57 (44.9%)	0.877
Age, median (IQR)	69 (59.75-73)	57 (50-70)	67 (57-72)	<0.001*
Range	43 - 90	40 - 79	40 - 90	
Chronic conditions, mean (SD)	7.4 (3.6)	5.8 (5.5)	7 (3.6)	0.017*
Range	2 - 17	1 - 16	1 – 17)	
CIRS score, median (IQR)	15 (12-19)	12 (10-15.5)	14 (11-19)	0.003*
Range	8 - 30	2 - 27	21 - 30	
Medications, median (IQR)	6.5 (4.75- 10)	5 (2.5-7.5)	6 (4-9)	<0.001*
Range	1 - 24	0 - 11	0 - 24	

Legend: PIMs = potentially inappropriate medications, IQR = inter-quartile range, CIRS = cumulative illness rating scale

Logistic regression was used to determine the influence of age, gender, burden of co-morbidities as defined by CIRS and number of medications on the likelihood of receiving a PIP as defined by OncPal criteria. The results are detailed in **Table 4.20**. Both age and number of medications were significantly and positively associated with an increased risk of being prescribed a PIM according to OncPal criteria, taking into consideration the patients' gender and level of morbidity. For every one extra

medication prescribed, the odds of being prescribed a PIM increased by 21.4% (Odds ratio 1.214, 95% CI 1.038 – 1.420, P =0.015). For every one year increase in age, the odds of receiving a PIM increased by 7.3% (Odds ratio 1.073, 95% CI 1.023 – 1.126, P =0.004).

Table 4.20: Risk factors for receiving a potentially inappropriate medication according to OncPal criteria

Variable	B (SE)	Wald	df	p-value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Gender	-.309 (.463)	0.447	1	0.504	0.734	0.296	1.819
Age	-.071 (.024)	8.387	1	0.004*	1.073	1.023	1.126
Meds	.194 (.080)	5.863	1	0.015*	1.214	1.038	1.420
CIRS	.009 (.059)	.023	1	0.879	1.009	0.900	1.132
Constant	.4.681 (1.458)	10.30 2	1	0.001	0.009		

Legend: Hosmer and Lemeshow $\chi^2(8) \geq 12.563$, p=128 0; B = beta value; Snell $R^2=0.176$; Nagelkerke $R^2 = 0.253$; SE = standard error; df = degrees of freedom; Exp (B) = Odds ratio; CIRS = cumulative index rating scale

Key Findings 6:

- Three of every four (70.8%) adults' who died within 6 months of enrolment were prescribed at least one potentially inappropriate medication (PIM) according to OncPal criteria.
- For every one extra medication prescribed, the odds of being prescribed a PIM increased by 21.4%.
- For every one year increase in age, the odds of receiving a PIM increased by 7.3%.

4.3.17 Patients in whom both STOPP and OncPal criteria were applied

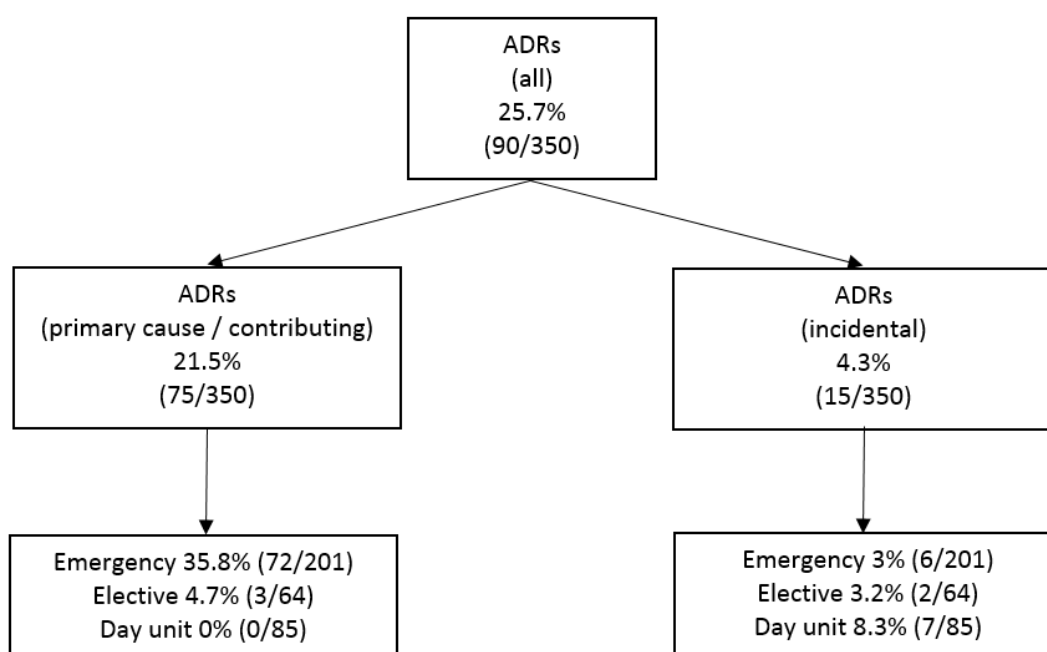
One in five patients (n=77) were aged ≥ 65 years and died within six months of enrolment. These patients were therefore eligible for the application of both STOPP and OncPal criteria. Sixty six of these 77 patients (85.7%) were prescribed at least 1 PIM as per STOPP criteria and 83.1% (n=64) and at least 1 PIM as per OncPal criteria. On further analysis, these patients, were more likely to be on more PIMs according to OncPal than those patients who met the criteria for OncPal alone and not STOPP criteria ($U = 1243$, $p = 0.001$). This was also the case for STOPP criteria ($U = 2742$, $p < 0.001$)

4.3.18 Adverse Drug Reactions in patients with cancer

A total of 274 adverse events (AEs) were identified in 166 (47.4%) participants, of which 139 were identified as being drug related in 90 (25.7%) participants (**Table 4.21**). For 15 of these 90 participants, ADRs did not cause or contribute significantly to admission and were thought to be an incidental findings and therefore trivial. Accordingly, for 75 (21.5%) patients, an ADR caused or contributed significantly to hospital admission (**Figure 4.14**). Of these 75 ADRs, 72 (35.8%) presented as emergency admissions, whereas 3 (4.7%) presented electively i.e. one out of every three *emergency* oncological admissions were drug related and one out of every twenty *elective* oncological admissions were drug related.

Table 4.21: Adverse events (AE) and adverse drug reactions (ADR)

AE name	AE	All ADR	ADR (causing / contributing to admission)
New onset fall/s	16 (4.6%)	6 (1.7%)	5 (1.4%)
New onset unsteady gait	9 (2.6%)	3 (0.9%)	2 (0.6%)
Acute kidney injury	26 (7.4%)	5 (1.4%)	5 (1.4%)
Symptomatic orthostatic hypotension	4 (1.1%)	3 (0.9%)	3 (0.9%)
Major serum electrolyte disturbance	49 (14%)	13 (3.7%)	12 (3.4%)
Symptomatic bradycardia	1 (0.3%)	1 (0.3%)	1 (0.3%)
New major constipation	30 (8.6%)	19 (5.4%)	14 (4%)
Acute bleeding	13 (3.7%)	6 (1.7%)	6 (1.7%)
Acute dyspepsia / nausea / vomiting	52 (14.9%)	30 (8.6%)	29 (8.3%)
Acute diarrhea	25 (7.1%)	17 (4.9%)	10 (2.9%)
Acute delirium	21 (6%)	8 (2.3%)	8 (2.3%)
Symptomatic hypoglycaemia	0 (0%)	0 (0%)	0 (0%)
Other	28 (8%)	28 (8%)	28 (8%)
Total Number	274	139	123
Number of patients involved	166	90	75

Figure 4.14: Adverse drug reactions classification

4.3.19 Types of adverse drug reactions

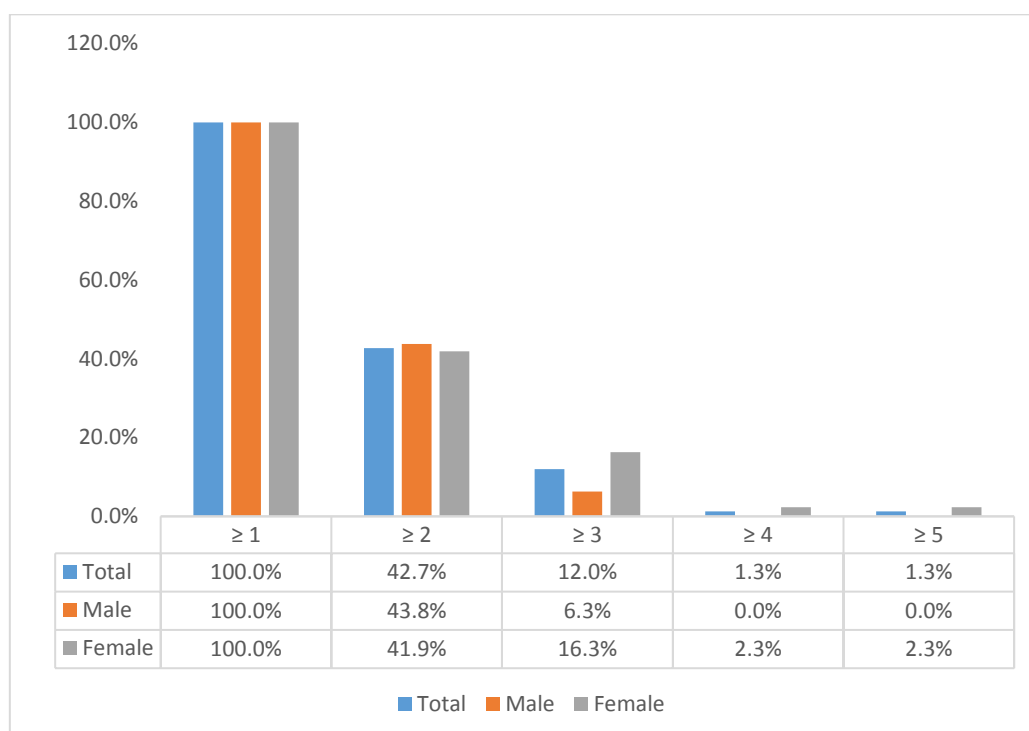
The primary ADR symptoms causing clinical presentation are listed in **table 4.22**. The 12 point **AE Trigger List** identified 64% (n=48) of all ADRs. Older and younger adults were equally like to experience the same type of ADRs ($X^2(17) = 16.434$, $p = 0.493$), as were men and women ($X^2(17) = 23.230$, $p = 0.142$).

Table 4.22: Types of ADRs in order of frequency and according to age

Variable	< 70 years n=229	≥ 70 years n=121	Total n = 350	P-value
				0.493
Neutropenia with infection	15 (6.6%)	3 (2.5%)	19 (5.1%)	
Acute dyspepsia / nausea / vomiting	10 (4.4%)	5 (4.1%)	15 (4.3%)	
New major constipation	10 (4.4%)	2 (1.7%)	12 (3.4%)	
Acute diarrhea	5 (2.2%)	3 (2.5%)	8 (2.8%)	
Acute bleeding	3 (1.3%)	3 (2.5%)	6 (1.7%)	
Acute delirium	0 (0%)	2 (1.7%)	2 (0.6%)	
Symptomatic orthostatic hypotension	1 (0.4%)	1 (0.8%)	2 (0.6%)	
New unsteady gait	1 (0.4%)	1 (0.8%)	2 (0.6%)	
Steroid induced hyperglycaemia	1 (0.4%)	1 (0.8%)	2 (0.6%)	
Steroid induced insomnia	1 (0.4%)	0 (0%)	1 (0.3%)	
Symptomatic bradycardia	1 (0.4%)	0 (0%)	1 (0.3%)	
Electrolyte disturbance	0 (0%)	1 (0.8%)	1 (0.3%)	
Acute liver failure	1 (0.4%)	0 (0%)	1 (0.3%)	
Pancreatitis	1 (0.4%)	0 (0%)	1 (0.3%)	
Urinary retention	0 (0%)	1 (0.8%)	1 (0.3%)	
Anxiety secondary to levothyroxine	1 (0.4%)	0 (0%)	1 (0.3%)	
Mouth sores and neutropenia	1 (0.4%)	0 (0%)	1 (0.3%)	

Thirty two (42.7%) of participants that experienced an ADR had a **Sequence of events** e.g. one patient that presented with new major constipation had associated vomiting and acute kidney injury. Men and women were equally likely to experience a **Sequence of Events**, 43.8% vs 41.9%, $X^2(1) = 0.027$, $p = 0.870$, as were all age groups, $X^2(3) = 1.423$, $p = 0.700$ (**Figure 4.15**).

Figure 4.15: Percentage of patients who experienced adverse drug reactions who had a Sequence of Events (n=75)



Key Findings 7:

- The three most common ADRs experienced by participants were neutropenia with infection, nausea and vomiting and major constipation.
- Less than 1 in 2 (42.5%) participants who experienced an ADR had a ***Sequence of Events***.

4.3.20 Adverse drug reaction causality

As per the WHO causality criteria, medication probably/certainly caused or contributed significantly to admission in 75 (21.5%) cases. ADRs occurred in similar frequencies for older and younger secondary to cancer specific treatment ($\chi^2(1) = 1.292$, $p = 0.295$), non-cancer specific treatments ($\chi^2(1) = 2.603$, $p = 0.107$) and a combination of both ($\chi^2(1) = 1.382$, $p = 0.240$) (**Table 4.23**). Women were more likely to experience an ADR secondary to cancer specific treatment (15.8 vs 6.6%, $\chi^2(1) = 8.060$, $p = 0.005$) and men secondary to non-cancer specific treatment (10.8 vs 7.7%,

$\chi^2(1) = 4.210$, $p = 0.040$) or a combination of both (1.8 vs 0%, $\chi^2(1) = 4.199$, $p = 0.040$)

(Table 4.24). The specific drug classes involved in ADRs are listed in Table 4.25.

Table 4.23: ADR causality according to age

Variable	< 70 years n=229	≥ 70 years n=121	Total n = 350	P-value
ADRs secondary to cancer specific treatments	30 (13.1%)	10 (8.3%)	40 (11.4%)	0.295
ADRs secondary to non-cancer specific treatment	19 (8.3%)	13 (10.7%)	32 (9.1%)	0.107
ADRs secondary to a combination of both	3 (1.3%)	0 (0%)	3 (0.9%)	0.240

Table 4.24: ADR causality according to gender

Variable	Male n = 167	Female n = 183	Total n = 350	P-value
ADRs secondary to cancer specific treatments	11 (6.6%)	29 (15.8%)	40 (11.4%)	0.005
ADRs secondary to non-cancer specific treatment	18 (10.8%)	14 (7.7%)	32 (9.1%)	0.040
ADRs secondary to a combination of both	3 (1.8%)	0 (0%)	3 (0.9%)	0.040

Table 4.25: Drug classes involved in ADRs

Drug class	Total n=75
1 Cancer specific treatments	40 (53.3%)
2 Opioids	13 (17.3%)
3 Steroids	5 (6.7%)
4 Non-steroidal anti-inflammatories	4 (5.3%)
5 Antibiotics	2 (2.7%)
6 Diuretics	2 (2.7%)
7 Thyroid hormone	1 (1.3%)
8 DMARD	1 (1.3%)
9 Anti-cholinergic	1 (1.3%)
10 Alpha blocker	1 (1.3%)
11 Proton pump inhibitor	1 (1.3%)
12 Laxative	1 (1.3%)
13 Cancer specific treatment and anti-emetic	1 (1.3%)
14 Benzodiazepine and opioid	1 (1.3%)
15 Warfarin and DOAC	1 (1.3%)

Legend: DMARD = Disease modifying anti-rheumatic drug, DOAC = Direct-oral anti-coagulants

Key Findings 8:

- ADRs were equally likely to be caused by cancer specific treatment as non-cancer specific treatment in both younger and older (≥ 70 years)
- The three most common drug implicated were cancer specific treatments, opioids and steroids.

4.3.21 Adverse drug reaction severity, predictability and preventability

Of the 75 ADRs causing or contributing significantly to admission 73 (97.3%) were graded as “four” on the Hartwig and Siegel severity scale i.e. any ADR which was the reason for the admission *or* increased the length of stay by at least 1 day. Two ADRS (2.7%) required intensive medical input (grade 5 on Hartwig and Siegel severity scale). Of 75 ADRs, 67 (89.3%) were predictable i.e. were listed in the ‘drugs’ summary of product characteristics of the drugs as being common or very common adverse effect. Using Hallas criteria of avoidability, 22 of 75 ADRs (29.3%) were definitely avoidable, 25 (33.3%) possibly avoidable and 28 (37.4%) unavoidable i.e. 2 out of every 3 ADRs were potentially avoidable.

4.3.22 ADR Risk factors and Outcomes

There were no differences between participants who experience ADRs and those who did not (**Table 4.26**). However, when day unit admissions (patients who attended for a couple of hours for treatment) were removed from analysis, all of whom had no significant ADR, it was identified that patients on chemotherapy had a significantly higher chance of experiencing an ADR than those not currently receiving

chemotherapy ($\chi^2 (1) = 7.749$, $p = 0.005$) (**Table 4.27**). There was no significant difference between patients who experienced an ADR and those who did not in relation to the length of stay (5 (3-10) vs 6 (4-11), $U = 6642$, $p = 0.389$), incidence of death during the index admission (8% vs 5.3%, $\chi^2 (1) = 0.088$, $p = 0.339$) and incidence of death during the 6 months following admission (43.9% vs 44.2%, $\chi^2 (1) = 0.361$, $p = 0.0548$).

Table 4.26: Comparisons between those who experienced ADRs and those who did not

Variable	ADRs (n = 75)	No ADRs (n=275)	Total n = 350	P-value
Gender (female)	47 (57.3%)	140 (50.9%)	183 (52.3%)	0.323
Age, median (IQR) range	65 (56 – 70) 16 - 89	66 (57-72) 18 - 90	65.5 (57-72) 16 - 90	0.599
Chronic conditions, median (IQR) range	6 (4-8) 1 - 15	6 (4-8) 1 - 18	6 (4-8) 1 - 18	0.816
CIRS score, median (IQR) range	13 (10-17) 4 - 29	12 (9-16) 2 - 30	13 (9-16) 2 - 30	0.292
Medications, median (IQR) range	5 (3-8) 0 - 24	5 (3-8) 0 - 22	5 (3-8) 0 - 24	0.502
Length of stay, median (IQR)	5 (3-10)	6 (4-11)	6 (3-10)	0.389
RIP during index admission	6 (8%)	10 (3.6%)	16 (4.6%)	0.109
RIP within 6 months of enrolment	29 (38.7%)	99 (36%)	127 (39.1%)	0.364
Currently on chemotherapy	55 (73.3%)	187 (68%)	242 (69.1%)	0.375

Table 4.27: Risk factors associated with ADRs (Day unit patients excluded)

Variable	ADRs n = 75	No ADRs n=190	Total n = 265	P-value
Gender (female)	43 (57.2%)	99 (52.1%)	142 (53.6%)	0.442
Age, median (IQR) range	65 (56-70) 16 - 89	66 (57-72) 18 - 90	66 (57-72) 16 - 90	0.494
Chronic conditions, median (IQR) range	6 (4-8) 1 - 15	6 (4-8.25) 1 - 18	6 (4-8) 1 - 18	0.753
CIRS score, median (IQR) range	14 (10-18) 2 - 30	13 (10-17) 4 - 29	14 (10-17.5) 2 - 30	0.503
Medications, median (IQR) range	5 (3-8) 0 - 24	6 (3-9) 0 - 18	6 (3-9) 0 - 24	0.637
Length of stay, median (IQR) range	5 (3-10) 0 - 41	6 (4-11) 0 - 68	6 (3-10) 0 - 69	0.389
Death during index admission	6 (8%)	10 (5.3%)	16 (6%)	0.399
Death within 6 months of enrolment	29 (43.9%)	84 (44.2%)	113 (47.1%)	0.548
Currently on chemotherapy	55 (73.3%)	104 (54.7%)	157 (60%)	0.005*

Logistic regression was used to determine the influence of age, gender, chemotherapy, number of conditions and number of medications on the risk of experiencing an ADR (**Table 4.28**). No predictor variables were identified.

Table 4.28: Risk factors for experiencing an ADR

Variable		B (SE)	Wald	df	p-value	95% CI for Exp (B)	
						Lower	Upper
Gender	Female	-.255 (.267)	.913	1	.339	.775	.459 1.307
Age		-.004 (.012)	.104	1	.747	.996	.973 1.020
chemo		-.297 (.307)	.939	1	.333	.743	.407 1.356
Medications		.007 (.057)	.017	1	.897	1.007	.901 1.127
Conditions		-.028 (.043)	.430	1	.512	1.029	.945 1.120
Constant		-.1.061 (.698)	2.310	1	.339	.775	.459 1.307

Homer and Lemeshow $\chi^2 (8) \geq 5.054$, $p=0.752$, Model $\chi^2 = 361.003$, Cox and Snell $R^2 = 0.008$, Nagelkerke $R^2 = 0.012$, B = beta-value, SE = standard error, df = degrees of freedom, CI = confidence interval, Exp (B) = Odds ratio, Medications = number of medications, Conditions = number of conditions

Key Findings 9:

- Nine of every ten (89.3%) ADRs were predictable.
- Twenty two (29.3%) of ADRs were definitely avoidable.
- Twenty five (33.3%) were possibly avoidable.

4.4 DISCUSSION

This is the first study in Ireland to identify and classify patients with cancer according to age, morbidity burden, medication and PIM use. It is also the first study internationally to assess ADRs in a robust manner in this population.

This study identified that 1 in 3 (34.5%) patients attending oncologists are 70 year and older. It also identified that nearly all patients (96.9%) attending oncologists

are multimorbid with 68% of participants having ≥ 5 chronic conditions. Four in every five (81.1%) older adults (≥ 70 years) have ≥ 5 chronic conditions compared to more than one in every two (60.7%) younger adults. Older adults had a significantly higher burden of comorbidity as determined by their CIRS scores. Cardiovascular conditions were highly prevalent with approximately 1 in 2 having a diagnosis of hypertension and dyslipidaemia, 1 in 7 having a diagnosis of IHD and DM and 1 in 10 having a diagnosis of atrial fibrillation.

Polypharmacy and high level polypharmacy were identified in 47.1% and 11.4% respectively. Their prevalence was significantly higher in older adults compared to younger adults, 63.6% vs 38.4% and 19% vs 7.4% respectively. Older adults were less likely to be prescribed chemotherapy and less likely to have received chemotherapy in the past. Three out of every four (73.1%) adults' ≥ 65 years were prescribed at least one PIM according to STOPP criteria, one in four received ≥ 3 PIMs. This was also the case for those eligible for the application of OncPal criteria; 3 in every 4 (70.8%) were prescribed at least 1 PIM and 1 in every 3 received ≥ 3 PIMs.

Ninety (25.7%) patients experienced an ADR. For 75 (21.5%) patients admissions to the oncology service (emergency, elective or day unit), ADRs caused or contributed significantly to hospital admission. ADRs were more prevalent in those presenting as emergency admissions i.e. ADRs cause/significantly contributed to 1 in 3 (35.8%) emergency admissions. ADRs were equally likely to be caused by cancer specific treatment as non-cancer specific treatment with no difference in rates identified between older and younger adults. Of these ADRs, 89.3% were predictable and 62.6% possibly or definitely avoidable i.e. approximately 2 of every 3 were

potentially avoidable. Chemotherapy, opioids, steroids and NSAIDs were the most common drugs implicated. One in twenty (4.6%) patients enrolled died during the index admission with 4 out of 10 (39.1%) dying within the following 6 months.

As predicted for patients with cancer, cancer is often one of several diagnoses. This has implications for the management and treatment of cancer as many of the medications involved in cancer treatment regimens have the potential to worsen other diagnoses e.g. corticosteroid use in diabetes mellitus. Despite their multimorbidity, these patients were almost exclusively functionally independently and cognitively intact, with a lower average age than expected of 63.6 years. This suggests that perhaps older adults with medium to severe level dependency or moderate to severe cognitive impairment either (i) do not get referred to oncology specialists for assessment or (ii) do but they are not put forward for intensive treatment regimens. This could mean that appropriate patient selection occurs, however we have to ensure that patients who could benefit from treatment, have a discussion regarding this with a thorough risk benefit assessment.

In accordance with earlier studies the prevalence of polypharmacy and high level polypharmacy was high. Approximately every second patient (47.1%) was prescribed 6 or more medications and 1 out of every 10 (11.4%) were prescribed ≥ 11 medications. Some of the most commonly prescribed drugs identified in this study have the potential to interact with chemotherapy e.g. 5-fluorouracil increases the level of warfarin. During treatment with chemotherapeutic agents up to 30% will experience nausea, vomiting or diarrhoea. This can have implications for other medications specifically antihypertensive agents, which when fluid depleted, could

provoke dizziness and falls. Ongoing diuretic use in this context could increase the risk of a patient developing an acute kidney injury with continued use. The vast majority of cancer drugs, as expected, are prescribed by oncologists but the vast majority of other drugs are prescribed by patients' General Practitioners (GP) or other hospital specialists. It is pertinent that there is clear communication between these specialists. An extensive knowledge of chemotherapeutic agents and medications required to treat other conditions is required to assess risk and adjust medications accordingly. At present, this is not the sole responsibility of any one doctor. Often once a cancer diagnosis is made, patients and other doctors defer to the treating oncologist for treatment of all ailments.

Similar to other patient populations, PIM prescription was highly prevalent in this cohort. This increases medication burden and places patients at an increased risk of ADRs. Additionally, this can place a financial burden on an already stretched healthcare system. The discussion around deprescribing of medications with patients with cancer is challenging. Deprescribing of medications, even if inappropriate, can be viewed by patients as withdrawal of care, in a time that presents many psychological difficulties. This is supported by the findings of this study that identified that 1 in 4 patients had a diagnosis of depression or anxiety and that 13.4% of patients were prescribed benzodiazepines on a daily basis. Tapering or stopping of medications can often lead to a discussion around end of life care. It is important a clear discussion is had with patients regarding medication use addressing the risks of continued use so that patients understand that it is not withdrawing of care, but rather the optimisation of prescribing to reduce potential risks e.g. interactions between a regular medication and chemotherapy.

Worryingly, 1 in 10 patients continued to smoke despite their cancer diagnosis and 1 in 10 continued to drink more than the recommended weekly alcohol allowance. Alcohol in small amounts can be good for patients (e.g. appetite stimulation), but in excess can be harmful and can interact with chemotherapy. Its use in patients who are already on many high risk medications i.e. chemotherapy (69.1%), anticoagulation (14%), opioids (30%), steroids (12.3%), benzodiazepines (3.4%), z-drugs (11.1%) and neuroleptics (5.1%), potentially places these patients at a higher risk of ADRs.

The most common non-cancer specific treatments implicated in ADRs were medications that are commonly implicated in ADRs in the acute (non-cancer) population i.e. opioids, steroids and NSAIDs. This highlights that the high risk medicines, regardless of the patient population, are the ones that most likely cause ADRs. This offers an opportunity to intervene in prescribing practices early and thus either avoid ADRs or improve their recognition so that they can be identified early and adverse consequences can be minimised or avoided.

This study has some limitations. Firstly it was limited by the small sample size. For the sample size calculation at the start of the study, it was predicted that 313 older adults would be required to estimate the true prevalence of PIM according to STOPP criteria in this population. Unfortunately, this was not feasible for two reasons; (i) time allocated to the study and (ii) inability to recruit from the radiation oncology day unit. In total, 186 older adults were enrolled i.e. 59% of the target amount required. In the pilot phase of this study, the logistics of recruiting radiation oncology patients was identified as challenging secondary to (i) limited space and (ii)

the time patients spend in hospital undergoing treatment. Space was allocated to this research for one afternoon a week. Frequently patients attend for radiation treatment weekly at the same day, with patients with the same cancer diagnoses allocated the same time slots. This would have biased our sample. Additionally, patients spend a short time receiving radiotherapy (i.e. approximately 10 -15 minutes), and are therefore eager to receive treatment and leave. Perhaps if the radiation oncology day unit had been included in this study our overall sample population would have been older, more functionally and cognitively impaired and on more medications. Even so, our results are consistent with the rates of PIM identified by the Nightingale study (179), supporting this high PIM prevalent rate.

Another limitation of this study was the exclusion criteria i.e. the ability to only recruit patients on one admission. Prevalence rates of multimorbidity, medication use and PIM are accurate because of this, however it is possible that ADRs were missed due to the exclusion of repeat admissions.

This study highlights the importance of an integrated care approach for patients with cancer, particularly older adults. Older adults could benefit from gerontology input, as well as ongoing GP input at the time of cancer diagnosis as well as during treatment. During treatment for cancer, the risk of drug-drug and drug-disease interactions is likely at its highest. This is a key time for comprehensive geriatric assessment to (i) adjust medications, (ii) optimise other chronic conditions and (iii) optimise both cognitive and functional ability through a multi-disciplinary approach. The application of prescribing tools such as STOPP and OncPal could assist in reducing medication burden in a structure fashion as well as avoiding ADRs. Going

forward medication reviews are an important part of the treatment of cancer and both oncologists and GPs need to be educated regarding their potentially for harm during this high risk time. The use of the ADR trigger list could assist oncologists to identify ADRs and in doing so deprescribe or adjust medications accordingly, so that repeated ADRs do not occur.

The prescription of preventative medications, as determined by OncPal criteria, in patients with cancer and a poor prognosis, was highly prevalent. The prescription of preventative medications in the acute (non-cancer) older frailer population with a poor survival prognosis is an evolving entity with limited evidence available to guide best practice. On reviewing all common explicit prescribing tools to date, none address this. STOPP (36, 37), Beers (63-67) and FORTA (68, 69) criteria all look at PIMs in the general older population and NORGEF-NH (135) criteria addresses PIMs in the nursing home population. However no prescribing tool to date addresses the deprescription of preventative medications in older frailer multimorbid patients with a poor survival prognosis, regardless of place of residence. NORGEF-NH addresses prescribing in nursing homes, but fundamentally doesn't acknowledge that not all patients living in residential care are frail, multimorbid with a poor survival prognosis. The following chapters will discuss the development, validation and inter-rater reliability (IRR) of a new explicit prescribing tool (STOPPFrail criteria) to address this. The final chapter will apply STOPPFrail criteria to a representative population.

CHAPTER 5:

STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited
life expectancy): Consensus validation

5.1 INTRODUCTION

Many explicit prescribing tools have been developed to guide clinicians on cessation of potentially inappropriate medications (PIMs) in older adults; the most commonly cited are Beers criteria (63-67), STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert doctors to Right Treatment) criteria (36, 37) and FORTA (Fit FOR The Aged) criteria (68, 69). These explicit tools are designed to detect common instances of potentially inappropriate medication (PIM) use in the general older population. In chapters 3, I reported PIM prevalence according to STOPP/START criteria (36, 37) in an unselected population of older adults presenting with acute illness and requiring hospital admission. Similarly, in chapter 4, I reported on the prevalence of PIMs in patients attending a medical oncology service using STOPP/START criteria (36, 37) and OncPal (Oncological palliative care deprescribing guideline) (192). It is evident that existing explicit criteria for PIM identification are unsuitable for older frail adults with multiple co-morbidities, high levels of functional dependency and a poor survival prognosis, a population which is becoming increasingly prevalent and is increasingly encountered in clinical practice (3).

Older patients are now surviving longer with complex co-morbid illnesses including cancer, dementia, chronic kidney disease, cardiovascular disease, cerebrovascular disease and chronic lung disease, many of which contribute to frailty and poor survival prognosis (193, 194). Chronic illnesses, together with the effects of physiological ageing can impact negatively on cognitive and physical functional ability. In such patients, the final months of life are often characterised by frailty and increased dependency, necessitating re-evaluation of drug treatment goals. In these

circumstances, medications intended to have long-term preventative effects such as lipid-lowering drugs, anti-diabetic agents and cognitive enhancing drugs may no longer be appropriate. This is well recognised by doctors and patients. However, polypharmacy and inappropriate prescribing (IP) remain highly prevalent in this patient population (195, 196), placing these individuals at an increased risk of adverse drug reactions (ADRs), hospitalisation and death. Accordingly, appropriate deprescribing of medications needs to be considered in frailer, multi-morbid patients with a poor survival prognosis.

5.1.1 Deprescribing in frail older adults

Deprescribing is defined as “the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes” (131). It involves (i) reviewing all medications prescribed, (ii) identifying those medications that are inappropriate, (iii) deciding when and how these medications should be tapered, reduced or stopped and (iv) arranging adequate monitoring and follow-up (132). Healthcare professionals, patients and their relatives all acknowledge the burden of polypharmacy for older frail adults, yet all groups display passivity towards deprescribing (133). There are many barriers to deprescribing, which are listed in **Table 5.1** (132-134, 197, 198). As a consequence of these challenges, less than half of attending clinicians use a consistent approach to deprescribing (134) and many clinicians avoid it completely.

Table 5.1 Barriers to deprescribing

Patient factors
Patients' preference/resistance to change
Patients' communication ability
Organisational factors
Time constraints
Access and maintenance of medical and pharmacy records
Inter-professional relationships/prescribers from multiple specialties
Limited training of nursing staff
Nursing preferences/resistance to change
Co-ordinating and involving all relevant personnel e.g. pharmacists
Physician factors
Deficiency of knowledge
Fear of causing adverse events
Fear of litigation
Ease of following the "path of least resistance"
Concern that it may initiate end of life/life expectancy discussions
Lack of motivation
Research factors
Lack of deprescribing guidelines
Lack of evidence based research on deprescribing
Single-disease guidelines driving prescribing and hindering deprescribing

The growing burden of polypharmacy and IP has promoted national bodies in the UK and Ireland such as the National Institute for health and Care Excellence (NICE) (199-201) and Health Information Quality Authority (HIQA) (202, 203), to offer guidance on deprescribing. NICE recommends annual medication reviews for care home residents, during which appropriateness of medications should be optimised and medications deprescribed where necessary (199). Similarly they recommend review of medications for community dwelling older adults with chronic diseases, however no time frame is suggested (200, 201). Despite this, to date, no explicit guidelines exist for deprescribing in frailer older adults with poor one year survival prognosis, other than NORGE-PNH criteria, which are specific to the nursing home population (135).

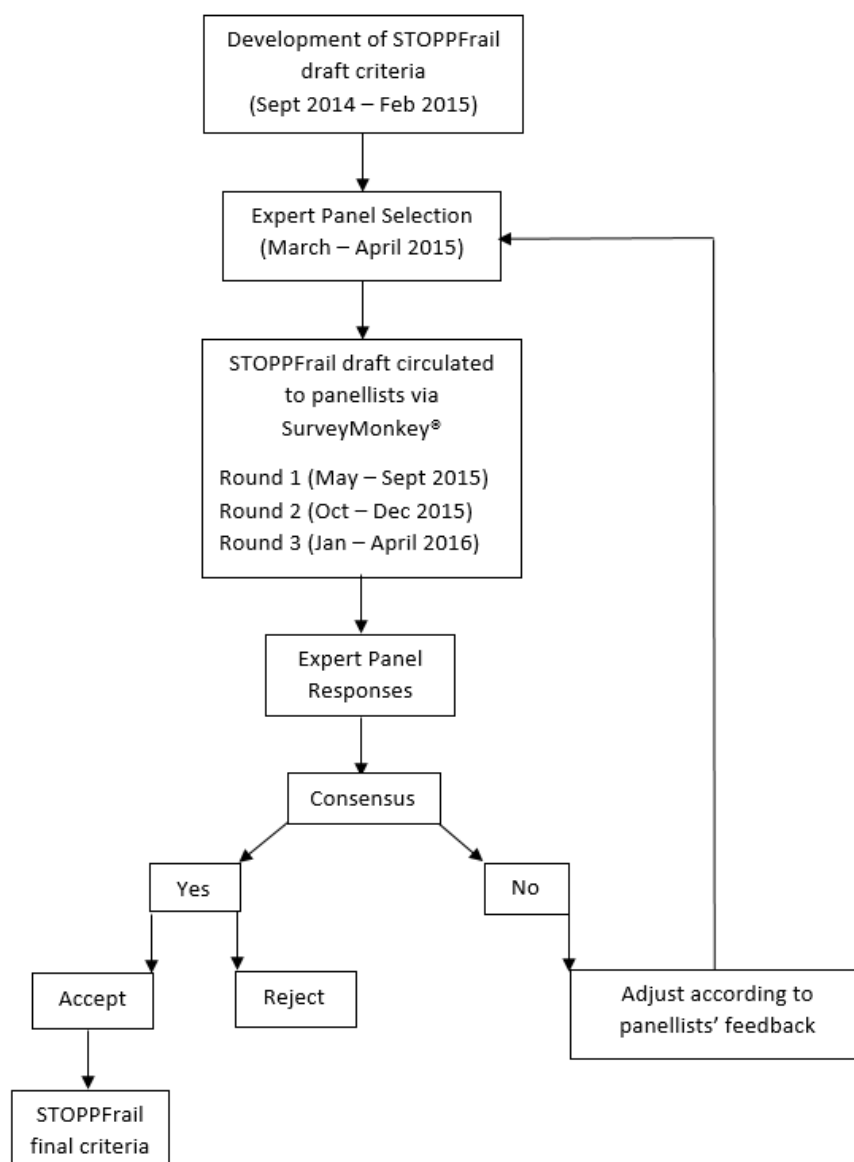
5.1.2 Objectives

There is an accepted need for deprescribing in the frailer older population and a clear associated need for specific explicit criteria to guide the prescriber. With these considerations in mind, the principal objective of this research was to devise and validate an explicit set of criteria, using the Delphi technique, aimed at assisting physicians with the challenging task of deprescribing medications in older frail adults with limited life expectancy. It was envisaged that this tool could be used in all healthcare settings where such patients are encountered. The work undertaken in this chapter, including study design, data collection and statistical analysis, is entirely my own.

