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Deprescribing long-term medications in frail older people approaching end-of-life

Volume 1 of 1

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October 2019

Dedicated to my wife, Sara

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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.

Signed: ______________________

Date: ________________________

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ACHI	Australian Classification of Health Interventions
ACS	Australian Coding Standards
ADE	Adverse Drug Event
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
ARB	Angiotensin Receptor Blocker
BBB	Blood Brain Barrier
BISEP	Burden of Illness Score for Elderly Persons
BPSD	Behavioural and Psychological Symptoms of Dementia
CCI	Charlson Co-morbidity Index
CFS	Clinical Frailty Scale
CI	Confidence Interval
CKD	Chronic Kidney Disease
Df	Degrees of freedom
DRS	Diagnostic Risk Score
Eavg	Average absolute difference in predicted and calibrated probabilities
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
Emax	Maximum absolute difference in predicted and calibrated probabilities
FI	Frailty Index
FP	Frailty Phenotype
GP	General Practitioner
HELP	Hospitalized Elderly Longitudinal Project

HIV	Human Immunodeficiency Virus
HOMR	Hospital patient One-year Mortality Risk
HYVET	Hypertension in the Very Elderly Trial
ICU	Intensive Care Unit
iQR	Interquartile Range
LMWH	low Molecular Weight Heparin
LRT	Likelihood Ratio Test
MI	Myocardial Infarction
MMSE	Mini-Mental State Examination
MPI	Multidimensional Prognostic Index
NH	Nursing Home
NICE	National Institute of Clinical Excellence
NNT	Number Needed to Treat
NPV	Negative Predictive Value
PIM	Potentially Inappropriate Medication
PPV	Positive Predictive Value
PRN	Pro ne rata
QALY	Quality Adjusted Life Year
QOL	Quality Of Life
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SAFES	Sujet Agé Fragile—Evaluation et Suivi
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulator
SPRINT	Systolic Blood Pressure Intervention Trial

SQ	Surprise Question
STOPP	Screening Tool of Older Peoples Prescriptions
STOPPFrail	Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy
TTB	Time To Benefit
TTH	Time To Harm
UTI	Urinary Tract Infection

List of Statistical Symbols

c	concordance statistic
CI	Confidence interval
Df	Degrees of freedom
Eavg	average absolute difference in predicted and calibrated probabilities
Emax	maximum absolute difference in predicted and calibrated probabilities
p	probability value

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THESIS OVERVIEW

One of the great successes of modern medicine is that it has transformed relatively acute causes of death (i.e. cardiovascular disease, organ failure and some cancers) into chronic diseases. In the developed world, most people will now grow old and, over decades, accumulate various chronic diseases before eventually succumbing to a final illness. Older people in their final years are commonly prescribed multiple medications to manage their chronic diseases. These medications may ameliorate symptoms, prevent future adverse health events and extend life. However, the use of multiple medications is also associated with higher risks of side-effects, adverse drug-interactions, and adherence problems. Furthermore, as older people become increasingly frail, the use of multiple medications may be considered burdensome for them or even futile. For frail older patients taking multiple medications, when does the scale shift from net benefit to net harm? If declining health and death are unavoidable, it follows logically that there must come a point when patients no longer benefit from certain chronic disease therapies.

This thesis primarily attempts to address two important questions. Firstly, how can we recognize when older people are approaching end-of-life? For such people, a personalized approach that prioritizes comfort and symptom relief is likely to be more appropriate than the pursuit of strict chronic disease targets. Secondly, when attempting to address a frailer older person’s complex and burdensome medication regimen, how do we separate essential medications from those that are dispensable?

The thesis consists of seven chapters. The first chapter is an introduction, divided into three sections: (i) what is deprescribing and why is it important? (ii) recognizing when older people are approaching end-of-life; (iii) operationalizing deprescribing for older people approaching end-of-life. Chapter 2 describes the application of a mortality prediction model, previously validated in North America, to a cohort of hospitalized older adults in Ireland. Chapter 3 examines the prevalence of potentially inappropriate prescribing in hospitalized older patients who are in the last year of life. Chapter 4 compares the performance of two structured deprescribing-decision tools using 100 standardized clinical cases. Chapter 5 examines the effect of applying a novel and recently validated deprescribing tool – STOPPFrail Criteria –to the medication regimens of frail, older, hospitalized patients who are undergoing transition to long-term nursing home care. A randomized controlled design is used to determine the impact of STOPPFrail on the number of prescribed medications, a variety of healthcare outcomes, quality of life and mortality. In chapter 6, applying information gathered from the previous chapters, a new version of STOPPFrail is developed and validated using modified Delphi methodology. Finally, in chapter 7, I discuss questions arising from these studies and suggest topics for future research.

The thesis is presented in the form of a Publication-based Thesis. The 'Methods' and 'Results' sections of chapters 2, 3, 4 and 5 are largely unchanged from how they are presented in respective peer-reviewed published papers; the 'Introduction' and 'Discussion' sections have been modified in certain instances to improve the coherence of the thesis. PDF versions of published articles and supplementary documents are presented in the appendices.

"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided. "

Paracelsus

CHAPTER 1

Introduction

1.1 WHAT IS DEPRESCRIBING AND WHY IS IT IMPORTANT?

1.1.1 **Definition:**

The term 'deprescribing' first appeared in the English literature in 2003.[1] Woodward, in an early review article, outlined the principals of deprescribing. These included:

i. reviewing all current medications,
ii. identifying medications to be discontinued, substituted or reduced
iii. planning a deprescribing regimen in partnership with the patient and
iv. frequently reviewing and supporting the patient. [1]

Since then, several new definitions have been proposed. [2-4] A 2015 systematic review of the literature by Reeve *et al.* was conducted to determine whether a standardized definition of deprescribing could be reached to inform future research on the subject.[5] The most common characteristics of the various definitions were used by the authors to develop a new definition:

"Deprescribing is the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."

1.1.2 **When is medication considered 'inappropriate'?**

It may be informative to firstly consider the concept of "appropriate" prescribing. Parish, in his influential paper, discussed this concept in the context of limited healthcare resources, and stated that prescribing is appropriate when it is safe, effective and economic.[6] Cribb and Barber later expanded on this framework and suggested that the appropriateness of prescribing could be evaluated by considering three overlapping domains:[7]

1. *The drug has the right technical properties* –broadly, this refers to the efficacy and safety of the medication. Can the drug fulfil its goal of benefitting the patient? Also, do the potential benefits of the drug outweigh the potential risks? Important considerations here include other prescribed drugs, co-morbidities and the prognosis of the patient.
2. *The drug aims to fulfil the goals of the patient* – Often the respective goals of the physician and patient easily align, for example, in the prescribing of analgesics for pain. Disease control (e.g. antihypertensive therapies) or preventive medications (e.g. anticoagulants) do not usually make the patient feel better and therefore it is important that the prescriber translates 'technical' goals into goals that are meaningful to the patient.[7] Shared-decision making is now widely advocated as the ideal model for treatment decision-making and failure to elicit and address patients' individual concerns contributes to treatment nonadherence.[8-10] Generally a patient wants to get better or remain well and this fact is the background against which prescribing decisions are made. When a patient is approaching end-of-life, achieving technical goals may be of limited or no benefit to the patient, and it is more appropriate to place greater emphasis on important patient-related goals (i.e. control of symptoms).
3. *The drug serves the general good* –the wider implications of prescribing decisions also need to be considered. There are social, biological and economic consequences of poor prescribing practices. A low threshold for prescribing medicines to treat depressive or anxiety symptoms may

medicalize aspects of normal life experience.[11] Indiscriminate prescribing of broad-spectrum antibiotics is a major contributor to the growing problem of bacterial resistance. Finally, healthcare resources are limited and there is an opportunity cost to interventions. The opportunity cost of prescribing an ineffective or unsafe medication can be measured by the health benefits (life years saved, quality adjusted life years [QALYs] gained) that could have been achieved had the money been spent on an alternative intervention or healthcare programme.[12]

Using this model, a medication could be considered *inappropriate* if it is not effective or safe, if it does not aim to fulfil the treatment goals of the patient, or if it does not serve 'the general good'. Ethical and practical judgement is of course necessary to weigh up competing considerations between these domains. For example, any expectation of efficacy or value for money depends on the patient adhering to the medication, and this is in itself, at least partly, contingent on the drug having meaningful value to the patient. Likewise, if a patient approaching end-of-life wishes to continue a medication (e.g. a benzodiazepine) despite concerns about safety, it may be considered inappropriate and potentially unethical to deprescribe the medication against the patient's wishes.[13]

1.1.3 Polypharmacy

Polypharmacy refers to the concurrent use of multiple medications by an individual. Various definitions are present in the literature but, most commonly, polypharmacy refers to the use of five or more daily medications.[14] In the United States, 39% of adults aged 65 years or older take 5 or more daily medications.[15] In

Europe, almost 25% of nursing home residents take 10 or more daily medications.[16]

Polypharmacy is strongly associated with multimorbidity (i.e. two or more chronic medical conditions in an individual[17]). The prevalence of multimorbidity increases steadily with age, and in developed countries, more than half of all adults aged 65 years or older have three or more chronic conditions. [18, 19] The management of multimorbidity in older people is challenging. Chronic disease treatment guidelines, which inform physician practice, are generally derived from single disease randomized trials. These trials also commonly exclude frailer multimorbid older individuals.[20] Thus, when multiple treatment guidelines are applied to multimorbid older adults, they commonly result in lengthy, problematic prescriptions.[20-24] **Figure 1.1** illustrates some of the difficulties associated with uncritically applying several single-disease treatment guidelines to an older patient with multimorbidity.

Polypharmacy is also likely to be driven by nonclinical factors. Available evidence suggests that prescribing decisions are strongly influenced by the expectations that patients bring to the consultation with their doctors.[25-29] For some patients, more investigations and more treatment may be perceived as better care.[30] Perhaps an even more important determinant, however, is the perception that doctors have of their patients' expectations. In two large primary care studies conducted in England and Australia, doctors' perceptions of their patients' expectations, rather than patients' *actual* expectations, were the strongest predictor of the decision to prescribe.[31,32] Clinicians are often poor at detecting expectations specific to the patient visit,[33] generally opt for *doing* rather than *not doing* in response to health threats (the so-called "treatment imperative"),[34,35] and

Figure 1.1: Problems associated with application of chronic disease guidelines a patient with multimorbidity.

Patient: 76-Year-Old Male **Medical History**	**Application of single-disease NICE treatment guidelines (First line recommended drugs)**	**Problems**
Type 2 diabetes mellitus Coronary artery disease (history of myocardial infarction) Heart failure with reduced ejection fraction (symptomatic) Chronic kidney disease (eGFR 38 ml/min/1.73 m2 Dementia 	**NG28** Metformin **CG172** Aspirin Atorvastatin Ramipril Bisoprolol **NG106** Ramipril Bisoprolol Furosemide Spironolactone	**General** Adherence problems due to memory loss **Potential Drug-Disease Interactions** CKD & metformin — *Risk of lactic acidosis* CKD & spironolactone — *Risk of hyperkalaemia* **Potential Drug-Drug Interactions** Ramipril & spironolactone — *Risk of hyperkalaemia*

may sometimes favour the perceived efficiency of prescribing a medication over spending additional time and effort explaining why it may not be necessary.[29, 36]

The enthusiasm for treatment on the part of doctors and patients reflects a tendency to overestimate the benefits and underestimate the harms of medical interventions.[30, 37, 38] Thomas, in 1978, referred to this tendency as the "therapeutic illusion".[39] He contended that "the patient who is made better with no treatment will also be made better with treatment".[39] When a patient is prescribed unnecessary treatment and later gets better, the improvement serves to confirm to the doctor and the patient that the correct course of action was taken (i.e. confirmation bias). This creates a relationship between treatment and recovery that is non-existent. When physicians, in particular, believe that the medications they prescribe are more effective than they actually are, the result can be unnecessary and costly care.

Inappropriate prescribing and polypharmacy in the context of ageing and declining health pose three important problems. Firstly, patients are placed at an increased risk of adverse drug reactions. Secondly, if treatments are unnecessary, patients are subjected to complicated, burdensome treatment regimens. Thirdly, inappropriate prescribing and polypharmacy are associated with increased healthcare costs.

1.1.4 Adverse drug reactions

Adverse drug reactions (ADRs) are defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the intentional 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'.[40] ADRs may be easy to recognize when the syndrome fits the known adverse effect pattern of the drug (e.g. acute kidney injury or gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs) and there is a time relation between use of the drug and the occurrence of the reaction. ADRs, however, can be difficult to recognize, particularly in older people with complex medical issues, and may manifest as nonspecific symptoms such as fatigue, poor appetite, memory loss, impaired balance and constipation.[41] Unfortunately, these symptoms may be misinterpreted as representing new clinical problems (prompting the prescription of new medications), or perhaps worse, may be attributed to normal ageing.[13, 42]

Older age, in addition to being accompanied by increased chronic disease burden and complexity, is also associated with a range of physiological changes that alter drug pharmacokinetics (i.e. absorption, distribution, metabolism, and excretion) and pharmacodynamics (the effect of the drug on the organism). These physiological changes, which may be enhanced by frailty and declining health, place older people at increased risk of ADRs. Some of the important physiological changes and their clinical implications are summarized in **Tables 1.1** and **1.2**. Due to difficulties with detection, varying ADR definitions, as well as inconsistencies in the application of rigorous standardized causality assessment methods in prospective studies, accurate and reliable data about the true incidence and consequences of ADRs in older people are limited.[41] Best available evidence indicates that approximately 5% -10% of hospital admissions involving older adults are attributable to ADRs.[43, 44] Amongst hospitalized older adults, the incidence of clinically significant ADRs ranges from 6.5% -21%.[45-48] Evidence from prospective studies indicate that ADRs prolong hospital admissions[46] and are an important cause of mortality in hospitalized older patients.[45, 49]

There are no well-designed prospective studies examining ADR incidence in older people approaching end-of-life. However, valuable ADR data are available for nursing home residents who are generally representative of the frailest population of older adults. The most important study is a prospective cohort study involving 2916 nursing home residents in 18 nursing homes in Massachusetts who were observed for a mean of 9.9 months. [50, 51] Adverse drug events (ADEs), defined as injuries resulting from the use of a drug, were categorized as preventable (i.e. related to errors in prescribing, dispensing, administration or monitoring) or non-preventable (i.e. not related to errors in these steps). Potential events were reviewed by two trained physicians and were included in the analysis only if an ADE was considered 'highly probable'. Overall, there were 546 ADEs during the observation period which equated to a rate of 1.89 ADEs per 100 resident-months. The authors of the study reported that, for an average-sized nursing home in the United States (106 residents), this would amount to approximately 24 ADEs per year.[50] Importantly, the number of daily medications was also associated with an increased risk of an ADE; the odds ratio (OR) associated with taking 5 to 6 medications (versus <5 medications per day) was 2.0 (confidence interval [CI] 1.2 -3.2); 7 to 8 medications, 2.8 (CI, 1.7 -4.7); and 9 or more medications, 3.3 (CI, 1.9 -5.6).[51] The association of polypharmacy with increased ADR/ADE risk in nursing home residents has also been demonstrated by other investigators.[52, 53]

Overall, the literature indicates that polypharmacy is an important risk factor for drug-related harm in older adults. ADRs seem to be particularly important in the acute setting when transitions of care (potentially resulting in prescribing errors), introduction of new medications (increased risk of prescribing errors, drug-drug and drug-disease interactions) and acute illness (increased risk of drug-disease interactions) render older people particularly vulnerable.

Table 1.1: Pharmacokinetic changes associated with ageing and declining health

	Changes in older adults	**Additional changes that may be important in older adults approaching end of life**	**Clinical implications**
Absorption	Reduced gastric acid secretion.[54]		Reduced absorption of calcium, iron and vitamin B12. This effect may be further enhanced by the use of anti-ulcer medications.
Distribution	Relative reduction in total body water and muscle mass and a relative increase in body fat. Decreases in albumin may be seen in older adults while α_1-acid glycoprotein is usually unchanged. Increased permeability of the blood brain barrier (BBB).[55]	*Body composition changes are likely to be exaggerated in older patients with frailty.* *Cachexia, which may be associated with terminal conditions or chronic inflammation, is associated with loss of equal amounts of fat and muscle mass with preservation in total body water.*[56] *Albumin may be very low in patients with terminal conditions while α_1-acid glycoprotein may increase.*	Hydrophilic drugs (e.g. gentamicin, digoxin, ethanol) have smaller volumes of distribution in older adults and therefore higher serum concentrations. Increased serum concentrations lead to an increase in elimination which limits the importance of this effect. Lipophilic drugs (e.g. diazepam, lignocaine) have larger volumes of distribution (lower serum concentrations) but may be more difficult to clear. The main factor determining drug effect is its free concentration. Increased levels of unbound drug (i.e. due to low albumin) lead to a proportionate increase in elimination, again, limiting the importance of this effect. Overall, alterations to body composition and serum drug-binding proteins, alone, are unlikely to have significant clinical implications in healthy older adults.[54, 57] Increased permeability of the BBB may increase risk of neurological ADRs.
Metabolism	Reduction in liver size and blood flow.[58] Reduced phase I metabolism (oxidation, reduction, hydrolysis). Unchanged phase II metabolism (glucuronidation, acetylation, sulfation)	*Frailty, inflammation reduce phase I metabolism.*[59, 60] *Frailty may lead to reduction in phase II metabolism.*[61, 62]	Several ACE inhibitors (e.g. enalapril, perindopril) are prodrugs and need to be activated in the liver. This activation may be impaired in older patients, especially those with severe heart failure and liver congestion, leading to delays in onset of action.[54, 63, 64] Bioavailability and half-life of certain opioids (e.g. tramadol) may be increased in patients with primary and secondary liver tumours.[65]

Excretion	Renal function reserve is reduced (reduced capacity to respond and recover from acute insults)[66]	*GFR may be reduced in older people with advanced disease.*	The majority of drugs and/or their metabolites are excreted by the kidneys. Reductions in GFR may lead to drug accumulation and toxicity. Accumulation of drugs with a narrow therapeutic index, such as gentamicin, lithium and digoxin, may cause serious adverse effects.[54] Frailty and cachexia are associated with reduced muscle mass and, therefore, serum creatinine and GFR calculators may underestimate renal impairment.[67]

Legend: ACE = angiotensin converting enzyme; ADRs = adverse drug reactions; BBB = blood brain barrier; GFR = glomerular filtration rate

Table 1.2: Pharmacodynamic changes associated with ageing

Drugs with age-related *increase* in pharmacodynamic effect		**Drugs with age-related *decrease* in pharmacodynamic effect**	
Drug	**Clinical implications**	**Drug**	**Clinical implications**
Anticholinergics	Risk of falls, cognitive decline, constipation[68]	Propranolol	Reduced chronotropic effect[54]
Benzodiazepines	Increased sedation, risk of falls, cognitive decline[69]	Furosemide	Reduced peak diuretic response (i.e. higher doses required to achieve diuresis)[54]
Morphine	Increased sedation, enhanced analgesic effect[70]		
Neuroleptics	Increased sedation, anticholinergic effects[71]	Isoprenaline	Reduced inotropic effect[73]
Warfarin	Increased anticoagulant effect[72]		

1.1.5 Burden and futility of medications at the end of life

Morin *et al.* examined patterns of prescribing in the last year of life in a nationwide longitudinal cohort study of 511,843 older adults in Sweden who died between 2007 and 2013.[74] Between the 12th month and the final month before death, the proportion of older adults with major polypharmacy (prescribed ≥10 regular medications) rose from 30.2% to 47.2% and the mean (standard deviation [SD]) number of prescription drugs increased from 7.6 (4.4) to 9.6 (4.7). Even when analgesic drugs were removed, the trend of increasing numbers of prescription medications in the last year of life persisted. In the month before death, 53.8% of patients were prescribed anti-thrombotics, 34.6% were taking supplements for anaemia, 20% were prescribed calcium or potassium supplements, 35.1% were prescribed gastric acid suppressants and 16.3% were prescribed lipid –lowering agents.[74] It is important to note that a significant proportion of these deaths may have been unexpected, and high-level polypharmacy, in many cases, may have been considered reasonable by attending physicians. However, several other investigators, focussing on patients with advanced cancer and other life-limiting illnesses, have also shown that low value medications are commonly prescribed at end of life.[75-77]

In a recent cross-sectional study of 5406 nursing home residents with advanced dementia, Tija *et al.* reported that just over half of all residents were prescribed at least one medication of questionable benefit.[78] Cholinesterase inhibitors (36.4%), memantine (25.2%) and lipid-lowering agents (22.4%) were the most commonly prescribed of such questionable medications. Most of these patients received between 5 and 15 medications daily.[79] These findings are important because nursing home residents with advanced dementia frequently have problems with dysphagia and aspiration and, therefore, drug administration, in addition to being potentially futile, may also be burdensome or even harmful. [80, 81]

The concept of therapeutic futility is an important one in medicine. Hippocrates wrote that physicians should “refuse to treat those who are overmastered by their diseases, realizing that in such cases medicine is powerless”.[82] The Oxford English Dictionary defines *futile* as “incapable of producing any useful result; pointless”.[83] The word futile relates to a specific action whereas *futility* refers to the relationship between an action and a specific goal. In the medical context, therefore, futility could be defined as a “clinical action serving no useful purpose in attaining a specified goal for a given patient.”[84]

“No useful purpose”, however, implies that there is no possibility of achieving a specified goal. There are always exceptions and some authors have suggested defining futility as a less than 1%, 2% or 5% chance of success.[85, 86] These thresholds can also be expressed as the number needed to treat (i.e. the number of patients that need to be treated for one patient to benefit [NNT]). Defining futility as a 1%, 2% or 5% chance of success translates into an NNT of 100, 50 or 20, respectively. While attractive in terms of concreteness, these thresholds need to be interpreted with caution. NNT figures are derived from randomized controlled trials that usually exclude older patients with significant frailty or advanced disease and reflect the chance of success for the “average” patient with an average set of risk factors.[21] Thus, applying RCT evidence to an individual older patient with marked frailty or advanced disease could substantially over- or underestimate chance of success for that individual. Even so, it is instructive to note most patients do not benefit from preventive medications that are commonly prescribed for them (**Table 1.3**).

Table 1.3: Number needed to treat data for commonly prescribed preventive therapy

Drug	Specified outcome	NNT for benefit
Statins	Primary prevention[87]	217 (nonfatal MI) 313 (nonfatal stroke)
	Secondary prevention (heart disease, treatment for 5 years)[88, 89]	83 (death) 39 (nonfatal MI) 125 (nonfatal stroke)
Bisphosphonates	Fracture prevention in postmenopausal women with no previous fracture (treatment for 3 years)[90, 91]	No benefit
	Fracture prevention in postmenopausal women with prior fracture or very low bone density (treatment for 3 years)[90, 91]	20 (vertebral fracture; many of these subclinical) 100 (hip fracture)
Calcium and vitamin D	Fracture prevention in community dwelling older adults[92, 93]	No benefit
	Fracture prevention in high risk older adults (residents in institutions)[94]	111 (hip fracture); no benefit with vitamin D alone
Aspirin	Primary prevention (treatment for 6.6 years)[95]	No benefit
	Secondary prevention (treatment for 2 years)[96, 97]	333 (death) 77 (non-fatal MI) 200 (non-fatal stroke)

Legend: MI = myocardial infarction; NNT = number needed to treat

As shown in **Table 1.3**, RCT evidence indicates that 100 postmenopausal women with a prior history of fracture would need to be treated for 3 years with a bisphosphonate to prevent one hip fracture. [90, 91] Treating 1000 patients for 3 years will prevent 10 hip fractures which, even at this level, is likely to represent an important public health intervention. However, when an older person is approaching end-of-life, and care needs to be individualized, bisphosphonate therapy may be considered a low-priority intervention.

1.1.6 Costs associated with inappropriate prescribing

Morgan *et al.* measured the frequency of prescribing and cost of potentially inappropriate medications (PIMs) dispensed to drug plan enrolees aged ≥65 years in 6 provinces in Canada in 2013.[98] PIMs were defined using the American Geriatrics Society's 2012 version of the Beers Criteria, an explicit list of medications to be avoided or used with caution in older adults. Overall, 37% of older people took one or more prescription Beers Criteria PIMs. Extrapolating from these data, it was estimated that $419 million in total, or $75 per older Canadian, was spent on PIMs in the community setting in 2013.[98] In a similar study conducted in Ireland by Cahir *et al.*, PIM prescribing (defined by Screening Tool of Older Peoples Prescriptions [STOPP]) was estimated to account for approximately 9% of the overall expenditure on pharmaceuticals in those aged ≥70 years.[99] Only the direct cost associated with PIM prescribing, and not the consequences, was measured in these studies.

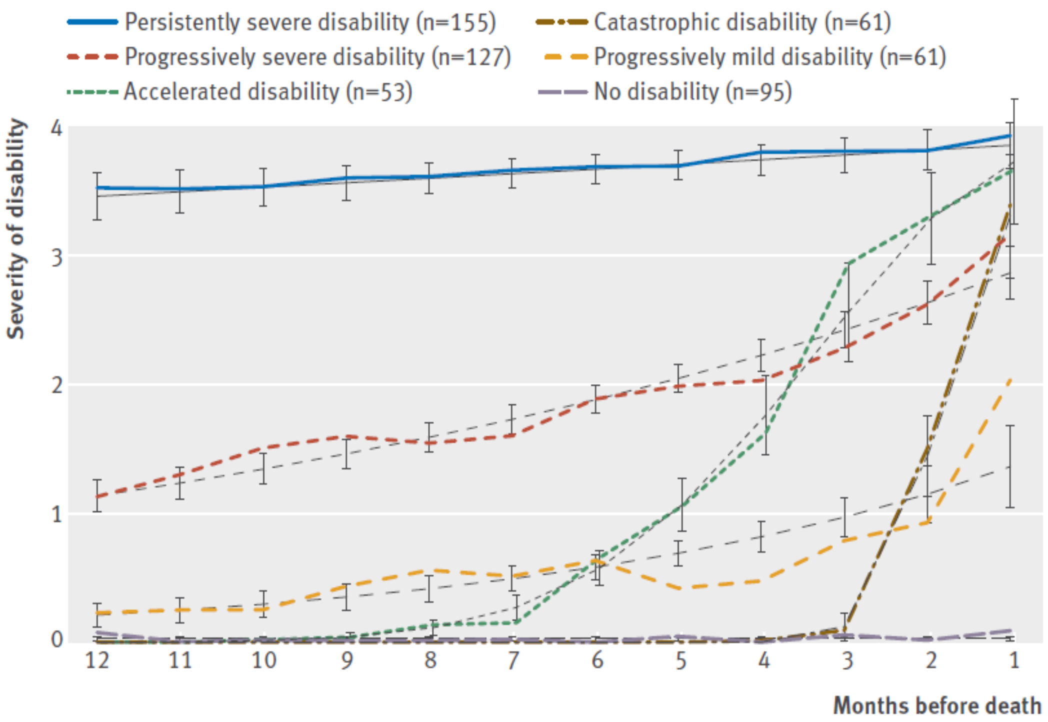
Recently Formica *et al.* conducted a systematic review of observational studies that evaluated the economic impact of preventable ADRs.[100] Only observational studies in the United States and Europe were included. While limited by heterogeneity in methods, outcome definitions and reporting, the review showed that costs due to preventable ADRs in a hospital inpatient setting ranged from €2,851 to a maximum of €9,015 while those in an outpatient setting ranged from €174 to €8515 per patient.[100]

1.2 RECOGNIZING WHEN OLDER PEOPLE ARE APPROACHING END OF LIFE

1.2.1 Trajectories of disability in the last year of life

Glaser and Strauss in 1968 described three patterns of dying: [101] sudden, unexpected deaths; expected deaths, both with a short and prolonged dying phase; and entry-re-entry deaths, where individuals had recurrent hospital admissions in the last months of life. More recently, these concepts have been expanded and expressed as trajectories of disability in the last year of life. The most important study examining these trajectories has been the Precipitating Events Project.[102-104] This longitudinal study originally enrolled 754 community dwelling older persons aged 70 years or older in the United States (US) between March 1998 and October 1999. In order to be eligible, participants had to be independent in 4 essential activities of daily living (ADLs): washing, dressing, walking and transferring from a chair to a standing position. Comprehensive home-based assessments were completed at baseline and patients were followed prospectively with further comprehensive assessments at 18-month intervals. Participants, or a designated surrogate, had monthly telephone interviews primarily focussed on determining participants' abilities across the 4 ADLs. Clinically distinct trajectories of disability in the last year of life were identified using a statistical method called trajectory modelling, which is a form of latent class modelling. The most recent update from this longitudinal study was in 2015 by which time 552 participants had died.[104] In the last year of life, six distinct trajectories of disability were identified (**Figure 1.2**): no disability, catastrophic disability, accelerated disability, progressively mild disability, progressively severe disability, persistently severe disability.[104]

Figure 1.2: Trajectories of disability in the last year of life among 552 older decedents.