5.2 METHODS

The study timeline is detailed in **Figure 5.1**. This study involved four phases: (i) local development of draft criteria; (ii) comprehensive literature review to support the inclusion of draft criteria; (iii), use of Delphi consensus methodology and selection of expert review panel and (iv) determination of content validity of the criteria using the aforementioned technique. Each of these phases are described below.

Figure 5.1 Delphi consensus method of validation



5.2.1 Local development of draft criteria

Prof. Denis O'Mahony (senior academic consultant/geriatrician, University College Cork), Dr. Paul Gallagher (senior academic consultant/geriatrician, University College Cork), Dr. Carole Parsons (academic pharmacist, Queen's University Belfast), all of whom have recognised expertise in geriatric pharmacotherapy, and I were involved in the original development of the deprescribing tool. It was decided that the tool should: (i) have an appropriate name to reflect its purpose, (ii) include a clear definition of the target patient population, (iii) incorporate common instances of PIM encountered in clinical practice in frail older people with poor survival prognosis, (iv) be concise and lend itself to be time-efficient and easy to use, and (v) be based on the most current up to date evidence available. Medication appropriateness would be assessed according to the risk-benefit definition i.e. it is appropriate to prescribe an indicated medication if its potential benefit outweighs its' potential risk of harm, while considering patients' comorbidities, co-prescribed medications and altered physiology associated with ageing and disease progression. These five components were considered to be mandatory for development of a deprescribing tool that could easily be used in both the clinical and research setting.

The deprescribing tool was named STOPPFrail (Screening Tool of Older Person's potentially inappropriate Prescriptions in Frail adults with limited life expectancy), in an attempt to highlight the proposed appropriate target subpopulation of older people. Similar to STOPP/START criteria (36, 37), the initial draft of STOPPFrail indicators was arranged according to physiological systems. For patients to be suitable for medication review according to STOPPFrail criteria, four eligibility criteria were proposed (**Table 5.2**). Since the most consistent predictors of

mortality are the number and severity of co-morbid conditions and associated functional impairment (140), our definition of patients in whom deprescribing would be appropriate or desirable according to STOPPFrail criteria was based on these essential indicators, rather than the presence of specific diseases, such as dementia or cancer. In addition, relevant challenges associated with medication use in this population, such as administration time and physical discomfort were proposed for incorporation into the tool, as these issues have been reported by healthcare professionals, patients and their families to be of concern in frail older adults (133).

It was envisaged that STOPPFrail criteria would be used by all physicians who come in contact with frailer older adults with a limited life expectancy, regardless of their own specialty and the location of the assessment (acute hospital, primary care or long-term residential units). However, in order to apply the STOPPFrail tool, physicians would need to have access to patients' diagnoses, and medication lists, as well as their measured cognitive and functional status details.

Table 5.2 Proposed definition of target population

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:
End-stage irreversible pathology
Poor one-year survival prognosis
Severe functional impairment or severe cognitive impairment or both
Symptom control is the priority rather than prevention of disease progression

5.2.2 Comprehensive literature review to support draft criteria inclusion

The evidence base to support the use of each drug or drug class in frailer older patients with limited life expectancy was checked using the British National Formulary and an extensive literature review, limited to the last 20 years. Drugs and drug classes were selected based on clinical judgement of the authors as well as available data on inappropriate prescribing in patients with limited life expectancy. Literature searches of the PubMed, Cinahl and Google Scholar databases were undertaken. Searches included the drug in question combined with key words i.e. “life expectancy”, “frailty”, “older adults”, “poor prognosis”, “deprescribing”, “inappropriate prescribing”, “adverse drug reactions” and “adverse drug events”. Randomised control trials (RCTs), systematic reviews and up-to-date guidelines were included. Where none of the above was found, observational studies were reviewed. Articles had to be written in the English language and include older adults. The panel was provided with an electronic repository containing supporting references for the proposed STOPPFrail criteria.

5.2.3. Use of Delphi consensus methodology and selection of expert panel

The Delphi consensus method was used for this research. It is a well-established method that aims to gather information from persons in the domain of their relevant expertise, with the goal of reaching a group consensus on a complex subject where information is lacking. In this instance, the complex subject in question is potentially inappropriate medication use in older frailer adults with poor survival prognosis. Delphi panellists must have expertise in the topic under consideration and the panel

as a whole should represent all relevant parties concerned with the topic. Anonymity should be maintained throughout the process to avoid counterproductive argument and confrontation between panellists. Discussion outside of the process is generally discouraged during the process, although face-to-face panel discussion at the end of the process when reaching conclusions is not unusual. This technique has been used for the successful development of other explicit prescribing criteria in the past e.g. Beers criteria (63-67) and STOPP/START criteria (36, 37). The Delphi consensus method is illustrated in **figure 5.1**. It was the chosen methodology for this research due to the paucity of randomised controlled clinical trial evidence supporting the long term benefits of preventive drugs in frailer older adults with complex co-morbidities and limited life expectancy. Such patients are commonly excluded from clinical trials of drug therapies (51).

In March 2015, twenty five experts, were invited to participate in the Delphi process. Panellists were selected on the basis of their recognised academic credentials, clinical practice, experience and geographical diversity. After the study design and aims were explained to each participant, seventeen of the twenty five agreed to participate. The eight individuals who declined were spread across the participating specialties (**Table 5.3**). The final panel consisted of academic consultant geriatricians (n=6), clinical pharmacologists (n=3), psychiatrists of old age (n=1), palliative medicine physicians (n=3), senior academic primary care physicians (n=2) and clinical pharmacists with an interest in geriatric pharmacotherapy (n=2) (**Table 5.4**). All of the panellists were affiliated with Irish university teaching hospitals and two were practicing in Northern Ireland. Panellists completed the Delphi process between May 2015 and April 2016.

Table 5.3 Description of the Delphi assessment panel according to occupation

Specialty	Invited	Participated
Physicians in Geriatric Medicine	8	6
Clinical pharmacologists	4	3
Palliative care physicians	6	3
General Practitioners	3	2
Old age psychiatrists	2	1
Clinical pharmacists	2	2

Table 5.4: Expert panellists who participated in Delphi validation of STOPPFrail

Name	Discipline	Place of practice
1 Prof. Joe Harbison	Geriatric Medicine	St James's Hospital, Dublin
2 Prof. Lorraine Kyne	Geriatric Medicine	Mater Misericordiae, Dublin
3 Prof. Riona Mulcahy	Geriatric Medicine	University Hospital Waterford
4 Prof. Sean O'Keeffe	Geriatric Medicine	University College Hospital Galway
5 Prof. Peter Passmore	Geriatric Medicine	Queen's University Belfast
6 Dr. Suzanne Timmons	Geriatric Medicine	Mercy University Hospital, Cork
7 Prof. Michael Barry	Clinical Pharmacology	St James's Hospital, Dublin
8 Prof. John Stinson	Clinical Pharmacology	Trinity College, Dublin
9 Prof. David Williams	Clinical Pharmacology	Beaumont Hospital, Dublin
10 Dr. Brian Creedon	Palliative care	University Hospital Waterford
11 Prof. Tony O'Brien	Palliative care	Marymount & Cork University Hospital
12 Prof. Max Watson	Palliative care	Northern Ireland Hospice, Belfast
13 Prof. Tom O'Dowd	General Practice	Trinity College, Dublin
14 Prof. Henry Smithson	General Practice	University College Cork
15 Prof. Brian Lawlor	Psychiatry of Old Age	St James's Hospital, Dublin
16 Prof. Stephen Byrne	Clinical Pharmacy	University College Cork, Cork
17 Dr. Cristin Ryan	Clinical Pharmacy	Royal College of Surgeons of Ireland

5.2.4 Determination of content validity of the criteria

Each round was sent to the panellists using an online survey [SurveyMonkey®]. The first Delphi round consisted of 30 proposed criteria with each criterion presented in a standardized format i.e. a drug or drug class deemed potentially inappropriate followed by an explanatory sentence (see **Appendix 10**). An example of such a statement is displayed in **Figure 5.2**. Panellists rated their agreement with each statement on a 5-point Likert scale, where 5 = strongly agree, 4 = agree, 3 = neutral, 2 = disagree, 1 = strongly disagree, 0 = unable to offer an opinion (204). In round 1, panellists were also asked to offer suggestions or comments (including new drugs) as appropriate on the proposed criteria.

For each statement, consensus was based on the median Likert scale response and interquartile range. A median value of 4 or 5 with a 25th centile of ≥ 4 was accepted for inclusion in the tool i.e. only statements with at least 75% of respondents agreeing or strongly agreeing were included. Proposed criteria with a median value of ≤ 3 were rejected: those with a median value of 4 or 5 and a 25th centile of < 4 were rephrased in accordance with panellists' suggestions and included in the next Delphi round. Statistical analysis was performed using IBM SPSS® Statistics version 22.

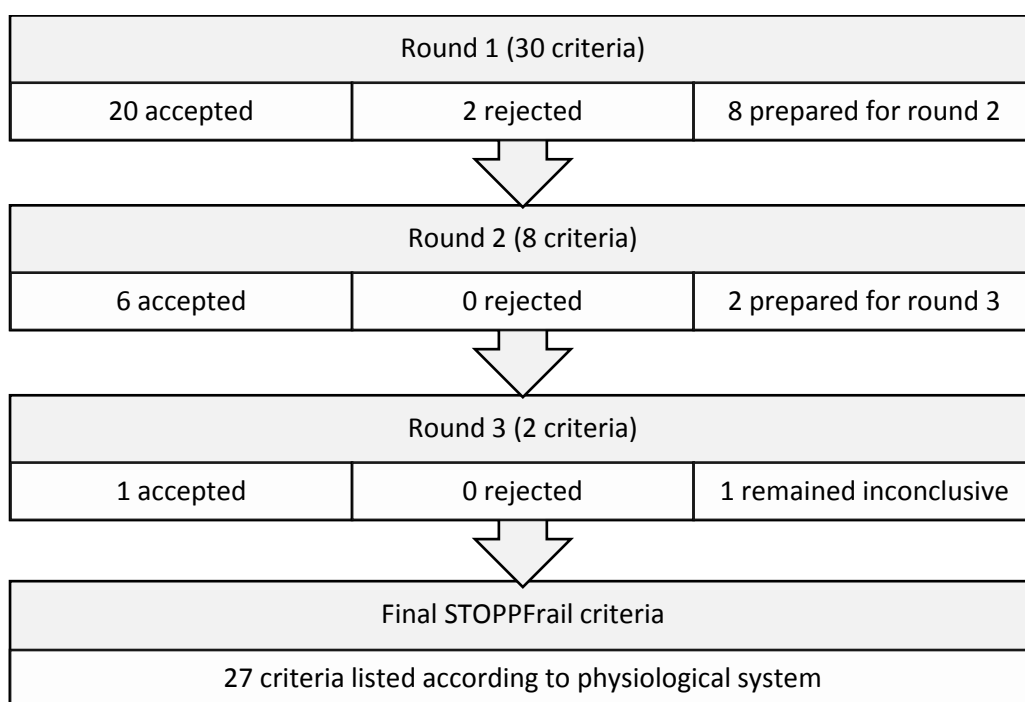
Figure 5.2: Sample question from round 1 of the Delphi consensus survey

Cardiovascular System:																									
STOPPfrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below. - End-stage irreversible pathology - Poor one year survival prognosis - Severe functional impairment or severe cognitive impairment or both - Symptom control is the priority rather than prevention of disease progression. The decision to prescribe/not to prescribed medications to the patients, should also be influences by the following issues: - Risk of the medication outweighing the benefit - Administration of the medication is challenging - Monitoring of the medication effect is challenging - Drug adherence/compliance is difficult The following prescriptions are potentially inappropriate for patients who meet the inclusion criteria above. Please select one response per statement: B1: Lipid lowering therapies (statins, ezetimibe, bile acid sequestrans, fibrates, nicotinic acid, acipimox). These medications needs to be prescribed for a long duration to be of benefit. For short term use ADE risk outweighs the potential benefit. <table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 80%;">Strongly agree</td><td style="width: 20%;"></td></tr><tr><td>Agree</td><td></td></tr><tr><td>Neutral</td><td></td></tr><tr><td>Disagree</td><td></td></tr><tr><td>Strongly disagree</td><td></td></tr><tr><td>Don't know</td><td></td></tr></table> B2: alpha blockers for hypertension. Stringent blood pressure control is not required in very frail people. Alpha blockers in particular cause marked vasodilation, which can result in marked symptomatic postural hypotension, falls and injuries. <table border="1" style="width: 100%; border-collapse: collapse;"><tr><td style="width: 80%;">Strongly agree</td><td style="width: 20%;"></td></tr><tr><td>Agree</td><td></td></tr><tr><td>Neutral</td><td></td></tr><tr><td>Disagree</td><td></td></tr><tr><td>Strongly disagree</td><td></td></tr><tr><td>Don't know</td><td></td></tr></table>		Strongly agree		Agree		Neutral		Disagree		Strongly disagree		Don't know		Strongly agree		Agree		Neutral		Disagree		Strongly disagree		Don't know	
Strongly agree																									
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Disagree																									
Strongly disagree																									
Don't know																									

5.3 RESULTS

All panellists completed the Delphi validation process in three rounds; 27 criteria comprise the final STOPPFrail tool (for summary, see **Figure 5.3**).

Figure 5.3: Flow chart of Delphi process



5.3.1 Round 1

Round 1 draft criteria were prepared and sent to panellists. The draft criteria, the responses received and their outcomes are displayed in **Table 5.5**.

Table 5.5: Round 1 results

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- Symptom control is the priority rather than prevention of disease progression

The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

	Med	IQR	Outcome
Section A: General			
A1. Any drug that the patient persistently fails to comply with for any reason	4.0	3.5-5	Inconclusive
A2. Any drug without clear clinical indication	5.0	5.0-5.0	Accepted
Section B: Cardiology System			
B1. Lipid lowering therapies (statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid and acipimox) These medications need to be prescribed for a long duration to be of benefit. For short-term use, the risk of adverse drug events outweighs the potential benefits	5.0	4.0-5.0	Accepted
B2. Alpha-blockers for hypertension Stringent blood pressure control is not required in very frail older people. Alpha blockers in particular can cause marked vasodilatation, which can result in marked postural hypotension, falls and injuries	5.0	4.0-5.0	Accepted
Section C: Coagulation System			
C1. Anticoagulants (warfarin/novel oral anticoagulants) Anticoagulation as a preventative measure (e.g. with atrial fibrillation) as distinct from treatment of acute venous thromboembolic (VTE) disease	3.0	2.0-4.0	Rejected
C2. Anti-platelet agents No role for anti-platelet agents in primary cardiovascular prevention, only beneficial for secondary cardiovascular prevention, therefore discontinue unless there is a previous history of ischaemic heart disease, cerebrovascular disease or arterial stent insertion	4.0	3.0-5.0	Inconclusive
Section D: Central Nervous System			
D1. Memantine Discontinue unless it has been prescribed for behavioural and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease and has been shown to improve symptoms	4.0	2.25-5.0	Inconclusive

D2. Acetylcholinesterase inhibitors There is no significant clinical benefit from continuation of these drugs in those with advanced Alzheimer's disease (Mini-Mental State Examination score <10/30 <u>and</u> functionally dependent). No role in other dementia syndromes in the advanced stages. D3. Anti-depressants There is no proven role for anti-depressants in advanced dementia (MMSE <10/30 and functionally dependent) D4. Neuroleptic antipsychotics Aim to reduce dose and discontinue these drugs in patients taking them for longer than 12 weeks if there are no current clinical features of behavioural and psychiatric symptoms of dementia (BPSD)	4.0	3.25-5.0	Inconclusive
Section E: Gastrointestinal System			
E1. Proton Pump Inhibitors Proton Pump Inhibitors at full therapeutic dose $\geq 8/52$, unless persistent dyspeptic symptoms at lower maintenance dose.	4.0	4.0-5.0	Accepted
E2. H2 Receptor Antagonists H2 Receptor Antagonists at full therapeutic dose for $\geq 8/52$, unless persistent dyspeptic symptoms or symptoms reoccur after discontinuation	4.0	3.5-5.0	Inconclusive
E3. Gastrointestinal antispasmodics Regular daily prescription of gastrointestinal antispasmodics agents unless the patient has frequent relapse of colic symptoms because of high risk of anti-cholinergic side effects	4.0	4.0-5.0	Accepted
Section F: Respiratory System			
F1. Theophylline This drug has a narrow therapeutic index, requires monitoring of serum levels and interacts with other commonly prescribed drugs putting patients at an increased risk of adverse drug events (ADEs)	5.0	4.0-5.0	Accepted
F2. Leukotriene antagonists (Montelukast, Zafirlukast) These drugs have no proven role in COPD, they are indicated only in asthma.	5.0	4.0-5.0	Accepted
Section G: Musculoskeletal System			
G1. Calcium and vitamin D supplementation Unlikely to be of any benefit in the short term	4.0	3.0-5.0	Inconclusive
G2. Anti-resorptive/bone anabolic drugs for osteoporosis (bisphosphonates, strontium, teriparatide, denosumab) Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated adverse drug events	4.0	3.0-5.0	Inconclusive
G3. Selective Estrogen Receptor Modulators (SERMs) for osteoporosis Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated ADEs particularly venous thromboembolism and stroke.	5.0	4.0-5.0	Accepted
G4. Long-term oral NSAIDs Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months	5.0	4.0-5.0	Accepted

G5. Long-term oral steroids Increased risk of side effects (peptic ulcer disease etc.) when taken regularly for ≥ 2 months. Consider careful dose reduction and discontinuation	5.0	4.0-5.0	Accepted
Section H: Urogenital System			
H1. 5-alpha reductase inhibitors No benefit with long term urinary bladder catheterisation	5.0	4.0-5.0	Accepted
H2. Alpha blockers with urinary catheter No benefit with long term urinary bladder catheterisation	5.0	4.0-5.0	Accepted
H3. Muscarinic antagonists No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity	5.0	4.0-5.0	Accepted
Section I: Endocrine System			
I1. Diabetic oral agents Aim for monotherapy. Target of HbA1c $<8\%$ /64mmol/mol. Stringent glycaemic control is unnecessary	4.0	4.0-4.5	Accepted
I2. ACE-Inhibitors for diabetes Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis	4.0	4.0-5.0	Accepted
I3. Angiotensin Receptor Blockers (ARBs) Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis	4.0	4.0-5.0	Accepted
I4. Systemic oestrogens for menopausal symptoms Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms	4.0	4.0-5.0	Accepted
Section J: Miscellaneous			
J1. Multi-vitamin combination supplements Discontinue when prescribed for prophylaxis rather than treatment	5.0	4.0-5.0	Accepted
J2. Nutritional supplements (other than vitamins) Discontinue when prescribed for prophylaxis rather than treatment	5.0	4.0-5.0	Accepted
J3. Prophylactic antibiotics No firm evidence for a role for prophylactic antibiotics for recurrent cellulitis or recurrent UTI	4.0	3.0-5.0	Inconclusive

*Legend: Med = median; IQR = inter-quartile range; ADE=adverse drug event

5.3.1.1 Criteria accepted for inclusion after round 1

In round 1, twenty criteria were accepted (**Table 5.5**). The first proposed criterion included in STOPPFrail was a general statement that any drug prescribed without a clinical indication should be discontinued. The remaining 19 criteria accepted included deprescribing of lipid-lowering agents, alpha-blockers for hypertension, neuroleptics, proton pump inhibitors, theophylline, leukotriene receptor antagonists, selective oestrogen receptor modulators, non-steroidal anti-inflammatories, steroids, 5-alpha reductase inhibitors and alpha-blockers in catheterised patients, muscarinic antagonists, diabetic oral agents, Ace-inhibitors, angiotensin receptor antagonists, multivitamins and nutritional supplements.

5.3.1.2 Criteria rejected for inclusion after round 1

Two criteria were rejected in round 1 (**Table 5.5**). See **Table 5.6** for the comments received by panellists.

(i) Anticoagulants as a preventative measure.

Our research group proposed discontinuation of anticoagulation because bleeding risk and cost of treatment outweighed the potential benefits to patients in whom cognition and activities of daily living function were poor. Panellists agreed that in the majority of people meeting the inclusion criteria for STOPPFrail, anticoagulants should be stopped. However, this criterion was rejected due to the panel's concern over the minority of patients in whom stopping anticoagulants could be potentially

inappropriate. Specifically, the majority of panel members considered that, regardless of frailty and life expectancy, stroke or systemic embolism was an unfavourable outcome in patients with atrial fibrillation deprived of anticoagulant therapy. The panellists and authors agreed that individual clinical judgement should be applied based on individual clinician and patient preferences and individual priorities with regard to anti-coagulation therapy. In recent years, anticoagulation has become easier, safer and more efficient due to the development of direct oral anticoagulants i.e. apixaban, rivaroxaban, edoxaban and dabigatran. Therefore panellists felt that in patients receiving anti-coagulants with a good indication and incurring minimal or no side-effects, continuation was reasonable.

(ii) Use of anti-depressants in patients with advanced dementia

Reasons for rejection of this proposed criterion included possible benefits outside of anti-depressant effects, such as analgesic effects, appetite stimulation and anxiolytic properties. Panellist feedback suggested that cessation of antidepressants in patients with severe dementia was a generally reasonable approach, but not in all such patients with limited life expectancy as a general rule. Panellists feared that antidepressant therapy could be stopped in patients who derived benefit from treatment that was not measureable because of the communication problems associated with severe dementia and that overall, the risk of relapse of symptoms outweighed the potential benefit of discontinuation.

Table 5.6: Comments received from panellists for criteria rejected in round 1

Criterion	Med	IQR	Outcome
C1. Anticoagulants (warfarin/novel oral anticoagulants) Anticoagulation as a preventative measure (e.g. with atrial fibrillation) as distinct from treatment of acute venous thromboembolic (VTE) disease	3.0	2.0-4.0	Rejected
“This must be balanced with how you will respond to a patient if they have an A.fib-related stroke” “Depends on vascular risk. Having a stroke not a good way to go ...” “Good evidence from BAFTA that there may be some benefit. Suggestive evidence from AVERROES.” “It does depend on the individual case but the majority will gain no benefit. The poor cost benefit of the NOAC drugs should make them only a rare second line” “Suppose strong history of previous TIAs or small strokes, and A fib, and can take a NOAC- not very burdensome to continue this despite poor prognosis - would not like to see a stroke on top of the other disease, even if frail” “In general I strongly agree. As before easier to use these indicators to justify not starting anticoagulants, rather than stopping. The DOACs do seem to have less issues with administration and monitoring than warfarin, but renal impairment causes many problems with them” “Must assess each individual patient in respect of risk/benefit. It may be reasonable to continue for example in a hyper-coaguable patient with distressing symptoms”			
Criterion	Med	IQR	Outcome
D3. Anti-depressants There is no proven role for anti-depressants in advanced dementia (MMSE <10/30 and functionally dependent)	3.0	2.0-4.0	Rejected
“No proof agreed, but if BPSD troublesome and seems related to depression use” “Anti-depressants have uses outside depression, e.g. analgesia, appetite stimulation” “suggest to clarify wording; is it for patients who meet the frailty criteria or just advanced dementia” “I would not stop antidepressants in people with limited life expectancy until end of life - may not be of proven benefit in advanced dementia / functionally dependent people, but that doesn't mean they don't work. Lots of end of life care we use all the time has NO proven benefit! Also, would not withdraw in a person with previous severe depression and relapse on previous withdrawal” “my only comment here is that some anti-depressants have good anxiolytic effects, can be helpful” “Needs careful individual clinical assessment. TCADs for example are commonly used in neuropathic pain or may be used to reduce oro-pharyngeal secretions”			

*Legend: Med = median; IQR = inter-quartile range

5.3.1.3 Criteria deemed inconclusive after round 1

Eight criteria were deemed inconclusive after round 1 (**Table 5.5**). The first was a general criterion of deprescribing any drug with which patients fail to comply. Feedback suggested that the explanatory sentence should remind users to try all appropriate measures to improve medication adherence before deprescribing; this criterion was rephrased accordingly for round 2. Other drugs for which there was uncertainty among the panel were anti-platelet agents, memantine, acetylcholinesterase inhibitors, H2-receptor antagonists, calcium and vitamin D supplements, bone anti-resorptive/anabolic agents and prophylactic antibiotics. See **Table 5.7** for the comments received from panellists. Feedback was incorporated into rephrasing the criteria for round 2.

Table 5.7: Comments from panellists for criteria found to be inconclusive

Criterion	Med	IQR	Outcome
A1. Any drug that the patient persistently fails to comply with for any reason	4.0	3.5-5	Inconclusive
“Obviously the patient compliance issues will need to be explored to rule out a misunderstanding from the individual patient’s perspective.” “Provided appropriate measures have been taken to enhance compliance.” “Depends on clinical situation and whether symptomatic as the situation may change although they may not admit to this.” “The reason why the patient fails to comply would need to be clarified.” “If it helps symptoms, efforts should be made to find a way to improve compliance or find alternative administration route -stopping may not be the best result.” “As you state “<i>potentially inappropriate</i>” I can strongly agree. If you had stated “<i>inappropriate</i>” alone, I would have ticked agree.” “Having spoken to the patient to clarify his / her reasons for non-compliance if possible.”			
Criterion	Med	IQR	Outcome
C2. Anti-platelet agents No role for anti-platelet agents in primary cardiovascular prevention, only beneficial for secondary cardiovascular prevention, therefore discontinue unless there is a	4.0	3.0-5.0	Inconclusive

previous history of ischaemic heart disease, cerebrovascular disease or arterial stent insertion.			
"Would not stop if symptomatic ischaemic heart disease until last days of life - agree with the wording used" "I think 75 mg aspirin is still useful in most elderly patients requiring secondary prevention...."			
Criterion	Med	IQR	Outcome
D1. Memantine Discontinue unless it has been prescribed for behavioural and psychological symptoms of dementia (BPSD) in patients with Alzheimer's disease and has been shown to improve symptoms.	4.0	2.25-5.0	Inconclusive
"As per previous comments, patients (& families) can have a sense of "I must take this drug to help." "Don't know this one." "Agree totally unless the indication was behavioural symptoms/ hallucinations and these responded well to memantine - would then be reluctant to rock the boat. Would not limit to AD however- we use for PDD also when intolerant of AChI due to tremor." "Must always explain rationale to patient and family."			
Criterion	Med	IQR	Outcome
D". Acetylcholinesterase inhibitors There is no significant clinical benefit from continuation of these drugs in those with advanced Alzheimer's disease (Mini-Mental State Examination score < 10/30 <u>and</u> functionally dependent). No role in other dementia syndromes in the advanced stages.	4.0	3.25-5.0	Inconclusive
"No experience with this one." "Again, unless for hallucinations in PD dementia -would NOT stop in this case as definitely provokes return of symptoms."			
Criterion	Med	IQR	Outcome
E2. H2 Receptor Antagonists H2 Receptor Antagonists at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms or symptoms reoccur after discontinuation.	4.0	3.5-5.0	Inconclusive
"Hardly ever use these now."			
Criterion	Med	IQR	Outcome
G1. Calcium and vitamin D supplementation Unlikely to be of any benefit in the short term.	4.0	3.0-5.0	Inconclusive
"Would not initiate, but less definite about stopping altogether. Bone fractures cause symptoms....."			
Criterion	Med	IQR	Outcome

G2. Anti-resorptive/bone anabolic drugs for osteoporosis (bisphosphonates, strontium, teriparatide, denosumab) Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated adverse drug events.	4.0	3.0-5.0	Inconclusive
“More inclined to stop these due to ADEs, and administration challenges are greater.....” “Then indication is the important consideration. May be used in symptomatic hypercalcaemia of malignancy for example.”			
Criterion	Med	IQR	Outcome
J3. Prophylactic antibiotics No firm evidence for a role for prophylactic antibiotics for recurrent cellulitis or recurrent UTI.	4.0	3.0-5.0	Inconclusive
“Act on advice from microbiology.”			

*Legend: Med = median; IQR = inter-quartile range; ADEs = adverse drug events

Panellists agreed with the inclusion of anti-platelet agents, but raised concerns over their cessation when their indication was secondary prevention. Similar to the feedback for anti-coagulants, panellists were concerned about the minority of patients in whom deprescribing of anti-platelet agents may be inappropriate. It was felt that secondary prevention of conditions such as ischaemic heart disease, peripheral vascular disease and stroke should incorporate bespoke judgement, and that a general statement would therefore not be appropriate in relation to anti-platelet therapy. Hence, it was decided that primary prevention should be the focus of this criterion i.e. anti-platelet agents for primary cardiovascular prevention (as distinct from secondary prevention) in this category of patient is probably inappropriate.

Panellists welcomed the inclusion of calcium supplementation and anti-resorptive therapy in STOPPFrail, but asked for clarity around the explanatory sentence i.e. cessation where the indication was osteoporosis and not malignancy or

hypercalcaemia. Evidence is lacking on whether long term use of calcium is beneficial due to methodological flaws in studies and high dropout rates (205). Patient compliance with calcium supplements is generally poor (31); those patients most likely to be non-compliant usually have a history of smoking, poor mobility and previous fractures (206). Anti-resorptive medications may be challenging to administer, have a less favourable side-effect profile and in some cases have been shown to have ongoing clinical benefits after cessation e.g. bisphosphonates. For these reasons the panellists agreed to cessation in those with limited life expectancy.

5.3.2 Round 2

Round 2 draft criteria were prepared, incorporating suggestions and comments received and sent to panellists. The draft criteria, the responses received and their outcomes are displayed in **Table 5.8**. Consensus could not be reached on two criteria after round 2 i.e. cessation of (i) memantine and (ii) acetylcholinesterase inhibitors in advanced dementia. **Table 5.9** displays the comments received by the panellists. A third Delphi round was therefore prepared for circulation.

Table 5.8: Round 2 results

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- Symptom control is the priority rather than prevention of disease progression

The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

	Med	IQR	Outcome
Section A: General			
A1. Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations	5.0	4.0-5.0	Accepted
Section C: Coagulation System			
C2. Anti-platelet agents Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit).	5.0	4.0-5.0	Accepted
Section D: Central Nervous System			
D1. Memantine Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD	4.0	3.5-5.0	Inconclusive
D2. Acetylcholinesterase inhibitors Discontinue and monitor in patients with severe dementia.	4.0	3.0-5.0	Inconclusive
Section E: Gastrointestinal System			
E2. H2 Receptor Antagonists H2 Receptor Antagonists at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose.	4.0	4.0-5.0	Accepted
Section G: Musculoskeletal System			
G1. Calcium supplementation Unlikely to be of any benefit in the short term.	5.0	4.0-5.0	Accepted
G2. Anti-resorptive/bone anabolic drugs <u>FOR OSTEOPOROSIS</u> (bisphosphonates, strontium, teriparatide, denosumab)	4.0	4.0-5.0	Accepted
Section J: Miscellaneous			
J3. Prophylactic antibiotics No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTI.	4.0	4.0-5.0	Accepted

*Legend: Med = median; IQR = inter-quartile range; BPSD = Behavioural and psychological symptoms of dementia

Table 5.9: Comments received from panellists for criteria rejected in round 2

Criterion	Med	IQR	Outcome
D1. Memantine Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD.	4.0	3.5-5.0	Inconclusive
“there is a study in palliative care where memantine was stopped and quite a percentage of patients rebounded in terms of behaviours. it does depend as you say on the behavioural responses before to the drug” (this person agreed). “If patient has moderate-severe dementia and is tolerating memantine, I see no reason to discontinue. It may have benefits that are not recognised until it is stopped” (this person agreed).			
Criterion	Med	IQR	Outcome
D2. Acetylcholinesterase inhibitors Discontinue and monitor in patients with severe dementia.	4.0	3.0-5.0	Inconclusive
“Would not stop if tolerated. May have unrecognised benefits (this person agreed).			

*Legend: Med = median; IQR = inter-quartile range; BPSD = Behavioural and psychological symptoms of dementia

5.3.3 Round 3

Round 3 draft criteria were prepared and sent to panellists. The draft criteria, the responses received and their outcomes are displayed in **Table 5.10**.

Table 5.10 Round 3 Results

STOPP frail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:			
• End-stage irreversible pathology • Poor Prognosis • Severe functional impairment or severe cognitive impairment or both • Symptom control is the priority rather than prevention of disease progression			
The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:			
• Risk of the medication outweighing the benefit • Administration of the medication is challenging • Monitoring of the medication effect is challenging • Drug adherence/compliance is difficult			
	Med	IQR	Outcome
Section D: Central Nervous System			
D1: Memantine Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved behavioural and psychological symptoms of dementia (BPSD) (specifically in frail patients who meet the criteria above).	4.0	4.0-5.0	Accepted
D2. Acetylcholinesterase inhibitors Discontinue and monitor in patients with severe dementia (specifically in frail patients who meet the criteria above).	4.0	3.25-5.0	Inconclusive
*Legend: Med = median; IQR = inter-quartile range, BPSD = Behavioural and psychological symptoms of dementia			

In this round, consensus was obtained for memantine and it was included in the STOPPFrail tool. Consensus was not achieved for acetylcholinesterase inhibitors (AChEI's) with no clear trend towards acceptance (**Table 5.11**). **Table 5.12** displays the comments received from the panellists. Panellists reported that the evidence base for acetylcholinesterase inhibitors in advanced dementia was still developing

and the possibility that unrecognised benefits existed could not be dismissed. The DOMINO-AD trial was cited to support their argument in favour of retaining AChEI's (207, 208). This trial suggests that in patients where AChEI's are stopped, the admission rate to nursing homes in the year following cessation is significantly increased compared to those patients who continue to receive AChEI's. However, this difference is only seen in the first year following cessation.

After three Delphi rounds, no additional concerns were raised by the panel and it was decided by the authors not to proceed to a fourth Delphi round as it was deemed unnecessary. The final consensus STOPPFrail criteria are presented in **Table 5.13**.

Table 5.11: Acetyl Cholinesterase Inhibitors Delphi Results

Acetyl Cholinesterase Inhibitor			
	Round 1	Round 2	Round 3
Median	4.000	4.000	4.000
25 th centile	3.250	3.000	3.250

Table 5.12: Comments received from panellists for criteria rejected

Criterion	Med	IQR	Outcome
D2. Acetylcholinesterase inhibitors Discontinue and monitor in patients with severe dementia (specifically in frail patients who meet the criteria above).	4.0	3.25-5.0	Inconclusive
" if very late then yes but the DOMINO study in NEJM would indicate that in people with MMSE 5-13, Donepezil at least should be continued for a year. I feel that the definition above is probably not concise enough." "Evidence that in severe dementia, stopping acetyl cholinesterase inhibitors is detrimental. If no adverse events, I would continue for symptomatic benefit (DOMINO-AD)." "Patients (and more over family members) may place an over significance in the stopping of this medications."			