Values for 'Severity of disability' represent the mean number of disabled activities of daily living (from 0 to 4). Black lines depict predicted trajectories, and companion lines depict observed trajectories. Ī bars represent 95% confidence intervals for predicted disability scores. Reproduced with permission.[104]

Importantly, the results indicate that approximately 50% of older people need assistance with basic ADL functioning 12 months prior to death. This finding has also been reported in larger, albeit less rigorous, cohort studies.[105, 106] Of those who were disability-free 12 months prior to death, one third remained disability-free, while the remainder varied in terms of the timing and rate of development of disability. Apart from advanced dementia, which was characterized by high levels of disability throughout the last year of life, other common causes of death (i.e. cancer, organ failure and frailty) did not follow a predictable disability trajectory.[103, 104]

1.2.1 Hospitalizations as a marker of declining health

The majority of people in the last year of life are admitted to hospital on at least one occasion and, for many of these people, hospitalizations are frequent and prolonged.[107, 108] Goldbury *et al.* measured healthcare utilization amongst all adults who died in a 12 month period in New South Wales, Australia.[107] Of the 45,749 decedents, 82% were admitted to hospital in the last year of life, 24% had more than 3 hospital admissions and 35% spent more than 30 days in hospital. Lyons and Verne reported similar findings in England where 78% of people had at least one hospital admission in the year before death and the mean length of stay in hospital was 29.7 days.[108]

Because older people are frequently admitted to hospital in the year prior to death, it follows then that there is an opportunity to identify people who have a high one-year mortality risk. The value of identifying high risk patients is that important discussions about values, priorities and goals of care can take place. Amongst adults of all ages hospitalized with acute illness, 20%-28% will be deceased within 1 year.[109, 110] Important factors associated with an increased 1-year mortality risk in hospitalized patients include increased age,[109-111] impaired functional status,[111, 112] delirium,[113] and low socioeconomic status.[109]

Impaired functional status, as well as ADL decline during hospitalization, appears to be particularly important. Boyd *et al.* examined outcomes in the year following discharge for older people with hospitalization associated disability.[112] Compared with older people who were discharged from hospital with no change in ADL functioning, those discharged with new or additional disability were significantly more likely to be deceased at one year (41.3% versus 17.8%).[112] In the Precipitating Events Project, Gill *et al.* evaluated the role of intervening hospital admissions on the course of disability in the last year of life.[104] All six disability trajectories were closely matched by the monthly prevalence of hospital admissions and these findings were confirmed using a set of multivariable models that adjusted for several potential confounders.[104] The results indicate that acute illness leading to hospitalization plays a significant role in the disabling process at the end of life. The results of these studies also suggest that new or additional disability associated with hospitalization in an older person is often a sentinel event and should, perhaps, prompt a discussion about goals of care.

1.2.3 Prognostic estimation

Prognostication relies upon an ability to accurately estimate survival. Prognostic estimates may be formulated subjectively (i.e. clinician prediction) or objectively (i.e. using prognostic models). Clinician prediction has the advantage of being instantaneous and convenient, and while it may incorporate known prognostic factors in its determination, accuracy will undoubtedly vary depending on the knowledge, experience and personality of the clinician. Indeed, most studies have found that clinicians generally give optimistic estimations of life expectancy.[114-116] Christakis and Lamont described clinicians' prognostic accuracy in terminally ill patients.[115] In this study, 343 doctors provided survival estimates for 468 terminally ill patients at the time of hospice referral. Just 20% of predictions were accurate (i.e. predicted survival rate within ±33% of actual survival) and overall, doctors overestimated survival by an average factor of 5.3. The most experienced clinicians tended to be most accurate, while, counterintuitively, the longer the duration of the doctor-patient relationship, the greater the likelihood of an inaccurate prediction.[115]

The accuracy of clinician prediction may depend on how the question the question is asked.[117-118] As outlined, the temporal question – "how long will this patient live?" –is likely to be associated with overly-optimistic predictions. The surprise question asks the clinician "would you be surprised if this patient were to die within the next (insert *specific time frame*; usually 12 months)?"[119] Of course, the threshold for "surprise" will inevitably vary between healthcare professionals. But, rather than being asked to provide an estimate of life expectancy, as in the temporal question, the answer is binary (yes or no), and essentially functions as a method of separating those with an intermediate-to-high probability of dying (the clinician answers that he/she would *not* be surprised if the patient died within the specified time period i.e. surprise question positive [SQ+]) from those with a low probability of dying (the clinician *would be* surprised i.e. surprise question negative [SQ-]). The surprise question is widely used as a method for identifying patients who might benefit from hospice and palliative care.[120, 121] Its accuracy was recently assessed in two systematic reviews: Downar *et al.*[122]included studies where the primary outcome (death) was measured at least 6 months after the surprise question was asked; in contrast, White *et al.*[123] included all studies that examined the use of the surprise question, even those that used time scales as short as 7 days. Downar *et al.*'s review demonstrated that the surprise question has better discrimination for patients with cancer that those patients with non-cancer illnesses (concordance [c] statistic 0.83 versus 0.77). The pooled accuracy for White *et al.*'s review was 0.75. While, the reviews showed that the surprise question will lead to the detection of many 'false positives', this simple method appears to be very effective at excluding patients with longer survival times (negative predictive value >90% in both reviews). Overall, it seems that the surprise question has value as part of a wider prognostic assessment and, in particular, may be helpful in excluding patients who are *not* necessarily approaching end of life.

Multiple prognostic models have been developed in recent years to predict mortality risk in older people. The quality and limitations of non-disease-specific prognostic models for older people were evaluated in 2012 systematic review by Yourman *et al*.[124] The authors concluded that there was insufficient evidence to recommend any of the 16 models that met the study requirements for clinical use. Very few of the indices had been tested in terms of transportability (i.e. tested in different patients, in different geographical regions, at different times). Of particular concern was the fact that just two of the indices had been validated by investigators who were not involved in the development of the same indices.

Since that review, two important prognostic models have been developed and validated. The first is the Hospital patient One-year Mortality Risk (HOMR) model which uses administrative data to predict one-year mortality risk in hospitalized adults aged 18 years and older. [125, 126] It was developed and validated in over 3 million hospitalized adult (i.e. ≥18 years) non-psychiatric patients in Canada and the United States. The HOMR model was highly discriminative, with a c statistic ranging from 0.89 to 0.92. The HOMR model has not been validated in an exclusively older hospitalized population nor has it been externally validated by independent investigators not involved in its development. The second recently developed prognostic model, the Q-Mortality risk algorithm, uses routinely collected primary care data to predict 1-year mortality risk in older community dwelling adults. [127] It was developed and validated using data from almost 2 million patients in the United Kingdom and was shown to be highly discriminative (c statistic 0.85). Similar to the HOMR model, the Q-mortality risk algorithm has yet to be independently validated.

1.2.4 Frailty status and risk of death

Frailty is broadly characterized as a late-life vulnerability to adverse health outcomes [128-131] A single operational definition of frailty has yet to gain widespread acceptance among experts primarily because there has been a proliferation of frailty measurement tools with differing conceptual bases in the medical literature in the last 2 decades. The two conceptual models that have been most cited in the literature, and therefore merit particular attention, are the frailty phenotype (FP) and the frailty index (FI).

The FP, developed by Fried *et al.*, recognizes frailty as a distinct clinical syndrome that commonly, though not always, overlaps with disability and co-morbidity.[131] The core characteristics of the phenotype were first identified and validated in 2001 through a consensus survey of 62 geriatricians and then operationalized in the Cardiovascular Health Study, a large-cohort study of over 5,300 community-dwelling older men and women in the United States.[132] An individual is considered frail if he or she meets three of the following five criteria: (i) weakness as measured by low grip strength, (ii) slow walking speed, (iii) low level of physical activity, (iv) low energy or self-reported exhaustion, and (v) unintentional weight loss. Individuals who meet one or two criteria are classified as pre-frail while those who meet none of the criteria are considered non-frail. The relevant thresholds for each of these measurements are shown in **Table 1.4.**

The FI, developed by Rockwood *et al.*, conceptualizes frailty as an accumulation of health deficits over the course of one's life.[133, 134] Health deficits are defined by clinical symptoms, signs, diseases, disability, laboratory, radiological or electrocardiographic abnormalities or social characteristics. Frailty is then measured by dividing the number of health deficits present by the number of health deficits measured. Therefore, a person with 8 deficits out of 40 measured has a frailty index of 0.20. In general, health deficits should be acquired, age-related and associated with adverse outcomes.[133] The number (usually 30 to 70 items) and type of deficits measured can vary depending on the population studied but the construction of the index should follow established guidelines.[135]

Table 1.4: The Frailty Phenotype

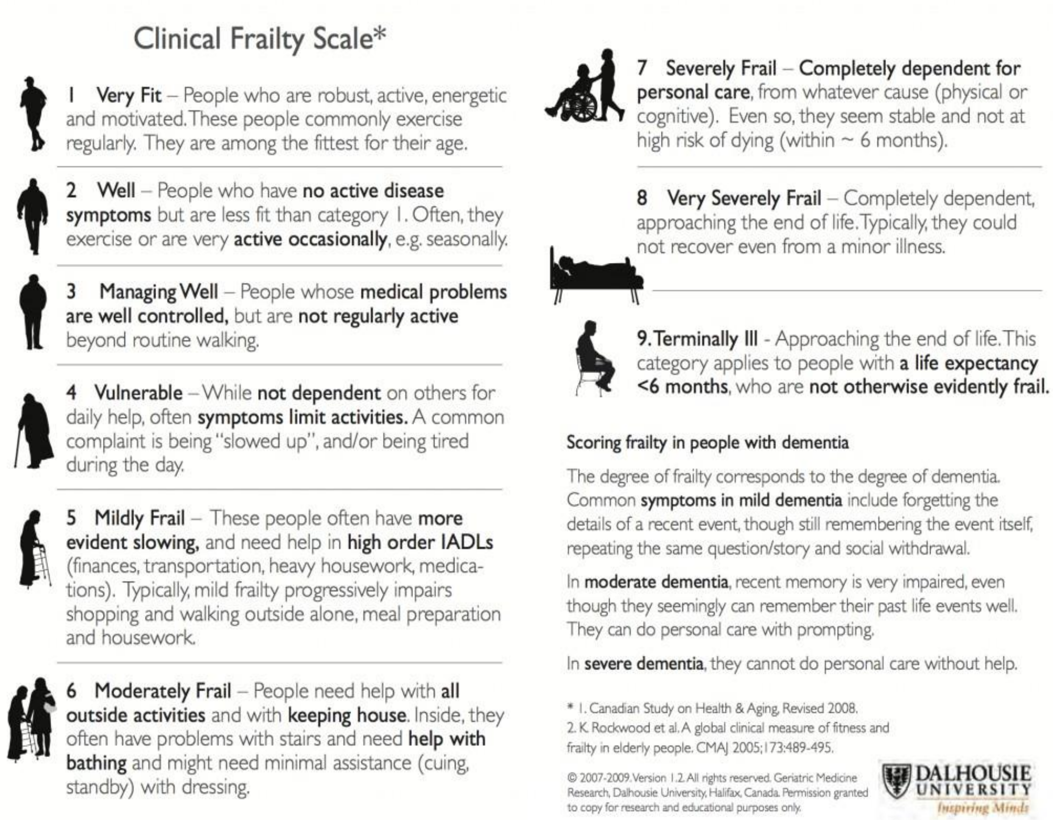
Frailty Phenotype Criteria	**Measurement**
Weakness	Grip strength: lowest 20% (by sex, body mass index)
Slowness	Walking time/ 15 feet: slowest 20% (by sex, height)
Low level of physical activity	Kcal/ week: lowest 20% Males: 383 Kcal/week; Females 270 Kcal/week
Exhaustion; poor endurance	"Exhaustion" (self-report)
Weight loss	> 10Ib (4.5kg) lost unintentionally in prior year

A recent systematic review and meta-analysis of 19 studies indicated that the FI was a significant predictor of mortality, with higher FI scores associated with a significantly higher mortality risk.[136] Indeed, in head-to-head comparisons, the FI has been shown to be superior to the FP in predicting mortality in older people.[137, 138] However, the FI has certain inherent limitations. In addition to limited face validity for practicing clinicians, counting deficits is likely to be onerous and impractical in routine clinical practice. Recognizing this, Rockwood *et al.*

developed the Clinical Frailty Scale (CFS; see **Figure 1.3**).[139] Here, the care provider assigns a frailty score ranging from 1 (very fit) to 9 (terminally ill) using a decision support chart with succinct, clear descriptors for each of the nine levels of frailty. Clinical judgement is required of the care provider to assign the appropriate score. The CFS has been shown to correlate very closely with the FI in terms of predicting adverse outcomes in older people including institutionalization and death.[139] In recent studies by Ritt *et al.*, the performance of the CFS when used to predict 1-year mortality in 307 older hospitalized patients exceeded that of the FI, several other frailty measurement tools, and also measures of co-morbidity burden and dependency.[140, 141]

The use of the CFS to identify older people who are approaching end-of-life is appealing because of its ease of use, good face validity and strong predictive performance. However, it is a graded tool designed to identify people who are at risk of a range of clinical outcomes (e.g. falls, dependency, institutionalization, complications related to invasive procedures etc.) *in addition* to risk of death. Successive scores on the scale are defined in terms of increasing disability and this may be a limitation if it is to be used to identify people approaching end-of-life. Longitudinal studies indicate that approximately half of all disability develops slowly and progressively in association with advancing age and severity of disease; the remainder develops rapidly in association with acute events such as stroke or trauma.[142] A patient who develops acute severe disability due to trauma may be relatively stable in other physiological systems and therefore may have a low short-term risk of death despite a high score on the CFS.