Table 5.13 Final STOPPFail criteria

STOPPFail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:	The decision to prescribe/not prescribe medications to the patients, should also be influenced by the following issues:
1. End-stage irreversible pathology 2. Poor one-year survival prognosis 3. Severe functional impairment or severe cognitive impairment or both 4. Symptom control is the priority rather than prevention of disease progression	1. Risk of the medications outweighing the benefit 2. Administration of the medication is challenging 3. Monitoring of the medication effect is challenging 4. Drug adherence/compliance is difficult
Section A: General	Section G: Musculoskeletal System
A1: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate information A2: Any drug without clear clinical indication	G1: Calcium supplementation Unlikely to be of any benefit in the short term G2: Anti-resorptive/bone anabolic drugs FOR OSTEOPOROSIS (bisphosphonates, strontium, teriparatide, denosumab) Unlikely to be of any benefit in the short term G3: Selective Estrogen Receptor Modulators [SERMs] for osteoporosis Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated ADEs particularly venous thromboembolism and stroke (190) G4: Long-term oral NSAIDs Increased risk of side effects [peptic ulcer disease, bleeding, worsening heart failure etc.] when taken regularly for ≥ 2 months (227-229) G5: Long-term oral steroids Increased risk of side effects [peptic ulcer disease etc.] when taken regularly for ≥ 2 months. Consider careful dose reduction and gradual discontinuation (230)
Section B: Cardiovascular	Section H: Urogenital System
B1. Lipid lowering therapies [statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid and acipimox] These medications need to be prescribed for a long duration to be of benefit. For short-term use, the risk of adverse drug events [ADEs] outweighs the potential benefits (209-211) B2. Alpha-blockers for hypertension Stringent blood pressure control is not required in very frail older people. Alpha blockers in particular can cause marked vasodilatation, which can result in marked postural hypotension, falls and injuries (212)	H1. 5-alpha reductase inhibitors No benefit with long term urinary bladder catheterisation (231, 232) H2. Alpha blockers No benefit with long term urinary bladder catheterisation (231, 232) H3. Muscarinic antagonists No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity (231, 232)
Section C: Coagulation system	Section I: Endocrine System
C1: Anti-platelets Avoid anti-platelet agents for primary [as distinct from secondary] cardiovascular prevention [no evidence of benefit] (213)	I1. Diabetic oral agents Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary (233) I2. ACE-Inhibitors for diabetes Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis (234) I3. Angiotensin Receptor Blockers [ARBs] Stop where prescribed only for prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis (234) I4. Systemic oestrogens for menopausal symptoms Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms (190)
Section E: Gastrointestinal System	Section J: Miscellaneous
E1. Proton Pump Inhibitors Proton Pump Inhibitors at full therapeutic dose ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose (190) E2: H2 receptor antagonist H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose (190) E3. Gastrointestinal antispasmodics Regular daily prescription of gastrointestinal antispasmodics agents unless the patient has frequent relapse of colic symptoms because of high risk of anti-cholinergic side effects (190)	J1. Multi-vitamin combination supplements Discontinue when prescribed for prophylaxis rather than treatment J2. Nutritional supplements [other than vitamins] Discontinue when prescribed for prophylaxis rather than treatment (235) J3: Prophylactic Antibiotics No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs (236-238))
Section F: Respiratory System	
F1. Theophylline This drug has a narrow therapeutic index, requires monitoring of serum levels and interacts with other commonly prescribed drugs putting patients at an increased risk of ADEs (223-226) F2. Leukotriene antagonists [Montelukast, Zafirlukast] These drugs have no proven role in COPD, they are indicated only in asthma (226)	

5.4 DISCUSSION

The final STOPPFrail criteria is an explicit list of 27 PIMs in older frail adults with limited life expectancy, arranged according to physiological systems. Each criterion is presented in the same manner i.e. a drug/drug class followed up by an explanatory sentence to support and guide deprescribing. This list of PIMs was developed and validated using the Delphi technique. Delphi panellists included a variety of specialists with expertise in geriatric pharmacotherapy. The first two criteria recommend deprescribing medications without indication or where compliance is poor. The remaining 25 criteria include lipid-lowering therapies, alpha-blockers for hypertension, anti-platelets, neuroleptics, memantine, proton-pump inhibitors, H2-receptor antagonists, anti-spasmodic agents, theophylline, leukotriene antagonists, calcium supplements, bone anti-resorptive therapy, selective oestrogen receptor modulators, non-steroidal anti-inflammatories, corticosteroids, 5-alpha-reductase inhibitors, alpha-1-selective blockers, muscarinic antagonists, oral diabetic agents, ACE-inhibitors, angiotensin receptor blockers, systemic oestrogens, multivitamins, nutritional supplements and prophylactic antibiotics. Consensus could not be reached on the inclusion of acetylcholinesterase inhibitors. Full consensus was reached on the exclusion of anticoagulants and antidepressants from the list.

The criteria are not designed to replace clinical judgement, but rather to assist clinicians with medication reviews and assessment of treatment goals in this specific patient population. Recognition of those patients in whom STOPPFrail criteria are applicable may be challenging for less experienced physicians; in these circumstances, the use of simple mortality predictive tools may be helpful to guide

life expectancy e.g. the Walter Index (139) or the Cumulative Illness Rating Scale adapted for geriatric patients (CIRS-G) (239). However, one anticipates that the majority of clinicians who use STOPPFrail will be experienced in recognising patients who are appropriate for deprescribing i.e. general practitioners who regularly attend nursing home patients and hospital specialists with prognostic knowledge of the diseases in older patients that they manage on a regular basis. In the interest of simplicity and user-friendliness, we did not want STOPPFrail criteria to be contingent on the use of another tool to determine eligibility.

Unnecessary or potentially harmful polypharmacy is a well described problem in frailer older people with limited life expectancy. This research aims to put a framework on the guiding principle of deprescribing in late life i.e. that the benefits of many preventive medications are unlikely to be realised in those with a limited life expectancy. Although many IP explicit tools exist (71), there is an unmet need for a concise explicit tool to assist deprescribing in this specific patient population. STOPPFrail is a concise deprescribing assistive tool, focusing on 27 specific indicators, suggesting that it will be easy to use, time efficient and therefore more likely to be implemented in routine clinical practice. Like STOPP/START criteria (36, 37), STOPPFrail criteria are listed according to physiological systems, thereby allowing users to structure their approach to deprescribing. We aimed for a concise set of criteria that can be easily deployed in paper and electronic format.

Developing this tool required discussion of many controversial treatments in frail, end-stage older patients e.g. hypertension. The Delphi panellists agreed that a generalised statement about discontinuing all anti-hypertensives would be

contentious. Therefore, it was decided to focus on the drug class least likely to be prescribed as a first line agent and most likely to cause orthostatic hypotension and falls in an older cohort i.e. alpha-1 receptor blockers.

Appropriate use of STOPPFrail criteria may have pharmacoeconomic benefits. Older frailer adults with a poor survival prognosis account for a growing proportion of the population and a disproportionately high level of medication consumption. Implementation of safe, evidence-based deprescribing in this population, may improve patients' quality of life through reduced adverse drug reactions, related hospitalisations and mortality. Before the true value of STOPPFrail can be used as a measure of prescribing appropriateness in older frailer patients with poor one year survival prognosis or tested by means of RCTs, its inter-rater reliability needs to be evaluated. This is the subject of chapter 6 of this thesis. Following on from this, the prevalence of PIMs according to STOPPFrail criteria need to be assessed. This is the subject of chapter 7.

CHAPTER 6

Inter-rater reliability of STOPPFrail criteria amongst physicians from three clinical
specialty services

6.1 INTRODUCTION

The development and validation of STOPPFrail criteria was described in Chapter 5. In brief, STOPPFrail criteria were validated using a Delphi consensus methodology to highlight commonly encountered instances of potentially inappropriate medication (PIM) use in frail older adults with limited life expectancy. The primary goal of STOPPFrail is to assist clinicians with the decision to deprescribe medications that are of limited value or appropriateness in this population (240). However, before the STOPPFrail tool can be used in clinical practice, its reliability between clinical practitioners and generalizability between specialist disciplines must be demonstrated.

6.1.1. Objectives

The objective of this study is to determine the inter-rater reliability (IRR) of STOPPFrail criteria between physicians practising in different clinical specialties. The work undertaken in this chapter, including study design, data collection and statistical analysis, is entirely my own.

6.2 METHODS

6.2.1 Clinical case histories

Twenty detailed clinical case histories were collated by Dr. Paul Gallagher (Consultant Geriatrician / Senior Lecturer, University College Cork) (PG) and I (AL), modified from real world anonymised clinical cases. These clinical cases were obtained from a

sample of participants enrolled in the prevalence study described in Chapter 3. Recorded data included the participant's co-morbid illnesses, concurrent medication use and cognitive and functional abilities. . The Structured History of Medication use (SHiM) was employed to accurately capture concurrent medications, including medication adherence (241). Case details were amended, where necessary, to ensure, the 20 clinical cases described frail multi-morbid patients with an appreciable incidence of potentially inappropriate prescriptions (PIPs), according to STOPPFrail criteria. Each clinical case history was presented in a standardized format and included the patient's age, gender, co-morbidities, a detailed medication history, medication allergies, and cognitive status and activities of daily living (ADL) functional status.

The participants featured in the 20 clinical cases had a mean ($\pm$ standard deviation) age of 79.3 ($\pm$ 5.68) years, twelve were female. The total number of prescribed medications was 181, median 9 (IQR 7-11). The median number of conditions was 7 (IQR 4-8). Eighteen of the twenty clinical cases (90%) were eligible for the application of STOPPFrail criteria i.e. end stage irreversible pathology, a poor one year survival prognosis, severe cognitive or functional impairment or both and symptom management was the priority. The irreversible diagnoses for the 18 cases meeting STOPPFrail inclusion criteria were severe dementia (n=6), advanced metastatic cancer (n=4), severe disabling stroke (n=2), stage IV chronic obstructive pulmonary disease (COPD) (n=2), advanced Parkinson's disease with associated dementia (n=1), motor neuron disease (n=1), stage 4 congestive cardiac failure (n=1) and rheumatoid arthritis with dementia (n=1).

6.2.2 Expert Gold Standard Assessment of PIM use according to STOPPFrail criteria

For each of the 20 clinical cases, two physicians (AL and PG), with expertise in geriatric pharmacotherapy, first determined if the patient described in the clinical case was eligible for application of STOPPFrail criteria. STOPPFrail criteria were then applied to identify potentially inappropriate medications that could be deprescribed. Complete agreement between the two expert assessors was reached in terms of prescribing appropriateness according to STOPPFrail criteria. This combined level of agreement (labelled “rater 1”) was set as the gold standard [GS], against which other physicians’ ratings were compared.

6.2.3 Physician recruitment

Twelve physicians were invited to participate; 6 geriatricians (3 consultant geriatricians and 3 specialist registrars in geriatric medicine), 3 general practitioners (GPs) (2 qualified GPs and 1 specialist trainee in general practice) and 3 palliative care physicians (**Appendix 11**). This was a convenience sample with an optimum proportion of raters to subjects. It was anticipated that raters would agree 80% of the time with a relative error of 30%, thus a minimum of 17 cases was required for review (242). Invited participants had no prior knowledge of STOPPFrail criteria and did not routinely use other IP tools.

The study's objectives were explained to each invited physician. Subsequently, all physicians agreed to participate. Physicians independently completed the exercise between January and February 2017. Each physician was supplied, in paper format, (i) the STOPPFrail criteria (**Chapter 5, Table 5.13 page 222**) (ii) the 20 clinical cases (**Appendix 12**) and (iii) an answer booklet with clear instructions (**Appendix 13**). Participants were asked to decide, for each individual clinical case, (i) if the patient was eligible for application of STOPPFrail criteria (ii) for the cases that were eligible, to identify PIPs listed in STOPPFrail criteria and (iii) suggest which ones, in theory, could be deprescribed, but *only if* they deemed it clinically appropriate to do so. Participants were asked, after they had familiarised themselves with STOPPFrail criteria, to measure the time taken to apply STOPPFrail criteria in each case.

For criterion A1 (any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all formulations), raters were instructed to assume that all formulations and delivery mechanisms had been tried without success, unless stated otherwise. For criterion A2 (drugs with no clear indication), raters were asked to base this on the known indications of the medications, as per the summary of product characteristics (SPC) of the medicine, the British National Formulary (BNF) and/or their clinical judgement.

Physicians were allocated the following rater numbers: consultant geriatricians [raters 2, 3, 4], specialist registrars in geriatric medicine [raters 5, 6, 7], general practitioners [raters 8, 9], specialist trainee in general practice [rater 10] and palliative care physicians [raters 11, 12, 13].

6.2.4 Statistical analysis

Physician responses were dichotomized into whether each STOPPFrail indicator was applied or not. Some criteria could be relevant to more than one drug e.g. criterion A2 advises deprescribing any drug which does not have a clear indication. The response of raters 2 -13 were cross-tabulated with those of the gold standard (GS) assessment. Statistical analysis was performed using IBM SPSS® Statistics version 22. Cohen's Kappa Statistic was used to determine the level of agreement between each rater and the GS. This is a chance-corrected measure of agreement on how raters classify individual items into the same category, in this instance the presence or absence of a potentially inappropriate prescription according to STOPPFrail criteria. The Fleiss Kappa statistic was used to determine the overall mean kappa statistics between subgroups of raters (geriatricians, GPs and palliative care physicians) and the GS. The calculation of the kappa statistic is detailed in **Figure 6.1**. The kappa statistic was interpreted as poor if ≤ 0.2 , fair if 0.21–0.40, moderate if 0.51–0.6, substantial if 0.61–0.8 and good if 0.81–1.00 (153).

Figure 6.1: Calculation of the kappa statistic and proportions of positive and negative agreement between raters 1 and 2

STOPPFrail criteria		Rater 1 (GS)		
		Appropriate	Inappropriate	Total
Rater 2	Appropriate	438 (76.4%)	12 (2.1%)	450 (78.5%)
	Inappropriate	37 (6.5%)	86 (15%)	123 (21.5%)
Total		475 (82.9%)	98 (17.1%)	573

Kappa co-efficient = (observed agreement – chance agreement) / (1 – chance agreement)
 Observed agreement = (438 + 86) / 573 = 0.92
 Chance agreement = (0.785 * 0.829) + (0.171 * 0.215) = 0.68
 Kappa = (0.91 – 0.68) / (1 – 0.68) = 0.73
 Proportion of positive agreement (ppos) = 2 (438) / (573 + 438 – 86) = 0.95
 Proportion of negative agreement (pneg) = 2 (86) / (573 - 438 + 86) = 0.78

6.3 RESULTS

6.3.1. Identification of clinical cases eligible for STOPPFrail criteria

application

Of the 12 independent raters, 9 raters identified *all* 18 cases that met STOPPFrail inclusion criteria. Two GPs identified 16 cases and one consultant geriatrician identified 17 cases as being eligible for the application of the STOPPFrail tool. No rater incorrectly identified the two cases which did not meet STOPPFrail eligibility criteria, as doing so.

6.3.2 Time taken to deploy the criteria

Geriatricians, GPs and Palliative Medicine physicians took an average of 2.33, 3.41 and 2.7 minutes respectively to apply STOPPFrail criteria to each clinical case, a combined overall mean ($\pm$ standard deviation) of 2.7 (0.94) minutes. During this time the physician read the clinical case in question and applied STOPPFrail accordingly. This time did not include the time taken for participants to read the instruction manual and familiarise themselves with the STOPPFrail tool.

6.3.3 Medications identified for deprescribing

Of the 165 medications prescribed to 18 patients, the gold standard (GS) determined that 91 medications were potentially inappropriate according to STOPPFrail criteria and should be deprescribed. **Table 6.1** displays the kappa statistics for each rater compared to the GS. Columns A, B, C and D indicate the status of agreement between raters and the GS. For example, rater 1 (GS) and rater 3 agreed that STOPPFrail criteria were not identified in 471 instances (column A). In 27 instances, rater 1 did not identify a STOPPFrail criterion but rater 3 did (column B). There were 20 instances where rater 3 identified a STOPPFrail criterion that rater 1 did not (column C). In 83 instances, both rater 1 and rater 3 identified a STOPPFrail criterion (column D). The Fleiss kappa co-efficient between all 12 raters and the GS was **0.76 (SD 0.059)**. The Fleiss kappa co-efficient between the GS and geriatricians, GPs and palliative care physicians were **0.80 (SD0.6)**, **0.77 (SD0.9)** and **0.75 (SD0.1)** respectively, with no significant difference noted between groups or between participants within groups, as determined by one way ANOVA ($df (2, 9) = 0.712, p=0.516$).

Table 6.1: Level of agreement in numbers of STOPPFrail criteria applied and numbers of drugs recommended for deprescribing

	Rater Combination	A	B	C	D	ppos	pneg	Kappa	IP (n)
Consultant Geriatricians vs GS	Rater 1 * Rater 2	461	37	17	86	0.94	0.76	0.71	116
		438	37	12	86	0.95	0.78	(*0.73)	
	Rater 1 * Rater 3	471	27	20	83	0.95	0.78	0.73	102
	Rater 1 * Rater 4	477	21	14	89	0.96	0.84	0.80	108
Specialist registrars geriatric medicine vs GS	Rater 1 * Rater 5	483	15	12	91	0.97	0.87	0.84	94
	Rater 1 * Rater 6	486	12	10	93	0.98	0.89	0.87	96
	Rater 1 * Rater 7	494	4	27	76	0.97	0.83	0.80	80
GP Registrars vs GS	Rater 1 * Rater 8	485	13	11	92	0.98	0.88	0.86	100
	Rater 1 * Rater 9	484	14	41	62	0.95	0.69	0.64	84
		435	14	31	62	0.95	0.73	(*0.69)	
	Rater 1 * Rater 10	491	7	37	66	0.96	0.77	0.71	74
		442	7	27	66	0.96	0.80	(*0.76)	
Pall Care vs GS	Rater 1 * Rater 11	488	10	30	73	0.96	0.79	0.75	77
	Rater 1 * Rater 12	479	19	25	78	0.96	0.78	0.74	94
	Rater 1 * Rater 13	490	8	30	73	0.96	0.79	0.76	77
Mean (SD)								0.76 (SD0.059)	

Legend: A = Both raters agreed criterion not fulfilled; B = Rater 1 scored criterion as being not fulfilled, rater 2 scored criterion as being fulfilled; C = Rater 1 score criterion as fulfilled, rater 2 scored criterion as not fulfilled; D = Both raters scored criterion fulfilled; ppos = proportion of positive agreement; pneg = proportion of negative agreement; IQR = interquartile range; *adjusted for cases not identified by raters as meeting the inclusion criteria for STOPPFrail.

6.3.4 Variations between raters

Total agreement between all raters and the GS was observed for 4 STOPPFrail criteria. Minor variations (defined as the identification or omission of up to 2 STOPPFrail criteria by a rater other than the gold standard rater) were observed for 16 STOPPFrail criteria. Major variations (defined as the identification or omission of ≥ 3 STOPPFrail criteria by a rater other than the gold standard rater) were observed for 7 STOPPFrail criteria. These rater variations are detailed in **Tables 6.2**. The reasons for variations of each STOPPFrail observation according to each rater is shown in **Table 6.3**. The breakdown of variations between each rater and the GS and for each case is presented in **Table 6.4**.

Table 6.2: Criteria where total agreement, minor variations or most variations were noted

Total Agreement (n=4)	
D2	Memantine.
E3	Gastrointestinal antispasmodics.
I4	Systemic oestrogens for menopausal symptoms.
J3	Prophylactic Antibiotics.
Minor Variations (n=16) (Defined as the identification or omission of up to 2 STOPPFrail criteria by a rater other than the gold standard rater)	
B1	Lipid lowering therapies.
B2	Alpha-blockers for hypertension.
C1	Anti-platelets.
D1	Neuroleptic antipsychotics.
E2	H2 receptor antagonist.
F1	Theophylline.
F2	Leukotriene antagonists.
G3	Selective Estrogen Receptor Modulators [SERMs] for osteoporosis.
G4	Long-term oral NSAIDs.
G5	Long-term oral steroids.
H1	5-alpha reductase inhibitors.
H2	Alpha blockers.
H3	Muscarinic antagonists.
I2	ACE-Inhibitors for diabetes.
I3	Angiotensin Receptor Blockers.
J2	Nutritional supplements.
Major Variations (n=7) (Defined as the identification or omission of ≥3 STOPPFrail criteria by a rater other than the gold standard rater)	
A1	Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate information.
A2	Any drug without clear clinical indication.
E1	Proton Pump Inhibitors.
G1	Calcium supplementation.
G2	Anti-resorptive/bone anabolic drugs for Osteoporosis.
I1	Diabetic oral agents.
J1	Multi-vitamin combination supplements.

Table 6.3: Reasons for major variations in identification of STOPPFrail indicators

Major Variation (n=7)	
(Defined as the identification or omission of ≥ 3 STOPPFrail criteria by a rater other than the gold standard rater)	
STOPPFrail criterion	Reasons for variations
A1: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate information.	For 1 or more cases, 10 physicians overlooked that patients were having difficulty with medication adherence.
A2: Any drug without clear clinical indication	Senior consultant geriatricians and those involved in caring for nursing home patients more frequently suggested discontinuation of warfarin, benzodiazepines and acetyl cholinesterase inhibitors due to the lack of an ongoing clear indication.
E1: Proton Pump Inhibitors (PPI)	This criterion suggests reducing high dose PPIs to a lower dose; 7 physicians suggested discontinuation of the lower dose.
G1: Calcium supplementation	This criterion suggestion stopping calcium alone; 3 physicians suggested discontinuation of vitamin D with calcium.
G2: Anti-resorptive/bone anabolic drugs for Osteoporosis	This criterion suggests stopping anti-resorptive therapy in patients with osteoporosis; 6 physicians suggested discontinuation in patients with metastatic cancer.
I1: Diabetic oral agents	When ≥ 1 diabetic oral agent was prescribed, physicians differed in their approach to deprescribing; some suggested discontinuing one agent alone whereas others suggested discontinuation of all oral diabetic agents.
J1: Multi-vitamin combination supplements	Three physicians suggested discontinuing folic acid and vitamin b12 supplementation as part of this criterion. Other physicians either continued these medications or suggested discontinuing them as part of criterion A2 i.e. no clear indication.

Table 6.4: Frequency of STOPPFrail observations according to each rater

Criterion	Raters (n)												
	GS	2	3	4	5	6	7	8	9	10	11	12	13
A1: Any drug the patient persistently fails to take/tolerate	11	11	6	6	10	11	2	9	9	2	5	4	5
A2: Drugs with no clear indication	21	41	23	18	17	16	9	21	8	11	11	14	20
B1: Lipid lowering therapies	13	14	13	14	14	14	13	14	12	12	14	14	14
B2: Alpha blockers for HTN	2	2	2	2	2	2	2	2	2	2	1	2	1
C1: Anti-platelets	1	3	0	1	1	1	1	0	0	1	1	1	1
D1: Neuroleptics	2	1	2	2	2	2	2	1	2	1	0	0	0
D2: Memantine	2	2	2	2	2	2	2	2	2	2	2	2	2
E1: Proton pump inhibitors	4	8	5	7	4	5	4	9	7	5	5	8	4
E2: H2 Receptor Antagonists	0	1	1	1	1	1	0	1	1	1	1	1	1
E3: Gastrointestinal antispasmodics	0	0	0	0	0	0	0	0	0	0	0	0	0
F1: Theophylline	1	1	1	1	1	1	1	1	1	1	0	1	0
F2: Leukotriene antagonists	1	0	1	1	1	1	0	1	1	1	1	1	1
G1: Calcium supplementation	6	6	9	6	12	11	6	6	6	5	6	6	6
G2: Anti-resorptive/Bone anabolic drugs for Osteoporosis	2	2	4	4	3	3	0	1	2	1	3	1	3
G3: SERMs for Osteoporosis	1	1	1	1	1	0	1	1	0	0	1	1	1
G4: Long term oral NSAIDs	3	2	3	2	2	3	3	2	3	2	3	3	3
G5: Long term oral steroids	1	0	1	1	1	1	1	1	0	0	0	0	0
H1: 5 alpha reductase inhibitors	1	1	1	3	1	1	1	1	1	1	1	1	1
H2: alpha blockers	3	3	3	5	3	2	3	3	3	3	3	3	3
H3: Muscarinic antagonists	0	0	0	1	0	1	0	0	0	0	1	1	1

I1: Diabetic oral agents	5	4	4	6	5	5	5	5	5	3	2	8	2
I2: Ace inhibitors for Diabetes Mellitus	0	1	0	0	0	0	0	0	0	0	0	0	0
I3: Angiotensin receptor blockers [ARBs] for Diabetes Mellitus	1	0	1	1	1	0	0	2	0	1	0	1	0
I4: Systemic oestrogens for menopausal symptoms	0	0	0	0	0	0	0	0	0	0	0	0	0
J1: Multivitamin combination tablets	3	3	8	3	3	3	4	3	6	2	3	3	3
J2: Nutritional Supplements	13	10	11	16	13	13	14	12	1	11	13	14	13
J3: Prophylactic Antibiotics	5	5	5	5	5	5	5	5	5	5	5	5	5

6.3.5 Criteria with major variations

The criteria where most variations between raters were observed are listed in **Table 6.3**. Differences in opinion regarding drug indication was identified for warfarin, benzodiazepines and acetyl cholinesterase inhibitors. Two Consultant Geriatricians and one GP with experience in attending patients in residential care units were more likely to identify these prescriptions as being potentially inappropriate. Ten raters did not observe that patients were having difficulty with medication adherence for all cases. Seven raters identified the lower dose of a proton pump inhibitor (PPI) as being inappropriate as part of criterion E1; this criterion suggests reducing the higher dose to a lower dose. Three raters suggested Vitamin D was inappropriate as part of criterion G1. However, this criterion suggests stopping calcium alone i.e. it does not mention Vitamin D. When three diabetic oral agents were prescribed, raters' opinion on appropriateness varied. Raters either identified that one agent alone was inappropriate and suggested that deprescribing should occur in a staggered fashion i.e. one agent at a time. Others identified all diabetic oral agents as inappropriate and suggested that they could, in theory, be deprescribed all at the one time. For 3 raters, folic acid and vitamin b12 supplementation were identified as inappropriate as part of STOPPFrail criterion J1 (combination multivitamins) criterion. Other raters either deemed these drugs appropriate and suggested continuation or else deemed them inappropriate as part of criterion A2 i.e. prescription of a medication without a clear indication.

6.4 DISCUSSION

The Inter-rater reliability of STOPPFrail criteria is substantial to good (mean 0.76 (SD 0.059)), when tested between multiple physicians practising across three different specialities, despite physicians having no prior knowledge of the tool or experience of using it. It takes approximately 3 minutes to apply STOPPFrail criteria to one clinical case. No discrepancies in its application were identified for 4 STOPPFrail criteria. Minor variations were identified for 16 criteria and major variations were identified for 7 criteria. There was no difference between the three different physician groups, or between the participants within each group, in their ability to apply STOPPFrail criteria ($df (2, 9) = 0.712, p=0.516$).

The strength of this study is the robust methodology employed. Three groups of physicians, all of whom had no experience in using IP criteria and who were given the same clear instructions, participated in this research. The clinical cases used were based on real patients and therefore reflected common clinical practice. However, there were limitations. Firstly, this was a theoretical exercise i.e. physicians assessed the suitability of STOPPFrail criteria according to a clinical case history presented to them in a structured format and identified IP accordingly. Assessments were *not* completed on patients in person and medications were *not* actually deprescribed. It could be suggested that physicians are more conservative when dealing with real life patients rather than theoretical cases. However, it could also be suggested that the IRR could be under-estimated here. Where there is perceived ambiguity in the information provided and patients are not there to clarify information, physicians could also assume medications are appropriate.

Efficient and safe deprescribing depends on the quality of the available clinical data. The more comprehensive the clinical information, the more accurate IP criteria can be applied leading to higher levels of IRR (243). However, ambiguity is often present in clinical practice due to incomplete records (244, 245), and consequently, physicians often make decisions based on limited information. Therefore, these cases, in this theoretical exercise, do reflect common clinical scenarios.

Major variations, found in 7 STOPPFrail criteria, were as a result of (i) differences in physician opinion regarding clinical indications, (ii) criteria mis-interpretation and (iii) failure to acknowledge problems with medication adherence. Differing opinions on clinical indication for medications could be as a consequence of physician specialty and/or physician level of training e.g. Consultant Geriatricians deemed acetyl-cholinesterase inhibitors inappropriate in late stage dementia more frequently than their trainee geriatricians or GP colleagues. Mis-interpretation of criteria was identified for the prescription of Vitamin D and low dose PPIs. The identification of both these prescriptions as inappropriate was not necessarily incorrect, however for the purpose of this exercise, they were deemed incorrect as they were not specifically listed as PIP in STOPPFrail criteria. STOPPFrail criteria was developed and validated to guide physicians on deprescribing, as well as open dialogue around the appropriateness of all medications and in doing so encourage medication review in its entirety, thus these variations seen here cannot be assumed to be inappropriate.

Despite clear documentation of medication adherence in the clinical cases, physicians did not observe this every time. This was probably the result of a reading error and once not identified in one case, was unlikely to be identified in other cases. This is a challenge with a theoretical exercise as participants rely on their ability to assess the clinical information as it is presented to them, rather than confirming medications and adherence with a patient directly. This could also be explained by user fatigue as the exercise progressed and the process became repetitive.

Physicians are frequently under time pressure where completing medication reviews and using criteria like STOPPFrail can encourage identification of medications that can potentially be deprescribed in a time-efficient structured fashion. Explicit criteria that require time to deploy often do not translate to clinical practice and inevitably are used primarily as research tools (19). STOPPFrail criteria has shown itself here to, not only assist physicians with identifying inappropriate medications in frailer older adults with a poor survival prognosis, but to also do this in a time efficient manner, which suggests it will translate across to clinical practise, where it hopefully, will have impact.

Deprescribing requires a culture change for many physicians, particularly physicians wherein contact with frail older adults with a poor one year survival prognosis comprises a small part of their everyday clinical practice. Deprescribing requires extensive knowledge around disease trajectory, pharmacological actions of medications and the likely risks involved with their use. Deprescribing in patients with a poor survival prognosis is more challenging than deprescribing specific drugs for specific reasons in older adults as this process can often initiate a more extensive

discussion around end of life care. Future studies, using STOPPFrail criteria, will be needed to ascertain the extent of PIP in this population cohort. The substantial to good IRR demonstrated in this study, indicates that prevalence studies of PIP, according to STOPPFrail criteria, will be comparable between researchers and across research centres. Following this, randomised controlled trials can be planned to assess whether deprescribing in this population can affect patient outcomes and provide the evidence required to support physicians undertaking deprescribing. Our data suggests that STOPPFrail provides reliable explicit guidance for any clinician undertaking routine medication review in frailer older patients with poor one year survival prognosis.

CHAPTER 7:

Prevalence of potentially inappropriate prescribing as determined by
STOPPFrail criteria in a representative population of older patients
undergoing assessment for long term nursing home placement and of older
adults presenting with acute illness to hospital.

7.1 INTRODUCTION

STOPPFrail criteria were devised to highlight instances of potentially inappropriate prescribing practices in frail older adults with a poor one year survival prognosis. Their content was validated by Delphi consensus methodology, in which 17 senior academic clinicians participated (240). As demonstrated in Chapter 6, the inter-rater reliability (IRR) of STOPPFrail criteria was good when deployed by physicians practising in different specialties (246).

The prevalence of potentially inappropriate prescribing in older frail adults with a poor survival prognosis is unknown. One population of older adults with such functional impairment are those who require long term nursing home admission. Such patients are often very frail (16), with multiple co-morbidities (17), carry a high burden of medication (195) and often have a very poor survival prognosis (247).

In Ireland, the Health Service Executive (HSE) operates the Nursing Home Support Scheme (NHSS) to provide assessment and subsequently financial support to older adults requiring long term nursing home care. Prior to nursing home application, a care needs assessment must be performed by appropriate healthcare professionals. Through this assessment, applicants' medical, functional and cognitive status details are established. The completion of this comprehensive report is overseen by a consultant in Geriatric Medicine or Old Age Psychiatry, who provides a detailed clinical assessment and confirms that long term nursing care is required for the person. This application document contains a large amount of relevant clinical information on frail older adults suitable for long term care. For this reason, it was deemed a reliable source of relevant information on this population of older people.

In Ireland, older frailer people with a poor one year survival prognosis are commonly referred to hospital with acute illness. As pointed out previously, these patients are commonly exposed to major polypharmacy as a result of multi-morbid illness. The extent to which such patients are exposed to medications that are likely not appropriate for them is unknown.

7.1.1 Objectives

The objectives of this study were:

- (i) To determine the proportion of older adults requiring long-term nursing care eligible for the application of STOPPFrail criteria.
- (ii) To determine the prevalence of potentially inappropriate prescribing using STOPPFrail criteria, and the risk factors for prescription of STOPPFrail medications.
- (iii) To determine the proportion of older adults presenting to hospital with an acute illness to hospital (see Chapter 3) who are eligible for the application of STOPPFrail criteria.
- (iv) To determine the prevalence of potentially inappropriate prescribing using STOPPFrail criteria in this acutely ill hospitalised cohort.

The work undertaken in this chapter, including study design, data collection and statistical analysis, is entirely my own.

7.2 METHODS

7.2.1 Study population

Using an estimated prevalence of ≥ 1 potentially inappropriate medication of 20%, a margin of error of 5% and a 95% level of confidence, a minimum sample of 246 patients was required for this study (**Figure 7.1**).

Figure 7.1: Same size calculation

Formula	$n = \frac{Z^2 \times P (1 - P)}{D^2}$
n = sample size	
Z = Z statistic for the level of confidence (1.96)	
P = Expected prevalence (20% or 0.20)	
D = margin of error (5% or 0.05)	
	$n = \frac{(1.96)^2 \times (0.20) (1 - 0.2)}{0.05^2} = 246$

7.2.2 Cork City and County Local Placement Forum and the Common

Summary Assessment Report

All patients applying for nursing home or long-term residential placement through the Irish Nursing Home Support Scheme (248) must undergo a comprehensive multidisciplinary assessment of their illnesses, ADL function, cognition and personal care needs. The results of this assessment are presented in the form of a Common Summary Assessment Report (CSAR) (**appendix 14**) which is reviewed and discussed by a multidisciplinary panel each fortnight.

The CSAR contains details on patients' co-morbid illnesses, concurrent medications and doses, Barthel Index (157) score and cognitive status using either a

Mini-mental state examination (MMSE) (158) or the Montreal cognitive assessment (MoCA) (162). The Barthel Index and the MMSE have been described in detail in Chapter 3. The MoCA is a 30-point cognitive assessment tool, which has been validated in patients with mild cognitive impairment and dementia (**Appendix 15**). It assesses several cognitive domains including short-term memory, visuospatial abilities, executive function, language, attention, concentration, abstract thinking and orientation.

7.2.3 Study period

All CSARs submitted as part of the applications for long term nursing home or residential facility care to the Cork Nursing Home Support Scheme office, between Jan 1st and June 30th 2016, were retrospectively reviewed. The local Clinical Research Ethics Committee approved the study protocol (**appendix 16**).

7.2.4 Data Collection

The following data were transferred from the CSARs onto an excel spreadsheet: (i) standard demographic details, (ii) medical diagnoses, (iii) concurrent medications and doses, (iv) functional ability (Barthel Index score) (157), (vi) cognitive ability (MMSE (158) or MOCA score (162), and (vii) frailty using the Rockwood clinical frailty scale category (163). Where available, supplementary clinical information was obtained from case records.

Recorded medications were those prescribed at the time of nursing home application. Short term medications documented on the CSAR were excluded from evaluation e.g. heparinoids for deep vein thrombosis prophylaxis. Co-morbidities were quantified according to the Cumulative Illness Rating Scale (CIRS) (156). Details of both the Clinical Frailty Scale and CIRS have been described in Chapter 3.

7.2.5 Determination of potentially inappropriate prescribing practices using STOPPFrail criteria

STOPPFrail criteria for potentially inappropriate prescriptions were applied to patients who meet STOPPFrail eligibility criteria i.e. the presence of an end-stage irreversible pathology, a poor one year survival prognosis, severe cognitive or functional impairment or both and patients in whom symptom management was the overriding priority, as opposed to long-term prevention.