Figure 1.3: The Clinical Frailty Scale[139] (reproduced with permission)



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.

DALHOUSIE UNIVERSITY *Inspiring Minds*

1.3 OPERATIONALIZING DEPRESCRIBING FOR OLDER PEOPLE APPROACHING END OF LIFE

1.3.1 Identifying medications to be deprescribed

In addition to NNT, Holmes *et al.* suggest incorporating time to benefit (TTB) and time to harm (TTH) data into deprescribing decisions.[143] TTB refers to the time that a statistically significant benefit was observed in trials of people receiving a particular drug compared to an appropriate control group.[143] Similarly, TTH is the time period that elapses before a statistically significant adverse effect of a treatment occurs in the treatment group compared to the control group.[143] Using all this information for any particular drug and comparing it with an estimate of the patient's remaining life expectancy, the authors postulate that a better estimate of net benefit (or net harm) can be made.[143] The approach has clear limitations: firstly, drug data are derived from trials that generally exclude older patients approaching end-of-life and therefore may have limited applicability;[21] secondly, as discussed, estimates of remaining life expectancy are commonly inaccurate;[114-116] thirdly, the approach is likely to be time-consuming in a clinical setting. In light of these complexities, several tools have been developed in recent years to support clinicians with deprescribing decisions in older people approaching end of life. These tools can broadly be categorized as implicit (judgement-based) or explicit (criterion-based).

The two most prominent implicit deprescribing tools in the medical literature are the Geriatric-Palliative algorithm (**Figure 1.4**)[144] and the deprescribing algorithm proposed by Scott *et al.* (**Figure 1.5**).[145] Both tools require the user to answer a series of questions about each individual medication in the patient's drug regimen. While comprehensive and patient-centred, the outcome of applying such algorithms will depend on the knowledge, experience and attitudes of the user. Judgement is required: the user is not provided with resources or decision aids to estimate treatment benefit-harm trade-offs in individual patients. The use of implicit medication assessment tools such as these, in general, is time-consuming, and is likely to result in variations in practice between physicians; for these reasons integration into routine clinical practice has been very limited.[146]

Figure 1.4: The Geriatric-Palliative algorithm

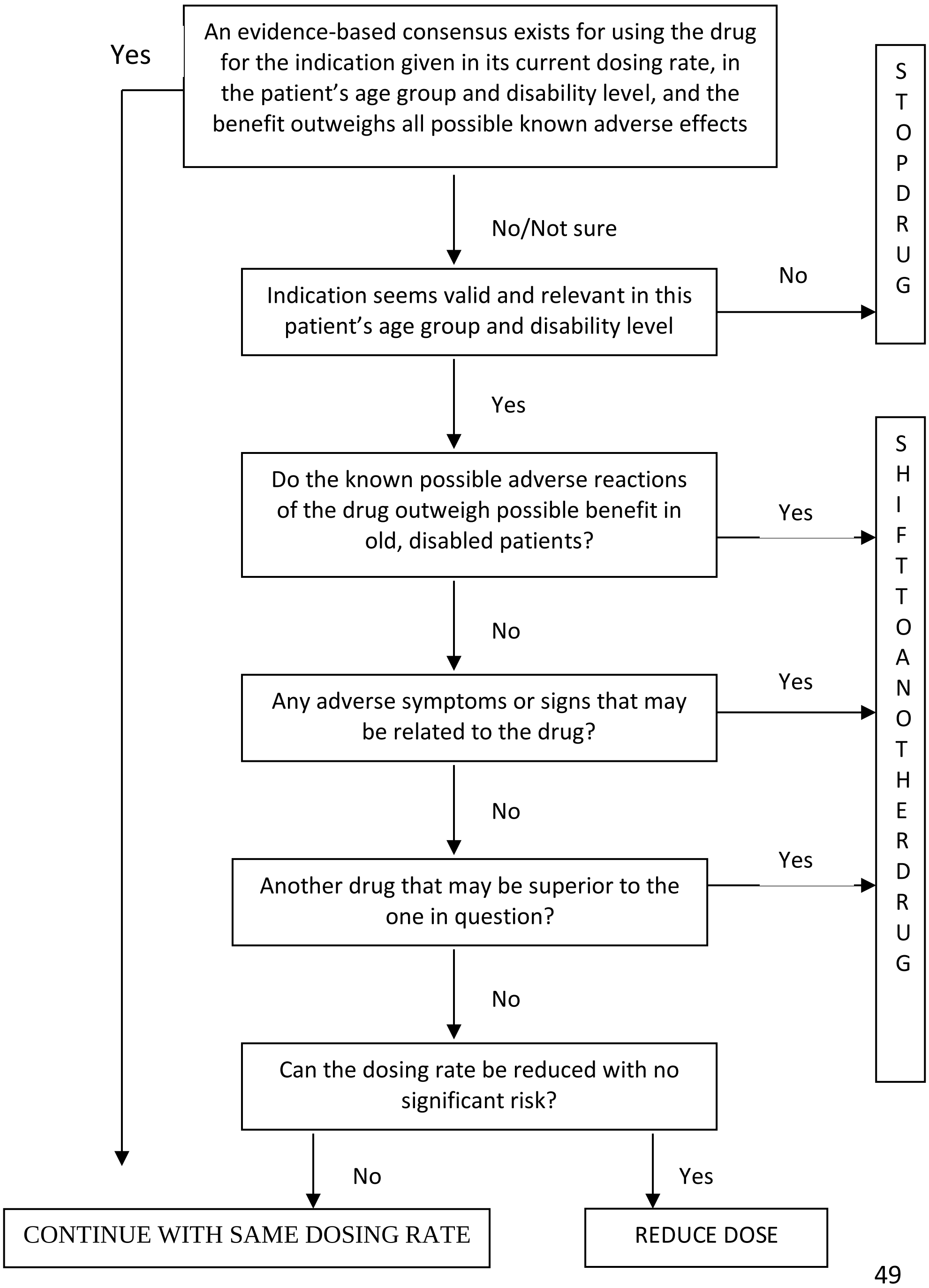
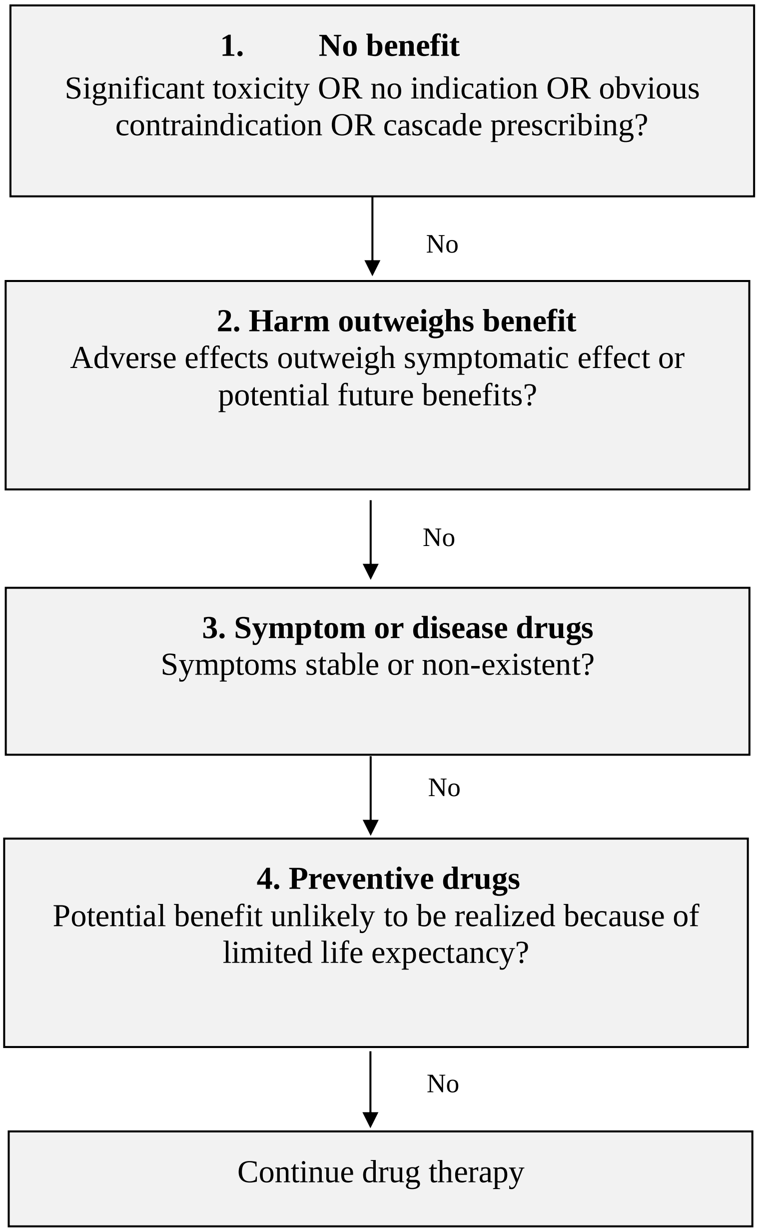


Figure 1.5: Scott *et al.'s* deprescribing algorithm. Each medication is individually assessed using the decision tree shown below.



STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy; **figure 1.6**) criteria were published in 2017 and consist of 27 mostly explicit indicators to assist physicians with deprescribing decisions in frail older individuals with poor 1 year survival prognosis.[147] The criteria were created following a literature appraisal and two rounds of Delphi consensus validation involving 17 panellists with expertise in geriatric medicine, clinical pharmacology, palliative medicine, general practice and psychiatry. Of the 27 indicators, 26 are explicit (i.e. clearly defined statements highlighting the potentially inappropriate use of particular drug/ drug classes in a particular clinical situation) and one is implicit (i.e. Criterion A2: Stop any drug without a clear clinical indication). The criteria are organized according to physiological systems and are designed to be used by physicians of all disciplines who commonly provide care for frailer older people. The inter-rater reliability of STOPPFrail in a recent study was shown to be substantial (mean kappa 0.76 ± 0.6) when evaluated among general practitioners, geriatricians and palliative care physicians using theoretical test cases.[148] This suggests that STOPPFrail-guided deprescribing, as an intervention, is likely to be reproducible in different settings. However, STOPPFrail has important limitations. Firstly, it is unclear how prevalent the prescribing of the listed medications is amongst older frailer adults and whether discontinuation would result in important patient-related outcomes. Secondly, the user is not prompted to explore symptoms such as poor appetite, nausea, altered bowel habit, sedation and gait disturbance, which could represent the adverse effects of prescribed drugs. Finally, shared decision making is not emphasized in the deprescribing process.

Figure 1.6: STOPPFrail Criteria

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: **1) End-stage irreversible pathology** **2) Poor one-year survival prognosis** **3) Severe functional or severe cognitive impairment or both** **4) 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:** **1) Drug adherence/compliance is difficult** **2) Administration of the medication is challenging** **3) Monitoring of the medication effect is challenging** **4) Drug adherence/ compliance is difficult**
Section A: General **A1:** Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations. **A2:** Any drug without clear clinical indication. **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 (ADEs) outweighs the potential benefits **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 **Section C: Coagulation system** **C1: Anti-platelets** Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit) **Section D: Central Nervous System** **D1. 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) **D2: Memantine** Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD (specifically in frail patients who meet the criteria above)	**Section G: Musculoskeletal System** **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)** **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 **G4. Long-term oral NSAIDs** Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months **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 **Section H: Urogenital System** **H1. 5-alpha reductase inhibitors** No benefit with long term urinary bladder catheterisation **H2. Alpha blockers** No benefit with long term urinary bladder catheterisation **H3. Muscarinic antagonists** No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity **Section I: Endocrine System** **I1. Diabetic oral agents** Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary **I2. ACE-Inhibitors for diabetes**

Section E: Gastrointestinal System **E1. Proton Pump Inhibitors** Proton Pump Inhibitors at full therapeutic dose ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose **E2: H2 receptor antagonist** H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose **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	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 **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 **I4. Systemic oestrogens for menopausal symptoms** Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms
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 **F2. Leukotriene antagonists (Montelukast, Zafirlukast)** These drugs have no proven role in COPD, they are indicated only in asthma (50)	**Section J: Miscellaneous** **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 **J3: Prophylactic Antibiotics** No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs
Disclaimer (STOPPFrail) **Whilst every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence-based, it is emphasized that the final decision to avoid or initiate any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that prescribing decisions should take account of current published evidence in support of or against the use of drugs or drug classes described in STOPPFrail.**	

1.3.2 Shared decision-making

Shared decision making involves the sharing of information between the patient and physician, building consensus about preferred treatments and their rationale, and then reaching agreement on the treatment to be implemented.[8] Patient involvement in healthcare decisions is a key component of patient-centred care.[149] When patients engage in shared decision making, they feel more knowledgeable, better informed and clearer about their values.[150] Furthermore, patients are more likely to choose more conservative options when they engage in shared decision making.[150] There is also evidence that patients prefer to participate in medical decision making. A recent systematic review of peer reviewed journal articles found that, in 63% of articles most patients expressed a wish to actively participate in decisions around their treatment.[151]

Qualitative studies have indicated that clinicians are often reluctant to initiate discussions about deprescribing with older people, believing that they would resist having their medications discontinued or that they would interpret deprescribing as withdrawing of care or "giving up" on active treatment.[152, 153] These perceptions, however, have not been borne out in patient-focussed research.[154, 155] Reeve *et al.* recently examined attitudes of older people towards deprescribing in a nationally representative sample of Medicare beneficiaries in the United States.[154] In this study, 92% of people indicated a willingness to discontinue one or more of their medications if their physician said it was possible and appropriate to do so, and 66% reported a desire to reduce the number of medications that they were taking. The greatest predictor of willingness to deprescribe was the taking 6 or more daily medications.[154] The results are important for clinical decision-making and suggest that physicians can be reassured that broaching the topic of deprescribing with their older patients is generally acceptable to them.