The presence or absence of a potentially inappropriate medication (PIM) was categorised as a dichotomous variable i.e. a medication was either potentially inappropriate according to STOPPFrail criteria or not. Some prescriptions could pertain to 1 or more STOPPFrail criteria (e.g. a drug may have no clear indication and also be listed elsewhere in the criteria as being inappropriate) but for the purpose of this study the identification of one drug was categorised as being inappropriate, regardless of whether or not it fulfilled one or more STOPPFrail criteria i.e. the potentially inappropriate drug was the unit of measurement, not the numbers of STOPPFrail criteria it breached. Uncertainty regarding the appropriateness of a

prescription was treated conservatively i.e. the prescribing decision was deemed to be appropriate in such circumstances.

7.2.6 Statistical analysis

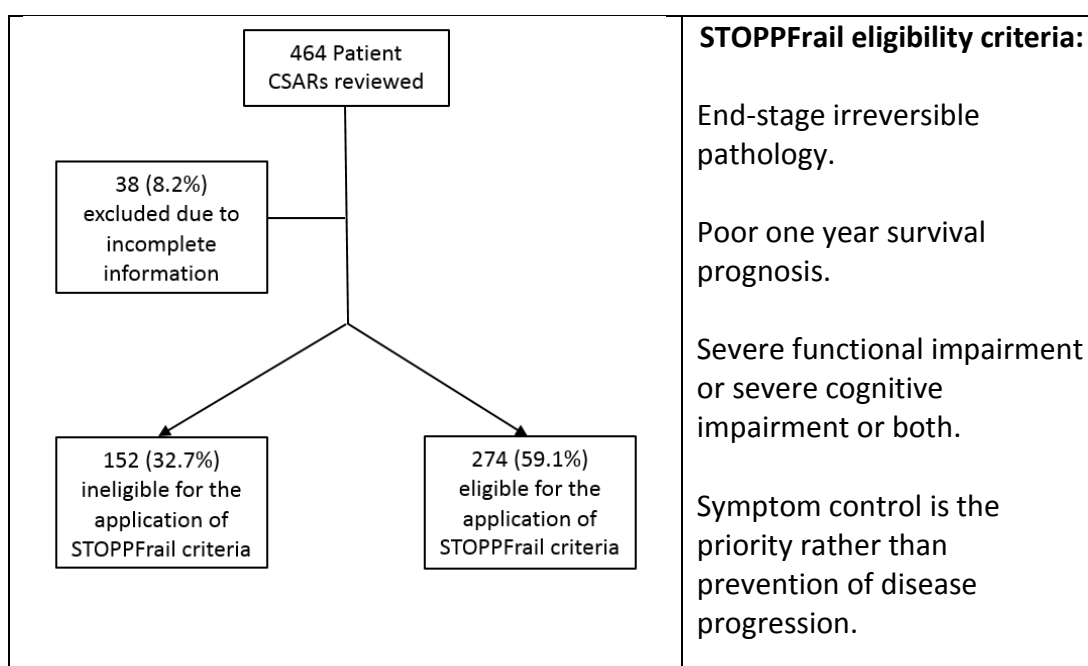
Statistical analysis was performed using SPSS[®] version 22. Descriptive data were reported using the mean and standard deviation (SD) for variables normally distributed and median and interquartile range (IQR) for non-parametric variables. Differences in the distribution of categorical variables were compared using the Pearson Chi-square (X^2) test and continuous variables using the independent t-test. The Mann Whitney U and Kruskal-Wallis tests were used to determine independence of two or more non-parametric variables respectively. Multivariable logistic regression was used to examine the influence of gender, age, presence of dementia, the number of medical conditions and the number of medications on the presence of potentially inappropriate prescribing practices. The Hosmer & Lemeshow statistic was used to test the goodness-of-fit of the regression model. A probability value of < 0.05 was considered statistically significant.

7.3. RESULTS

7.3.1 Screening

Four hundred and sixty four CSARs were retrospectively reviewed, of which 38 were excluded due to incomplete information (**Figure 7.2**). Two hundred and seventy four patients (59.1%) met STOPPFrail eligibility criteria, thus comfortably fulfilling the study power calculation requirement to evaluate at least 246 patients. All patients, those that met STOPPFrail eligibility criteria and those that did not, were evaluated in this study.

Figure 7.2: Participant screening, exclusion and enrolment



7.3.2 Population characteristics (n = 426)

Fifty five percent (n=233) of the 426 study patients were female (**Table 7.1**). The median (IQR) age was 83 (77.2 – 88) years, with an overall range of 40 to 99 years. Thirty three patients (7.7%) were < 65 years old. Approximately two thirds of patients (64.1%) requiring long term care resided in hospital at the time of nursing home application; 15.7% were already in emergency nursing home accommodation. The remainder of patients were at home (19.7%), in hospice care (0.2%) or in temporary hostel accommodation (0.2%).

7.3.3 Characteristics of patients who were eligible for the application of STOPPFrail criteria

Differences between older adults that met STOPPFrail eligibility criteria and those that did not are displayed in **Table 7.1**. Two hundred and eighty four (66.7%) of adults had a MMSE score available, whereas 58 (13.6%) adults had a MOCA score only. Older adults who met STOPPFrail eligibility criteria were older (83.5 (IQR78.75 – 88) vs 80 (70.25 – 86) years, $U = 15940$, $p < 0.001$), had lower mean MMSE scores (14.6 (SD7) vs 21 (5.6) $t_{248.48} = 7.47$, $p < 0.001$) and had lower mean Barthel Index scores (7.6 (SD4.3) vs 12 (3.9) $t_{341.281} = 10.86$, $p = 0.03$) compared to older patients who did not meet STOPPFrail criteria.

Older adults meeting STOPPFrail eligibility criteria had a higher level of frailty on the Rockwood Clinical Frailty Scale ($\chi^2 (7) \geq 93.616$ $p < 0.001$) (**Figure 7.3**) than

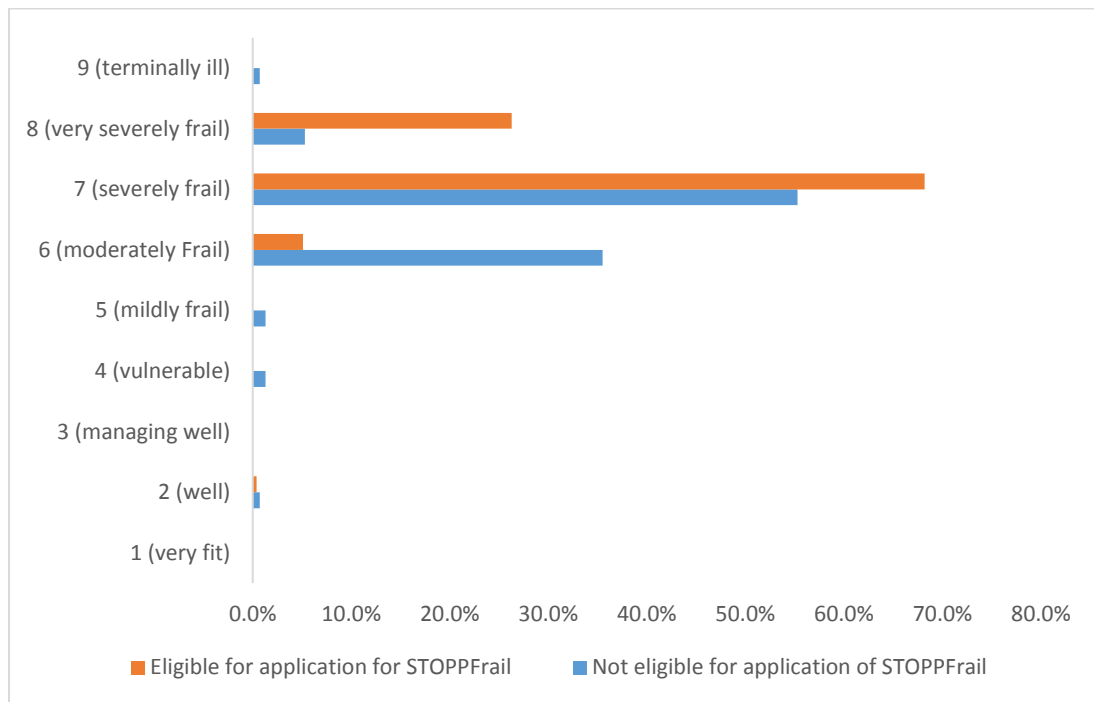
those who did not. Older adults meeting STOPPFrail eligibility criteria more likely to be severely frail (68.2% vs 55.3%, $X^2(1) \geq 7.122$ $p=0.008$) or very severely frail (26.3% vs 5.3%, $X^2(1) \geq 28.305$ $p \leq 0.001$) compared to patients who did not meet STOPPFrail eligibility criteria.

Table 7.1: Characteristics of study population

Variable	Eligible for application for STOPPFrail n = 274	Not eligible for application of STOPPFrail n = 152	Total n = 426	P-value
Female gender	155 (56.6%)	78 (51.3%)	233 (54.7%)	0.297
Age distribution				
Median (IQR)	83.50 (78.75-88)	80 (70.25-86)	83 (77.25-88)	<0.001*
≤ 64	0 (0%)	33 (21.7%)	33 (7.7%)	<0.001*
65 – 74	37 (13.5%)	11 (7.2%)	48 (11.3%)	0.050*
75 – 84	109 (39.8%)	60 (39.5%)	169 (39.7%)	0.950
85 - 94	118 (43.1%)	44 (28.9%)	162 (38%)	0.004*
≥ 95	10 (3.6%)	4 (2.6%)	14 (3.3%)	0.572
Cognition				
Patients completed MMSE (n)	181 (66.1%)	103 (67.8%)	284 (66.7%)	0.721
Mean (SD)	14.6 (7)	21 (5.6)	16.6 (7)	<0.001*
Normal cognition (24–30)	16 (8.8%)	25 (24.3%)	44 (14.4%)	<0.001*
Mild CI (19–23)	34 (18.8%)	43 (41.7%)	77 (27.1%)	<0.001*
Moderate CI (10-18)	92 (50.8%)	32 (31.1%)	124 (43.7%)	0.001*
Severe CI (0 – 9)	39 (21.5%)	3 (2.9%)	42 (14.8%)	<0.001*
Function (Barthel Index)				
Mean (SD)	7.6 (4.3)	12 (3.9)	9.2 (4.7)	0.03*
Independent (≥ 20)	0 (0%)	4 (2.6%)	4 (0.9%)	0.007*
Low dependency (16– 19)	9 (3.3%)	27 (17.8%)	36 (8.5%)	<0.001*
Moderate dependency (11 – 15)	61 (22.3%)	70 (46.1%)	131 (30.8%)	<0.001*
High dependency (6 – 10)	110 (40.1%)	43 (28.3%)	153 (35.9%)	0.015*
Maximum dependency (0 – 5)	94 (34.3%)	8 (5.3%)	102 (23.9%)	<0.001*

Legend: IQR = inter-quartile range, MMSE = mini-mental state examination, CI = cognitive impairment, SD = standard deviation, p-value pertains to the probability of there being a difference between groups in the variable of interest.

Figure 7.3: Level of frailty according to STOPPPFrail eligibility criteria (n=274)



7.3.4 Level of morbidity

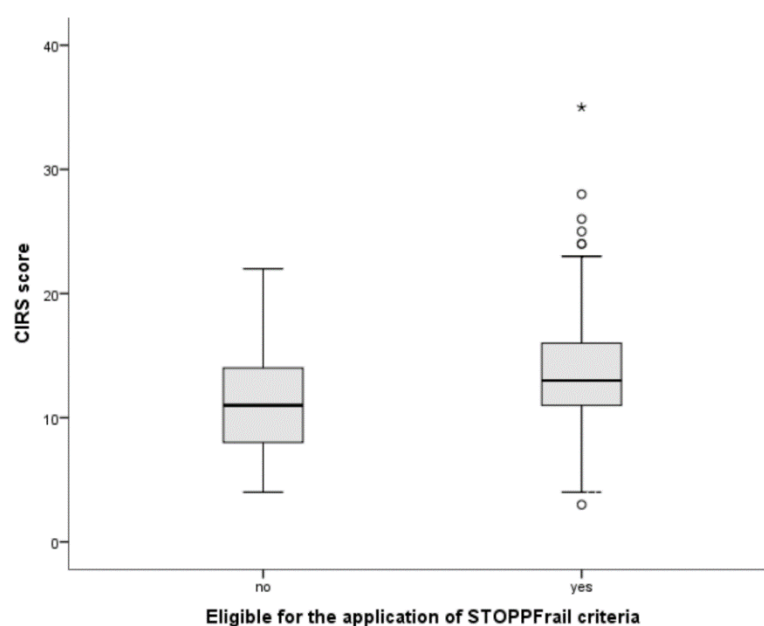
Patients had an average of 7.3 (SD 2.6) conditions, with 3.8 (SD 1.9) illnesses requiring regular medications. The prevalence of conditions, in order of frequency, is presented in **Table 7.2**. Patients meeting STOPPPFrail eligibility criteria were more likely to have a diagnosis of dementia (73.4% vs 42.8%, $\chi^2(1) \geq 9.02$, $p < 0.001$), faecal incontinence (55.8% vs 30.9%, $\chi^2(1) \geq 24.736$, $p < 0.001$), urinary incontinence (81% vs 54.6%, $\chi^2(1) \geq 34.385$, $p < 0.001$) and osteoporosis (25.2% vs 15.1%, $\chi^2(1) \geq 5.833$, $p < 0.016$), as well as a higher burden of co-morbid illness, (CIRS scores 13.6 (SD4.4) vs 10.9 (SD3.8), $t_{(424)} = 6.386$, $p < 0.001$) (**Figure 7.4**) than patients who did not meet STOPPPFrail eligibility criteria. Anxiety was more prevalent in those ineligible for STOPPPFrail criteria (11.2% vs 2.9%, $\chi^2(1) \geq 12.088$, $p < 0.001$).

Table 7.2: Comparison of patients eligible for STOPPFrail criteria and patients not eligible for STOPPFrail criteria in terms of morbidity specific details

Variable	Eligible for application of STOPPFrail n = 274	Not eligible for application of STOPPFrail n = 152	Total n = 426	P-value
Conditions				
Mean (SD)	7.3 (2.6)	6.4 (2.5)	7 (2.6)	<0.001*
Conditions requiring regular medications				
Mean (SD)	4 (2)	3.8 (1.9)	3.9 (2)	0.172
Co-morbid Index (CIRS)				
Mean (SD)	13.6 (4.4)	10.9 (3.8)	12.7 (4.4)	<0.001*
Conditions				
Urinary Incontinence	222 (81%)	83 (54.6%)	305 (71.6%)	<0.001*
Faecal Incontinence	153 (55.8%)	47 (30.9%)	200 (46.9%)	<0.001*
Dementia	201 (73.4%)	65 (42.8%)	266 (62.4%)	<0.001*
Hypertension	134 (48.9%)	62 (40.8%)	196 (46%)	0.107
Constipation	122 (44.5%)	54 (35.5%)	176 (41.3%)	0.071
Depression	94 (34.3%)	59 (38.8%)	153 (35.9%)	0.353
Dyslipidaemia	70 (25.5%)	42 (27.6%)	112 (26.3%)	0.640
Falls	70 (25.5%)	41 (27%)	111 (26.1%)	0.748
Atrial Fibrillation	64 (23.4%)	36 (23.7%)	100 (23.5%)	0.939
Osteoporosis	69 (25.2%)	23 (15.1%)	92 (21.6%)	0.016*
Cancer	60 (21.9%)	25 (16.4%)	85 (20%)	0.178
Osteoarthritis	52 (19%)	30 (19.7%)	82 (19.2%)	0.849
Stroke	51 (18.6%)	24 (15.8%)	75 (17.6%)	0.464
Ischaemic Heart Disease	51 (18.6%)	22 (14.5%)	73 (17.1%)	0.227
Diabetes Mellitus	42 (15.3%)	29 (19.1%)	71 (16.7%)	0.320
Previous fracture	47 (17.2%)	19 (12.5%)	66 (15.5%)	0.204
Hypothyroidism	34 (12.4%)	25 (16.4%)	59 (13.8%)	0.248
COPD	34 (12.4%)	15 (9.9%)	49 (11.5%)	0.431
Heart Failure	33 (12%)	11 (7.2%)	44 (10.3%)	0.118
Chronic kidney disease	23 (8.4%)	15 (9.9%)	38 (8.9%)	0.609
Benign prostatic hypertrophy	29 (10.6%)	9 (5.9%)	38 (8.9%)	0.106
Epilepsy	23 (8.4%)	12 (7.9%)	35 (8.2%)	0.857
Neck of femur fracture	23 (8.4%)	8 (5.3%)	31 (7.3%)	0.233
Anaemia	22 (8%)	6 (3.9%)	28 (6.6%)	0.103
Recurrent UTIS	18 (6.6%)	8 (5.3%)	28 (6.6%)	0.997
Alcohol dependency	14 (5.1%)	13 (8.6%)	27 (6.3%)	0.162
GORD	13 (4.7%)	12 (7.9%)	25 (5.9%)	0.185
Anxiety	8 (2.9%)	17 (11.2%)	25 (5.9%)	0.001*
Glaucoma	17 (6.2%)	6 (3.9%)	23 (5.4%)	0.323
Parkinson's Disease	14 (5.1%)	6 (3.9%)	20 (4.7%)	0.587

Legend: CIRS = Cumulative illness rating scale, SD = standard deviation, COPD = chronic pulmonary obstructive disease, UTI = urinary tract infection, p-value pertains to the probability of there being a difference between groups in the variable of interest.

Figure 7.4: CIRS score according to STOPPPFrail eligibility criteria



7.3.5 Prescription medications

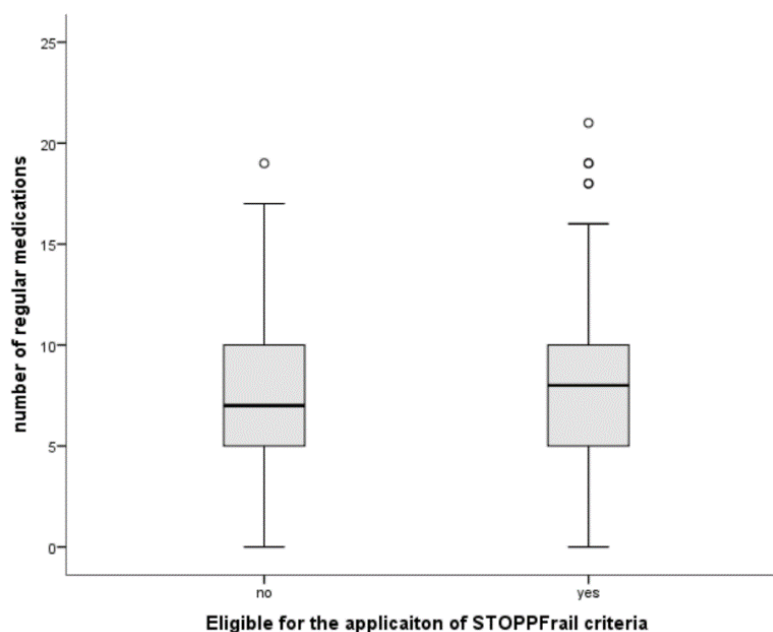
A total of 3765 medications were prescribed to this cohort of 426 patients; 2512 medications (66.8%) to those eligible for application of STOPPPFrail criteria and 1253 medications (33.2%) to all others. Polypharmacy (≥ 6 medications) and high level polypharmacy (≥ 11 medications) were observed in 294 (69%) and 98 (23%) patients respectively, with no significant difference noted between groups, (67.1% vs 69%, $\chi^2(1) \geq 1.425$, $p = 0.233$) and (24.8% vs 19.7%, $\chi^2(1) \geq 0.403$, $p = 0.526$) respectively. There was no significant difference in the mean number of medications prescribed to those that were eligible for application of STOPPPFrail criteria and those that were not, a mean of 8.0 (SD 4) vs 7.5 (SD 3.7), $t_{(424)} = 1.334$, $p = 0.183$ (**Figure 7.5**).

Table 7.3: Number of prescription medications in 426 patients applying for nursing home care

Variable	Eligible for application of STOPPFrail n = 274	Not eligible for application of STOPPFrail n = 152	Total n = 426	P-value
Medications (regular)				
Mean (SD)	8 (4)	7.5 (3.7)	7.8 (3.9)	0.183
range	0 - 21	0 - 19	0 - 21	
	268 (97.8%)	149 (98%)	417 (97.9%)	0.882
Number of patients on at least 1 medication				
1 – 5 medications	76 (27.7%)	47 (30.9%)	123 (28.9%)	0.487
6 – 10 medications	124 (45.3%)	72 (47.4%)	196 (46%)	0.675
≥ 11 medications	68 (24.8%)	30 (19.7%)	98 (23%)	0.233
≥ 6 medications	102 (67.1%)	294 (69%)	294 (69%)	0.526

Legend: IQR = inter quartile range, p-value pertains to the probability of there being a difference between groups in the variable of interest

Figure 7.5: Numbers of medications according to eligibility for STOPPFrail criteria



There was no significant difference between the numbers of medications prescribed to those aged ≤ 74 years, those between 75 and 84 years, 75 and those ≥ 85 years ($\chi^2 (4) \geq 5.932$, $p = 0.204$) (**Table 7.4**). The numbers of prescribed medications increased significantly with the number of conditions increasing from ≤ 5 to 6 – 10 but this was not the case when the number of conditions increased to ≥ 11 ($\chi^2 (4) \geq 102.692$, $p < 0.001$).

Table 7.4: Number of prescription medications and numbers of co-morbid illnesses according to age group

Variable	Number of medications			Total 426	P- value
	0 - 5	6 - 10	≥ 11		
Age					0.204
≤ 74	23 (28.4%)	37 (45.7%)	21 (25.9%)	81 (19%)	
75 – 84	45 (26.6%)	79 (46.7%)	45 (26.6%)	169 (39.7%)	
≥ 85	64 (36.4%)	80 (45.4%)	32 (18.2%)	176 (41.3%)	
Conditions					<0.001
0 – 5	75 (56.8%)	46 (23.5%)	5 (5.1%)	126 (29.6%)	
6 – 10	56 (42.4%)	41 (71.9%)	73 (74.5%)	270 (63.4%)	
≥ 11	1 (0.8%)	9 (4.6%)	20 (20.4%)	30 (7%)	

Legend: p-value pertains to the probability of there being a difference between groups in the variable of interest

7.3.6 General prescribing trends

Medication classes prescribed to this cohort are shown in **Table 7.5**.

Table 7.5: Common prescriptions

Variable	Eligible for application of STOPPFrail n = 274	Not eligible for application of STOPPFrail n = 152	Total n = 426	P-value
Medication				
Anti-hypertensives	172 (62.8%)	86 (56.5%)	258 (60.6%)	0.210
Beta blocker	92 (33.6%)	41 (27%)	133 (31.2%)	0.159
Diuretic (loop)	61 (22.3%)	26 (17.1%)	87 (20.4%)	0.206
ACE inhibitor	38 (13.9%)	21 (13.8%)	59 (13.8%)	0.988
Calcium channel blocker	34 (12.4%)	22 (14.5%)	56 (13.1%)	0.546
ARBs	27 (9.9%)	11 (7.2%)	38 (8.9%)	0.364
Alpha blockers	23 (8.4%)	10 (6.6%)	33 (7.7%)	0.502
Aldosterone antagonists	16 (5.8%)	2 (1.3%)	18 (4.2%)	0.026*
Analgesia	134 (48.9%)	70 (46.1%)	204 (47.9%)	0.572
Paracetamol	110 (40.1%)	53 (34.9%)	163 (38.2%)	0.283
Local anaesthetic	37 (13.5%)	13 (8.6%)	50 (11.7%)	0.128
Opioids (strong)	30 (10.2%)	20 (13.2%)	50 (11.7%)	0.497
Neuropathic agent	19 (6.9%)	13 (8.6%)	32 (7.5%)	0.544
Opioids (weak)	14 (5.1%)	8 (5.3%)	22 (5.2%)	0.945
NSAIDs (oral)	5 (1.8%)	2 (1.3%)	7 (1.6%)	0.692
NSAIDs (topical)	5 (1.8%)	1 (0.7%)	6 (7%)	0.328
Proton pump inhibitors	138 (50.4%)	66 (43.4%)	204 (47.9%)	0.169
Laxatives	130 (47.7%)	51 (33.6%)	181 (42.5%)	0.005*
Osmotic	110 (40.1%)	47 (30.9%)	157 (36.9%)	0.059
Stimulant	71 (25.9%)	27 (17.8%)	98 (23%)	0.056
Enema	1 (0.4%)	2 (1.3%)	3 (0.7%)	0.261
Bulk-forming	1 (0.4%)	0 (0%)	1 (0.2%)	0.456
Anti-platelet agents	100 (36.5%)	42 (27.6%)	142 (33.3%)	0.063
Neuroleptics	82 (29.9%)	48 (31.6%)	130 (30.5%)	0.723

Legend: ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, NSAID = non-steroidal anti-inflammatory, p-value pertains to the probability of there being a difference between groups in the variable of interest

Table 7.5: Common prescriptions continued

Variable	Eligible for application of STOPPFrail n = 274	Not eligible for application of STOPPFrail n = 152	Total n = 426	P-value
Anti-depressants	76 (27.7%)	53 (34.9%)	129 (30.3%)	0.125
SSRIs	62 (22.6%)	39 (25.7%)	101 (23.7%)	0.481
NASSa	33 (12%)	20 (13.2%)	53 (12.4%)	0.739
TCAs	14 (5.1%)	15 (9.9%)	29 (6.8%)	0.062
SNRIs	1 (0.4%)	1 (0.7%)	2 (0.5%)	0.672
Vitamin D supplements	88 (32.1%)	40 (26.3%)	128 (30%)	0.211
Calcium supplements	65 (23.7%)	33 (21.7%)	98 (23%)	0.636
Statin	79 (28.8%)	42 (27.6%)	121 (28.4%)	0.792
Anti-dementia drugs	90 (32.8%)	29 (19.1%)	119 (27.6%)	0.002*
- Memantine	60 (21.9%)	17 (11.2%)	77 (18.1%)	0.006*
- AChEi	52 (19%)	16 (10.5%)	68 (16%)	0.023*
Nutritional supplements	72 (26.3%)	26 (17.1%)	98 (23%)	0.029*
Benzodiazepines	62 (22.6%)	33 (21.7%)	95 (22.3%)	0.828
Anticoagulants	41 (15%)	35 (23%)	76 (17.8%)	0.037*
- Warfarin	14 (5.1%)	6 (3.9%)	20 (4.7%)	0.597
- DOACs	27 (9.9%)	29 (19.1%)	56 (13.1%)	0.007*
Thyroxine	32 (11.7%)	23 (15.1%)	55 (12.9%)	0.309
Z-drug	32 (11.7%)	16 (10.5%)	48 (11.3%)	0.719
Anti-epileptic drugs	32 (11.7%)	14 (9.2%)	46 (10.6%)	0.432
Folic acid	28 (10.2%)	14 (9.2%)	42 (9.9%)	0.738
Vitamin B1	26 (9.5%)	0 (0%)	42 (9.9%)	0.731

Legend: SSRI = selective serotonin re-uptake inhibitors, NASSa = nor adrenergic and specific serotonergic anti-depressant, TCAs = tricyclic anti-depressants, SNRI = Serotonin-norepinephrine reuptake inhibitors, AChEi = acetyl cholinesterase inhibitors, DOAC = Direct oral anti-coagulants, p-value pertains to the probability of there being a difference between groups in the variable of interest

The three most commonly prescribed medications were: (i) proton pump inhibitors (47.9%), (ii) paracetamol (38.2%) and (iii) osmotic laxatives (36.9%). Opioids were prescribed to 17.2% of patients, 30.5% were prescribed neuroleptics, 30.3% were prescribed antidepressants and 11.3% of patients were prescribed Z drug hypnotics.

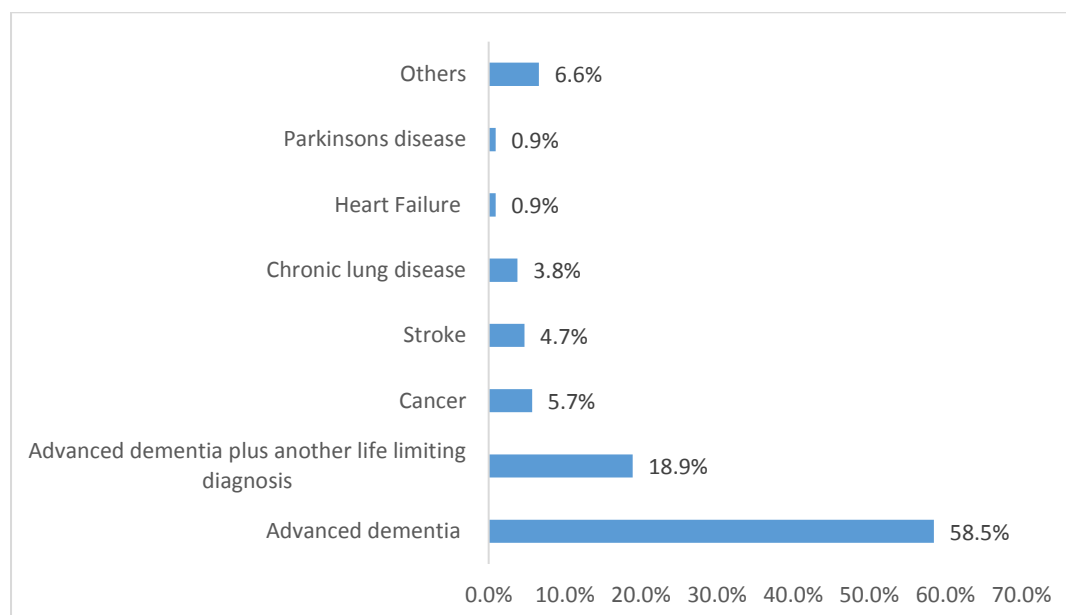
Patients meeting STOPPFrail eligible criteria were more likely to be prescribed aldosterone antagonists (5.8% vs 1.3%, $\chi^2(1) \geq 4.944$, $p = 0.026$), laxatives (40.1% vs 30.9%, $\chi^2(1) \geq 7.722$, $p = 0.005$) and nutritional supplements (26.3% vs 17.1%, $\chi^2(1) \geq 4.789$, $p = 0.029$). Consistent with a higher prevalence of dementia in these patients, they were also more likely to be prescribed acetyl cholinesterase inhibitors (21.9% vs 11.2%, $\chi^2(1) \geq 5.206$, $p = 0.023$) and memantine (19.0% vs. 10.5%, $\chi^2(1) \geq 7.578$, $p=0.006$). In contrast, anti-coagulants were less frequently prescribed to these STOPPFrail eligible patients (15% vs 23%, $\chi^2(1) \geq 7.287$, $p = 0.037$).

7.3.7 Life limiting diagnoses of older adults meeting STOPPFrail eligibility criteria

STOPPFrail eligibility criteria requires a patient to have end-stage irreversible pathology with an associated poor one year life expectancy e.g. advanced dementia with recurrent infections. Life-limiting conditions for those meeting STOPPFrail eligibility criteria are displayed in **Figure 7.6**. One in two patients (51%) had a diagnosis of advanced dementia with major cognitive and functional impairment, a further 19% had advanced dementia with another life-limiting diagnosis. Those who had dementia as a life-limiting illness were either experiencing recurrent infections

or maximum dependency with significant dysphasia. Those classified as “others” included end-stage liver disease, multi-system atrophy, motor neuron disease, multiple sclerosis and severe peripheral vascular disease.

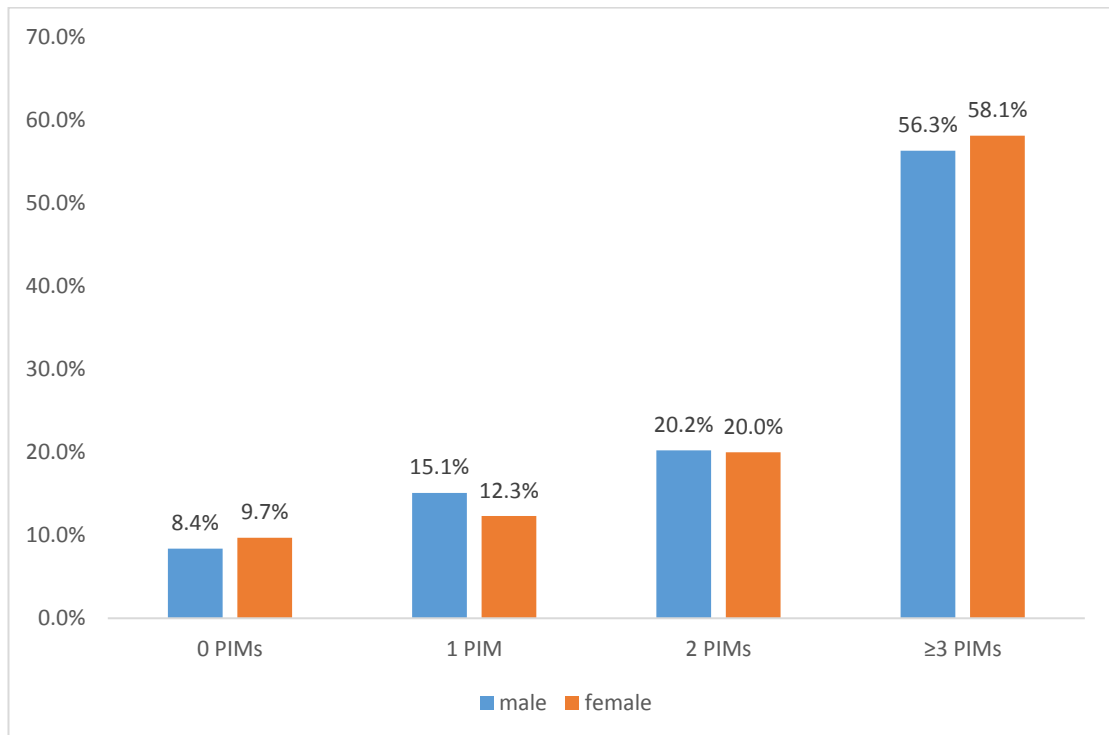
Figure 7.6: Life limiting diagnoses in those eligible for STOPPFrail criteria (n = 274)



7.3.8 Potentially inappropriate Medication (PIM) use as determined by STOPPFrail criteria

Applying STOPPFrail criteria, 828 of 2512 (33.0%) medicines were potentially inappropriate. These were identified in 250 of 274 patients (91.2%) who were eligible for STOPPFrail criteria. One PIM was identified in 38 patients (13.9%), 2 PIMs in 55 patients (20.1%), 3 PIMs in 48 patients (17.5%), 4 PIMs in 50 patients (18.2%), 5 PIMs in 34 patients (12.4%), 6 PIMs in 17 patients (6.2%), 7 PIMs in 4 patients (1.5%), 8 PIMs in 2 patients (0.7%), 10 PIMs in 1 patient (0.4%) and 11 PIMs in 1 patient (0.4%). Both males and females were equally likely to be prescribed 1, 2 or ≥ 3 PIMs ($\chi^2(3) \geq 0.567$, $p = 0.904$) (Figure 7.7).

Figure 7.7: Numbers of patients on potentially inappropriate medications as determined by STOPPFrail criteria (n = 274)



The most frequently encountered PIMs identified by STOPPFrail criteria are detailed in **Table 7.6**. These include (i) medications with no clear indication (47.0%), (ii) high dose proton pump inhibitors (31.4%), (iii) lipid-lowering therapies (29.6%), (iv) nutritional supplements (25.5%) and (v) neuroleptics (24.5%). Females were more likely to be inappropriately prescribed medications with no clear indication (52.6% vs 24.1%, $X^2(1) \geq 3.84$, $p = 0.05$), anti-platelets for primary prevention, (23.3% vs 5.5%, $X^2(1) \geq 9.261$, $p = 0.002$), calcium, (33.5% vs 6%, $X^2(1) \geq 20.7$, $p < 0.001$) and anti-resorptive therapy for osteoporosis, (16.3% vs 2.5%, $X^2(1) \geq 9.822$, $p = 0.002$). Males were more likely to be prescribed alpha blockers for hypertension, (3.5% vs 0.65%, $X^2(1) \geq 6.514$, $p = 0.011$), and neuroleptics (19.6% vs 18%, $X^2(1) \geq 7.884$, $p = 0.005$).

and alpha blockers with long term catheterisation (1.5% vs 0%, $\chi^2(1) \geq 3.951$, $p = 0.047$).

Table 7.6: Most frequently encountered potentially inappropriate prescriptions according to STOPPFrail criteria in 274 eligible patients

STOPPFrail Criterion		Total n=274
A2	No clear indication	182 instances in 129 patients (47%)
E1	High dose PPI	86 instances in 86 patients (31.4%)
B1	Lipid lowering therapies	83 instances in 81 patients (29.6%)
J2	Nutritional Supplements	108 instances in 70 patients (25.5%)
D1	Neuroleptics	73 instances in 67 patients (24.5%)
G1	Calcium	64 instances in 64 patients (23.4%)
D2	Memantine	49 instances in 49 patients (17.9%)
C1	Anti-platelet for primary prevention	47 instances in 47 patients (17.1%)
G2	Anti-resorptive therapies for OP	30 instances in 30 patients (10.9%)
J1	Multivitamins	22 instances in 22 patients (8%)
I1	Diabetic oral agents	22 instances in 20 patients (7.3%)
G5	Long term oral steroids	14 instances in 14 patients (5.1%)
B2	Alpha blockers for HTN	8 instances in 8 patients (2.9%)

Legend: PPI = proton pump inhibitor; OP = osteoporosis; HTN = hypertension

7.3.9 Risk factors for being prescribed a PIM as determined by

STOPPFrail criteria

Logistic regression was used to determine the influence of age, gender, dementia, number of conditions and number of medications on the risk of receiving a potentially inappropriate prescription according to STOPPFrail criteria. The results are detailed in **Table 7.7**.

Table 7.7: Risk factors for receiving a PIM as determined by STOPPFrail criteria

Variable		B (SE)	df	p-value	Exp (B)	95% CI for Exp (B)	
						Lower	Upper
Gender	Female	0.10 (0.50)	1	.837	1.11	0.42	2.95
Age	65 – 74		3	.233			
	75 – 84	0.50 (0.72)	1	.490	1.65	0.40	6.76
	85 – 94	1.14 (0.75)	1	.131	3.12	0.71	13.69
	≥ 95	-0.37 (1.04)	1	.724	0.69	0.09	5.34
Dementia		-0.07 (0.58)	1	.902	0.93	0.30	2.88
Medications		0.46 (0.09)	1	<0.001*	1.58	1.32	1.89
Conditions		-0.11 (0.10)	1	.262	0.89	0.73	1.09
Constant		-0.30 (1.00)	1	.763	0.74		

Homer and Lemeshow χ^2 (8) ≥ 2.795 , $p=0.947$, Model $\chi^2 = 125.022$, Cox and Snell $R^2 = 0.141$, Nagelkerke $R^2 = 0.309$, B = beta-value, SE = standard error, df = degrees of freedom, CI = confidence interval, Exp (B) = Odds ratio, Medications = number of medications, Conditions = number of conditions

The number of medications a patient was prescribed was significantly associated with an increased risk of receiving a STOPPFrail criteria PIM, controlling for gender, age, presence of dementia and the number of medical conditions. For every one extra medication prescribed, the odds of receiving a STOPPFrail PIM increased by 57.9% (Odds ratio 1.579, 95% CI 1.318 – 1.89, $P < 0.001$).

7.3.10 Application of STOPPFrail criteria to hospitalised older adults

In Chapter 3, 240 older patients were studied to determine the prevalence of ADRs causing hospitalisation and the prevalence of PIMs according to STOPP/START criteria. These patients were retrospectively reviewed to assess their eligibility for the application of STOPPFrail criteria; 48 (20%) patients met the STOPPFrail eligibility criteria. The differences identified between these patients and those who did not meet STOPPFrail eligibility criteria are displayed in **Table 7.8**.

Those who met STOPPFrail eligibility criteria were significantly older (mean age 81.4 (SD 6.8) years vs 77.2 (SD 7.6) years, $t_{238}=3.495$, $p = 0.001$), more cognitively impaired (median MMSE scores 20 (IQR 11-25) vs 27 (IQR 23.75-28.75), $U = 926$, $p < 0.001$), more functionally impaired (median Barthel Index scores 11 (IQR 7.25) vs 20 (IQR 18 – 20), $U = 519$, $p < 0.001$), had a higher burden of co-morbid illness (mean CIRS score 20.5 (SD 4.5) vs 14 (SD 5.7), $t_{89,454}=5.845$, $p < 0.001$), were prescribed a higher number of medications (mean 10.8 (SD 4.6) vs 8.2 (SD 4.4), $t_{70,546}=3.696$, $p = 0.001$) and were significantly frailer on the Rockwood Frailty Scale ($X^2(8) \geq 163.627$ $p < 0.001$) (**Figure 7.8**) than those that did not. Reasons for both groups not completing the MMSE score are displayed in **Table 7.9**. Those patients who met STOPPFrail eligibility criteria were more likely to die during the index admission (14.6% vs 1%, $X^2(2) \geq 18.844$, $p < 0.001$) and more likely to die within 6 months of enrolment (39.6% vs 3.6%, $X^2(2) \geq 50.782$ $p < 0.001$) than those who did not meet STOPPFrail eligibility criteria.

Table 7.8: Characteristics of study population (n=240)

Variable	Eligible for application for STOPPFrail n = 48	Not eligible for application of STOPPFrail n = 192	Total n = 240	P-value
Female	20 (41.7%)	99 (51.6%)	119 (49.6%)	0.220*
Age, Mean (SD)	81.4 (6.8)	77.2 (7.6)	78 (7.6)	0.001*
Cognitive ability				
MMSE completed	27 (56.3%)	172 (89.6%)	199 (82.9%)	<0.001*
Median, (IQR)	20 (11-25)	27 (23.25-28.75)	26 (22-28)	<0.001*
Functional ability				
Function (Barthel), med (IQR)	11 (7.25-13)	20 (18-20)	19 (15-20)	<0.001*
Conditions, mean (SD)	11.8 (3.7)	8.2 (3.9)	8 (4.1)	<0.001*
CIRS, mean, (SD)	20.5 (4.5)	14 (5.7)	15.3 (6.1)	<0.001*
Medication use				
Medications, mean (SD)	10.8 (4.6)	8.2 (4.4)	8.7 (4.6)	0.001*
Number of patients on ≥1 med	48 (100%)	188 (97.9%)	236 (98.3%)	0.313
1 – 5	6 (12.5%)	47 (24.5%)	53 (22.1%)	0.074
6 – 10	22 (45.8%)	83 (43.2%)	105 (43.8%)	0.745
≥11	20 (41.7%)	58 (30.2%)	78 (32.5%)	0.130
≥6	42 (87.5%)	142 (74%)	184 (76.7%)	0.047*
Follow up data				
Data available on death	38 (79.2%)	146 (76%)	184 (76.7%)	
Death during index admission	7 (14.6%)	2 (1%)	9 (3.8%)	<0.001*
Death within 6 months of index admission	19 (39.6%)	7 (3.6%)	26 (10.8%)	<0.001*
LOS, med (IQR)	9 (5-21.5)	7 (3-12)	8 (3-13.75)	0.022*

Legend: IQR = inter-quartile range, MMSE = mini-mental state examination, med = median, IQR = inter quartile range, SD = standard deviation, CIRS = Cumulative illness rating scale, LOS = length of stay, p-value pertains to the probability of there being a difference between groups in the variable of interest.

Figure 7.8: Clinical Frailty Scale status of patients (n = 240) according to STOPPFrail eligibility criteria

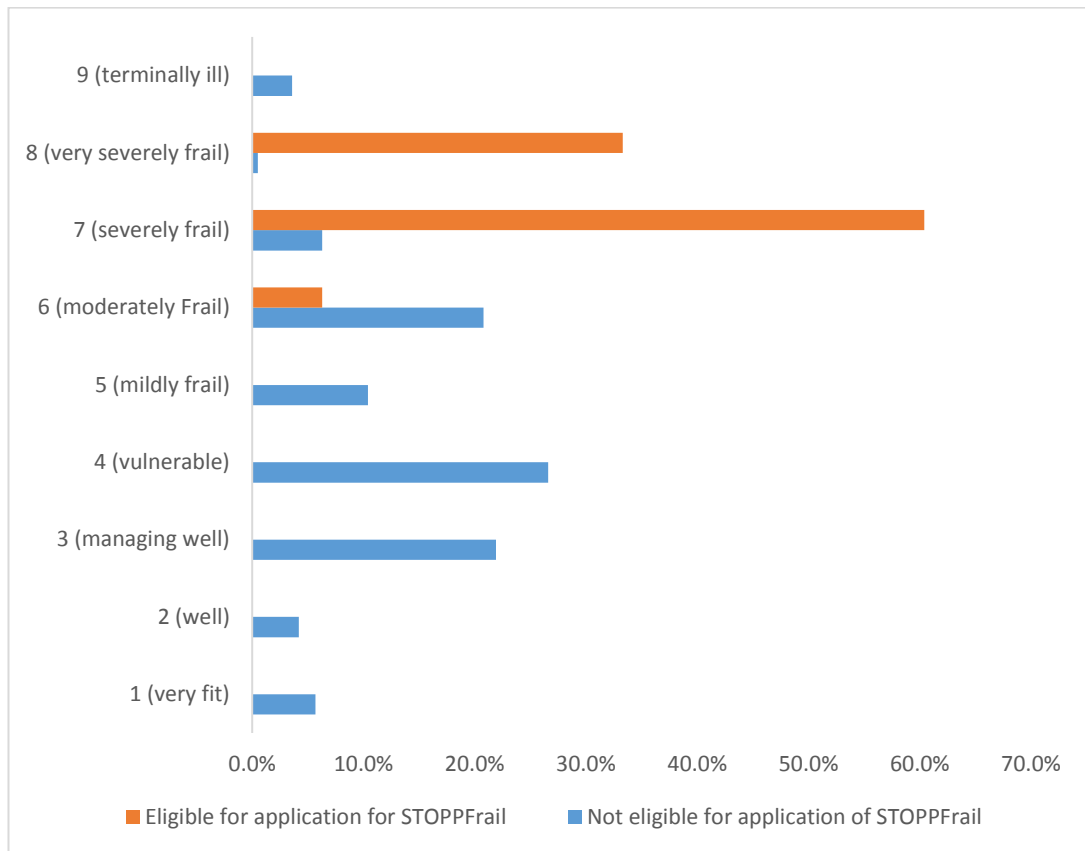
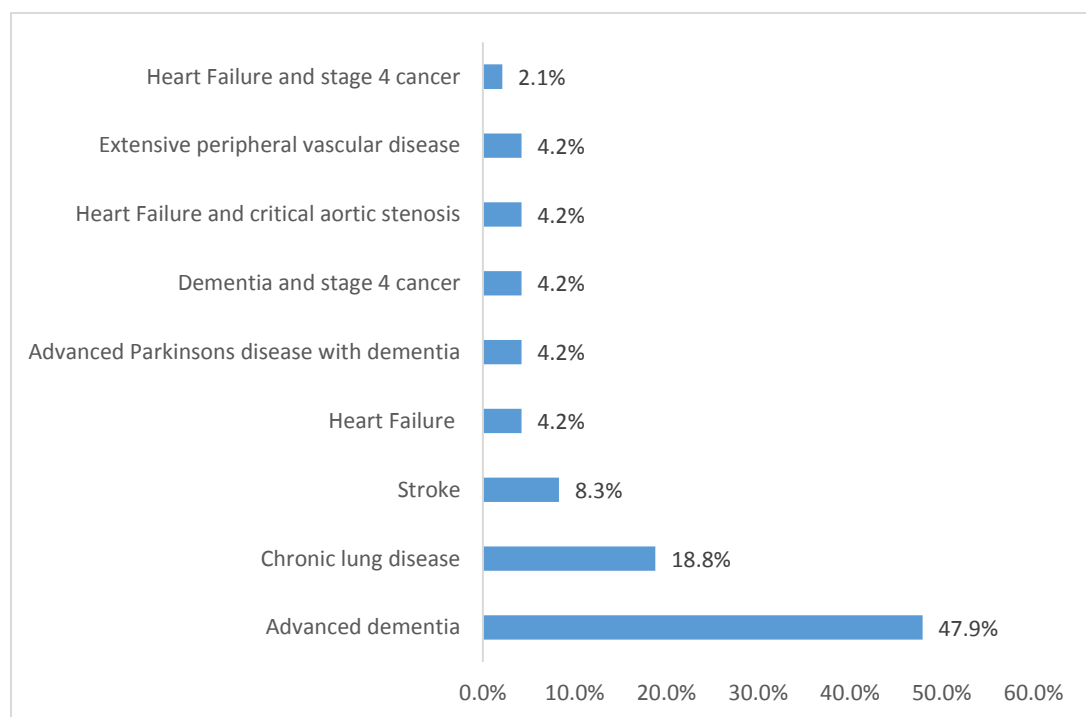


Table 7.9: Reasons for participants not completing the Mini Mental State Examination (MMSE) (n= 41)

Reasons	Eligible for application for STOPPFrail n = 21	Not eligible for application of STOPPFrail n = 20
Severe dementia	15 (71.4%)	0 (0%)
Too delirious/too drowsy	4 (19%)	3 (15%)
Severe hearing impairment	1(4.8)	2 (10%)
Patient unable to speak English	0 (0%)	3 (15%)
Aphasia	1 (4.8%)	1 (5%)
Declined	0 (0%)	7 (35%)
Time restraints	0 (0%)	4 (20%)

STOPPFrail eligibility criteria requires a patient have an end-stage irreversible pathology with an associated poor one year life expectancy e.g. advanced dementia with recurrent infections. Life-limiting diagnoses among those meeting STOPPFrail eligibility criteria are displayed in **Figure 7.9**. Almost 1 in 2 patients (47.9%) had a diagnosis of advanced dementia with major cognitive and/or functional impairment, a further 18% of patients had severe chronic lung disease with recurrent exacerbations and were requiring long term oxygen.

Figure 7.9: Life limiting diagnoses in those eligible for STOPPFrail application (n=48)

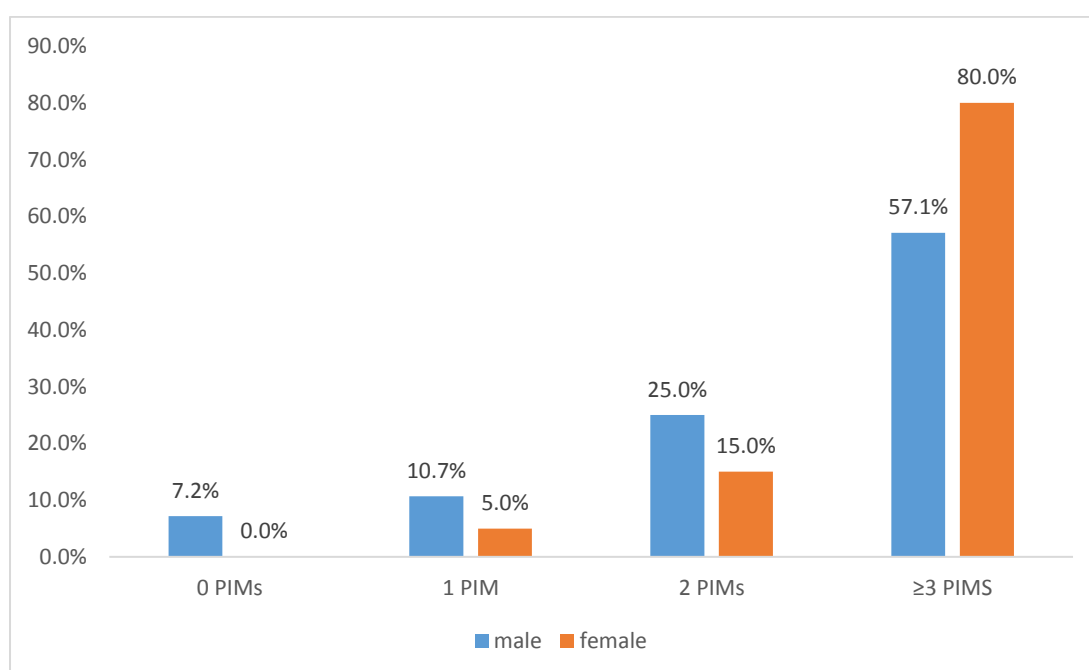


7.3.11 Potentially inappropriate medication (PIM) use as determined by STOPPFrail criteria in hospitalised older adults

According to STOPPFrail criteria, 198 of 519 (38.2%) medicines were potentially inappropriate. These were identified in 46 of the 48 patients (95.8%) who were

eligible for application of STOPPFrail criteria. One PIM was identified in 4 patients (8.3%), 2 PIMs in 10 patients (20.8%), 3 PIMs in 5 patients (10.4%), 4 PIMs in 6 patients (12.5%), 5 PIMs in 8 patients (16.7%), 6 PIMs in 6 patients (12.5%), 7 PIMs in 3 patients (6.3%), 9 PIMs in 2 patients (4.2%) and 10 PIMs in 2 patients (4.2%). Both males and females were equally likely to be prescribed 1, 2 or ≥ 3 PIMs ($\chi^2(3) \geq 3.360$, $p = 0.339$) (**Figure 7.10**).

Figure 7.10: Percentage of patients on potentially inappropriate medications as determined by STOPPFrail criteria (n = 48)



The most frequently encountered PIMs identified by STOPPFrail criteria are detailed in **Table 7.10**. These include: (i) medications with no clear indication (58.3%), (ii) lipid lowering therapies (45.8%), (iii) high dose proton pump inhibitors (PPIs) (35.4%), (iv) calcium supplementation (31.3%) and (v) neuroleptics (22.9%). There was no significant difference in PIM use between men and women.

Table 7.10: Most frequently encountered potentially inappropriate prescriptions according to STOPPFrail criteria in 48 patients

STOPPFrail Criterion		Total n=48
A2	No clear indication	53 instances in 28 patients (58.3%)
B1	Lipid lowering therapies	22 instances in 22 patients (45.8%)
E1	High dose PPI	17 instances in 17 patients (35.4%)
G1	Calcium supplements	15 instances in 15 patients (31.3%)
D1	Neuroleptics	12 instances in 11 patients (22.9%)
J2	Nutritional Supplements	17 instances in 10 patients (20.8%)
C1	Anti-platelet for primary prevention	8 instances in 8 patients (16.7%)
D2	Memantine	8 instances in 8 patients (16.7%)
G5	Long term oral corticosteroids	7 instances in 7 people (14.6%)
A1	Drugs the patients persistently fails to take or tolerate	13 instances in 6 people (12.5%)
G2	Anti-resorptive therapies for OP	6 instances in 6 people (12.5%)
I1	Diabetic oral agents	5 instances in 5 people (10.4%)
B2	Alpha blockers for HTN	4 instances in 4 people (8.3%)
I2	ACE inhibitors for Diabetes Mellitus	3 instances in 3 people (6.3%)
J1	Multivitamins	2 instances in 2 people (4.2%)

Legend: PPI = proton pump inhibitor; OP = osteoporosis; HTN = hypertension, ACE = angiotensin converting enzyme

7.4 DISCUSSION

This study shows that a high proportion of older adults (59.1%) who apply for nursing home long-term care in Ireland meet STOPPFrail eligibility criteria i.e. end stage irreversible pathology, poor 1 year survival prognosis, severe functional impairment or severe cognitive impairment of both and patients wherein symptoms control is the priority rather than prevention of disease progression. In US nursing homes, 65% of patients die within one year from the time of admission (247). In the present study, as expected, those who met STOPPFrail eligibility criteria were older, had higher

levels of cognitive impairment, were more functionally impaired and were objectively frailer than those who did not meet STOPPFrail eligibility criteria.

Those who met STOPPFrail eligibility criteria had a significantly higher mean number of medicated conditions (7.3 (SD 2.6) vs 6.4 (SD 2.5), $p < 0.001$). For patients that met STOPPFrail eligibility criteria, the most prevalent life limiting diagnosis was advanced dementia, seen in 70% of cases. Dementia was also present, but generally in its earlier stages in 42.8% of those not meeting STOPPFrail eligibility criteria.

Despite the fact of those who met STOPPFrail eligibility criteria having a poor one year survival prognosis, they nevertheless received the same median number of daily medications as those patients who did not meet STOPPFrail eligibility criteria (8 (SD4) vs 7.5 (SD3.7), $p = 0.183$). Approximately two thirds (69%) of all study participants experienced polypharmacy (≥ 6 daily medications) and one quarter (23%) experienced high-level polypharmacy (≥ 11 daily medications). No significant differences in rates of overall polypharmacy and high-level polypharmacy were identified between those that met STOPPFrail eligibility criteria and those that did not (67.1% vs 69% $p = 0.233$ and 24.8% vs 19.7% $p = 0.526$, respectively). Similar prevalence rates of 48.7% and 24.3% for overall polypharmacy (5-9 medications) and high-level polypharmacy (≥ 10 medications), have been reported by the SHELTER study (195).

Nearly two-thirds (60.6%) of patients were prescribed an anti-hypertensive, approximately 1 in 2 patients (47.9%) were prescribed a proton pump inhibitor, approximately 1 in 3 patients (33.3%) were prescribed an anti-platelet, almost 1 in 3

patients (30.5%) were prescribed neuroleptics, over 1 in 4 patients (28.4%) were prescribed a statin and almost 1 in 4 (22.3%) were prescribed long-term benzodiazepines. The prevalence of neuroleptic prescriptions in nursing homes in the US is reported to be approximately 22% to 25% (249, 250). In other countries, varying daily neuroleptic prevalence rates have been reported: 11% in Hong Kong, 26-27% in Canada, 34% in Switzerland, 38% in Finland (251) and 32.8% in Europe (252). This study suggests that the prescription of regular daily anti-psychotic medication often precedes nursing home placement in frailer, older people in Ireland.

Potentially inappropriate prescribing was highly prevalent in this sample population with 1 in 3 prescriptions being potentially inappropriate according to STOPPFrail criteria and 90% of patients receiving at least 1 STOPPFrail PIM. Approximately 1 in 7 patients (13.9%) received 1 PIM alone, 1 in 5 patients (20.1%) received 2 PIMs and 1 in 2 patients (57.7%) received ≥ 3 PIMs. Approximately 1 in 2 of these patients (47%) were prescribed a medication without any clear indication. Approximately 1 in 3 of these patients (31.4%) were prescribed a high dose, long-term proton pump inhibitor without any clear reason. Approximately 1 in 3 (29.6%) of these patients were prescribed a statin for long-term cardiovascular prevention. The odds of receiving a PIM increased by 57.9% for every extra medication prescribed.

One in five older adults (20%) presenting to hospital with an acute illness met STOPPFrail eligibility criteria. Similar to patients who applied for nursing home placement, those that met STOPPFrail eligibility criteria and were being admitted to

hospital with acute illness were older, more cognitively impaired, more functionally impaired, had a higher burden of co-morbid illness and were frailer than those that did not meet STOPPFrail eligibility criteria; they were also prescribed more medications. These findings are not surprising, since eligibility for STOPPFrail criteria means higher levels of frailty and dependency. Approximately 1 in 7 (14.6%) of those who met STOPPFrail eligibility criteria died during the index admission. More than 1 in 3 (39.6%) patients died within 6 months of enrolment in the study. For nearly half (47.9%) of the patients, the life-limiting diagnosis was advanced dementia. For approximately 1 in 5 (18%) patients, the life-limiting diagnosis was chronic lung disease with recurrent exacerbations and a need for long-term oxygen therapy.

For older adults admitted with an acute illness to hospital, nearly all patients (95.8%) who met STOPPFrail eligibility criteria were on at least 1 STOPPFrail PIM. The most prevalent PIMs were drugs with no clear indication, statins, high dose PPIs, calcium supplements and neuroleptics.

Clinicians who undertake medication review of multi-morbid older people with poor survival prognosis need to be aware of these highly prevalent PIMs, particularly at points of care transition, such as hospital discharge and admission to nursing homes for long-term care. Given the high prevalence of STOPPFrail PIMs identified in the present study, there is potential for STOPPFrail to be beneficial in routine medication review in older nursing home residents, both on admission and during routine clinical review thereafter.

This study indicates that regardless of poor survival prognosis, IP, according to STOPPFrail criteria, is highly prevalent. This suggests that prescribers are either (a) failing to identify when patients have a poor survival prognosis, or (b) identifying patients with a poor survival prognosis but are not adjusting their prescribing practices accordingly. Polypharmacy and IP contribute to ADRs (160), and associated increased morbidity and mortality. Older adults who reside in nursing homes are at the highest risk from iatrogenic morbidity and mortality (195).

Deprescribing of PIMs in this particular population not only has the potential to reduce ADRs, but could be economically highly beneficial, given the direct and indirect costs associated with STOPPFrail-defined PIMs. Adults aged 85 years and older are the fastest growing segment of the population in most developed nations (3, 4). Multimorbidity is more prevalent in this population cohort than in any other cohort, with prevalence rates of over 80% reported (13), with proportionately high levels of polypharmacy and associated IP. Internationally, several studies demonstrate the potential magnitude of health budget wastage resulting from ADRs (113-116). In addition, the overall expenditure on prescription medications in older people is substantial with drug costs being one of the fastest growing areas of all healthcare expenditure in general. In Ireland, Europe and the US the annual expenditure on drugs continues to rise in recent years (253-255). STOPPFrail criteria, through (i) identifying the correct patient population that would benefit from deprescribing and (ii) identifying medications that are potentially inappropriate in a systems-based structured fashion, has the potential to guide physicians with

deprescribing decisions and consequently to lower costs of drug treatment and thereby to have a positive impact on the current healthcare expenditure.

Prescribing for the older patients is often complex, particularly prescribing for older, frailer multimorbid adults. One continuing challenge is the paucity of clinical trial evidence to support prescribing and deprescribing in this group. Older adults with multimorbid illness are often excluded from clinical trials and when they are included they are, more often than not, under-represented compared to other adult age groups (256, 257). Clinical trials often concentrate on reporting on how efficaciously a drug works, with very little research focused on the potential impact of deprescribing. This observational study is important in the planning of future randomised control trials of deprescribing in older frail adults with a poor one year survival prognosis. Power calculation in particular will be facilitated by the present study as well as the choice of appropriate clinical trial endpoints.

The global ageing demographic shift also increases the demand for more specialist geriatricians than are currently available. Unfortunately, in many countries, the proportion of geriatricians to the number of persons aged over 75 is diminishing, not rising. This results in many older complex patients being prescribed for primarily by their General Practitioners or hospital specialists who do have specialist training in Geriatric Medicine and pharmacotherapy. In this context, explicit tools like STOPPFrail criteria, can assist and empower less experienced physicians with medication management and deprescribing in complex, multimorbid older patients.

CHAPTER 8:

Summary & Conclusions

8.1 Summary of research findings

In the introduction to this thesis, I reported the demographic changes predicted for Ireland, Europe and worldwide i.e. substantial increases in the numbers of older frailer patients surviving with complex co-morbid illnesses. I discussed the various challenges and considerations when prescribing for such patients. I discussed the role of prescribing indicators in identifying potentially inappropriate prescribing in older adults and highlighted an important deficiency in the literature, namely the lack of an IP screening tool to guide deprescribing in frail multimorbid older adults with poor survival prognosis. I subsequently described the negative outcomes associated with IP, including ADRs and their associated morbidity, higher mortality and greater healthcare costs. I discussed the challenges with current approaches employed by researchers and physicians for identifying, classifying and reporting ADRs. I also discussed the negative impact these varied methodologies have on the accurate ascertainment of ADR prevalence in older adults. I emphasized how such heterogeneity in reporting of ADRs results in difficulty with comparing prevalence studies in the literature to date.

This thesis aimed to contribute to the medical literature by presenting a standardized method for identification, assessment and reporting of ADRs in older adults. To do this, I reviewed the existing literature relevant to ADR ascertainment, including the various ADR definitions and ADR causality tools. The concept of an Adverse Event (AE) **Trigger List** was subsequently developed and validated to assist with identification of the most commonly occurring ADRs in older people using a

structured and unbiased process. This novel ADR assessment methodology was found to have good inter-rater reliability (IRR) amongst physicians chosen from a variety of clinical disciplines in everyday clinical practice. This new process of evaluating potential ADRs related to commonly encountered AEs was then applied to two high risk populations' i.e. (i) older multimorbid adults attending hospital with acute illness and (ii) patients with cancer requiring hospitalisation.

In addition, I developed and validated a new explicit prescribing tool, called STOPPFrail criteria, through the Delphi consensus technique, to assist deprescribing in older frailer multimorbid adults with a poor survival prognosis. This tool was designed to aid the deprescription of commonly prescribed pharmacotherapies that are unlikely to be beneficial in this particular patient population. The IRR of STOPPFrail criteria was then assessed amongst physicians practising across three different specialties and subsequently STOPPFrail criteria was applied to two representative populations. The principle findings and conclusions of these studies are listed below.

8.1.1 Development and validation of an *AE Trigger List*

The newly developed and validated ***AE Trigger List*** consists of twelve commonly occurring clinical symptoms or syndromes that may be indicative of underlying ADRs and thus require investigation using a standardized process to determine if this is the case. This ***AE Trigger List*** was developed based on the type of ADRs identified in a previous robust study of ADR prevalence in older adults (146) and augmented by

group consensus. The group consensus involved in the refinement of this ***AE Trigger List*** comprised co-principal investigators and primary researchers involved in the FP7-funded SENATOR project which began in 2012 (147). Each AE on the ***AE Trigger List*** was given a concise definition to remove any ambiguity for the user.

This study also aimed to standardise the approach to assessing the morbidity associated with ADRs and thus the ***AE Trigger List*** was also used to assess the inter-dependent relationships between symptoms experienced secondary to an ADR; this assessment was referred to as ***Sequence of Events***. Not only were all AEs on the ***Trigger List*** assessed for a drug cause but when a drug cause was found, the relationship between AEs was also assessed, allowing the associated morbidity to be captured in a structured process. The assessment of AEs on the ***AE Trigger List*** was then sent to an adjudication committee for review where senior academic clinicians with extensive experience in Geriatric Medicine and pharmacotherapy could agree or disagree with the assessment undertaken.

The IRR of using this ***AE Trigger List*** was assessed amongst 21 persons, all of whom were principal investigators and primary researchers on the SENATOR project. The median IRR was found to be substantial for identifying ADRs. This method of evaluating adverse events and determining whether or not they are caused by ADRs has been used to determine the principal outcome measure in the SENATOR clinical trial which is a large randomised controlled trial to determine the effect of SENATOR software on incident ADRs in multimorbid older patients who are hospitalised with acute medical and surgical illnesses (147, 150).

8.1.2 Prevalence of ADRs causing hospitalisation in older adults

This is one of the first studies to use a standardized approach to identify, classify and report ADRs in older people. The ***AE Trigger List*** was applied prospectively to 240 older adults presenting to hospital with an acute unselected illness. This population included many older frailer patients with complex co-morbid illnesses. Of the participants studied, 44.2% were aged ≥ 80 years and 84.6% had ≥ 5 conditions. In addition, 16.3% had moderate or severe dementia. Using Rockwood's clinical frailty scale, 1 in 4 older adults were severely frail, very severely frail or terminally ill. Approximately three quarters of the patients experienced polypharmacy i.e. ≥ 6 daily prescription drugs and one third experienced high level polypharmacy i.e. ≥ 11 daily prescription drugs.

Potentially inappropriate prescribing practices were identified in 67.5% of patients using STOPP criteria. Among these patients, 19.2% of prescriptions were potentially inappropriate according to STOPP criteria. The most frequently encountered PIMs identified by STOPP criteria were: (i) medications prescribed beyond a recommended duration (41.3%), (ii) PPI's for uncomplicated peptic ulcer disease/reflux oesophagitis at full therapeutic dosage for > 8 weeks (24.6%), (iii) medications prescribed without an evidence-based clinical indication (20%), and (iv) use of benzodiazepines for ≥ 4 weeks (17.9%). For every additional medication prescribed, the odds of being prescribing a PIM increased by 41.5% (odds ratio 1.415, 95% CI 1.237 – 1.619, $p < 0.001$).

START criteria for potentially inappropriate prescribing omissions were applicable in 170 of the 240 participants (70.8%). For the remaining 70 participants, a more palliative approach to pharmacotherapy was appropriate. More than one half of participants (52.9%) ≥ 1 PPO. The most common PPOs were: (i) omission of an ACE inhibitor in patients with systolic heart failure and/or coronary artery disease (12.4%), (ii) omission of bone anti-resorptive or anabolic therapy with osteoporosis (8.2%), (iii) omission of vitamin D and calcium with osteoporosis (7.6%) and (iv) vitamin D when housebound or experiencing falls (7.6%).

ADRs caused or significantly contributed to acute admission in 22.1% of these patients. The most common ADRs were bleeding, falls and clinically relevant electrolyte disturbances. The ***AE Trigger List*** identified 79.3% of these ADRs. Twenty nine (54.7%) patients who experienced an ADR had a clear ***Sequence of Events*** according to the Adverse Event assessment process, with women being more likely to experience this phenomenon than men (67.9% vs 40%). The most commonly implicated drugs were opioids, direct oral anti-coagulants and benzodiazepines. The vast majority of ADRs (85%) were predictable. Using Hallas ADR avoidability criteria, 45.3% were definitely avoidable and 45.3% possibly avoidable. Those who experienced ADRs had a higher burden of co-morbid illness, were prescribed more medications and more likely to die during the index admission than patients who did not have ADRs. For each additional prescribed medication, the odds of experiencing an ADR increased by 10.3% (Odds ratio 1.103, 95% CI 1.006 – 1.210, $p < 0.001$).

8.1.3 Prevalence of ADRs causing hospitalisation in patients with cancer

This is the first study in Ireland to identify and classify patients with cancer according to age, burden of co-morbidity, medication and PIM use. It is also the first study internationally to assess ADRs attributable to drugs other than cytotoxic chemotherapeutic agents in a comprehensive manner in this population. In this prospective study, 34.5% of all patients attending an oncology service were aged ≥ 70 years and 81.1% of these older patients had ≥ 5 chronic comorbid clinical conditions. A higher prevalence of polypharmacy and high level polypharmacy were identified in the older patients compared to the younger patients i.e. 63.6% vs 38.4% and 19.0% vs 7.4% respectively. In addition, older adults were less likely to be prescribed chemotherapy. According to STOPP criteria, 73.1% of patients aged ≥ 65 years were prescribed at least one PIM and 25.3% were prescribed ≥ 3 PIMs. Similar results emerged from application of OncPal criteria; 70.8% of older patients were prescribed ≥ 1 PIM and 30.7% were prescribed ≥ 3 PIMs.

The 12 point ***AE Trigger List*** identified 64% of all ADRs in this population. ADRs caused or contributed significantly to 21.5% of all oncology admissions (emergency, elective and day unit). ADRs were more prevalent in those patients presenting to hospital as an emergency (35.8%). ADRs were equally likely to result from cancer-specific pharmacotherapy as non-cancer specific pharmacotherapy, with no difference in prevalence rates identified between older and younger patients. The three most common ADRs in the cohort were: (i) neutropenia with infection, (ii) nausea/vomiting and (iii) major constipation. Thirty two (42.7%) of all participants

who experienced an ADR had a ***Sequence of Events***. Of the 75 ADRs identified, 67 (89.3%) were entirely predictable. Using Hallas criteria of avoidability, 29.3% were definitely avoidable, 33.3% possibly avoidable and 37.4% were unavoidable. Chemotherapeutic agents, opioids, corticosteroids and NSAIDs were the most commonly implicated drugs in relation to identified ADRs.

8.1.4 Validation of STOPPFrail criteria

STOPPFrail is a novel validated list of prescribing indicators for older frailer patients with a poor survival prognosis. It is comprised of 27 prescribing indicators designed to assist with deprescribing in a structured fashion in this particular patient population. STOPPFrail criteria are organised according to physiological systems for ease of use and each indicator is accompanied by a concise statement which explains why the prescription is potentially inappropriate.

Its content validity was established by a Delphi consensus methodology, in which a panel of seventeen experts in geriatric pharmacotherapy participated. The inter-rater reliability of STOPPFrail application was found to be substantial amongst twelve physicians practising in Geriatric Medicine, Palliative Medicine and General Practice.