In that same study, Reeve *et al.* suggested that clinicians could initiate discussions about deprescribing by explaining that "benefits and risks (of medications) can change over time" and that, therefore, some long-term medications may no longer be necessary in some older patients.[154] For patients approaching end of life however, deprescribing decisions may form part of a wider discussion around goals of care. Indeed, communication around goals of care is a central element in ensuring that patients receive the care that they want, in alleviating anxiety, and in supporting patients' families.[156-158] While patients expect their physician to initiate discussions about goals of care and end of life preferences,[159] in reality physicians often do not approach these discussions until late in the course of older patients' final illness. Mack *et al.*, in a large prospective cohort study of patients with metastatic colorectal and lung cancer, found that the initial conversations around end-of-life care took place an average of 33 days before death.[160] These findings are significant because patients who are not aware that they are approaching end of life may overuse treatments of limited benefit (i.e. preventive medications) and underuse services that support quality of life (e.g. specialist palliative care, psychosocial and spiritual support).[161, 162]

Decisions about medications represent just one aspect of the many decisions that patients and their physicians face when they discuss goals of care and usually other aspects of the discussion take priority. For this reason, a focus on the patient's values, such as whether the patient favours a primary focus on extending life or a primary focus on palliation may be more worthwhile than concentrating on the merits of individual therapies.[162, 163] Some patients may desire more detailed information and, in general, the discussion should be tailored to the patient's level of knowledge about their overall condition and information preferences.[162] While withdrawal of certain treatments may be recommended, commitment to supporting patients through their illness should be re-emphasized.[164]

1.4 EVIDENCE OF EFFICACY FOR DEPRESCRIBING

Two recent systematic reviews examined the impact of deprescribing interventions on prescribing and clinical outcomes.[165, 166] Thillainadesan *et al.*[165] focussed on older hospitalized patients (i.e. ≥65 years old) while Dills *et al.*[166] included adult patients aged ≥18 years old in outpatient, assisted living, nursing home and acute care settings. Only RCTs were included. Both reviews concluded that deprescribing interventions can reduce medication burden but evidence of a positive impact on important clinical outcomes such as ADRs, falls, rehospitalisation, quality of life and mortality is weak and of low quality.

There is very limited high-quality evidence evaluating the impact of deprescribing specifically in older people approaching end of life. Kutner *et al.*, in a multicentre unblinded randomized trial, examined the safety and clinical implications of discontinuing statin drugs for patients with advanced disease and limited prognosis.[167] The 'surprise question',[119] as well as evidence of recent functional decline, was used to identify eligible patients. In total, 381 patients were included in the study. There were no significant difference in mortality or cardiovascular events between the intervention and control group at 60 days but quality of life (QoL) was better in the patients who discontinued statin therapy. While the difference in QoL scores was statistically significant, the difference was small (mean McGill QoL score 7.11 versus 6.85; $p = 0.04$) and, therefore, of uncertain clinical relevance.[167]

At the time of writing this thesis, there are no other RCTs of deprescribing interventions involving older people approaching end of life. However, various medication optimization interventions have been tested in nursing home residents. Because nursing home residents usually represent an older, frailer population and because the median time from admission to a nursing home to death generally ranges from 5 to 15 months, these data are likely to be relevant.[168, 169] A 2016 Cochrane review evaluated RCTs of medication optimization interventions in nursing home residents.[170] Overall, 12 studies involving 10,953 residents in 355 nursing homes in ten countries were included. In five of the studies, interventions resulted in improvements in measures of prescribing quality. Overall, however, there was no clear evidence of benefit with respect to reducing adverse drug reactions or mortality.[170]

Most interventions in these studies involved a pharmacist and/or a physician conducting a formal medication review. Identifying deprescribing targets, as discussed, is complex and healthcare professionals will vary in their assessment of the importance and appropriateness of medications.[171, 172] Therefore, structured interventions, which can be reproduced in different settings, are preferable.[173] The Geriatric –Palliative algorithm and Scott's algorithm described earlier have both been evaluated in the nursing home setting: these studies are summarized in **Table 1.5**.[174, 175] While both interventions significantly reduced the number of medications in intervention patients, the Geriatric-Palliative algorithm was also associated with a significant reduction in mortality and acute hospital transfers.[175] However, these outcomes should be interpreted with caution. This was not a randomized controlled trial and the process of allocating participants to the intervention and control groups was not well described suggesting a high risk of bias.

Table 1.5: Characteristics of studies involving Scott's deprescribing algorithm and the Geriatric-Palliative algorithm

Study	Intervention	Design	Population	Outcomes measured	Results
Potter et al., 2016[174]	Scott's algorithm	RCT Follow-up: 1 year	Nursing home residents. 95 patients (47 intervention patients; 48 control patients) Mean age: 85	Primary: change in number of medications Secondary: mortality, falls, fractures, unplanned hospital presentations, cognitive status, functional status, QOL, sleep	Mean change in number of medications -1.9 ± 4.1 in intervention group compared with +0.1 ± 3.5 in control group. No statistically significant differences between groups for secondary outcomes.
Garfinkel et al., 2007[175]	Geriatric – Palliative algorithm	Case control study Follow-up: 1 year	Nursing home residents 190 patients (119 intervention patients; 71 control patients)	Change in number of medications Mortality Unplanned hospital presentations	Mean of 2.8 medications discontinued in the intervention group. Mortality 45% in control group vs 21% in intervention group ($p<0.001$) Transfers to acute hospital 30% in control group vs 11.8% in the intervention group ($p<0.002$)

Legend: QOL = quality of life; RCT = randomized controlled trial

1.5 CONCLUSION

Older people with multimorbidity and frailty are amongst the highest consumers of prescription medications. While it may be possible to justify individual drugs on the basis of medical indication, the cumulative effect of multiple medications may result in net harm to the patient. The pharmacotherapy evidence base has serious limitations when applied to frail multi-morbid older people and, as older people enter the final phase of life, polypharmacy may be associated with unnecessary burden, adverse drug reactions and increased healthcare costs.

An acute hospital admission in an older person often signals a change in survival trajectory and therefore could serve as a trigger to review medications and goals of care. As discussed, approximately one-in-four older adults admitted to hospital with acute illness will be deceased within a year. [109, 110] The challenge for clinicians is to distinguish between those who are likely to regain health and those who are in irreversible decline. In this regard, the HOMR model appears promising but requires independent validation in an older hospitalized sample.

The last year of life for many older people is a period of high symptom burden with frequent and prolonged hospital admissions. It follows then that the last year of life is also likely to be a period of high medication burden, especially during periods of acute illness. To date, this has not been demonstrated in any clinical study. If shown to be true, it reinforces the value of conducting a formal medication review for frail older people when they present to hospital with acute illness. The goal of such a review would be to strike a balance between high quality evidence-based care and burdensome and potentially harmful polypharmacy.

Identifying deprescribing targets is challenging, especially in multimorbid older adults who are at high risk of clinical deterioration. The use of explicit deprescribing criteria (e.g. STOPPFrail) is appealing because it could simplify the process of deprescribing for physicians of different disciplines, who do not necessarily have expertise in geriatric pharmacotherapy. However, at this point, it is unclear whether STOPPFrail criteria are comprehensive enough to be considered a reasonable alternative to specialist medication review. In addition, up to now, there have been no randomized controlled trials using STOPPFrail criteria as an intervention tool. Therefore, it is uncertain whether application of STOPPFrail criteria can reduce medication burden for frail older people without adversely affecting clinical outcomes.

In subsequent chapters, through a series of original studies, I will attempt to address some of these key issues.

CHAPTER 2

Predicting one-year risk of death in older hospitalized patients: external independent validation and update of the Hospital-patient One-year Mortality Risk (HOMR) model

2.1 INTRODUCTION

An important principle when caring for an older person with frailty and multi-morbidity is to align treatments and interventions to the patient's condition, preferences, and prognosis.[176] When life expectancy is limited, interventions to optimize quality of life may be prioritized over invasive procedures and potentially futile treatments. Patient-centred discussions about goals of care and, indeed, decisions about the deprescribing of long-term medications, are often deferred in frailer older patients because of physician discomfort and lack of confidence in making accurate prognostic assessments.[177, 178] As discussed in Chapter 1, physicians commonly over-estimate remaining life expectancy in their patients.[114, 116] It follows then that they may unnecessarily treat their patients with potentially futile medications. An accurate estimate of prognosis, especially when risk of death is high, could inform and motivate discussions between physicians and their patients about values, priorities, and therapeutic goals.

The Hospital patient One-year Mortality Risk (HOMR) model has recently been shown to accurately predict one-year mortality risk at the time of hospital admission for adult (i.e. ≥ 18 years), non-psychiatric patients.[125, 126] It is comprised of covariates that include demographics, co-morbidities, severity of acute illness, and recent acute hospital care utilization (**Figure 2.1**). These covariates are determined at hospital admission using health administrative data. Over 3 million patients aged 18 or older were included in the validation studies in Ontario and Alberta (Canada), and Boston (United States).[125, 126] The HOMR model had a very high discriminative performance (an area under the receiver operating characteristic (ROC) curve of 0.89 -0.92) and there was a less than 1% difference between the observed and expected percentages of deceased patients at 1 year.

Figure 2.1: Covariates used to calculate a patient's Hospital-patient One-year Mortality Risk (HOMR) score.

Sex	Points
Female	0
Male	1

ED visits	Points
Female	0
Male	1

Home O_2	Points
No	0
Yes	1

Admission directly to ICU	Points
No	0
Yes	1

Admissions by ambulance	Points
0	0
1	3
2	4
≥3	5

Sex	Points
No	0
Yes	1

Diagnostic Risk Score
See **Appendix 2**

Charlson Comorbidity Index score			
Diagnosis	Points	Diagnosis	Points
Myocardial infarction	1	Diabetes with chronic complications	2
Heart failure	2	Hemi- or paraplegia	1
Peripheral vascular disease	1	Renal disease	3
Cerebrovascular disease	1	Nonmetastatic cancer	2
Dementia	3	Moderate to severe liver disease	4
Chronic respiratory disease	2	Metastatic cancer	6
Mild liver disease	2	HIV infection	4
Diabetes without complications	1	**Total comorbidity score**	

Charlson Comorbidity Index score: Age x comorbidity

Age, yr.	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**
20-24.9	0	3	5	7	8	9	10
25-29.9	2	5	7	9	10	11	11
30-34.9	4	7	9	11	12	12	13
35-39.9	7	9	11	12	13	14	15
40-44.9	8	11	13	14	15	15	16
45-49.9	10	13	14	15	16	17	17
50-54.9	12	14	16	17	17	18	18
55-59.9	14	16	17	18	19	19	17
60-64.9	15	17	18	19	20	20	18
65-69.9	17	19	20	21	21	22	20
70-74.9	18	20	21	22	22	23	21
75-79.9	20	21	22	23	23	24	22
80-84.9	21	23	23	24	24	25	25
85-89.9	23	24	25	25	25	26	26
90-94.9	24	25	26	26	26	27	27
≥95	25	26	27	27	27	28	28

Living status/ admission urgency x admissions by ambulance

	No. of admissions by ambulance			
	0	**1**	**2**	**≥3**
Living status				
Home, independent	0	0	0	0
Rehabilitation facility	3	3	2	2
Home with home care	4	3	3	3
Nursing home	4	4	4	3
Chronic care hospital	8	6	5	5
Admission urgency				
Elective	0	0	0	0
ED, no ambulance	3	1	0	0
ED, ambulance	5	2	1	0

Admitting service	Points
Medicine	
General medicine	10
Cardiology	8
Gastroenterology/ nephrology/ neurology	9
Palliative care	28
Haematology/ oncology	14
Gynaecology	7
Surgery	
General surgery	8
Cardiovascular surgery	9
Neurosurgery	10
Orthopaedic/ plastic surgery	7
Thoracic/ transplant surgery	7
Trauma	8
Urology	6

Covariate	Total points
Sex	
ED visits	
Home O_2	
Diagnostic Risk Score	
Admission to ICU	
Admissions by ambulance	
Urgent readmission	
Admitting service	
Age x comorbidity	
Living status x admissions by ambulance	
Admission urgency x admissions by ambulance	
Total HOMR score	_____

Legend: ED = emergency department; HIV = human immunodeficiency viruses; ICU = intensive care unit.

The HOMR model's performance exceeds that of other similar prognostic models. However, it has not been validated in an exclusively older hospitalized patient population. In addition, like many published prognostic models, the HOMR model has yet to be externally validated by investigators who were not involved in its development. This is important because before a model can be applied in clinical practice with confidence, it needs to be tested in new patients and in different geographical regions.[179] The aim of this study was to evaluate the performance of the HOMR model in a population of older hospitalized patients in a large teaching hospital in Ireland.

2.2 METHODS

2.2.1 Data collection

The HOMR model was retrospectively applied to all hospitalized patients aged 65 years or older that were under the care of the specialist geriatric medicine service in Cork University Hospital from January 1st 2013 to March 6th 2015. When patients were admitted more than once during that period, a single hospital admission was chosen at random as the index hospitalization. Most of the information required to calculate the HOMR model was obtained using administrative data from the Hospital In-Patient Enquiry system (HIPE -a national database of coded discharge summaries). The *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification* (ICD-10-AM), Australian Classification of Health Interventions (ACHI) and *Australian Coding Standards* (ACS) apply to all activity coded in HIPE in Ireland.[180] Details about home supports prior to admission as well as provision of home oxygen therapy, which are not routinely collected by administration staff in Ireland, were obtained from the consultant geriatrician hospital discharge reports. When information was missing from these sources, the patients' medical records were reviewed. Covariate values were determined independently by two researchers with discrepancies resolved through consensus.

Deaths within one year of hospital admission were determined by accessing the hospital clinical information system, an online death notification system (https://www.RIP.ie), the Births, Deaths and Marriages Registry Office in Cork City, and, if required, by contacting the patient's general practitioner. Unlike the initial HOMR derivation and validation studies, patients who died during the index hospital admission were not included. There were two reasons for this. Firstly, geriatrician discharge reports were used to obtain information about home supports for the HOMR model, and these details were generally not included when the patient died during hospitalization. Secondly, the value of the predictive model, for the present project, is to calculate 1-year mortality risk after the acute hospital episode. Predicting in-hospital deaths largely depends on specific clinical factors.