8.1.5 Prevalence of potentially inappropriate prescribing as determined by STOPPFrail criteria

STOPPFrail criteria were applied to eligible patients from two study cohorts: (i) older adults undergoing comprehensive geriatric assessment when applying for the Irish Nursing Home Support Scheme towards long-term nursing home care, and (ii) older adults presenting to hospital with an acute unselected illness admitted under the care of specialist services other than Geriatric Medicine.

Two hundred and seventy four (59.1%) of patients applying for nursing home placement were eligible for application of STOPPFrail criteria. Potentially inappropriate prescribing according to STOPPFrail criteria was highly prevalent in these patients, with 91.2% having ≥ 1 PIM and 33.0% of all prescribed medications being potentially inappropriate according to STOPPFrail criteria. The most frequently prescribed STOPPFrail PIMs in these frail older patients with a poor one year survival prognosis were: (i) medications without a clear clinical indication (47%), (ii) long-term, high dose proton pump inhibitors without a clinical indication for high-dose therapy (31.4%), and (iii) lipid lowering therapies (statins in the great majority) (29.4%).

Twenty percent of older adults presenting to hospital with an acute illness were eligible for the application of STOPPFrail criteria. Potentially inappropriate prescribing was highly prevalent in this subgroup of 48 patients, with 46 patients (95.8%) being regularly prescribed at ≥ 1 PIM. Over one-third (38.2%) of all medications prescribed to these frail older patients with limited life expectancy were

potentially inappropriate according to STOPPFrail criteria. The most frequently prescribed STOPPFrail PIMs were: (i) medications without a clear indication (58.3%), (ii) lipid lowering therapies (45.8%) and (iii) high dose proton pump inhibitors without a clinical indication for high-dose therapy (35.4%). The prevalence of PIM use in older adults eligible for STOPPFrail criteria was the same in both studies i.e. at the point of admission to hospital with acute illness and at the point of consideration for transition to long-term nursing home care. Such “transition of care” time points could present viable opportunities for application of STOPPFrail criteria and effective deprescribing of unnecessary and potentially futile medications in this particular older patient population.

8.2 Limitations of these research findings

All participants who completed the IRR exercise on the assessment of ADRs, using the ***AE Trigger List***, were part of the SENATOR project. This research consortium’s main purpose is to develop a software engine capable of advising on medication appropriateness for older multimorbid patients with polypharmacy. In the second phase of this project, which is currently ongoing, a multi-centred RCT is in progress investigating whether the use of SENATOR software at the point of admission to hospital in older multimorbid adults will reduce *incident* hospital ADRs compared to standard pharmaceutical management in 6 European medical centres. It could be argued that because these participants had a good knowledge and background on ADR assessment prior to the IRR exercise these results are not generalizable to the

average physician, pharmacist or nurse working in hospital setting. However, of the 21 persons who participated, 15 were junior researchers who were either working for their first time on a large research project or were working in the area of Geriatric Pharmacotherapy where they hadn't worked before. Thus, it is likely that with the appropriate training, most healthcare staff could learn to use the ***AE Trigger List*** effectively and identify, assess and report ADRs in a standardized manner. Furthermore, if this standardized approach to assessing ADRs were to be used in future research studies and RCTs, comparisons between studies would be more reliable and determination of ADRs as trial outcomes would consequently be more robust.

In both prospective observational studies investigating the prevalence of ADRs (Chapters 3 and 4), ADR assessments were completed entirely by me. These studies could possibly have been strengthened by all ***AE Trigger List*** assessments had been sent to an adjudication panel to assess whether or not an ADR had occurred. This has been done for the SENATOR feasibility study (150) and is currently the methodology employed for ADR ascertainment in the SENATOR RCT. In the SENATOR feasibility study, 21.6% of all participants experienced an incident ADR during acute hospital admission under the care of specialist teams other than Geriatric Medicine or Clinical Pharmacology (150). In my study investigating the prevalence of ADRs in older patients presenting to hospital, ADRs accounted for 22.1% of all hospital admissions, consistent with the SENATOR feasibility study. In previous meta-analyses of ADRs causing hospitalisation and ADRs occurring during hospitalisation in older

adults, ADR occurrence rates of 10.0% of (83, 144) and 11.5% (84, 144), respectively have been reported. This suggests that although under-reporting of ADRs is likely, older adults experience ADRs at similar frequency prior to (*prevalent* ADRs) and during hospital admission (*incident* ADRs). However, more recent studies at Cork University Hospital have reported higher rates of 26.3% (45) and 21% (74) for *prevalence* and *incident* ADRs respectively. My research results presented in this thesis concur with these higher ADR prevalence and incidence findings than had been reported previously.

The use of Delphi Consensus Methodology for the development and validation of STOPPFrail criteria has some intrinsic limitations. This approach is not based on rigorous scientific evidence, but rather on the informed opinions of experts where robust scientific evidence may be lacking. Methodological concerns have been raised regarding the Delphi method, specifically the selection of expert panellists and the potential for bias at this stage of the process. Expertise can sometimes be overstated and clinical knowledge in a particular area does not necessarily equate with expert status. I have tried to be as methodologically robust with the Delphi panel selection as possible. Panellists from 5 different and relevant clinical practice backgrounds, who were senior academic clinicians regularly dealing with the patient cohort in question, were selected. In addition, panellists had to have extensive knowledge of the current literature on pharmacotherapy in frail older people. In this way, potential bias in the Delphi panel was minimized.

The Delphi consensus technique employs anonymity in each of its assessment rounds. This allows panellists to react in an unbiased fashion without influence from other panellists when presented with particular items for assessment/judgement. Thus each panellist's opinion carries the same weight and importance as every other panellist. Concerns have been raised regarding the true anonymity of this process, with some researchers suggesting that anonymity isn't employed when the researcher overseeing the process knows the answers given by each panellists (258). To avoid this, I ensured answers were returned to panellists in an anonymous fashion. I was aware of panellists' disciplines and was unaware of which answers were given by whom. However, some panellists did know each other and could possibly have discussed particular aspects of the research without my knowledge. Lack of communication between panellists can be viewed as a strength as well as a weakness in a particular Delphi consensus process. However, despite these intrinsic limitations, the Delphi technique is a widely recognized and accepted approach to achieving consensus when there is a paucity of evidence. It also allows the development of tools which can be used to further develop or refine the evidence base and reaffirm the original Delphi consensus. Use of the Delphi technique has proven beneficial in the development and validation of other IP prescribing tools (36, 63, 69, 199).

STOPPFrail is a novel tool consisting of explicit deprescribing indicators in frail older people with a poor one year survival prognosis. Therefore, it does not take into consideration the clinical context of the prescribing decision for each individual

patient but rather focuses on general prescribing principles. This means that the criteria may not be generalizable to all patients in the population that it is designed for. However, to minimise this effect we included clinical eligibility criteria that patients needed to have for the criteria to be appropriate and applicable. However, some clinicians may take the view that not all of the STOPPFrail deprescribing indicators are appropriate to all frail older patients with poor one year survival prognosis. Nonetheless, STOPPFrail criteria provides explicit guidance and assistance to physicians with deprescribing in this population in a structured fashion. As guidelines and not dictats, STOPPFrail criteria allow physicians the freedom to refrain from deprescribing if they consider that stopping a particular drug it is not in a particular patient's best interest.

8.3 Directions for future research

This thesis has identified several areas that warrant further investigation. Firstly, the ***AE Trigger List*** needs to be validated in other patient populations. This method of ADR ascertainment could potentially reduce the element of subjectivity in ADR identification and reporting in patient populations other than multimorbid older people with polypharmacy. If deployed in a standardized process, the ***AE Trigger List*** has the potential to improve comparison between studies and the accuracy of the study results. It would also make it easier for researchers to undertake meta-analyses reporting ADR prevalence and incidence in various clinical settings. However, the ***AE***

Trigger List process does not identify *all* potential ADRs and will always require an additional 'unspecified' adverse event criterion.

Patients with cancer frequently have complex co-morbidities, complex medication regimes and higher susceptibility to ADRs. Traditionally, these patients are managed by specialist oncologists. However, with the increasing complexity of prescribing regimes and high prevalence of ADRs from non-cancer pharmacotherapy in this cohort, there is a clear role for specialist geriatricians and clinical pharmacologists in contributing to the non-cancer therapeutic decisions in this vulnerable patient group. The data from my study should be replicated in other cancer centres to see if the results are similar and to identify potential areas for intervention to reduce the risk of ADRs and related negative outcomes. Future research could also investigate IP and ADRs in patients attending specialist radiation oncology services. These patients represented only a small proportion of my study population and are likely to comprise a higher number of older frailer patients than those hospitalized under the care of medical oncologists. There is a need to investigate *incident* ADRs in this population using this methodology as limited research has been completed on this to date. Potential interventional studies could examine the role of comprehensive geriatric assessment (CGA), IP screening tools, prescriber education, computer-based prescribing/decision support systems and clinical pharmacist assessments on reducing ADRs in this population.

The prevalence of potentially inappropriate prescribing according to STOPP/Frail criteria needs to be determined in other patient groups such as those

residing in nursing home facilities, those attending specialist palliative care services as well as those living in the community attending hospital outpatients. Furthermore, the practical value of implementation of STOPPFrail criteria *as an intervention* needs to be tested by way of a randomised controlled trial. Its effect on key health outcomes such as ADRs, falls, quality of life, morbidity, mortality, health care utilisation and medication cost needs to be investigated. There is the potential for this tool to be used in RCTs across different healthcare settings. This would allow the evidence base to expand and support physicians with deprescribing.

Finally, many IP prescribing tools have been incorporated into electronic prescribing decision support systems e.g. STOPP/START criteria in the current SENATOR and OPERAM clinical trials. There is the potential for STOPPFrail to be incorporated into an electronic prescribing system in a similar manner in both primary and secondary care. However, this would require considerable ICT developmental work and close collaboration between clinical and ICT experts.

Ultimately, this thesis aimed to devise strategies to improve identification, classification and reporting of ADRs in older adults who are at particularly high risk of serious ADRs. The work described above has also tried to develop strategies to improve prescribing in older frailer patients with complex multimorbidity and a limited life expectancy. Hopefully, these research findings facilitate better prescribing decisions made for these highly vulnerable patient groups in the future.

CHAPTER 9:

Publications in peer-reviewed journals and awards

9.1 PUBLICATIONS

Chapter 1: Introduction
• Lavan AH, O'Mahony D, Gallagher P. Comments on "intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. <i>J Am Geriatr Soc</i> 2015; 63(5): 1043-4. PMID 25989577 • Lavan AH, O'Grady J, Gallagher P. Appropriate prescribing in the elderly: Current Perspectives. <i>World J Pharmacol</i> 2015; 4(2): 193-209 • Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. <i>Ther Adv Drug Saf</i> 2016; 7(1): 11-22. PMID 26834959 • Lavan AH, Gallagher P, O'Mahony. Future perspective in drug therapy of older adults in "Developing Drug Products in an Aging Society". Springer international Publishing, 2016. 737-757 (Book Chapter) • Lavan AH, Gallagher P, O'Mahony D. Methods to reduce prescribing errors in elderly patients with multimorbidity. <i>Clin Interv Aging</i> 2016; 11: 857-866. PMID 27382268 • Gallagher P, Lavan AH, O'Mahony D. Prescribing for Older Patients in "Geriatric Emergency Medicine". Springer International Publishing, 2018. 299-313 (Book Chapter)
Chapter 2: Development and validation of an adverse drug reaction trigger list
• Lavan AH, Eustace J, Dahly D, Flanagan E, Gallagher P, Cullinane S, Petrovic M, Perehudoff K, Guðmundsson A, Sverrisdóttir Á, Samuelsson O, Cherubini A, Dimitri F, Rimland J, Cruz-Jentoft A, Vélez-Díaz-Pallarés M, Lozano-Montoya I, Soiza R, Subbarayan S, O'Mahony D. Incidence of adverse drugs

reactions in a cohort of older inpatients – a multi-centred prospective observational study. <i>Ther Adv Drug Saf</i> 2018; 9 (1): 13-23
Chapter 5: STOPPFrail (<u>S</u>creening <u>T</u>ool of <u>O</u>lder <u>P</u>ersons <u>P</u>rescriptions in <u>F</u>rail adults with limited life expectancy): Consensus validation
• Lavan AH, Gallagher P, Parsons C, O’Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. <i>Age Ageing</i> 2017; 46 (4): 600-607. PMID 28119312 • Lavan AH, O’Mahony D, Gallagher P. Response to Dr Caballero-Mora's comments. <i>Age Ageing</i> 2017; 46 (5): 875. PMID 28874009
Chapter 6: Inter-rater reliability of STOPPFrail criteria amongst physicians from three clinical specialty services
• Lavan AH, Gallagher P, O’Mahony D. Inter-rater reliability of STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy) criteria amongst 12 physicians. <i>Eur J Clin Pharmacol</i> 2018; 74 (3): 331-338. PMID 29159488

9.2 SUBMITTED PAPERS

Chapter 4: Prevalence of multimorbidity, potentially inappropriate prescribing and adverse drug reactions (ADRs) in patients with cancer
Adverse drug reactions in an oncological population; prevalence, predictability and preventability (The Oncologist)
Chapter 7: Prevalence of potentially inappropriate prescribing as determined by STOPPFrail criteria in a representative population of older patients undergoing assessment for long term nursing home placement and of older adults presenting with acute illness to hospital
STOPPFrail criteria: application to a representative population awaiting long term care (European Journal of Clinical Pharmacology)

9.3 AWARDS

Irish Gerontology Society, oral presentation award 2016
STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation (Chapter 5)
European Geriatric Medicine Society, best poster award 2016
STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation (Chapter 5)
Irish Society of Medical Oncology, oral presentation award 2017
The prevalence of adverse drug reactions causing hospitalisation in patients with cancer (Chapter 4)

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Appendices

Appendix 1 - Clinical case histories

Case 1

PC: 66 year old male presented with a 3 day history of new painless jaundice.

Recruitment: Patient recruited within 24 hours of admission.

HPC: He presented with cellulitis of his right leg to his GP 5 days earlier. At this time he was commenced on Flucloxacillin. After two days of treatment he noticed a yellow discoloration of his skin which became worse over the following days. After 5 days of treatment he stopped the antibiotics and presented to the emergency department. Otherwise well. No nausea, no diarrhoea, no constipation, no vomiting, on confusion, no falls.

Medical History:

1. Varicose veins
2. Gastro-oesophageal reflux disease (GORD)
3. Hiatus hernia – Gastroscopy 6 months ago
4. Hypertension

Medications (regular):

1. Tramadol 50mg, Oral, Once a day: 2 weeks
2. Diclofenac gel, One application, Topical, Three times a day: 2 weeks
3. Esomeprazole 40mg, Oral, Once a day: 6 months – 1 year
4. Bisoprolol 5mg, Oral, Once a day: >5 years
5. Ramipril 10mg, Oral, Once a day: >5 years

Medications (as required):

1. Paracetamol 1g, Oral, As required (last took 6 weeks ago): >5 years

Recent short courses of treatment:

1. Flucloxacillin 500mg, Oral, Four times a day, 5 days
(Courses was started 5 days prior to admission)

Allergies: Amoxicillin/clavulanate – history of jaundice

Social History: Ex-smoker, No alcohol, Lives with wife, Fully independent of ADLs

Barthel: 20/20, **MMSE:** 30/30, **4AT:** 0

Bloods (at admission):

Creat 70, eGFR 104, Na 137, K 4.8
Hb 12.8, WCC 9.8, Neuts 5.4, Plts 304
Alb 36, Bilirubin 242, Ca (corrected) 2.30, ALT 40, ALP 753, GGT 162

ECG: Normal sinus rhythm, No atrial fibrillation, 65 bpm, No blocks

Course of events in hospital:

Diagnosis per team: Acute liver failure
The patient spent a total of 6 weeks in hospital
Liver function recovered with watchful monitoring but took 6 weeks until they were within normal limits
During the hospitalisation he had no falls, no nausea, no vomiting, no diarrhoea, no constipation.

Medications changes during admission:

1. Tramadol stopped
2. Flucloxacillin stopped by patient the day before admission

Copy of page: Case 2

PC: 64 year old male presented with abdominal pain and new constipation.

Recruitment: Patient recruited within 24 hours of admission.

HPC: No bowel motion for 5 days. Normally passes a bowel motion every day or every second day. Previously well, although has unintentionally lost weight over the last 6 months. He had been complaining of worsening back pain for the last 3 to 4 weeks. Associated nausea. No confusion. No recent falls.

Medical History:

1. Prostate cancer diagnosed 2002
2. Insulin dependent diabetes mellitus
3. Macular degeneration
4. Hypertension
5. Hypercholesterolemia
6. Osteoarthritis
7. Cataracts

Medications (regular):

1. Perindopril 2.5mg, Oral, Once a day: >5 years
2. Bendroflumethiazide 2.5mg, Oral, Once a day: >5 years
3. Rosuvastatin 10mg, Oral, Once a day: >5 years
4. Tamsulosin 400mg, Oral, Once a day: >5 years
5. Paracetamol 1g, Oral, Once a day: 6 months – 1 year
6. Esomeprazole 20mg, Oral, Once a day: >5 years
7. Aspirin 75mg, Oral, Once a day: >5 years
8. Lidocaine Patch, One Patch, transdermal, 12 hours on, 12 hours off: 3 – 6 months
9. Novomix (Insulin Aspart) 32 Units, Sub cut, Twice a day: >5 years
10. Oxycodone 10mg, Oral, Twice a day: 2 weeks

Medications (as required):

1. Oxycodone 10mg, oral, as required (started taking once a day, last week twice to three times a day): 2 weeks

Recent short courses of treatment: nil

Allergies: NKDA

Social History: Ex-smoker, No alcohol, Lives with wife and son, No home help.

Barthel: 17/20 (dependent for bathing, unable to climb stairs), **MMSE:** 27/30, **4AT:** 0

Bloods:

Creat 74, eGFR 93, Na 131, K 3.6, Ca 2.3 (corrected)
Hb 12.1, WCC 10, Neuts 6, Platelets 401
Bilirubin 46, Alb 36, ALT 30, ALP 100

ECG: Normal sinus rhythm, No atrial fibrillation, 75bpm, No blocks

Course of events in hospital:

- Day 1: PR exam stool in rectum
Day 1: Plain film abdomen confirmed constipation
Day 1 medication changes:
- Given one phosphate enema
- Regular senna two tablets at night commenced
- Nivolumab (one sachet three times a day) commenced
- Regular and as required oxycodone stopped
- Started paracetamol regularly 1g three times a day
- Continued on all long-standing medications
Day 2: Small hard bowel motion
Day 3: Another small hard bowel motion. CT abdomen ordered in view of weight lost and ongoing back pain
Day 4: Large normal bowel motion
Day 5: CT abdomen showed a suspicious mass in his pancreas and lesion in his liver
- ? pancreatic malignancy with liver metastasis
Day 6: Patient well in the morning but later in the day found dead in bed

Copy of page: Case 3

PC: 75 year old male presented with a 3 day history of shortness of breath, wheezing, productive cough and temperatures.
Recruitment: Patient recruited within 24 hours of admission

HPC: Patient well up until 3 days ago when the above symptoms started with reduced oral intake. No nausea/vomiting. No constipation. No confusion prior to or at the time of assessment. No falls.

Medical History:

1. Diabetes Mellitus type 2
2. Depression
3. Chronic obstructive pulmonary disease - recurrent exacerbations (on home oxygen)
4. Congestive cardiac failure
5. Ischaemic heart disease
6. Atrial fibrillation
7. Diverticular disease
8. Gout
9. Polymyalgia rheumatica
10. Chronic kidney disease
11. Benign prostatic hyperplasia

Medications (regular):

1. Tamsulosin 400mcg, oral, once a day: > 5 years
2. Omeprazole 40mg, oral, once a day: > 1 year
3. Finasteride 5mg, oral, once a day: > 1 year
4. Sertraline 100mg, oral, once a day: > 1 year
5. Bisoprolol 7.5mg, oral, once a day: > 1 year
6. Furosemide 40mg, oral, twice a day: > 5 years
7. Allopurinol 300mg, oral, once a day: > 1 year
8. Atorvastatin 10mg, oral, once a day: > 1 year
9. Zolpidem 10mg, oral, once a day: 6 months - 1 year
10. Rivaroxaban 15mg, oral, once a day: > 1 year
11. Prednisolone 20mg, oral, once a day: < 1 week
12. Fluticasone/salmeterol one puff, inhaled, twice a day: > 5 years
13. Tiotropium one puff, inhaled, once a day: > 5 years

Medications (as required): nil

Recent short courses of treatment: nil

Allergies: nil

Social History: Ex-smoker, No alcohol, Lives with wife, help for domestic tasks

Barthel: 18/20 (unable to climb stairs), **MMSE:** 29/30, **4AT:** 0

Bloods (at admission):

Creat 166 $\uparrow$, eGFR 40.2 $\downarrow$, Baseline creat 110 $\uparrow$, baseline eGFR 60.16 $\downarrow$

Na 128 $\downarrow$, K 3.6, Ca 2.2 (corrected)

Hb 12, WCC 13 $\uparrow$, Neuts 10 $\uparrow$, Platelets 304, CRP 80 $\uparrow$

Alb 36, ALT 32, ALP 80

ECG: Normal sinus rhythm, no atrial fibrillation, 80 bpm, no blocks

Course of events in hospital:

Day 1: Patient commenced on IV amoxicillin/clavulanate 1.2g, ipratropium bromide/salbutamol nebuliser and hydrocortisone 100mg IV. Furosemide held. All regular medications continued

Day 2: Patient had clinically improved, furosemide 40mg twice a day restarted, Sodium now 132, patient eating and drinking well

Day 3: Patient improving. IV antibiotics and IV steroids changed to oral preparations. Sodium 133

Day 4: Patient started mobilising

Day 5: Discharged

Copy of page: Case 4

PC: 67 year old female presented with drowsiness and confusion.
Recruitment: Patient recruited within 24 hours of admission.

HPC: Recent acute flare of Rheumatoid Arthritis 4 weeks earlier. Commenced on oral Prednisolone and Oxycodone which helped. Over the last week she took more oxycodone. In the last 2/3 days, she became confused, ++ drowsy on day of admission. She began coughing. Drowsiness got worse. Per daughter, the patient is passing bowel motions, no vomiting, no recent falls.

Medical History:

1. Pernicious anaemia
2. Hyperthyroidism
3. Aortic stenosis (moderate)
4. Hypertension
5. Antral gastritis on gastroscopy 2004
6. Gastrointestinal bleed secondary to aspirin 2004
7. Rheumatoid arthritis
8. Osteoporosis
9. Hypercholesterolaemia

Medications (regular):

1. Carbimazole 10mg, oral, once a day: > 5 years
2. Prednisolone 5mg, oral, once a day: < 4 weeks
3. Amlodipine 10mg, oral, once a day: > 5 years
4. Pantoprazole 40mg, oral, once a day: > 5 years
5. Folic acid 5mg, oral, once a day: > 6 month
6. Alendronate 70mg, oral, once a week: > 1 year
7. Atorvastatin 40mg, oral, once a day: > 5 years
8. Ferrous fumarate 305mg, oral, once a day: 3 - 6 months
9. Tramadol 100mg, oral, three times a day: < 1 month
10. Oxycodone 10mg, oral, twice a day: < 2 weeks

Medications (as required):

1. Paracetamol 1g, oral, As required (last took 6 weeks ago): >5 years
2. Oxycodone 2.5mg, oral, (increased use to three times a day for the week preceeding admission): < 2 weeks

Recent short courses of treatment: Cefuroxime: 1 week (Finished 3 weeks ago)

Allergies: NKDA

Social History: Life long non-smoker, no alcohol, lives with her husband and daughter

Barthel: 20/20, **MMSE:** 18/30 (disorientated in time, place and person), **4AT:** 12, **DSM-V:** 7

Bloods (at admission):

Creat 84, eGFR 62.35 $\downarrow$, Na 136, K 4.8, Ca 2.23 (corrected)

Hb 11.2, WCC 25 $\uparrow$, Neuts 15 $\uparrow$, Pits 400, CRP 110 $\uparrow$, INR 1.1

Alb 32, ALT 35, ALP 75

ECG: Normal sinus rhythm, No atrial fibrillation, 80 bpm, No blocks

Course of events in hospital:

Day 1: Diagnosed with delirium secondary to opioid toxicity with an associated pneumonia. Tramadol and oxycodone held. Started on piperacillin/tazobactam.

Day 4: Developed profuse diarrhoea (6-7 times/day). Creat increased from 84 to 150, commenced on IV fluids.

Day 5: Creat 90. Clostridium difficile diagnosed. Commenced on metronidazole 3 days later, diarrhoea settled. Fluctuating confusion till day 6 admission. Discharged on day 20.

Copy of page: Case 5

PC: 80 year old female presented with dysuria, foul smelling urine and fevers.

Recruitment: Patient recruited within 24 hours of admission.

HPC: Patient was well up until 2 days ago when she woke feeling generally unwell. Noted dysuria and foul smelling urine. No bowel motion for 4 days. Usually has a bowel motion every second day. Feels constipated. Came to hospital due to fever and feeling nauseous. Unable to eat. Continued to take her medication

Medical History:

1. Hypertension
2. Aortic valve replacement (bioprosthetic) secondary to severe aortic stenosis
3. Coronary artery disease
4. Hypercholesterolaemia
5. Previous ischaemic stroke
6. Left carotid artery stent secondary to stroke and carotid artery disease
7. Endometrial cancer diagnosed 2011 (Total abdominal hysterectomy bilateral salpingo oophorectomy)
8. ↑BMI
9. Gastro-oesophageal reflux disease (GORD)
10. Large incisional hernia
11. Chronic constipation
12. Diverticular disease

Medications (regular):

1. Amlodipine 10mg, oral, once a day, >5 years
2. Valsartan 80mg, oral, once a day, > 5 years
3. Bisoprolol 10mg, oral, once a day, > 5 years
4. Clopidogrel 75mg, oral, once a day, 3 - 6 months
5. Aspirin 75mg, oral, once a day, > 5 years
6. Pantoprazole 40mg, oral, once a day, > 1 year
7. Atorvastatin 40mg, oral, once a day, > 5 years

Medications (as required):

1. Triazolam 0.25mg, oral, uses 2-3 times a week, > 5 years

Recent short courses of treatment: nil

Allergies: nil

Social History: Lifelong non-smoker, no alcohol, lives with husband, daughter does domestic care

Barthel: 20/20, **MMSE:** 24/30, **4AT:** 0

Bloods (at admission):

Creat 89, eGFR 56.26_l (no major change from baseline), Na 130_l, K 4, Ca 2.25 (corrected)
Hb 10.4_l, WCC 12_l, Neuts 8_l, Plts 342
Bili 12, Alb 36, ALT 20, ALP 75

ECG: Normal sinus rhythm, no atrial fibrillation, no blocks

Course of events in hospital:

Admitted and treated with IV amoxicillin/clavulanate and fluids. Nausea settled within 24 hours. Commenced on lactulose and bowels began to move on day 2. Changed to oral antibiotics on day 3 and discharged home 4 days after admission.

Copy of page: Case 6

PC: 87 year old male admitted with a fall/collapse. Unwitnessed. Recruited within 24 hours of admission

Recruitment: Patient recruited within 24 hours of admission.

HPC: Patient found on the floor by his carer. Laceration to the back of his head. He had been lying on the floor for a few hours. Unable to remember exactly what happened. Found in the sitting room. No incontinence. No fractures. More confused than usual. Carer had noticed over the preceding week that he appeared more confused and that this confusion was fluctuating. Per carer, no constipation, no vomiting.

Medical History:

1. Osteoarthritis
2. Constipation
3. Cataracts
4. Iron deficiency anaemia
5. Basal cell carcinoma
6. Ischaemic stroke 2006
7. Heart failure
8. Atrial fibrillation
9. Vascular dementia

Medications (regular):

1. Atorvastatin 20mg, oral, once a day, > 5 years
2. Warfarin, as per INR, oral, once a day, > 5 years
3. Lactulose 10mls, oral, once a day, > 5 years
4. Furosemide 40mg, oral, once a day, > 1 year
5. Buprenorphine patch, 12mcg/hr, transdermal, > 1 year
6. Esomeprazole 40mg, oral, once a day, > 5 years

Medications (as required): nil

Recent short courses of treatment:

1. Prednisolone 5mg, oral, once a day, on intermittently for the last year. Last course 1 week ago

Allergies: nil

Social History: Lifelong non smoker, no alcohol, lives alone, home help three times a day for personal and domestic tasks

Barthel: 13/20 (help with dressing, bathing, grooming, unable for stairs, minor help with transfers. **MMSE:** 16/30 (baseline score 21/30), **4AT:** 7,

DMS-V: yes

Bloods (at admission):

Creat 83, eGFR 80.79_l, Na 115_l (127 one week ago, baseline 125 - 130 over the last year), K 4.1, Calcium 2.22 (corrected)
Hb 11.1_l, WCC 7, Neuts 4, Plts 212
Bili 12, Alb 36, ALT 18, ALP 65

ECG: Atrial Fibrillation, no blocks

Course of events in hospital:

On admission found to be hyponatraemic and more confused than usual. Furosemide and buprenorphine held. On day 4, got out of the chair when the nurses weren't with him and fell. No damage and no changes in medications. On day 14 sodium still 124 despite changes in medications. Synacthen test done. Diagnosed with Addison's. Commenced on hydrocortisone. Sodium recovered within 3 days of starting steroids to 133. Discharged to a nursing home at day 50

Copy of page: Case 7

PC: 84 year old female, admitted following a fall.

Recruitment: Patient recruited within 24 hours of admission.

HPC: Patient was with her daughter, She dropped to the ground. Some mild dizziness prior to falling. Otherwise very well. No warning. No sensation of vertigo. No history of falls but mobility has dis-improved over the last 6 months. Requiring more assistance with ADLs. Daughter witnessed the fall. No obstacles. Didn't trip. No loss of consciousness, no seizure activity.

Medical History:

1. Atrial fibrillation diagnosed 1991
2. Heart failure
3. Hypercholesterolaemia
4. Cataracts
5. Glaucoma
6. Hypertension
7. Varicose eczema
8. Gastro-oesophageal reflux disease
9. Hiatus hernia
10. Osteoarthritis with a previous right hip replacement
11. Depression
12. Pulmonary hypertension (moderate)
13. Mitral Regurgitation (moderate)

Medications (regular):

1. Furosemide 40mg, oral, once a day 3 - 6 months
2. Warfarin, per INR, oral, once a day, > 5 years
3. Omeprazole 20mg, oral, once a day, > 5 years
4. Latanoprost/timolol eye drops, topical, once a day, > 5 years
5. Beclomethasone, two puffs, inhaled, twice a day, > 5 year
6. Dosulepin 75mg, oral, three times a day, > 5 years
7. Diltiazem 180mg, oral, once a day, > 5 years
8. Pravastatin 20mg, oral, once a day, > 5 years
9. Temazepam 10mg, oral, once a day, > 5 years

Medications (as required):

1. Salbutamol inhaler, one puff, inhaled, as required, > 5 years

Recent short courses of treatment: nil

Allergies: nil

Social History: Lifelong non-smoker, no alcohol, lives with her daughter

Barthel: 18/20 (occasional urinary incontinence and help climbing stairs)

MMSE: 20/20 (baseline score), **4AT:** 1 (orientated to time, place and person)

Bloods (at admission):

Creat 60, eGFR 88, Na 131, K 3.8, Ca (corrected) 2.3
Hb 11.4, WCC 6.4, Neuts 4, Plts 155
Bili 16, Alb 36, ALT 20, ALP 55

ECG: Atrial fibrillation, no heart blocks

Course of events in hospital:

Patient admitted for work up. Lying and standing BP showed a significant drop (Lying BP 120/85, standing BP 98/72). Furosemide held. On day 4 admission, patient noted to be constipated by the nursing staff. Last bowel motion was the day before admission. The only new medications received by the patient were one dose of paracetamol and one dose of Zolpidem. Patient discharged two days later

Copy of page: Case 8

PC: 76 year old female presented with a 3 day history of a productive cough of green sputum and fevers.

Recruitment: Patient recruited within 24 hours of admission.

HPC: Previously well prior to this. During the above symptoms she continued to take her regular medications as normal. She was able to eat and drink as normal. Shortness of breath and wheeze got worse so she presented to the emergency department. No confusion, no constipation, no diarrhoea.

Medical History:

1. Chronic obstructive pulmonary disease
2. Bronchiectasis
3. Breast cancer 1990 (mastectomy and radiotherapy)
4. Previous hyponatraemia in context of lower respiratory tract infections
5. Osteoporosis
6. Previous hysterectomy
7. Transient ischaemic attack
8. Peripheral neuropathy secondary to chemotherapy
9. Hypercholesterolaemia
10. Bilateral cataracts
11. Gastro-oesophageal intestinal disease

Medications (regular):

1. Long term oxygen 2 litres, nasal, 16 hours a day, > 1 year
2. Calcium carbonate 500mg, oral, twice a day, > 5 years
3. Colecalciferol 400IU, oral, twice a day, > 5 years
4. Fluticasone/salmeterol, one puff, inhaled, twice a day, > 5 years
5. Tiotropium, one puff, inhaled, once a day, > 5 years
6. Lansoprazole 15mg, oral, once a day, > 5 years
7. Alendronate 70mg, oral, once a week, 1 - 5 years
8. Aspirin 75mg, oral, once a day, > 5 years
9. Letrozole 2.5mg, oral, once a day, > 5 years

Medications (as required):

Paracetamol 1g as required (last took 2 weeks ago)

Recent short courses of treatment: nil

Allergies: Penicillin - rash

Social History: Ex-smoker (20 a day for 40 years), no alcohol, lives with husband, home help once a day

Barthel: 18/20 (unable for stairs), **MMSE:** 30/30, **4AT:** 0

Bloods (at admission):

Creat 130, eGFR 36.7, baseline creat 70, baseline eGFR 75, Na 118, K 3.8, Ca 2.21 (corrected)
Hb 12.2, WCC 14, Neuts 10, Plts 240, CRP 90

ECG: Normal sinus rhythm, no atrial fibrillation, no block

Course of events in hospital:

Treated for infective exacerbation of COPD with amoxicillin/clavulanate and inhaled ipratropium bromide and salbutamol. Sodium resolved in three days coinciding with treatment of infection. No changes in medications. No new events while in hospital

Appendix 2 - Ethical approval from the Clinical Research Ethics Committee (CREC) for acute medicine and oncology observational studies

 **UCC**
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University College Cork, Ireland

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

CORK UNIVERSITY HOSPITAL
29 SEP 2014
GERIATRIC DEPT Our ref: ECM 4 (w) 07/10/14

23rd September 2014

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Potentially inappropriate medications defined by STOPP version 2 and Beers Version 4 and the risk of adverse drug events causing hospitalisation in older adults.

Dear Dr Gallagher

Expedited approval will be granted to carry out the above study subject to receipt of the following:

- Fully Completed Application Form: Page 1 Protocol Section is blank.
- Study Protocol – No study title
- Revised Participant Consent Form – (a) Study title different from application checklist and (b) correct spelling errors specifically "you" should read "your" in a number of sentences
- Information Leaflet and Consent Form for Family/Caregivers. Application Form states "Patients and their families/care givers will be interviewed"
- Interview Questions for Families/Caregivers
- Confirmation – Please confirm the the Patients Information Document is the Patient Interview Guide.

The following documents have been approved:

- CV for Chief Investigator
- Study Protocol including Data Collection Sheet.

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

- Dr Amanda Lavan.

Yours sincerely


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

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COISTE EITICE UM THAIGHDE CLINIÚIL
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Lancaster Hall,
6 Little Hanover Street,
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CORK UNIVERSITY HOSPITAL
16 JAN 2015
GERIATRIC DEPT Our ref: ECM 3 (rmmr) 06/01/15

6th January 2015

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Potentially inappropriate medications defined by STOPP version 2 and Beers Version 4 and the risk of adverse drug events causing hospitalisation in older adults.

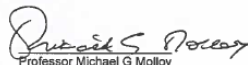
Dear Dr Gallagher

The Chairman approved the following:

- Application Form
- Detailed Protocol
- Information Leaflet/Consent Form
- Information Leaflet on Study
- Data Collection Sheet.

Full approval is now granted to carry out the above study.

Yours sincerely


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



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Clinical Research Ethics Committee

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

Our ref: ECM 3 (uuu) 03/11/15 & ECM 4 (w) 07/10/14

28th October 2015

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Potentially inappropriate medications defined by STOPP version 2 and Beers Version 4 and the risk of adverse drug events causing hospitalisation in older adults.