2.2.2 Statistical analysis

A sample size that results in at least 100 events, and preferably 200 or more events, is recommended to externally validate a prognostic model.[181] It was estimated that one-year mortality *after* hospital discharge would very likely exceed 15%,[109,182] and on that basis I calculated that a sample size of 1400 patients would be required.

To validate the HOMR model, the linear predictor for each patient was calculated based on the coefficient values provided in Appendix E of the original HOMR model development study.[125] The HOMR model was then evaluated in terms of its overall performance, discrimination and calibration. The model's overall performance was evaluated using the Brier score, rescaled to range from 0 to 1, with higher values indicating better performance.[183] Discrimination, which refers to how well the model distinguishes those with the outcome from those without the outcome (i.e. death in this case), was measured using the concordance (c) statistic. Calibration refers to the agreement between observed outcomes and predicted outcomes and is usually displayed using a calibration plot. For a perfectly calibrated model, the plotted values should lie on a 45˚ straight line.[184] In addition to calibration plots, the maximum and average difference in predicted versus loess-calibrated probabilities (Emax and Eavg) are reported.[185] Finally, bootstrapped 95% confidence intervals for these metrics are reported, based on 500 resampled replicates.[186]

To recalibrate the HOMR Model, the procedure described by Vergouwe *et al.* was followed and three additional logistic regression models were estimated.[187] The first additional model included the HOMR linear predictor, with its coefficient set to equal 1, and a freely estimated intercept (**Recalibration in the Large**). The second model then allowed the coefficient on the HOMR linear predictor to be freely estimated (**Logistic Recalibration**). The third model included the complete set of variables used in the HOMR model, including the same transformations and interactions, and allowed their respective coefficients to be freely estimated (**Model Revision**). The performance of each of these models was assessed using the same metrics used to validate the original HOMR model. In addition, optimism corrected c-statistic and shrinkage factor were estimated for the Model Revision using bootstrapping (with 500 re-sampled replicates). All analyses were conducted using the R language for statistical computing,[188] version 3.4.3 (2017-11-30). Expert statistical support for this study was provided by Dr. Darren Dahly, senior lecturer in the School of Public Health, University College Cork.

2.3 RESULTS

2.3.1 Characteristics of study population

Between January 1st 2013 and March 6th 2015, 1654 individual patients aged 65 year or older were hospitalized under the care of the specialist geriatric medicine service in Cork University Hospital. Of these, 206 patients (12.4%) died during the index hospitalization and therefore were not included in the analysis. After removing 39 patients with missing outcome data (2.7%), a final cohort of 1409 patients were analysed. Of these, 259 (18.4%) died within 1 year of admission to hospital. The median age of the study patients was 80 years (interquartile range 74 -85), two thirds were living independently prior to their hospital admission, and 94.5% of patients were admitted through the emergency department. The baseline characteristics of the study participants are summarized in **Table 2.1**.

Table 2.1: Baseline characteristics of study participants (and how they compare to original derivation cohort[125]).

Variable	Mean SD	Median [IQR]	(Min, Max)	HOMR derivation cohort
Sex				
Female	800 (56.8%)			61.8%
Male	609 (43.2%)			38.2%
Age	79.3 ± 7.4	80 (74, 85)	(65, 101)	59 (IQR 37 - 75)
Living Status*				
Independent	933 (66.2%)			83%
Rehabilitation Unit	33 (2.3%)			0.2%
Homecare	295 (20.9%)			12.1%
Nursing Home	148 (10.5%)			4.5%
Urgency of admission				

Elective	78 (5.5%)			47.4%
ED without Ambulance	498 (35.3%)			25.7%
ED with Ambulance	833 (59.1%)			26.9%
Number of ambulance transfers**	0.3 ± 0.7	0 (0, 0)	(0, 5)	N/A
Admitting Service***				
General Medicine (including geriatric medicine)	1365 (96.9%)			31.4%
General Surgery	3 (0.2%)			11%
Cardiology	17 (1.2%)			6.4%
Orthopedics	8 (0.6%)			8.4%
Gastroenterology/Nephrology/ Neurology	16 (1.1%)			4.9%
ICU admission (directly from emergency department)	3 (0.2%)			7.4%
Home O_2*	0			2.3%
ED Visits**				
0	828 (58.8%)			55.1%
≥1	581 (41.2%)			44.9%
Urgent readmission within 30 days	131 (9.3%)			4.5%
DRS	-1.9 ± 4.8	0 (-1, 0)	(-22, 9)	N/A
CCI****				
0	23.3%			57.8%
1-2	34.2%			21.7%
≥3	42.5%			20.5%

Legend: CCI =Charlson Comorbidity Index; DRS = Diagnostic Risk Score; ED = emergency department; HOMR = Hospital-patient One-year Mortality Risk; ICU = intensive care unit; IQR = interquartile range; N/A = not available; SD = standard deviation. *Prior to index hospitalization. ** In 12 months prior to index hospitalization.*** All patients, after hospital admission, were under the care of the specialist geriatric medicine service. **** Not adjusted for patient age.

2.3.2 HOMR model external validation

When the HOMR model was applied directly to the sample of 1409 older patients, it showed good discrimination (c statistic =0.78). Calibration, however, was poor (see **Figure 2.2** for calibration plot) with the model consistently over-estimating mortality at all but the lowest levels of risk (see **Table 2.2** for performance metrics).

Figure 2.2: Calibration plot of the unadjusted Hospital patient One-Year Mortality Risk (HOMR) model

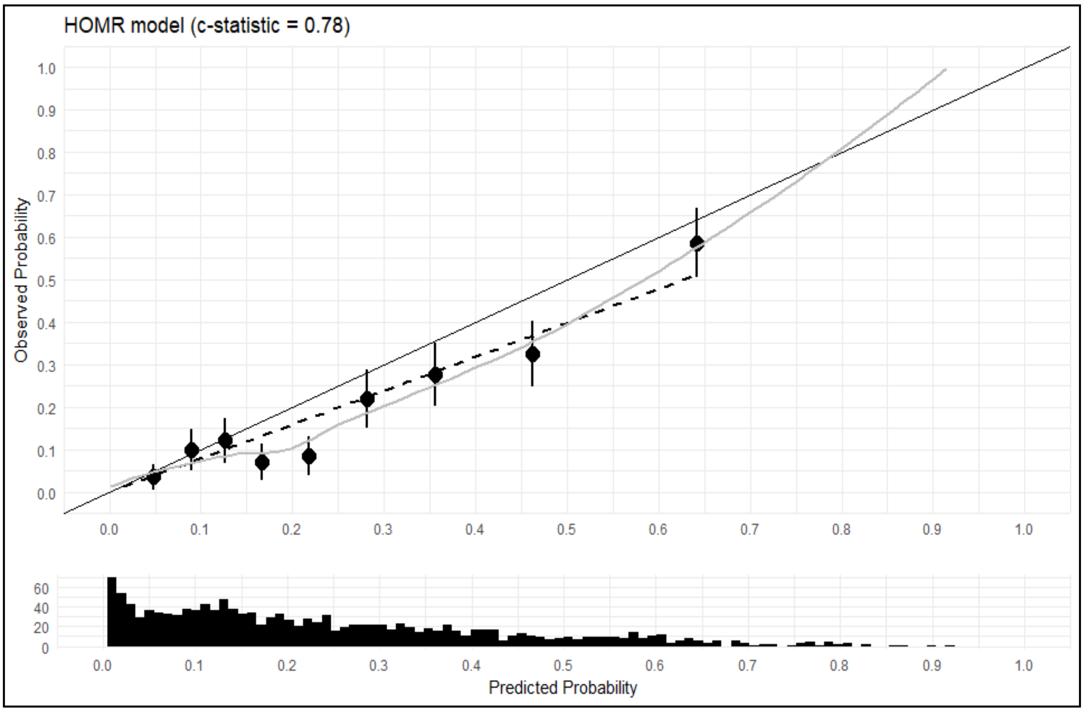


Table 2.2: Performance of the unadjusted and updated Hospital patient One-Year Mortality Risk (HOMR) models.

	HOMR model	**Calibration in the Large**	**Logistic Recalibration**	**Model Revision**
Intercept	0	-0.42	-0.43	-
Slope	1	1	0.99	-
Residual deviance	1139.96	1107.76	1107.73	1046.55
Df	1409	1408	1407	1389
LRT Chi sq p-value	-	<0.001	0.85	-
Brier score (rescaled)	0.15 (0.1 to 0.21)*	0.19 (0.13 to 0.25)	0.19 (0.13 to 0.26)	0.23 (0.18 to 0.31)
Emax	0.103 (0.085 to 0.146)	0.111 (0.03 to 0.225)	0.121 (0.03 to 0.236)	0.017 (0.016 to 0.094)
Eavg	0.058 (0.046 to 0.072)	0.016 (0.01 to 0.028)	0.017 (0.009 to 0.029)	0.008 (0.005 to 0.016)
c-statistic	0.78 (0.76 to 0.81)	0.78 (0.75 to 0.81)	0.78 (0.76 to 0.81)	0.82 (0.8 to 0.85)
* Bootstrapped 95% confidence intervals				

Legend: Df = degrees of freedom; LRT = likelihood ratio test; Emax = maximum absolute difference in predicted and calibrated probabilities; Eavg = average absolute difference in predicted and calibrated probabilities.

2.3.3 Performance of updated HOMR model

All three updating methods improved calibration over the original model (**Figure 2.3**). Recalibration in the Large resulted in a lower intercept (-0.42; see **Table 2.2**) and a significant improvement in model fit over the HOMR model (likelihood ratio test [LRT] Chi-square p value= <0.001). Logistic Recalibration did not lead to additional improvements in model fit (LRT Chi-square p value = 0.85), with a recalibration slope of 0.99 (i.e. close to 1). The Brier score and Eavg were improved by recalibration (**Table 2.2**). Calibration plots for Recalibration in the Large (which is virtually identical to the plot for Logistic Recalibration) and Model Revision are shown in **Figure 2.3**. In addition to improving calibration, Model Revision also improved discrimination (c statistic =0.82) which indicates that the relationship of the predictors and the outcome is different in our older patient sample. The optimism corrected c-statistic for the Model Revision was 0.8, and the shrinkage factor was 0.91, indicating some overfit. The re-estimated HOMR model, with regression coefficients, is shown in **Table 2.3**.

Figure 2.3: Calibration plots of the updated Hospital patient One-year Mortality Risk (HOMR) models.

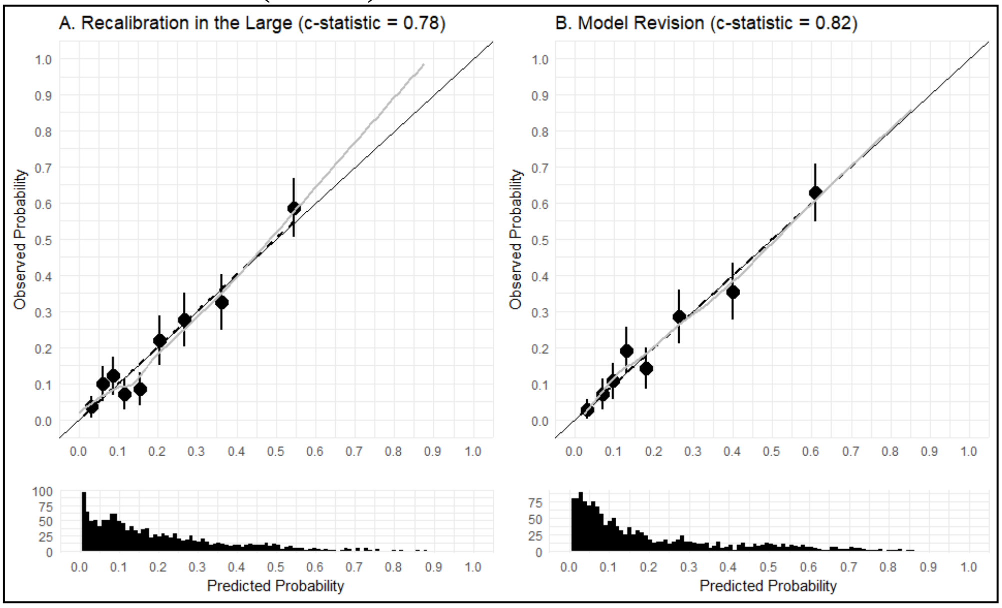


Table 2.3: HOMR Model Revision with regression coefficients

Variable	1-year post-hospitalization mortality
DRS	0.11 (0.07, 0.15)
sqrt (Age)	1.45 (0.60, 2.30)
Male (vs Female)	0.44 (0.12, 0.77)
Rehab	0.82 (-1.75, 3.38)
Homecare	1.16 (-0.24, 2.56)
Nursing Home	1.56 (0.13, 2.99)
log (CCI)	2.78 (-2.76, 8.33)
sqrt (Ed visits in the previous year + 1)	0.16 (-1.23, 1.55)
1/ (Admissions by ambulance in previous year +1)	-2.03 (-4.75, 0.70)
Other (vs General Medicine)	-0.68 (-1.58, 0.22)
ED w/o Ambulance	-0.83 (-3.16, 1.49)
ED w/Ambulance	-1.21 (-3.41, 0.98)
Urgent readmission	0.60 (0.07, 1.12)
Sqrt (Age) log (CCI)	-0.23 (-0.84, 0.38)
Rehab 1/ (Admissions by ambulance in previous year +1)	-0.15 (-3.66, 3.36)
Homecare 1/ (Admissions by ambulance in previous year +1)	0.31 (-1.23, 1.85)
Nursing Home 1/ (Admissions by ambulance in previous year +1)	-0.20 (-1.91, 1.52)
ED w/o Ambulance 1/ (Admissions by ambulance in previous year +1)	1.04 (-1.73, 3.81)
ED w/Ambulance 1/ (Admissions by ambulance in previous year +1)	1.91 (-0.71, 4.53)
Intercept	-14.79 (-22.86, -6.72)
Observations	1,409
Log Likelihood	-523.28
Akaike Information Criterion	1,086.55

Note:

1. Admitting service recoded to General Medicine vs Other, due to small cell sizes. ICU admission from the model was omitted as there were only 3 cases of this happening. Home O2 was omitted from the model since no patients in our sample were using it.
2. One-year mortality risk for individual patients can be calculated with the formula: Risk = exp (linear predictor) / (1 + exp (linear predictor).