Dear Dr Gallagher

The Chairman approved the following:

- > Cover Letter dated 20th October 2015
- > Amendment Application Form signed 19th October 2015
- > Revised Consent Form: *Put Version 2 dated October 2015 on this document (header or footer) prior to use.*
- > Addition study sites at Mercy University Hospital and South Infirmary Victoria University Hospital.

Yours sincerely

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



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Our ref: ECM 3 (vvv) 06/09/16 & ECM 4 (w) 07/10/14

7th September 2016

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Potentially inappropriate medications defined by STOPP version 2 and Beers Version 4 and the risk of adverse drug events causing hospitalisation in older adults.

Dear Dr Gallagher

The Chairman approved the following:

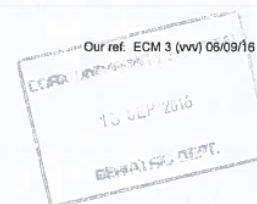
- > Cover Letter dated 11th August 2016
- > Amendment Application Form signed 10th August 2016.

Full approval to implement this amendment will be granted subject to receipt and approval of the following:

- > **Revised Study Protocol:** Changes must be clearly highlighted and the document must contain a new version and date
- > **Revised Data Collection Sheet:** Changes must be clearly highlighted and the document must contain a new version and date
- > Confirmation that patients consented to review of their medical charts.

Yours sincerely

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





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COISTE ÉITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

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Ireland.

Our ref: ECM 3 (qq) 11/10/16 & ECM 4 (w) 07/10/14

23rd September 2016

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Potentially inappropriate medications defined by STOPP version 2 and Beers
Version 4 and the risk of adverse drug events causing hospitalisation in older adults.

Dear Dr Gallagher

The Chairman approved the following:

- > Cover Letter dated 11th August 2016 (received 16th September 2016)
- > Revised Study Protocol
- > Data Collection Sheets
- > Participant Information Sheet and Informed Consent Form Version 2 dated October 2015.

Full approval is now granted to implement this amendment.

Yours sincerely

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



Appendix 3 - Data Collection Sheet

Study Number: _____

Hospital		Tick type of admission	
CUH		Emergency	
MUH		Elective	
		Day unit	

Baseline Characteristics:		
Age		
Gender	Male	Female
Smoker (ever)	Yes	No
Current Smoker	Yes	No
Weekly alcohol	Yes	No
Units per week		
Housing (circle)	Living in own home Living in child's home Sheltered accommodation Nursing Home Other	
Living arrangements (circle)	Alone Spouse Spouse and child Child/children Child and their family Living with other relative Living with other non-relative	
Supports in place <u>(in the last month)</u>		
PHN	Yes	No
Palliative care nurse	Yes	No
HSE Home Help/Paid non-relative	Yes	No
Paid relative	Yes	No
Unpaid Relative	Yes	No
Unpaid non-relative	Yes	No
Private Home help	Yes	No
Did they ever drive	Yes	No
Current driving	Yes	No
Hearing Impairment	Yes	No
Visual impairment	Yes	No
Walking Aid	Yes Walking stick/sticks Crutch x 1, Crutch x 2 Zimmer frame, rollator Wheelchair dependent	No

Study ID: _____

List Medical Diagnoses (and previous surgeries)

Name	ICD-10 code	Name chronic disease process	Treated yes/no

Cumulative Illness Rating Scale (CIRS) Index

Body system	Score
Cardiac (heart only)	0 – 1 – 2 – 3 – 4
Vascular (organ damage is rate separately)	0 – 1 – 2 – 3 – 4
Haemopoetic (blood, vessel, cells, bone marrow, spleen)	0 – 1 – 2 – 3 – 4
Respiratory	0 – 1 – 2 – 3 – 4
ENT (eye, ear, throat, larynx)	0 – 1 – 2 – 3 – 4
Upper GI	0 – 1 – 2 – 3 – 4
Lower GI	0 – 1 – 2 – 3 – 4
Hepatic	0 – 1 – 2 – 3 – 4
Renal	0 – 1 – 2 – 3 – 4
Other GU	0 – 1 – 2 – 3 – 4
Musculoskeletal	0 – 1 – 2 – 3 – 4
Neurological	0 – 1 – 2 – 3 – 4
Endocrine-metabolic	0 – 1 – 2 – 3 – 4
Psychiatric/Behavioural	0 – 1 – 2 – 3 – 4
Score (range 0 – 56)	

Study ID: _____

Medical Card: Yes No

All prescription medications (regular and PRN) the patient is currently taking (per pharmacy and patient vials) prior to admission to hospital – ring pharmacy first to get list and then corroborate with the patient

[illegible]

Study ID: _____

Recent changes to medications

Antibiotic in the last 2/12; yes or no	If yes specify
List any other changes/recent courses of medications	

Previous and current chemotherapy regimens

Current chemo: Name/s: When received the last cycle: Cycle number: Total cycles expected: Previous chemo: Yes or No Name if known:
--

Previous and current radiotherapy regimens and number of cycles

--

Study ID: _____

Modified Medications Reconciliation by Structure History of Medications

1.	Are you using your medication as prescribed (dosage, dose, freq, form) Check each medication on previous list according to dose, freq, form, time etc	Yes	No
2.	If no list medication/s here and find out reason why not taking as prescribed:		
3.	What is the reason for deviating (dose, dosage, freq, form) or not taking a drug at all (circle)	List reason/s:	
2.	Are you experiencing any side effect (at present, not previously) Name:	Yes	No
4.	Are you using any other prescription medication that are not mentioned on this list?(view medication containers) (in the last month) Name:	Yes	No
5.	Are you using non-prescription meds (in the last month) Name:	Yes	No
6.	Are you using homeopathic drugs or herbal remedies (Especially St John's wort) (in the last month) Name:	Yes	No
7.	Are you using any drugs belonging to friends or family members (in the last month) Name:	Yes	No
8.	Are you using 'as needed drugs' / on demand drugs (in the last month) Name:	Yes	No
9.	Are you using drugs that are no long prescribed (in the last month) Name:	Yes	No
10.	Are you taking your medications independently	Yes	No
11.	Are you using a dosage system	Yes	No
12.	Are you experiencing any problems taking your medication If yes what:	Yes	No
13.	Regarding Inhalation therapy what system are you using (circle)	Yes using Not using If yes Any problems using?	
14.	Regarding eye drops. Any difficulties using? (circle)	Yes using Not using If yes Any problems using?	
15.	Do you ever forget to take your medications (this question is N/A if they do not manage their medications alone) - Which medication _____ - Why _____ - What do you do _____	Yes	No
16.	Would you like to comment on or ask a question about your medication?		
	Do you have any allergies - Which drug - Symptoms	Yes	No
	Do you have any drug intolerances - Which drug - Symptoms	Yes	No

Study ID: _____

Barthel Index		
Bowels	0 = Incontinent or needs to be given enemas 1 = Occasional accident (1/wk) 2 = Continent	
Bladder	0 = Incontinent/catheterised and unable to manage 1 = Occasional accident (max 1/24hrs) 2 = Continent	
Grooming	0 = needs help with personal care 1 = Independent face/hair/teeth/shaving	
Toilet Use	0 = dependent 1 = needs some help but can do something alone 2 = Independent on and off	
Feeding	0 = unable 1 = needs help cutting, spreading butter etc 2 = independent	
Transfer	0 = unable – no sitting balance 1 = major help (on or two people) can sit 2 = minor help (verbal or physical) 3 = independent	
Mobility	0 = immobile 1 = wheelchair independent 2 = walks with help of one person (verbal or physical) 3 = Independent (may use any aid)	
Dressing	0 = dependent 1 = needs help but can do about half unaided 2 = Independent (including buttons, zips etc)	
Stairs	0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent up and down	
Bathing	0 = dependent 1 = Independent (or in shower)	
	SCORE	

Clinical frailty scale (score 1 – 9)	
--------------------------------------	--

MMSE		
Potential Score	Patients Score	Questions
5		What is the year? Season? Date? Day? Month?
5		Where are we now: Country? County? Town/city? Hospital? President?"
3		Recall (Ball, Flag Tree)
5		DLROW
5		Serial Sevens
3		Recall: Name the three objects
2		Name two objects
1		Repetition: 'No ifs ands or buts'
3		Three step command
1		Close your eye
1		Write a sentence
1		Copy this picture 

Study ID: _____

Delirium Assessment

4AT

- (1) Alertness
 - Normal: 0
 - Mild sleepiness for < 10 seconds after waking, then normal: 0
 - Clearly Abnormal: 4
- (2) AMT4 (age, date of birth, hospital, current year)
 - No mistakes: 0
 - 1 mistake: 1
 - 2 or more: 2
- (3) Attention
 - Achieves 7 months: 0
 - Starts but scores less than 7 months/refuses: 1
 - Untestable (unwell, drowsy, inattentive): 2
- (4) Acute Change or Fluctuating Course
 - No: 0
 - Yes: 4

Total: _____

DSM-V (yes to all 5)

- A. A disturbance of attention: yes no
- B. The disturbance develops over a short period of time: yes no
- C. An additional disturbance in cognition: yes no
- D. Disturbances in A and C are not better explained by another pre-existing illness: yes no
- E. There is evidence from history, exam, investigations etc that disturbance is a direct consequence of another medical condition, intoxication etc: yes no

Delirium: yes no

ECG completed, if yes:	Yes	No
Sinus	Yes	No
Atrial Fibrillation	Yes	No
Bradycardia (<50)	Yes	No
First degree heart block	Yes	No
Second Degree heart block	Yes	No
Complete heart block	Yes	No
Prolonged QT (QTc: _____)	Yes	No
Blood Work up (aim from this admission, if not put date beside)		
Date	Blood	Result
	Current Urea	
	Current Creatinine	
	Current eGFR (MDRD)	
	Baseline Urea (in the last year)	
	Baseline Creatinine (in the last year)	
	Baseline eGFR (MDRD)	
	Na	
	K+	
	Ca2+	
	Albumin	
	Alk Phos	
	ALT	
	HbA1c	
	CRP	
	Urate	
	Hb	
	WCC	
	Neuts	
	Plts	
	INR	
	Tfts (only if on levothyroxine)	

Study ID: _____

Did any of the following events/processes occur prior to admission:

Did the process occur		After filling out event form was the event secondary to a <u>non-cancer drug</u> (prob/certain)	Event secondary to recent chemo (prob/certain)	Event secondary to radiotherapy	Max WHO causality	Max H&S Severity	Max Avoidability
New onset fall	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
New onset Gait disturbance	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
AKI	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
New onset OH	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Major electrolyte derangement	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Symptomatic bradycardia	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
New onset major constipation	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Acute bleeding	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Acute dyspepsia	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Acute diarrhea	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Delirium	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Symptomatic hypoglycaemia	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			
Other (e.g. anaphylaxis, neutropenia, liver failure)	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐			

Appendix 4 - Barthel Index

Bowels	0 = Incontinent or needs to be given enemas 1 = Occasional accident (1/wk) 2 = Continent	
Bladder	0 = Incontinent/catheterised and unable to manage 1= Occasional accident (max 1/24hrs) 2 = Continent	
Grooming	0 = needs help with personal care 1 =Independent face/hair/teeth/shaving	
Toilet Use	0 = dependent 1= needs some help but can do something alone 2 =Independent on and off	
Feeding	0 = unable 1 = needs help cutting, spreading butter etc 2 = independent	
Transfer	0 = unable – no sitting balance 1 = major help (on or two people) can sit 2 = minor help (verbal or physical) 3 = independent	
Mobility	0 = immobile 1 = wheelchair independent 2 = walks with help of one person (verbal or physical) 3 = Independent (may use any aid)	
Dressing	0 = dependent 1 = needs help but can do about half unaided 2 = Independent (including buttons, zips etc)	
Stairs	0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent up and down	
Bathing	0 = dependent 1 = Independent (or in shower)	
	SCORE	

Appendix 5 – Mini Mental State Examination (MMSE)

Potential Score	Patients Score	Questions
5		<u>What is the year? Season? Date? Day? Month?</u>
5		<u>Where are we now: Country? County? Town/city? Hospital? President?"</u>
3		Recall (Ball, Flag Tree)
5		DLROW
5		Serial Sevens
3		Recall: Name the three objects
2		Name two objects
1		Repetition: 'No ifs ands or buts'
3		Three step command
1		Close your eye
1		Write a sentence
1		Copy this picture 

Appendix 6 - Structured History of Medication Use Questionnaire (SHiM)

Table 1. Structured History Taking of Medication Use Questionnaire

Questions asked per drug on the medication list, provided by the community pharmacist

1. Are you using this drug as prescribed (dosage, dose frequency, dosage form)?
2. Are you experiencing any side effects?
3. What is the reason for deviating (from the dosage, dose frequency, or dosage form) or not taking a drug at all?
4. Are you using any other prescription drugs that are not mentioned on this list? (view medication containers)
5. Are you using nonprescription drugs?
6. Are you using homeopathic drugs or herbal medicines (especially St. Johns wort)?
7. Are you using drugs that belong to family members or friends?
8. Are you using any "as needed" drugs?
9. Are you using drugs that are no longer prescribed?

Questions concerning the use of medicines

10. Are you taking your medication independently?
 11. Are you using a dosage system?
 12. Are you experiencing problems taking your medication?
 13. In case of inhalation therapy: What kind of inhalation system are you using? Are you experiencing any problems using this system?
 14. In case of eye drops: Are you experiencing any difficulties using the eye drops?
 15. Do you ever forget to take your medication? If so, which medication, why, and what do you do?
- Other
16. Would you like to comment on or ask a question about your medication?

Appendix 7 – Rockwood’s Clinical Frailty Scale

Clinical Frailty Scale*



1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.



2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.



3 Managing Well – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.



4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up", and/or being tired during the day.



5 Mildly Frail – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.



6 Moderately Frail – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.



7 Severely Frail – Completely dependent for **personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).



8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.



9. Terminally Ill - Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise evidently frail**.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.

2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Appendix 8 - STOPP/START criteria version 2

Screening Tool of Older Persons' Prescriptions (STOPP) version 2

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

Section A: Indication of medication

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

Section B: Cardiovascular System

1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).
4. Beta blocker with bradycardia ($< 50/\text{min}$), type II heart block or complete heart block (risk of complete heart block, asystole).
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side-effects than beta-blockers, digoxin, verapamil or diltiazem).
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available).
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome or renal failure (leg elevation and /or compression hosiery usually more appropriate).
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum $\text{K}^+ < 3.0 \text{ mmol/l}$), hyponatraemia (i.e. serum $\text{Na}^+ < 130 \text{ mmol/l}$) hypercalcaemia (i.e. corrected serum calcium $> 2.65 \text{ mmol/l}$) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic).
9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence).
10. Centrally-acting antihypertensives (e.g. methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).
11. ACE inhibitors or Angiotensin Receptor Blockers in patients with hyperkalaemia.
12. Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. $> 6.0 \text{ mmol/l}$ – serum K should be monitored regularly, i.e. at least every 6 months).
13. Phosphodiesterase type-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) in severe heart failure characterised by hypotension i.e. systolic BP $< 90 \text{ mmHg}$, or concurrent nitrate therapy for angina (risk of cardiovascular collapse).

Section C: Antiplatelet/Anticoagulant Drugs

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

Section D: Central Nervous System and Psychotropic Drugs

1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions).
2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs).
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenazine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention).
4. Selective serotonin re-uptake inhibitors (SSRI's) with current or recent significant hyponatraemia i.e. serum Na⁺ < 130 mmol/l (risk of exacerbating or precipitating hyponatraemia).
5. Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).

6. Antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extra-pyramidal symptoms).
7. Anticholinergics/antimuscarinics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic toxicity).
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment).
9. Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke).
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extra-pyramidal side effects, falls).
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (< 60 beats/min.), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta-blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury).
12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant anti-muscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care).
13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy).
14. First-generation antihistamines (safer, less toxic antihistamines now widely available).

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

1. Digoxin at a long-term dose greater than 125µg/day if eGFR < 30 ml/min/1.73m² (risk of digoxin toxicity if plasma levels not measured).
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR < 30 ml/min/1.73m² (risk of bleeding).
3. Factor Xa inhibitors (e.g. rivaroxaban, apixaban) if eGFR < 15 ml/min/1.73m² (risk of bleeding).
4. NSAID's if eGFR < 50 ml/min/1.73m² (risk of deterioration in renal function).
5. Colchicine if eGFR < 10 ml/min/1.73m² (risk of colchicine toxicity).
6. Metformin if eGFR < 30 ml/min/1.73m² (risk of lactic acidosis).

Section F: Gastrointestinal System

1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).
2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks (dose reduction or earlier discontinuation indicated).
3. Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation).

4. Oral elemental iron doses greater than 200 mg daily (e.g. ferrous fumarate > 600 mg/day, ferrous sulphate > 600 mg/day, ferrous gluconate > 1800 mg/day; no evidence of enhanced iron absorption above these doses).

Section G: Respiratory System

1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index).
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side-effects of systemic corticosteroids and effective inhaled therapies are available).
3. Anti-muscarinic bronchodilators (e.g. ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention).
4. Benzodiazepines with acute or chronic respiratory failure i.e. $pO_2 < 8.0 \text{ kPa}$ $\pm$ $pCO_2 > 6.5 \text{ kPa}$ (risk of exacerbation of respiratory failure).

Section H: Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H2 antagonist (risk of peptic ulcer relapse).
2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure).
3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief).
4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis (risk of systemic corticosteroid side-effects).
5. Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis (risk of systemic corticosteroid side-effects).
6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g. allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout).
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease).
9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).

Section I: Urogenital System

1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow-angle glaucoma (risk of acute exacerbation of glaucoma), or chronic prostatism (risk of urinary retention).

2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope).

Section J: Endocrine System

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

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

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

Section L: Analgesic Drugs

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

Section N: Antimuscarinic/Anticholinergic Drug Burden

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

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

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

Section A: Cardiovascular System

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

Section B: Respiratory System

1. Regular inhaled β_2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50% of predicted value and repeated exacerbations requiring treatment with oral corticosteroids.
3. Home continuous oxygen with documented chronic hypoxaemia (i.e. $pO_2 < 8.0$ kPa or 60 mmHg or $SaO_2 < 89\%$).

Section C: Central Nervous System& Eyes

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

Section D: Gastrointestinal System

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

Section E: Musculoskeletal System

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

Section F: Endocrine System

1. ACE inhibitor or Angiotensin Receptor Blocker (if intolerant of ACE inhibitor) in coa with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria ($>30\text{mg}/24$ hours) with or without serum biochemical renal impairment.

Section G: Urogenital System

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

Section H: Analgesics

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

Section I: Vaccines

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

Appendix 9 - OncPal criteria

Medication class	Medication	Considerations for limited benefit	Explanation
Blood and blood-forming organs	Aspirin	For primary prevention only.	Long-term benefits at population level. Little short or intermediate term risk of stopping (1). Drugs for primary prevention have, in general, no place in the treatment of end-of-life patients since the time-to-benefit usually exceeds life expectancy (2).
Cardiovascular system	Dyslipidaemia medications Statins Fibrates Ezetimibe	All indications.	Long-term benefits at population level. Little short or intermediate term risk of stopping (1).
	Antihypertensives ACE inhibitors Sartans Beta blockers Calcium channel blockers Thiazide Diuretics	If sole use is to reduce mild to moderate hypertension for secondary prevention of cardiovascular events or as management of stable coronary artery disease. ^{ab}	Long-term benefits at population level. Ongoing therapy unnecessary in most shortened life expectancy (1).
Musculo-skeletal system	Osteoporosis medications Bisphosphonates Raloxifene Strontium Denosumab	Except if used for the treatment of hypercalcaemia secondary to bone metastases.	Except if used for the treatment of hypercalcaemia secondary to bone metastases. Long-term benefits at population level. Little short or intermediate term risk of stopping (1).
Alimentary tract and metabolism	Peptic ulcer prophylaxis Proton pump inhibitors H2 antagonists	Lack of any medical history of gastrointestinal bleeding, peptic ulcer, gastritis, GORD or the concomitant use of anti-inflammatory agents including NSAIDs and steroids (3).	Ongoing therapy unnecessary in most shortened life expectancy (1).
Oral Hypoglycaemics Metformin Sulfonylureas Thiazolidinediones DPP-4 inhibitors GLP-1 analogues Acarbose	If sole use is to reduce mild hyperglycaemia for secondary prevention of diabetic associated events. ^c	Potential short-term complications outweigh benefit (1).	
Vitamins Minerals Complementary—alternative medicines	If not indicated to treat a low blood plasma concentration.	No evidence for effectiveness (4, 5). ^d	

Appendix 10 - STOPPfrail questionnaire on survey monkey

STOPPfrail

Survey Information

STOPPfrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥ 65 years) who meet ALL of the criteria listed below:

- End-stage irreversible pathology
- Poor Prognosis
- Severe functional impairment or severe cognitive impairment or both
- Symptom control is the priority rather than prevention of disease progression

The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:

- Risk of the medication outweighing the benefit
- Administration of the medication is challenging
- Monitoring of the medication effect is challenging
- Drug adherence/compliance is difficult

The criteria are presented according to the physiological system predominantly affected by the drug/drug class in question. There are a total of 10 sections with 2-3 criteria per section. In total there are 30 criteria. After each criterion you will be asked whether you agree/disagree, via a likert scale, with it being included in STOPPfrail. There will be room after each criterion for you to put in any suggestions/comments. After each physiological section there will also be another text box for you to make any further suggestions/comments e.g. another drug class you feel should be included.

I am undertaking this project under the guidance and supervision of Dr Denis O'Mahony and Dr Paul Gallagher. Your expertise and participation is very much appreciated. If you have any queries or questions have no hesitation in contacting me.

* 1. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
A1: Any drug the patient persistently fails to comply with for any reason.	☐	☐	☐	☐	☐	☐
Additional comments						

A2: Any drug without clear clinical indication.	☐	☐	☐	☐	☐	☐
Additional comments						

* 3. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
B1: Lipid Lowering Therapies (statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, acipimox). These medications need to be prescribed for a long duration to be of benefit. For short term use, ADE risk outweighs the potential benefit.	☐	☐	☐	☐	☐	☐
Additional comments						

B2: Alpha blockers for hypertension. Stringent blood pressure control is not required in very frail people. Alpha blockers in particular cause marked vasodilation, which can result in marked symptomatic postural hypotension, falls and injuries.	☐	☐	☐	☐	☐	☐
Additional comments						

* 5. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know
C1: Anticoagulants (warfarin/novel oral anticoagulants). Anticoagulation as a preventative measure (e.g. with atrial fibrillation) as distinct from treatment for venous thromboembolic (VTE) disease.	☐	☐	☐	☐	☐	☐
Additional comments						
C2: Anti-platelets. No role in primary cardiovascular prevention, only beneficial for secondary cardiovascular prevention, therefore discontinue unless there is a previous history of IHD, cerebrovascular disease or recent arterial stent insertion.	☐	☐	☐	☐	☐	☐
Additional comments						

* 7. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
D1: Memantine. Discontinue unless it has been prescribed for behavioural and psychological symptoms of dementia (BPSD) in patients with Alzheimers disease and has shown to improve symptoms.	☐	☐	☐	☐	☐	☐
Additional comments						
D2: Acetylcholinesterase Inhibitors. There is no significant clinical benefit from continuation of in those with advanced Alzheimers disease (MMSE <10/30 <i>and</i> functional dependent). No role in other dementia syndromes in the advanced stages.	☐	☐	☐	☐	☐	☐
Additional comments						

D3: Anti-depressants. There is no proven role for anti-depressants in advanced dementia (MMSE <10/30 <i>and</i> functionally dependent).	☐	☐	☐	☐	☐	☐
Additional comments						
D4: Neuroleptic antipsychotics. Aim to reduce dose and discontinue in patients taking them for longer than 12 weeks if there are no current clinical features of behavioural and psychiatric symptoms of dementia (BPSD).	☐	☐	☐	☐	☐	☐
Additional comments						

* 9. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	Don't know
E1: Proton Pump Inhibitors (PPIs). Proton Pump Inhibitors at full therapeutic dose for $\geq 8/52$, unless persistent dyspeptic symptoms at a lower maintenance dose.	☐	☐	☐	☐	☐	☐
Additional comments						
E2: H2 Receptor Antagonists (H2RA). H2 Receptor Antagonists at full therapeutic dose for $\geq 8/52$, unless persistent dyspeptic symptoms or symptoms reoccur after discontinuation.	☐	☐	☐	☐	☐	☐
Additional comments						

E3: Gastrointestinal antispasmodic Agents. Regular daily prescriptions of antispasmodic agents unless the patient has frequent relapse of colic symptoms because of high risk of anti-cholinergic side effects.

☐
☐
☐
☐
☐
☐

Additional comments

* 11. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
F1: Theophylline. This agent has a narrow therapeutic index, requires monitoring and interacts with other common drugs putting patients at an increase risk of adverse drug events (ADEs).	☐	☐	☐	☐	☐	☐
Additional comments						

F2: Leukotriene antagonists (Montelukast, Zafirlukast). These drugs have no proven role in those with COPD, they are only indicated in Asthma.

☐
☐
☐
☐
☐
☐

Additional comments

F2: Leukotriene antagonists (Montelukast, Zafirlukast). These drugs have no proven role in those with COPD, they are only indicated in Asthma.

☐
☐
☐
☐
☐
☐

Additional comments

* 13. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
G1: Calcium and vitamin D supplementation. Unlikely to be of any benefit in the short term.	☐	☐	☐	☐	☐	☐
Additional comments						

G2: Anti-resorptive/Bone anabolic drugs (bisphosphonates, strontium, teriparathyroid, denosumab). Benefits unlikely to be achieved within 1 year, increase short-intermediate term risk of associated ADEs.

☐
☐
☐
☐
☐
☐

Additional comments

G3: Selective oestrogen receptor modulators (SERMs) for osteoporosis. Benefits unlikely to be achieved within 1 year, increased short-intermediate term risk of associated ADEs, particularly venous thromboembolism and stroke.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

G4: Long-term oral non steroidal anti-inflammatories (NSAIDs). Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure) when taken regularly for ≥ 2 months.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

G5: Long-term steroids. Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc) when taken regularly for ≥ 2 months. Consider careful dose reduction and discontinuation.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

14. Do you have any other drug suggestions to add to this category or additional comments?

* 15. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above. Please select one response per statement.

Strongly agree Agree Neutral Disagree Strongly disagree Undecided

H1: 5-alpha reductase inhibitors. No benefit with long term urinary bladder catheterisation.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

H2: Alpha blockers. No benefit with long term urinary bladder catheterisation.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

H3: Muscarinic antagonists. No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

16. Do you have any other drug suggestions to add to this section or additional comments?

* 17. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above.
Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
I1: Diabetic oral agents. Stringent glycaemic control (Capillary blood glucose consistently < 10 and/or HbA1z consistently <45) is unnecessary. Avoid multiple hypoglycaemic agents where possible.	☐	☐	☐	☐	☐	☐
Additional comments						

I2: ACE-inhibitors for diabetes. Stop where prescribed for only prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

I3: Angiotension Receptor Blockers (ARBs). Stop where prescribed for only prevention and treatment of diabetic nephropathy. There is no clear benefit in older people with advanced frailty with poor survival prognosis.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

I4: Systemic oestrogens for menopausal symptoms. Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

18. Do you have any other drug suggestions to add to this section or additional comments?

* 19. The following prescriptions are potentially inappropriate for patients who meet the frailty criteria listed above.
Please select one response per statement.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	Don't know
J1: Multivitamin Combination Supplements. Discontinue when prescribed for prophylaxis rather than treatment	☐	☐	☐	☐	☐	☐
Additional comments						

J2: Nutritional Supplements. Discontinue when prescribed for prophylaxis rather than treatment

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

J3: Prophylactic Antibiotics. No evidence for a role for prophylactic antibiotics for recurrent cellulitis or recurrent UTIs.

☐ ☐ ☐ ☐ ☐ ☐

Additional comments

20. Do you have any other drug suggestions to add to this section or additional comments?

Appendix 11 - Physicians who participants in the IRR of STOPPFrail criteria

	Name	Discipline	Place of practice
1	Dr. Norma Harnedy	Geriatric Medicine (consultant)	Cork University Hospital, Cork
2	Dr. Liam Healy	Geriatric Medicine (consultant)	Cork University Hospital, Cork
3	Dr. Rónán O’Caoimh	Geriatric Medicine (consultant)	University Hospital Galway
4	Dr. Mary Buckley	Geriatric Medicine (specialist registrar)	Mercy University Hospital, Cork
5	Dr. Tim Dukelow	Geriatric Medicine (specialist registrar)	Mercy University Hospital, Cork
6	Dr. Bart Daly	Geriatric Medicine (specialist registrar)	Cork University hospital, Cork
7	Dr. Katie Boyle	General Practice	Cork City Medical Centre, 91 Patrick Street, Cork
8	Dr. Sadhbh Ní Lionáird	General Practice	Meadow Park surgery, Ballyvolane, Cork.
9	Dr. Denis O’Donovan	General Practice (trainee)	Cork Specialist training Scheme in General Practice.
10	Dr. Fiona Kiely	Palliative care (consultant)	Marymount University Hospital & Hospice & Cork University Hospital, Cork
11	Dr. Marie Murphy	Palliative care (consultant)	Marymount University Hospital & Hospice & Cork University Hospital, Cork
12	Dr. Coman Hennelly	Palliative care (specialist registrar)	Marymount University Hospital & Hospice & Cork University Hospital, Cork

Appendix 12 - Twenty clinical cases for assessment of STOPPFrail IRR

	Case 1		Case 2
Age:	78	Age:	89
Sex:	female	Sex:	male
Current location:	Acute hospital with pneumonia	Current location:	Acute hospital with pneumonia
Usual location:	Living at home but has applied for long term care secondary to severe functional and cognitive impairment. 24 supervision by family.	Usual location:	Nursing home resident for 1 year
Medical History:	1. Dementia diagnosed 2009 2. Diabetes Mellitus type 2 (HbA1c 6%) 3. Anxiety diagnosed 15 years ago (Currently no objective symptoms) 4. Intracerebral haemorrhage 2012 5. Orthostatic hypotension 6. Hypertension 7. Carotid stenosis 8. Diverticular disease – constipation on occasion 9. Urinary incontinence	Medical History:	1. Total anterior circulation stroke 2015 2. Post stroke epilepsy 2015 3. Atrial fibrillation (not for anti-coagulation) 4. Constipation 5. BPH (long term catheter in situ) 6. Recurrent infections (LRTIs, UTIs) 7. Faecal incontinence
Medications:	No problems with medication adherence 1. Calcium carbonate 500mg po bd (> 5 years) 2. Cholecalciferol 400IU po bd (> 5 years) 3. Atorvastatin 40mg po od (> 5 years) 4. Lansoprazole 30mg po od (4 years) 5. Senna one tablet po od (1 year) 6. Folic acid 5mg po od (4 years) 7. Lercandipine 10mg po od (> 5 years) 8. Valsartan 40mg po od (> 5 years) 9. Paracetamol 1g po tds (4 years) 10. Alprazolam 250mcg po od (1 year)	Medications:	No problems with medication adherence 1. Levetiracetam 250mg po bd (1 year) 2. Fluvastatin 20mg po od (> 5 years) 3. Lactulose 15ml po tds (1 year) 4. Digoxin 125mcg po od (1 year) 5. Fresubin 5kcal (energy + protein + fat) nutritional supplement one carton od (1 year) 6. Trimethoprim 100mg po od (1 year) 7. Tamsulosin 400mcg po od (> 5 years)
Social History:		Social History:	
Cognition:	MMSE score 8/30 six months ago	Cognition:	MMSE untestable (global aphasia)
Function:	Assistance of two for transfers, wheelchair dependent Urinary incontinent Fully dependent in all activities of daily living (ADLs)	Function:	Hoist transfer Faecal incontinence Fully dependent in all ADLs
Speech:	Verbalises but cannot express needs or wishes (random words)	Speech:	Global aphasia
Behaviour:	No behaviour problems	Behaviour:	No behaviour problems

Case 3

Age: 80
Sex: female
Current location: Acute hospital with acute agitation (delirium) and constipation
Usual location: Living at home with 24 hour supervision by her family

Medical History:

1. Dementia diagnosed 2010
2. Diabetes Mellitus type 2 (HbA1c 6.3% one month ago)
3. Dyslipidaemia
4. Depression
5. Hypertension
6. Osteoarthritis
7. Urinary incontinence
8. Constipation

Medications:

No problems with medication adherence

1. Escitalopram 10mg po od (> 5 years)
2. Esomeprazole 20mg po od (> 5 years)
3. Rosuvastatin 20mg po od (> 5 years)
4. Movicol one sachet po bd (2 years)
5. Rivastigmine patch 9.5mg od (> 5 years)
6. Gliclazide 60mg po od (> 5 years)
7. Metformin 500mg po bd (> 5 years)
8. Sitagliptin 50mg po od (2 years)

Social History:
Cognition: MMSE 10/30
Function: Walks with rollator
 Poor safety awareness
 Assistance required with all ADLs

Speech: Verbalises but cannot express needs of wishes
Behaviour: No behaviour problems generally

Case 4

Age: 86
Sex: female
Current location: GP surgery for flu vaccination
Usual location: Living at home with her husband and daughter

Medical History:

1. Anaemia
2. Congestive heart failure
3. Colorectal cancer – stage 4 – not for further treatment
4. GORD during previous treatment
5. Anxiety
6. Osteoporosis
7. COAD – GOLD stage 4
8. Atrial fibrillation

Medications:

Some problems with medication adherence (see each medication)

1. Ferrous fumarate 305mg po od (Hb 12.8) (1 year)
2. Warfarin as per INR (recently erratic – difficulty attending to get INRs checked) (>5 years)
3. Furosemide 40mg po bd (>5 years)
4. Ramipril 5mg po od (>5 years)
5. Rosuvastatin 10mg po od (>5 years)
6. Ranitidine 150mg po bd (1 year)
7. Diazepam 5mg po nocte (1 year)
8. Calcium carbonate 500mg po bd (>5 years)
9. Cholecalciferol 400IU po bd (>5 years)
10. Seretide (fluticasone/salmeterol) 250mcg inhaled bd – difficulty using (>5 years)
11. Theophylline 200mg po od (>5 years)
12. Centrum multivitamin one tablet od (1 year)
13. Fortisip (energy + protein + fat) nutritional supplement one carton od (1 year)

Social History:
Cognition: MMSE 24/30
Function: Walks with the help of two people very short distances.
 Assistance required with all ADLs
 Increasing frailty

Speech: Communicates ok, some repetition

Case 5

Age: 85
Sex: female
Current location: GP surgery for flu vaccination
Usual location: Living at home with her husband and daughter

Medical History:

1. Parkinson's disease diagnosed 2008
2. Parkinson's related dementia 2013
3. Orthostatic hypotension 2014
4. HTN
5. Diabetes
6. Osteoporosis: previous hip fracture 2012
7. Dyslipidaemia

Medications:

No problems with medication adherence

1. Betahistidine 16mg po tds (2 years)
2. Stalevo (levodopa/carbidopa/entacapone) 150mg/37.5mg/200mg po qds (>5 years)
3. Doxazosin 4mg po od (>5 years)
4. Amlodipine 10mg po od (>5 years)
5. Metformin 500mg po tds (>5 years)
6. Gliclazide 90mg po od (>5 years)
7. Sitagliptin 50mg po bd (>5 years)
8. Calcium carbonate 500mg po bd (4 years)
9. Cholecalciferol 400IU po bd (4 years)
10. Pravastatin 10mg po od (>5 years)
11. Aspirin 75mg po od (>5 years)

Social History:
Cognition: MMSE 10/30
Function: Walks with a rollator and assistance of 1
 Assistance required with all ADLs
 Increasing frailty

Speech: Verbalises but cannot express needs or wishes

Case 6

Age: 82
Sex: male
Current location: Acute hospital with pneumonia
Usual location: Nursing home resident

Medical History:

1. BPH (Previous TURP, long term catheter in situ for 1 year)
2. HTN
3. Alzheimer's dementia 2010
4. Osteoarthritis
5. GORD
6. Diverticular disease
7. Faecal incontinence

Medications:

Some problems with medication adherence (see each medication)

1. Dutasteride 0.5mg po od (>5 years)
2. Tamsulosin 0.4mg po od (>5 years)
3. Ramipril 10mg po od (>5 years)
4. Amlodipine 10mg po od (>5 years)
5. Donepezil 10mg po od (>5 years)
6. Memantine 20mg po od (3 years)
7. Paracetamol 1g po tds (1 year)
8. Naproxen 500mg po od (1 year)
9. Esomeprazole 40mg po od (1 year)
10. Lactulose 15mls po tds (1 year)
11. Fresubin 5 kcal (energy + protein + fat) nutritional supplement od (1 year) (patient refuses regularly)
12. Fresubin 2 kcal (energy + protein + fat) nutritional supplement od (1 year) (patient refuses regularly)

Social History:
Cognition: MMSE untestable
Function: Bed bound
 Hoist transfer
 Faecal incontinence
 No behavioural problems

Speech: Verbalises but cannot express needs or wishes

Case 7

Age: 75
Sex: female
Current location: Oncology outpatients
Usual location: Living at home with sister

Medical History:

1. Ulcerative colitis (colostomy in situ for 30 years)
2. HTN
3. Dyslipidaemia
4. Osteoarthritis
5. Diabetes Mellitus
6. Angiosarcoma - stage 4 – diagnosed 2015
 - Unresponsive to treatment
 - Bony metastases
 - Prognosis per oncologist 6 months
7. Anaemia

Medications:

No problems with medication adherence

1. Gliclazide 60mg po od (>5 years)
2. Atorvastatin 40mg po od (>5 years)
3. Morphine sulphate 10mg po od (3 months)
4. Lercandipine 10mg po od (>5 years)
5. Diclofenac 50mg po bd (4 months)
6. Alendronate 70mg po once a week (1 year)
7. Calcium carbonate 500mg po bd (1 year)
8. Cholecalciferol 400IU po bd (1 year)

Social History:

Cognition: MMSE 28/30

Function: Huge deterioration in function in the last 2 months
 Walks with rollator from bed to bathroom with assistance of 1
 Fully dependent in all ADLs

Speech: No issues

Case 8

Age: 80
Sex: female
Current location: Geriatric Outpatients
Usual location: Living independently

Medical History:

1. Congestive heart failure (NYHA II)
2. Anaemia (Hb 12)
3. Dyslipidaemia
4. Asthma

Medications:

No problems with medication adherence

1. Aspirin 75mg po od (3 years)
2. Perindopril 10mg po od (3 years)
3. Spironolactone 25mg po od (3 years)
4. Bisoprolol 10mg po od (3 years)
5. Ferrous fumarate 305mg po od (6 months)
6. Atorvastatin 10mg po od (3 years)
7. Salbutamol inhaler two puffs prn (> 5 years)
8. Symbicort (budesonide/formeterol) 400/12mcg inhaled bd (> 5 years)
9. Centrum multivitamin po od (1 year)
10. Bumetanide 1mg po bd (1 year)

Social History:

Cognition: MMSE 28/30

Function: Independent of all activities of daily living.