Legend: CCI = Charlson Comorbity Index; DRS = diagnostic risk score; ED = emergency department; ICU = Intensive care unit; sqrt =square root.

2.4 DISCUSSION

This study provides information about the performance of the HOMR model in new patients, in a different geographical region, when validated by investigators who were not involved in the model's development. The highly discriminative performance reported in the initial validation studies was substantially attenuated in the heterogenous multi-morbid hospitalized older cohort of the present study and calibration was found to be poor with the model consistently overestimating mortality risk. The results illustrate the importance of testing seemingly accurate prediction models in target populations before applying them widely in routine practice.

There are plausible reasons for the reduced predictive performance in this external validation study. Firstly, the patients in the present cohort were substantially older (median age was 80 years versus 59 years in the HOMR derivation cohort) and less likely to be living independently (66.3% versus 83%).[125] Secondly, unlike the initial validation studies, patients who died during their index hospital admission were excluded. This is likely to have had a significant impact on the HOMR-based mortality prediction because one of the HOMR covariates, the diagnostic risk score (see **Appendix 2**), quantifies risk of death based on specific admission diagnoses. High diagnostic risk scores associated with diagnoses such as intracerebral haemorrhage and sepsis reflect high risk of death during hospitalization. This risk may diminish significantly when patients survive the initial days of their acute hospital episode. Thirdly, it is unclear whether the diagnostic risk scores, which were derived from a large population of adult patients of all ages, are weighted appropriately for older hospitalized patients. An admission diagnosis of syncope, for example, is assigned a diagnostic risk score of -9 which probably reflects its usually benign prognosis in younger adults. In contrast, syncope, in older adults, is associated with reduced survival.[189] Finally, substantial differences in access to and organization of primary care services between North

America and Ireland may have had an important impact on covariates relating to recent acute hospital care utilization (i.e. ambulance transfers, emergency department visits, readmissions). [190, 191]

Our findings are not surprising: the accuracy of predictive models is often substantially lower in new patient populations compared to the accuracy found in patients of the development population.[192 -194] Rather than simply reject the model, updating methods were used to try to improve performance of in our older patient cohort. Updating methods adjust the prediction model to new patients by combining valuable information captured in the original development study (a very large data set) with the information of the validation cohort.[195] In this study, recalibration in the large (the simplest updating method where just one parameter of the original model [i.e. the intercept] is adjusted) substantially improved performance. While model revision resulted in further improvements, this more extensive updating method is less ideal because parameter estimates are redeveloped from the data of the validation set (a much smaller sample) and prior information from the larger derivation sample is neglected.[195]

The performance of the recalibrated HOMR model compares favourably with other validated prognostic models for older hospitalized patients that were included in a 2012 systematic review by Yourman *et al.* [124, 194 -204] (**Table 2.4**). Indeed, the predictive performance of the recalibrated HOMR model exceeds that of some risk models used widely in routine clinical practice, such as the CHADS2-VASc (c-statistic, 0.61)[205] and HAS-BLED (c-statistic, 0.72)[206] models. However, it is important to emphasize that the updated HOMR models, just like a newly developed model, require testing of their generalizability, as well as their impact on clinician behaviour and patient outcomes, before either can be recommended for use in daily clinical practice.[207]

Table 2.4: Summary of prognostic models used to predict mortality in hospitalized older patients.

Model	Description	c-Statistic: Derivation	Validation	Independent validation
HELP, 2000[196]	Patients ≥80 years, emergency admissions	c= 0.73 (N=1266)	C=0.74 (N=150)	-
Walter et al., 2001[197]	Patients ≥70 years, discharged from general medicine service	c=0.75 (N=1495)	C=0.79 (N=1427)	c=0.72[194] (N=100; patients ≥75; 1-year mortality prediction)
BISEP, 2003[198]	Patients ≥70 years, admitted under general medicine service	c=0.83 (N=525)	C=0.77 (N=1246)	c=0.72[194] (N=100; patients ≥75; 1-year mortality prediction)
CARING, 2006[199]	Adult patients admitted under general medicine service	c=0.82 (N=435)	C=0.79 (N=1064)	c=0.63[194] (N=100; patients ≥75; 1-year mortality prediction)
Levine et al., 2007[200]	Patients ≥65 years discharged from general medicine service	c=0.67 (N=2739)	C=0.65 (N=3643)	c=0.64[194] (N=100; patients ≥75; 1-year mortality prediction)
MPI, 2008[201]	Patients ≥65 years admitted to geriatric unit	c =0.75	C=0.75[202]	-
SAFES, 2008[203]	Patients ≥75 admitted through the emergency department	c=0.72 (N=870)	C=0.71 (N=436)	-
Silver Code, 2010[204]	Patients ≥75 admitted through the emergency department	c=0.66 (N=5457)	C=0.64 (N=5456)	c = 0.51[194] (N=100; patients ≥75; 1-year mortality prediction)
HOMR, 2014[125]	Adult patients of all ages admitted under non-psychiatric hospital services	c=0.92 (N=319 531)	C=0.89 - 0.92[126] (N= 2 862 996)	c =0.78 (N=1409; patients ≥65 years discharged from geriatric service; model re-calibrated for validation sample)

Legend: BISEP = Burden of Illness Score for Elderly Persons; CARING = cancer, ≥2 admissions, residence in a nursing home, intensive care unit admission with multiorgan failure, ≥2 noncancer hospice guidelines; HELP = Hospitalized Elderly Longitudinal Project; HOMR = Hospital patient One year Mortality Risk; MPI = Multidimensional Prognostic Index; SAFES = Sujet Agé Fragile—Evaluation et Suivi (Frail Elderly Subject – Assessment Follow-up).

With further revision, refinement and validation, it may be possible to optimize the performance of the HOMR model for older hospitalized patients. Even then, its impact on decision-making will need to be tested.[207] Determining the threshold for deviating from the standard of care may be difficult: a 50% one-year risk of death for an individual patient is highly relevant; however, at the end of that particular year, the patient is as likely to be alive as deceased. Prognostic estimates, therefore, even when very accurate, may not necessarily enhance certainty when making difficult clinical decisions.[208]

The HOMR model uses administrative data rather than specific clinical information (e.g. severity of chronic disease) to calculate one-year mortality risk. In addition, social supports (i.e. requirement for home care, residence in a nursing home) are used as a surrogate for functional status. Like other prediction models that have been derived from large databases, the HOMR model provides information about the probability of an outcome for the "average patient" with a given set of predictors. It tells us very little about the individual patient and his or her needs. Therefore, it is questionable whether this reductionist approach can add value to the delivery of end-of-life care at an individual patient level.

The present study has some limitations. Firstly, the HOMR model was applied and updated in a single medical centre where patients were cared for by specialist geriatricians. As discussed, this limits the generalizability of our findings and further validation in other centres is required. Secondly, we used the model differently to how it was originally designed by excluding patients who died during their index admission. However, we contend that the primary purpose of an accurate 1-year mortality prediction in a hospitalized patient would be to help guide decision-making and care-planning *after* the acute episode when the patient's condition has stabilized.

In conclusion, the exceptionally accurate 1-year mortality predictive performance of the HOMR model, reported in the North American validation studies, was significantly attenuated in a cohort of older hospitalized patients in a large teaching hospital in Ireland. Nevertheless, the performance of the HOMR model in our older patient cohort was demonstrably good and compares favourably to other validated non-disease specific mortality prediction tools for application in older people. Updating methods improved performance of the HOMR model but further refinement, validation, as well as clinical impact studies will be required before the model could be applied confidently in routine practice.

CHAPTER 3

Drug consumption and futile prescriptions: an observational study of hospitalized older patients in the last year of life

3.1 INTRODUCTION

Large observational studies have shown that hospitalizations are frequent in the last year of life.[104, 107, 108] Hospital physicians, therefore, have an opportunity to optimize medication regimens for older people with advanced frailty or end-stage chronic disease. This task involves tailoring treatments to the condition, preferences and prognosis of the individual patient.[176] In the context of burdensome polypharmacy, symptom control often takes priority over achieving strict chronic disease targets or preventing future adverse health events.

Many frail, multi-morbid older people may not have the benefit of a formal medication review while they are in hospital. Hospital physicians may not feel confident or competent with addressing potentially inappropriate polypharmacy or may believe that they are solely responsible for medicine management within their own particular specialty.[209] Status quo bias (a preference for continuing with usual medications, especially if they have been in place for years) and fear of negative consequences such as symptom relapse, litigation, increased workload are other barriers to deprescribing.[178, 210]

As discussed in Chapter 1, the STOPPFrail criteria (**Figure 1.6**) are an explicit list of 27 indicators to assist physicians with deprescribing decisions in frail older individuals with poor one year survival prognosis.[147] As a deprescribing tool, STOPPFrail is concise, easy-to-use and designed to be used by clinicians of all disciplines who commonly provide care for older people.[147] However, the relevance and potential applicability of the STOPPFrail list for older people hospitalized in the last year of life has not yet been studied.

Accordingly, the aims of this study were:

1. To determine the prevalence of potentially inappropriate medications (PIMs), as defined by the STOPPFrail tool, in the discharge prescriptions of older adults hospitalized in the last year of life.
2. To measure medication consumption by older people while in hospital in the last year of life.

3.2 METHODS

3.2.1 Study population

We included people aged ≥ 65 years who were hospitalized for ≥ 2 days under general medical services in a major teaching hospital in the year prior to death. The Hospital In-Patient Enquiry system (a national database of coded discharge summaries) was used to identify patients discharged between January 2013 to December 2014. When patients were admitted more than once during this period, a single hospitalization was randomly chosen as the index hospitalization. Patients who died during their index hospital admission and those discharged to a hospice, presumably in the final stages of a terminal illness, were excluded because the primary end point was to measure the prevalence of STOPPFrail-defined PIMs at the time of discharge. Deaths within one year of hospitalization were determined by accessing the Hospital Information System and an online death notification system (https://www.RIP.ie). In total, 603 patients were eligible for inclusion. We estimated that 50% of patients would be prescribed PIMs at discharge. Using a precision of 5% and a 95% level of confidence, we calculated that a minimum sample of 384 patients would be required for this study (**Figure 3.1**). To ensure an adequate final sample size, a random sample of 434 was generated using a randomization (RAND) function in Microsoft Excel©. The local Clinical Research Ethics Committee approved the study protocol (see **Appendix** x).

3.2.2 Data collection

A retrospective chart review was conducted on all study patients by a Geriatric Medicine trained physician (Dr. Denis Curtin) using a standardized data collection pro forma. The prevalence of STOPPFrail-defined PIMs was measured by accessing the discharge prescriptions from the patients' index hospitalization. Disease burden and performance status at the time of hospital discharge were determined using the Charlson Co-morbidity Index (CCI)[211, 212] and the Clinical Frailty Scale (CFS)[139] respectively. The CFS is a 9-item scale and, in this study, we categorized patients into 2 groups: (i) those with scores of ≥ 7 (indicating severe frailty and/or terminal illness and therefore potentially eligible for the STOPPFrail tool) and (ii) those with scores < 7 (indicating full independence, mild or moderate frailty). Medication consumption was determined by reviewing inpatient medication administration records from all hospitalizations in the last year of life. Medications that were prescribed but not consumed were not included, nor were nutritional products, blood products or intravenous fluids. A single ingredient constituted one medicine. For combination products, each ingredient was included as one drug as long as that ingredient was available as a medicine in the British National Formulary.

3.3 RESULTS

3.3.1 Patient characteristics

In total, 410 patients were included (24 patients were excluded because of missing data or because they were discharged to the care of community palliative services).

The principal characteristics of the decedents are summarized in **Table 3.1**. The mean age of patients was 80.8 years (standard deviation [SD] 7.9 years) and 49.3% were female. Polypharmacy was highly prevalent and the mean number of medications per patient at the time of hospital admission was 8.4 (SD 4.3). At the time of hospital discharge, 63.7% of patients were either severely frail or had an advanced terminal diagnosis (CFS ≥7).

Table 3.1: Baseline characteristics of study population

Variable	Total (n=410)
Mean age (SD) at time of index hospitalization	80.8 (7.9)
Female (%)	202 (49.3%)
Median no. of days (IQR) between index hospitalization and death	124 (47-225.5)
Home status prior to index admission: Independent	139 (33.9%)
Home with home care	198 (48.3%)
NH resident	73 (17.8%)
Discharge health/functional status: Mean (SD) CCI score	6.24 (2.3)
CFS ≥7	261 (63.7%)
Mean number (SD) of admission medications	8.4 (4.3)
Mean number (SD) of discharge medications	8.7 (4.2)

Legend: CCI = Charlson co-morbidity index; CFS = Clinical Frailty Scale; IQR = interquartile range; NH = nursing home; SD = standard deviation

3.3.2 Prevalence of STOPPFrail PIMs at hospital discharge

The mean number of medications prescribed per patient did not change significantly from index hospital admission to discharge (8.4 [SD 4.3] versus 8.7 [SD 4.2], p= 0.275). More than 80% of patients were prescribed at least one STOPPFrail-defined PIM in their discharge prescription and 34% had ≥ 3 PIMs prescribed (**Table 3.2**). The mean number of PIMs did not differ significantly between patients' potentially eligible for STOPPFrail-guided deprescribing (CFS ≥7) and those with less advanced stages of frailty (2.0 [SD 1.5] versus 1.8 [SD 1.4], p= 0.053). Full implementation of the STOPPFrail recommendations for those with polypharmacy (defined here as ≥ 5 long term medications) would have resulted in, on average, a 23% reduction in total medication burden. Lipid lowering medications, proton pump inhibitors, anti-psychotics and calcium supplements accounted for 59% of all STOPPFrail-defined PIMs (**Table 3.3**).

Table 3.2: STOPPFrail-defined potentially inappropriate medications (PIMs) prescribed per patient at hospital discharge

	Total
Mean no. of PIMs per patient (SD)	1.95 (1.4)
Mean no. of PIMs/patient (SD) in patients discharged ≥30 days from death	1.97 (1.4)
Mean no. of PIMs/patient (SD) in patients with CFS ≥7	2 (1.46)
≥1 PIM per patient	81.5%
≥3 PIMs per patient	34%

Legend: PIM = potentially inappropriate medication; SD = standard deviation

Table 3.3: Most frequently encountered potentially inappropriate prescriptions according to STOPPFrail criteria in 410 patients.