Speech: No issues

Case 9

Age: 82
Sex: female
Current location: Acute hospital due to recent seizure activity
Usual location: Nursing home resident

Medical History:

1. Dementia 2010
2. Recurrent UTIs
3. Seizures secondary to dementia
4. HTN
5. GORD
6. B12 deficiency (current B12 > 1500)

Medications: Some problems with medication adherence (see each medication)

1. Donepezil 10mg po od (>5 years)
2. Memantine 20mg po od (3 years)
3. Trimethoprim 100mg po od (2 years)
4. Levetiracetam 500mg po bd (2 years)
5. Bisoprolol 10mg po od (>5 years)
6. Perindopril 5mg po od (>5 years)
7. Ranitidine 150mg po bd (>5 years)
8. Hydroxycobalamin 1mg IM 3 monthly (2 years)
9. Fortisip (energy + protein + fat) nutritional supplement 1 carton od (patient refuses frequently) (2 years)

Social History:
Cognition: MMSE untestable
Function: Bed bound
 Hoist transfer
 Dependent in all ADLs
 No behavioural problems

Speech: mute

Case 10

Age: 74
Sex: male
Current location: Oncology outpatients
Usual location: Home with wife

Medical History:

1. BPH (no catheter)
2. Ischaemic heart disease (previous MI and CABG)
3. Heart failure
4. COAD
5. Lung cancer - stage 4, bony metastases
6. Dyslipidaemia
7. Atrial fibrillation
8. Constipation
9. Chronic kidney disease

Medications: Some problems with medication adherence (see each medication)

1. Aspirin 75mg po od (>5 years)
2. Bisoprolol 10mg po od (>5 years)
3. Dutasteride 0.5mg po od (>5 years)
4. Tamsulosin 0.4mg po od (>5 years)
5. Rosuvastatin 40mg po od (>5 years)
6. Ultibro (Indacaterol/glycopyrronium bromide) 85/43mcg inhaled od (>5 years) (difficulty using)
7. Combivent (ipratropium bromide/salbutamol) 500mcg/2.5mg nebulised qds (6 months)
8. Denosumab 120mg sc 4 weekly (6 months)
9. Movicol (macrogol) 1 sachet bd (6 months)
10. Fresubin 5 kcal (energy + protein + fat) nutritional supplement od (6 months)
11. Fresubin 2 kcal (energy + protein + fat) nutritional supplement od (6 months)
12. Quinine sulphate 300mg po od (>5 years)

Social History:
Cognition: MMSE 29/30
Function: Increasing frailty over the last 3 months
 Walks short distance with assistance of 2 indoors
 Dependent in all ADLs, wheelchair dependent outside home

Case 11

Age: 76
Sex: male
Current location: Acute hospital with aspiration pneumonia
Usual location: Nursing home resident

Medical History:

1. Stroke: TACS 2014
2. Post stroke depression
3. Atrial fibrillation
4. PE post stroke
5. Recurrent aspiration pneumonia (increasing frequency over the last 6 months)
6. PEG fed
7. HTN

Medications:

No problems with medication adherence

1. Escitalopram 10mg po od (2 years)
2. Ramipril 10mg po od (2 years)
3. Apixaban 5mg po bd (2 years)
4. Atorvastatin 10mg po od (>5 years)
5. Doxazosin 4mg po od (>5 years)
6. Lansoprazole 30mg po od (2 years)
7. Quetiapine 25mg po nocte (4 months)
8. Centrum B-complex multivitamin po od (2 years)

Social History:
Cognition: MMSE untestable (global aphasia) – no concerns regarding this
Function: Bed bound, Hoist transfer
Fully dependent in all ADLs
Poor sleep

Speech: Global aphasia
Behaviour: No behaviour problems

Case 12

Age: 80
Sex: female
Current location: Geriatric outpatients for review of anxiety
Usual location: Nursing home resident (moved in 4 weeks ago)

Medical History:

1. Recurrent cellulitis
 - Started prophylactic antibiotics 1 year ago
 - Three episodes per year pre and post antibiotics
2. Anxiety (new diagnosis)
3. Osteoarthritis
4. Constipation
5. Hypothyroidism
6. COAD stage 4 (on home oxygen)
 - Recurrent exacerbations
 - 4 hospital admission in the last 6 months

Medications:

No problems with medication adherence

1. Calvepen (penicillin V) 500mg po bd (1 year)
2. Paracetamol 1g po tds (1 year)
3. Diclofenac 50mg po bd (4 months)
4. Lactulose 10ml po tds (1 year)
5. Senna two tablets od (1 year)
6. Levothyroxine 75mcg po od (2 years)
7. Combivent (ipratropium bromide/salbutamol) 500mcg/2.5mg nebuliser qds (3 years)
8. Betahistidine 16mg po tds (1 year)
9. Folic acid 5mg po od (2 years)

Social History:
Cognition: MMSE 27/30
Function: Assistance of two to stand, restricted by SOB
Fully dependent of ADLs

Speech: No problems
Behaviour: No behaviour problems

Case 13

Age: 78
Sex: female
Current location: GP review for depression
Usual location: Nursing home resident

Medical History:

1. HTN
2. Osteoarthritis
3. Osteoporosis: hip fracture 2013)

Medications:

- No problems with medication adherence
1. Aspirin 75mg po od (>5 years)
 2. Bisoprolol 2.5mg po od (>5 years)
 3. Alendronate 70mg po once a week (3 years)
 4. Paracetamol 1g po tds (3 years)
 5. Calcium carbonate 500mg po bd (3 years)
 6. Cholecalciferol 400IU po bd (3 years)
 7. Diclofenac 75mg as required (3 months)

Social History:

Cognition: MMSE 30/30
Function: Independent of all ADLS, walks with one stick
Moved into the nursing home due to social isolation
Speech: No problems
Behaviour: No behaviour problems

Case 14

Age: 77
Sex: female
Current location: GP review in nursing to assess for a DNAR order
Usual location: Nursing home resident

Medical History:

1. Rheumatoid arthritis (burnt out disease)
2. Osteoarthritis
3. Diabetes Mellitus diagnosed 2012
4. Dementia
5. Constipation
6. GORD
7. Urinary incontinence (24 hour pads for the last year, no awareness)

Medications:

- No problems with medication adherence
1. Prednisolone 5mg po od (2 years)
 2. Paracetamol 1g po tds (>5 years)
 3. Metformin 500mg po tds (4 years)
 4. Gliclazide 60mg po od (4 years)
 5. Valsartan 80mg po od (4 years)
 6. Solifenacin 5mg po od (>5 years)
 7. Esomeprazole 20mg po od (>5 years)
 8. Movicol (macrogol) one sachet bd (1 year)
 9. Fortisip (energy + protein + fat) nutritional supplement one carton od (1 year)
 10. Centrum multivitamin one tablet od (1 year)
 11. Denosumab 60 mg sc 6-monthly (2 years)

Social History:

Cognition: MMSE 24/30
Function: Bed bound and hoist transfer due to RA
Totally dependent for all ADLS
Speech: No problems
Behaviour: No behaviour problems

Case 15

Age: 90
Sex: male
Current location: Acute hospital with urosepsis
Usual location: Nursing home resident

Medical History:

1. Dementia 2007
2. BPH – long term catheter in situ
3. Recurrent UTIs

Medications:

- No problems with medication adherence
1. Donepezil 10mg po od (>5 years)
 2. Memantine 20mg po od (4 years)
 3. Tamsulosin 400mcg po od (>5 years)
 4. Trimethoprim 100mg po od (2 years)
 5. Fortisip (energy + protein + fat) nutritional supplement one carton od (2 years)

Social History:

Cognition: MMSE untestable
Function: Bed bound and hoist transfer
 Totally dependent for all ADLs
Speech: Mute
Behaviour: No behaviour problems

Case 16

Age: 79
Sex: female
Current location: Acute hospital with superior vena cava obstruction (prognosis 30 days)
Usual location: Living in own home with family

Medical History:

1. Breast cancer - stage 4 (brain and bone metastasis) diagnosed 2015
2. PE
3. Subclinical hypothyroidism
4. Depression
5. Constipation
6. Dyslipidaemia
7. Low BMI
8. Recurrent UTIs
9. GORD

Medications:

- No problems with medication adherence
1. Capecitabine 500mg po tds (1 year)
 2. Tinzaparin 10,000IU sc od (1 day)
 3. Levothyroxine 25mcg po od (1 year)
 4. Escitalopram 10mg po od (1 year)
 5. Senna two tablets nocte (1 year)
 6. Atorvastatin 10mg po od (>5 years)
 7. Trimethoprim 100mg po od (1 year)
 8. Lansoprazole 15mg po od (>5 years)
 9. Fortisip (energy + protein + fat) nutritional supplement one carton po od (1 year)

Social History:

Cognition: MMSE 29/30
Function: Independent up until one month ago.
 Rapid deterioration since
 Currently dependent for all ADLs
 Assistance of two to stand up, can only walk one or two steps
Speech: No problems

Case 17

Age: 67
Sex: male
Current location: Acute hospital with pneumonia
Usual location: Living in own home with family

Medical History:

1. Motor neuron disease diagnosed 6 months earlier (rapid deterioration)
 - RIG (radiological insertion gastrostomy) in situ x 3 months
2. HTN
3. GORD
4. Dyslipidaemia

Medications:

No problems with medication adherence
1. Lansoprazole 15mg po od (>5 years)
2. Amlodipine 10mg po od (>5 years)
3. Rosuvastatin 10mg po od (>5 years)

Social History:**Cognition:****Function:**

MMSE untestable
Bed bound
Hoist transfer
Dependent for all ADLs

Speech:

Unable to communicate secondary to motor dysfunction

Case 18

Age: 77
Sex: male
Current location: Acute hospital with pneumonia
Usual location: Nursing home resident

Medical History:

1. Lung cancer (stage 4) (on home oxygen) diagnosed 2015
2. COAD (GOLD stage 4) (on home oxygen)
3. BPH
4. Dyslipidaemia
5. GORD
6. Depression
7. Diverticular disease

Medications:

No problems with medication adherence
1. Montelukast 10mg po od (>5 years)
2. Seretide (fluticasone/salmeterol) 500mcg mcg inhaled bd (>5 years)
3. Ventolin (salbutamol) inh prn (>5 years)
4. Aspirin 75mg po od (>5 years)
5. Dutasteride 0.5mg po od (>5 years)
6. Tamsulosin 0.4mg po od (>5 years)
7. Rosuvastatin 10mg po od (>5 years)
8. Esomeprazole 20mg po od (>5 years)
9. Escitalopram 10mg po od (1 year)
10. Fresubin 2Kcal (energy + protein + fat) nutritional supplement od (1 year)
11. Fresubin 5kcal (energy + protein + fat) nutritional supplement od (1 year)

Social History:**Cognition:****Function:**

MMSE 28/30
Assistance of two to stand
Unable to walk
Wheelchair dependent
Dependent for all ADLs

Speech:

No problems

Case 19

Age: 81
Sex: female
Current location: Geriatric outpatient for pharmacology review
Usual location: Nursing home resident

Medical History:

1. Dementia diagnosed 2009
2. Osteoporosis
3. Dyslipidaemia
4. Urinary incontinence

Medications: Some problems with medication adherence (see each medication)

1. Rivastigmine patch 9.5mg transdermal over 24 hours (>5 years)
2. Calcium carbonate 500mg po bd (>5 years) (difficulty taking)
3. Cholecalciferol 400IU po bd (>5 years) (difficulty taking)
4. Evista (raloxifene) (>5 years) 60mg po od (>5 years) (difficulty taking)
5. Rosuvastatin 10mg po od (>5 years) (difficulty taking)
6. Fortisip compact (energy + protein + fat) nutritional supplement one carton po od (1 year) (refuses regularly)
7. Quetiapine 50mg po od (1 year) (uses syrup preparation, no difficulty taking)

Social History:

Cognition: MMSE 12/30

Function: Assistance of two to stand
 Unable to walk
 Wheelchair dependent
 Dependent for all ADLs

Speech: No problems

Behaviour: No problems

Case 20

Age: 70
Sex: male
Current location: Acute hospital with pneumonia
Usual location: Nursing home resident

Medical History:

1. Osteoarthritis
2. Osteoporosis
3. Chronic lower back pain
4. Benign essential tremor
5. Gastritis 2010 (while on oral nsaids)
6. Peripheral vascular disease - Above knee right leg amputation
7. IHD - MI 2 months ago
8. Stroke disease
9. Carotid artery disease
10. HTN
11. CCF (NYHA 4)
12. Anxiety
13. Smoker

Medications: No problems with medication adherence

1. Aspirin 75mg po od (>5 years)
2. Atorvastatin 10mg po od (>5 years)
3. Perindopril 10mg po od (>5 years)
4. Eplerenone 25mg po od (>5 years)
5. Lansoprazole 30mg po od (>5 years)
6. Paracetamol 1g po tds (>5 years)
7. Buprenorphine patch 10micograms/hr (2 years)
8. Risedronate 35mg per week (4 years)
9. Calcium carbonate 500mg po bd (4 years)
10. Cholecalciferol 400IU po bd (4 years)
11. Sinemet (Levodopa / carbidopa) 125mg bd (1 year)
12. Flurazepam 30mg po nocte (1 year)

Social History:

Cognition: MMSE 28/30

Function: Hoist, wheelchair dependent, Dependent for all ADLs

Appendix 13 - Twenty answer sheets for assessment of STOPPFrail IRR

Case 1

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
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If yes, review the drug list and assess STOPPFrail criteria:

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Calcium carbonate 400mf po bd		
Cholecalciferol 400IU po bb		
Atorvastatin 40mg po od		
Lansoprazole 30mg po od		
Senna one tablet po od		
Folic acid 5mg po od		
Lercandipine 10mf po od		
Valsartan 40mg po od		
Paracetamol 1g po tds		
Alprazolam 250mcg po od		

Case 2

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria:

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Levetiracetam 250mg po bd		
Fluvastatin 20mg po od		
Lactulose 15ml po tds		
Digoxin 125mcg po od		
Fresublin 5kcal one carton od		
Trimethoprim 100mg po od		
Tamsulosin 400mcg po od		

Case 3

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria:

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Escitalopram 10mg po od		
Esomeprazole 20mg po od		
Rosuvastatin 20mg po od		
Movicol one sachet po bd		
Rivastigmine patch 9.5mg od		
Gliclazide 60mg po od		
Metformin 500mg po bd		
Sitagliptin 50mg po od		

Case 4

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
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If yes, review the drug list and assess STOPPFrail criteria:

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Ferrous fumarate 305mg po od		
Warfarin as per INR		
Furosemide 40mg po bd		
Ramipril 5mg po od		
Rosuvastatin 10mg po od		
Diazepam 5mg po nocte		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		
Seretide (fluticasone/salmeterol)		
Theophylline 200mg po od		
Centrum multivitamin od		
Fortisip one carton od		

Case 5

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Betahistidine 16mg po tds		
Stalevo(levodopa/carbidopa/entacapone) 150mg/37.5mg/200mg po qds		
Doxazosin 400mg po od		
Amlodipine 10mg po od		
Metformin 500mg po tds		
Gliclazide 90mg po od		
Sitagliptin 50mg po bd		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		
Pravastatin 10mg po od		
Aspirin 75mg po od		

Case 6

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Dutasteride 0.5mg po od		
Tamsulosin 0.4mg po od		
Ramipril 10mg po od		
Amlodipine 10mg po od		
Donepezil 10mg po od		
Memantine 20mg po od		
Paracetamol 1g po tds		
Naproxen 500mg po od		
Esomeprazole 40mg po od		
Lactulose 15mls po tds		
Fresubin 5 kcal od		
Fresubin 2Kcal od		

Case 7

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Gliclazide 60mg po od		
Atorvastatin 40mg po od		
Morphine sulphate 10mg po od		
Lercandipine 10mg po od		
Diclofenac 50mg po bd		
Alendronate 70mg po once a week		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		

Case 8

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Aspirin 75mg po od		
Perindopril 10mg po od		
Spironolactone 25mg po od		
Bisoprolol 10mg po od		
Ferrous fumarate 305mg po od		
Atorvastatin 10mg po od		
Salbutamol inhaler two puffs prn		
Symbicort (budesonide/formeterol) inh bd		
Centrum multivitamin po od		
Bumetanide 1mg po bd		

Case 9

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Donepezil 10mg po od		
Memantine 20mg po od		
Trimethoprim 100mg po od		
Levetiracetam 500mg po bd		
Bisoprolol 10mg po od		
Perindopril 5mg po od		
Ranitidine 150mg po bd		
Hydroxycobalamin 1mg IM 3 monthly		
Fortisip 1 carton od		

Case 10

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Aspirin 75mg po od		
Bisoprolol 10mg po od		
Dutasteride 0.5mg po od		
Tamsulosin 0.4mg po od		
Rosuvastatin 40mg po od		
Ultibro (Indacaterol/glycopyrronium bromide) inh od		
Combivent (ipratropium bromide/salbutamol) nebs inh qds		
Denosumab 120mg sc 4 weekly		
Movicol (macrogol) 1 bd		
Fresubin 5kcal od		
Fresubin 2kcal od		
Quinine sulphate 300mg po od		

Case 11

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Escitalopram 10mg po od		
Ramipril 10mg po od		
Apixaban 5mg po bd		
Atorvastatin 10mg po od		
Doxazosin 4mg po od		
Lansoprazole 30mg po od		
Quetiapine 25mg po nocte		
Centrum multivitamin po od		

Case 12

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Calvopen (penicillin V) 500mg po bd		
Paracetamol 1g po tds		
Diclofenac 50mg po bd		
Lactulose 10ml po tds		
Senna two tablets od		
Levothyroxine 75mcg po od		
Combivent (ipratropium bromide/salbutamol) nebuliser qds		
Betahistidine 16mg po tds		
Folic acid 5mg po od		

Case 13

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Aspirin 75mg po od		
Bisoprolol 2.5mg po od		
Alendronate 70mg po once a week		
Paracetamol 1g po tds		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		
Diclofenac 75mg as required		

Case 14

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Prednisolone 5mg po od		
Paracetamol 1g po tds		
Metformin 500mg po tds		
Gliclazide 60mg po od		
Valsartan 80mg po od		
Solifenacin 5mg po od		
Esomeprazole 20mg po od		
Movicol (macrogol) one sachet bd		
Fortisip one carton od		
Centrum multivitamin od		
Denosumab 60mg sc 6 monthly		

Case 15

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Donepezil 10mg po od		
Memantine 20mg po od		
Tamsulosin 400mcg po od		
Trimethoprim 100mg po od		
Fortisip one carton od		

Case 16

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Cepcitabine 500mg po tds		
Tinzaparin 10000IU sc od		
Levothyroxine 25mcg po od		
Escitalopram 10mg po od		
Senna two tablets nocte		
Atorvastatin 10mg po od		
Trimethoprim 100mg po od		
Lansoprazole 15mg po od		
Fortisip one carton po od		

Case 17

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Lansoprazole 15mg po od		
Amlodipine 10mg po od		
Rosuvastatin 10mg po od		

Case 18

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Montelukast 10mg po od		
Seretide (fluticasone/salmeterol) inh bd		
Ventolin (salbutamol) inh prn		
Aspirin 75mg po od		
Dutasteride 0.5mg po od		
Tamsulosin 0.4mg po od		
Rosuvastatin 10mg po od		
Esomeprazole 20mg po od		
Escitalopram 10mg po od		
Fresubin 2Kcal od		
Fresubin 5kcal od		

Case 19

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Rivastigmine patch 9.5mg transdermal over 24 hours		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		
Evista (raloxifene) 60mg po od		
Rosuvastatin 10mg po od		
Fortisip compact one carton po od		
Quetiapine 50mg po od		

Case 20

Does the patient meet the criteria for STOPPFrail to be applicable?

Criteria to meet:

End stage irreversible pathology	
Poor one year survival prognosis	
Severe functional impairment OR severe cognitive impairment OR both	
Symptom control is the priority rather than prevention of disease progression	

Yes		No	
-----	--	----	--

If yes, review the drug list and assess STOPPFrail criteria

Drug	Tick if this drug meets any STOPPFrail criteria AND you would stop it.	List STOPPFrail indicators relevant to this drug
Aspirin 75mg po od		
Atorvastatin 10mg po od		
Perindopril 10mg po od		
Eplerenone 25mg po od		
Lansoprazole 30mg po od		
Paracetamol 1g po tds		
Buprenorphine patch 10mcg/hr		
Risedronate 35mg per week		
Calcium carbonate 400mg po bd		
Cholecalciferol 400IU po bd		
Sinemet (Levodopa/carbidopa) 125mg bd		
Flurazepam 30mg po nocte		

Appendix 14 - Common Summary Assessment Report (CSAR)

COMMON SUMMARY ASSESSMENT REPORT

Please complete all sections clearly in block capitals. Read guidance notes before completing

I confirm that the assessment process and purpose has been explained to me. I consent that information may be shared as appropriate by relevant health and social care professionals in the processing of this application.

Signature _____ Applicant/Specified Person Date _____
(Date as appropriate)

1. SOURCE OF REFERRAL (PLEASE TICK):

Community Hospital ☐ Acute Hospital ☐ GP ☐
Mental Health ☐ Community ☐ Nursing Home ☐
Name of Referring Location: _____ Date of Referral: _____

2. PERSONAL DETAILS:

First Name: _____ Surname(s): _____ Preferred Name: _____
Current Address: _____ Home/Past Address (if relevant): _____ Tel No(s): _____
_____ Date of Birth (DD/MM/YYYY) _____
Medical Card No: _____ Hospital Number: _____
PPS No.: _____

3. PERSONAL CIRCUMSTANCES:

Marital Status: ☐ Single ☐ Married ☐ Widowed ☐ Separated ☐ Divorced ☐ Other
Living Circumstance: ☐ Alone ☐ With Spouse ☐ With partner ☐ With family ☐ With carer ☐ With Other
Describe Housing situation (See guidance document): _____
Who is the Principal Carer: _____
What level of support do they provide?
(Please include contact details): _____
Assessment of Carer's needs completed? Yes ☐ No ☐ (Please attach if available)
Identify any family members, neighbours, friends who provide support: _____
Contact Person/Specified Person/Care Rep: _____ Relationship to applicant?
(Contact details: address/phone/mobile): _____
GP: _____ Contact Details: _____
PHN &/or CMHN: _____ Contact Details Health Centre: _____

4. ALL APPLICANTS have the right to self-determination and capacity to do so is assumed unless otherwise proven.
His/her preference to stay at home or to be admitted to residential long-term care must be sought and recorded.

Has the person's above preference been discussed with him/her? Yes ☐ No ☐
If YES - brief outline of outcome

If No - Provide a reason and identify with whom it has been discussed & outline outcome

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____
(PRINT)

CSAR Applicant's Name _____ DOB: _____

5. RECORD OF CURRENT COMMUNITY/HOME SUPPORT SERVICES
(See Guidance Document before completing):

SERVICE (Tick)	Home Help/Support ☐	Day Care ☐	Respite ☐	Meals Supply ☐	Laundry ☐	Aids and Appliances ☐
Hours/Times p/w or relevant time or if refused services						
SERVICE (Tick)	PHN/CMHN ☐	Family support/ Private Carer ☐	Therapy or other discipline ☐	Day Hospital ☐	Services Refused ☐	
Hours/Times p/w or relevant time or if refused services						

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____
(PRINT)

6(a). CURRENT DIAGNOSIS AND MEDICAL SUMMARY:
(Please include only relevant conditions)

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____
(PRINT)

6(b). DETAILS OF THE PERSON'S MENTAL HEALTH STATUS:
(Please attach any supporting documentation, if available)

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____
(PRINT)

7. CURRENT MEDICATIONS (See Guidance Notes - Not for Purpose of Dispensing)

Name of Drug	Dosage	Frequency	Name of Drug	Dosage	Frequency

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____
(PRINT)

CSAR Applicant's Name _____ DOB _____

8: ASSESSMENTS

8 (A): BARTHEL INDEX

Please insert Date(s) Undertaken

WEIGHTING SCORE	3	2	1	0	SCORE	SCORE
Bowel (Feeding week)	Continued	Continued	Continued	Continued (If needs no more)		
Bladder (Feeding 24-48 hours)	Continued	Continued	Continued	Continued (If continues to be able to manage)		
Grooming				Needs Help		
Toilet Use	Independent	Needs Some Help	Dependent			
Feeding	Independent	Needs Some Help	Unable			
Transfer (from bed to chair & back)	Independent	Minimal Help Needed	Major Help (1-2 persons) Needed	Unable (No other help)		
Mobility	Independent	Needs with help of 1 person	Wheelchair Independent	Incappable		
Dressing	Independent (Dresses, age and hair)	Needs Help (Can do half needed)	Dependent			
Stairs	Independent (Up & down most carry walking aid)	Needs Help (Verbal or physical/carrying of aid)	Unable			
Bathing		Independent (Sitting in & out needed & wash self)	Dependent			
Findings	Independent (20)	Low Dependency (14-19)	Medium Dependency (11-15)	High Dependency (8-10)	Maximum Dependency (1-7)	TOTAL

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____

8 (B): COMMUNICATION

	Tick	Date	Signature
No problems	☐		
Retains most information and can indicate needs verbally	☐		
Difficulty speaking but retains information and indicates needs non-verbally	☐		
Can speak but cannot indicate needs or retain information	☐		
No effective means of communication	☐		

8 (C): COGNITIVE SCREENING REPORT - BY DATE ORDER IF MORE THEN ONE AVAILABLE

Cognitive Assessment (Specify Screening Tool)	Date	Result	Signature	Date	Result	Signature

8 (D): OTHER ASSESSMENTS (Specify Tool Used)

	Result	Date	Signature
Pressure Sore Risk			
Falls Risk			
Nutritional Risk			
Wandering Risk			
Other - Specify			

8 (E): OTHER SIGNIFICANT MEDICAL/SOCIAL/ RISK FACTORS THAT SHOULD BE CONSIDERED AS PART OF THE CARE NEEDS ASSESSMENT:

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____

CSAR Applicant's Name _____ DOB _____

9: ADDITIONAL COMMENTS e.g. Employment, Recreational or Social Needs (Attach supporting documentation):

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____

10(a). HEALTH PROFESSIONAL REPORTS.

(Please attach if relevant. Tick to indicate a report is appended)

Nursing ☐ Dietician ☐ Occupational Therapy ☐ Speech and Language ☐ Other ☐
 Physiotherapy ☐ Psychology ☐ Podiatry ☐ Social Work ☐

10(b). SPECIALIST ASSESSMENT

(Best practice recommends that all older people should have a Consultant Geriatrician/Old Age Psychiatry assessment prior to a decision being made about their future care needs.)

Specialist	Completed	Date	Signature
Geriatric Medicine	☐		
Old Age Psychiatry	☐		
Rehabilitation Consultant	☐		
Neurologist	☐		
Other (Specify)	☐		

Specialist Comment: (Or append report)

Completed by: NAME: _____ Role: _____ Date: _____ Signature: _____

11. RECOMMENDATION BY MDT. For Completion by MDT. See Guidance Notes

It is the recommendation of this MDT that this person's overall care needs are currently best met within a Long Term Residential Care Setting (Please Tick):

Yes ☐ No ☐

Confirmation of MDT's Recommendation	Confirmation of MDT's Recommendation
Name: _____	Name: _____
Role: _____	Role: _____
Signature: _____	Signature: _____

Name & Signature of Professional Co-ordinating completion of this CSAR Form

NAME: _____ Role: _____ Date: _____ Signature: _____

12. LPF DETERMINATION OF CARE NEEDS FOR COMPLETION BY LPF ONLY

It is the determination of this LPF that this person's overall care needs are currently best met by:

(Please Tick)

Long Term Residential Care Setting ☐
 Sheltered Housing ☐
 Other (Specify) ☐
 At Home with Community Supports ☐

Likelihood of change in personal circumstances Low Risk ☐ Medium Risk ☐ High Risk ☐

Confirmation of LPF's Determination	Confirmation of LPF's Determination	Confirmation of LPF's Determination
Name: _____	Name: _____	Name: _____
Role: _____	Role: _____	Role: _____
Signature: _____	Signature: _____	Signature: _____

IF LONG TERM CARE IS NOT DETERMINED TO BE APPROPRIATE THE FOLLOWING SERVICE(S) ARE RECOMMENDED BY LPF

Service Recommended	Home Help/Support	Day Care	Respite	Meals Supply	Laundry	Aids/ Appliances
PHN/CMIN	☐	☐	☐	☐	☐	☐
Therapy or other discipline	☐	☐	☐	☐	☐	☐
Day Hospital	☐	☐	☐	☐	☐	☐
Other (Specify)	☐	☐	☐	☐	☐	☐

Comment(s)

Appendix 15 - Montreal Cognitive Assessment (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA) Version 7.1 Original Version						NAME : Education : Sex :	Date of birth : DATE :																				
VISUOSPATIAL / EXECUTIVE						Copy cube		Draw CLOCK (Ten past eleven) (3 points)	POINTS																		
						[] []		[] [] []	___/5																		
NAMING								___/3																			
MEMORY						Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial						2nd trial						No points
	FACE	VELVET	CHURCH	DAISY	RED																						
1st trial																											
2nd trial																											
ATTENTION						Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [] 2 1 8 5 4 Subject has to repeat them in the backward order [] 7 4 2		___/2																			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [] FBACMNAAJKLBAFAKDEAAAJAMOFAB						___/1																					
Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt						___/3																					
LANGUAGE						Repeat : I only know that John is the one to help today. [] The cat always hid under the couch when dogs were in the room. []		___/2																			
Fluency / Name maximum number of words in one minute that begin with the letter F [] _____ (N ≥ 11 words)						___/1																					
ABSTRACTION						Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler		___/2																			
DELAYED RECALL						<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Has to recall words</td> <td>FACE</td> <td>VELVET</td> <td>CHURCH</td> <td>DAISY</td> <td>RED</td> </tr> <tr> <td>WITH NO CUE</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> <td>[]</td> </tr> </table>		Has to recall words	FACE	VELVET	CHURCH	DAISY	RED	WITH NO CUE	[]	[]	[]	[]	[]	___/5							
Has to recall words	FACE	VELVET	CHURCH	DAISY	RED																						
WITH NO CUE	[]	[]	[]	[]	[]																						
Optional						<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td>Category cue</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Multiple choice cue</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		Category cue						Multiple choice cue						Points for UNCUED recall only							
Category cue																											
Multiple choice cue																											
ORIENTATION						[] Date [] Month [] Year [] Day [] Place [] City		___/6																			
© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30						TOTAL		___/30																			
Administered by: _____						Add 1 point if ≤ 12 yr edu																					

Appendix 16 - Ethical approval for STOPPFrail observational study



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.

6th July 2015

Our ref: ECM 4 (mmm) 07/07/15

Dr Denis O'Mahony
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: STOPP frail criteria: application in a long term nursing care cohort.

Dear Dr O'Mahony

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

- > Public Community Nursing Units
- > Community Hospitals in the Kerry/Cork.

The following documents have been approved:

- > Protocol Submission Form
- > Study Protocol
- > Patient Information
- > Data Collection Sheets
- > Consent Form
- > CV for Chief Investigator.

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

- > Dr Paul Gallagher, Consultant Geriatrician
- > Dr Amanda Lavan, Specialist Registrar in Geriatrician Medicine.

Yours sincerely

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



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.

12th February 2016

Our ref: ECM 4 (mmm) 07/07/15 & ECM 3 (ooo) 01/03/16

Dr Denis O'Mahony
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: STOPP frail criteria: application in a long term nursing care cohort.

Dear Dr O'Mahony

I acknowledge receipt of an amendment application for the above study dated 4th February (received 10th February 2016). Please forward the following documents in order for us to review the application:

- > Revised Amendment Application Form: The form must be signed by Professor O'Mahony. There can only be one Chief Investigator on any study and the C.I. listed on file for this study is Professor O'Mahony.
- > Revised Study Protocol: All changes must be documented in a revised study protocol. The changes must be clearly highlighted and the protocol must have a new version and date.

The following documents have been approved:

- > Revised Data Collection Sheet
- > Survey for de-prescribing (for Patients and Families).

Yours sincerely

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





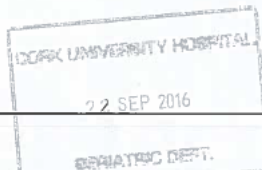
UCC

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 (mmm) 07/07/15 & ECM 3 (x) 11/10/16

19th September 2016

Dr Paul Gallagher
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: STOPP frail criteria: application in a long term nursing care cohort.

Dear Dr Gallagher

I acknowledge receipt of your amendment dated 13th September 2016.

Please note that we cannot approve this amendment until we receive the documents required to approve your previous amendment dated 4th February 2016. Also, Dr Denis O'Mahony is listed as the Chief Investigator in this study and all amendments would have to be signed by Dr O'Mahony. Study documents that change due to any study amendment must be submitted with the amendment application. The changes must be tracked and the documents must contain a new version and date.

Yours sincerely

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



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 (mmm) 07/07/15 & ECM 3 (nnnn) 15/11/16

9th November 2016

Dr Denis O'Mahony
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: STOPP frail criteria: application in a long term nursing care cohort.

Dear Dr O'Mahony

The Chairman approved the following:

- > Amendment Application Form signed 26th October 2016
- > Study Protocol Version 2 dated 26th October 2016
- > Amendment Application Form signed 26th October 2016
- > Study Protocol Version 3 dated 26th October 2016
- > Common Summary Assessment Report Form.

Full approval is now granted to implement Amendments 2 and 3.

Yours sincerely

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