STOPPFrail Criteria	n
A1: Any drug that the patient persistently fails to take or tolerate	8
A2: Any drug without clear clinical indication	70
B1: Lipid lowering therapies	147
B2: Alpha-blockers for hypertension	6
C1: Anti-platelets for primary cardiovascular prevention	15
D1: Neuroleptic antipsychotics	48
D2: Memantine	14
E1: Proton Pump inhibitors	166
E2: H2 receptor antagonists	3
E3: Gastrointestinal antispasmodics	0
F1: Theophylline	7
F2: Leukotriene antagonists	5
G1: Calcium supplementation	105
G2: Anti-resorptive/ bone anabolic drugs	36
G3: Selective Estrogen Receptor Modulators for osteoporosis	0
G4: Long-term oral NSAIDs	1
G5: Long-term oral steroids	31
H1: 5-alpha reductase inhibitors with long-term bladder catheterisation	0
H2: Alpha blockers with long-term bladder catheterisation	1
H3: Muscarinic antagonists with long-term bladder catheterisation	0
I1: Diabetic oral agents	24
I2: ACE-inhibitors for diabetes	5
I3: Angiotensin receptor blockers	0
I4: Systemic oestrogens for menopausal symptoms	0
J1: Multivitamin combination supplements	8
J2: Nutritional supplements (other than vitamins)	84
J3: Prophylactic antibiotics	12

3.3.3 Drug consumption while in hospital in the last year of life

In the year prior to death, the median number of days in hospital in this population of patients was 32 (interquartile range [IQR] 15-58). One-third of patients had 3 or more emergency department presentations in their last year. During all hospital stays in the last year of life, the mean number of individual medications consumed per patient was 23.8 (SD 10.1). One-in-six patients consumed ≥ 35 different medications (**Table 3.4**). Long-term preventive medications accounted for 9.5% of all medications consumed during hospitalization but 24.9% of medications prescribed at the time of hospital discharge.

Table 3.4: Acute hospital care utilization and medication consumption in the last year of life

Variable	**Total**
Median bed days (IQR)	32 (15-59)
Median hospital admissions (IQR)	2 (1.25 -3)
Median emergency department episodes (IQR)	2 (1-3)
≥ 30 Bed days	53.4%
≥ 3 hospital admissions	43.4%
≥ 3 emergency department episodes	34%
No. of medications (SD) consumed during hospitalization	
Mean (SD)	23.8 (10.1)
≥ 25 medications	43.6%
≥ 35 medications	17.3%
Types of medications consumed during hospitalization:	
Disease/ symptom control	87.3%
Long-term preventive (i.e. anti-thrombotics, lipid-lowering agents, calcium, vitamin D, bisphosphonates, bone anabolic drugs)	9.5%
Short-term preventive (i.e. LMWH, influenza vaccine)	3.2%

Legend: IQR = interquartile range; LMWH= low molecular weight heparin; SD = standard deviation

3.4 DISCUSSION

This is the first study of its kind using recently validated explicit deprescribing criteria designed for application in the frailest older people. Our data show that older people in their last year of life experience high levels of polypharmacy, a quarter of which includes long-term preventive therapies which are likely to be futile. Hospital physicians need to be able to recognize frailer older patients in their last year of life, and be prepared to deprescribe thoughtfully where appropriate, particularly long-term preventive drugs where benefit is unlikely to be realized.

Symptoms at end-of-life are often complex and multifaceted. A large nationally representative longitudinal survey of adults in the United States reported that symptoms such as depression, confusion, dyspnoea, incontinence, fatigue, anorexia, and vomiting were all common in the last year of life.[213] While improvements can usually be made regarding prescribing quality, high levels of medication consumption may be inevitable. This is important because the number of medications prescribed is the most important predictor of iatrogenic harm.[214] The challenge for the prescribing physician is to strike a balance between controlling multiple symptoms and minimizing the inherent risks of polypharmacy.

Full implementation of STOPPFrail recommendations for hospitalized patients would have resulted in almost 1-in-4 long-term medications being discontinued. The process of deprescribing must, of course, be individualized and patients' preferences, clinical contextual factors, and the potential for adverse drug withdrawal events given due consideration. As discussed in Chapter 1, many of other available deprescribing tools (e.g. Scott's algorithm, [145] Geriatric –Palliative algorithm [144]) are *implicit* and demand that the prescriber achieves a reasonable balance between the risks and benefits of each medication. The real-world applicability of these methods to all but expert prescribers is doubtful and this likely explains why implicit deprescribing tools are rarely applied in routine clinical practice. The value of STOPPFrail is that it is explicit, concise, easy-to-use, and, as we have shown, highly relevant to the practice of hospital physicians.

Recognizing when people are in the final phase of life is key to operationalizing deprescribing. As demonstrated in Chapter 2, the excellent performance of the Hospital-patient One-year Mortality Risk (HOMR) model in its initial validation studies was substantially attenuated when applied to a cohort of older hospitalized patients in a large teaching hospital in Ireland. Furthermore, Yourman and colleagues' 2012 systematic review concluded that there was insufficient evidence to recommend application of any of the other published prognostic models for older adults.[124] Therefore, physicians may need to rely on their clinical judgement and accept that there will always be uncertainty when making prognostic assessments. Acknowledging this uncertainty during the physician-patient discussion may allow for more attention to be directed towards the preferences and priorities of the patient. Even so, it is important to note that the majority of patients in this study were severely frail (i.e. CFS $\geq$7) as they approached end-of-life. Perhaps then, it is hospitalized patients who are severely frail or who have severe chronic disease that should be considered appropriate candidates for deprescribing interventions?

This study has some limitations. Firstly, the experience described does not apply to the 18-29% of older people who are not hospitalized in the last year of life.[104, 107] However, the burden of symptoms, disease and medication are presumably less marked in this cohort. Secondly, we may have underestimated medication exposure and acute hospital care utilization because information about hospitalizations outside of our institution was not captured.

In summary, hospitalizations are common and drug burden is high among people in the last year of life who are frequently discharged home with prescriptions for potentially futile medications. The STOPPFrail criteria are highly relevant and may assist physicians with deprescribing decisions in this patient population.

CHAPTER 4

Deprescribing in multi-morbid older people with polypharmacy: Agreement between STOPPFrail explicit criteria and Gold Standard deprescribing using 100 standardized clinical cases

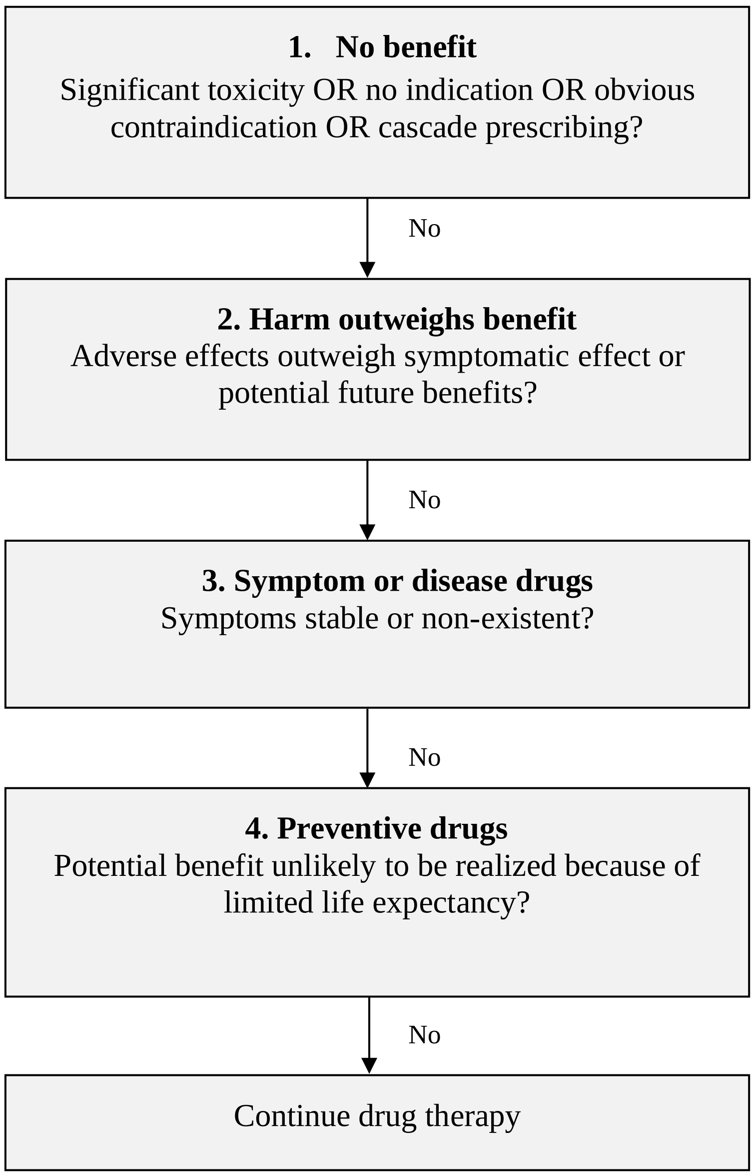
4.1 INTRODUCTION

The complexity associated with multimorbidity and polypharmacy necessitates a systematic approach to deprescribing potentially inappropriate medications. In Chapter 3, I showed that STOPPFrail-defined potentially inappropriate medications (PIMS) are commonly prescribed for older people approaching end-of-life. While this was important to demonstrate, it remains unclear whether the STOPPFrail criteria (which comprise just 26 explicit deprescribing indicators and one implicit indicator) are sufficiently comprehensive enough to be used as a tool to assist clinicians with deprescribing decisions in older people approaching end-of-life.

Scott and colleagues have recently proposed a 5-step deprescribing protocol (CEASE –**C**onfirm current medications; **E**stimate risk of drug-related harm; **A**ssess each medication for discontinuation; **S**ort/ prioritize medications for discontinuation; **E**liminate medications according to agreed deprescribing plan).[145] The third step –assessing each medication for discontinuation - requires the user to answer a series of questions about each medication in the patient's regimen (**Figure 4.1**).[145] While comprehensive and patient-centred, the outcome of this step will depend on the knowledge, attitudes and experience of the user. Implicit approaches, such as CEASE, are usually time-consuming, thereby greatly limiting their integration into routine clinical practice.[146]

The primary aim of the present study was to compare the utility of the structured predominantly explicit, STOPPFrail criteria with a gold standard comparator in frail older people with poor 1-year survival prognosis. Of the available published deprescribing tools, Scott's deprescribing algorithm has the strongest evidence of efficacy and physician acceptabilty,[173] and therefore, its use by a physician with expertise in clinical pharmacotherapy is likely to represent an appropriate gold standard for deprescribing. If STOPPFrail reproduces the results of this gold standard, then its brevity and easy usability may make it a more appropriate method of deprescribing in routine clinical practice for this particular older patient population. The secondary aim was to determine which potentially inappropriate or unnecessary medications are identified by the gold standard method but not by STOPPFrail. This information could inform future iterations of the STOPPFrail criteria.

Figure 4.1: Step 3 of the CEASE protocol: Scott's deprescribing algorithm[145]



4.2 METHODS

4.2.1 Clinical cases

To ensure that the comparison between the two deprescribing methods was valid, it was important to minimize external sources of variability.[215] For this reason, structured clinical cases were prepared to ensure timely and equal access to information relevant to the deprescribing decision (See **Appendix 3 f**or sample case). These clinical cases were based on anonymized patients included in the observational study that was described in Chapter 3. Each structured clinical case included a list of diagnoses, regular medications, functional and cognitive status and routine blood tests results prior to hospital discharge. All clinical cases were based on patients aged ≥65 years, prescribed ≥5 regular medications with moderate to severe frailty (Clinical Frailty Score ≥6 [139]). For each of the clinical cases, it was assumed that:

i. The patient was medically stable
ii. The patient had a poor 1-year survival prognosis
iii. The list of diagnoses was complete and correct
iv. Laxatives (unless potentially part of a prescribing cascade) and paracetamol were appropriate
v. There were no difficulties with medication administration (e.g. dysphagia, poor inhaler technique etc.) unless explicitly stated
vi. The patient's nutritional status was satisfactory unless otherwise stated
vii. Behavioural and psychological symptoms of dementia were present only if explicitly stated

4.2.2 Application of deprescribing methods

Four physicians, all trained in geriatric medicine, reviewed the clinical cases and identified medications that were potentially eligible for deprescribing. Two physicians (Dr. Denis Curtin and Dr. Desmond O'Donnell) rigidly applied STOPPFrail criteria while the other physicians (Dr. Kirstyn James and Dr. Tim Dukelow), who were not familiar with STOPPFrail criteria, identified drugs to be deprescribed using step 3 of the CEASE protocol (hereafter referred to as Scott's deprescribing algorithm; **Figure 4.1**). The physicians were instructed to document the primary reason for each deprescribing decision. Drugs that were not eligible for deprescribing were classified as 'important'. The physicians initially worked independently and then resolved any discrepancies in pairs to produce a final consensus list for each deprescribing method.

4.2.3 Sample size calculation and statistical analysis

A sample size of 100 was chosen to detect with 80% probability a Cohen's kappa coefficient of 0.70 under the alternative hypothesis when Cohen's kappa under the null hypothesis was 0.6. This sample size would also allow for more than 500 medications to be evaluated. Cohen's kappa coefficient 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 almost perfect if 0.81–1.00.[216] Statistical analysis was performed using SPSS® version 21.

4.3 RESULTS

4.3.1 Clinical cases

The mean number of medications per clinical case was 10.2 (standard deviation 3.3). The total number of medications to be evaluated (when paracetamol was excluded) was 994. Most medications were taken orally (88.7%), while the remainder were administered by inhaled (5.1%), transdermal (3%), topical (2%), or subcutaneous/ intramuscular (1.3%) routes.

4.3.2 Agreement between methods

The physicians using the Scott's deprescribing algorithm identified 524 medications (52.7% of the total) as potentially eligible for deprescribing; the physicians using STOPPFrail criteria identified 412 medications for deprescribing (41.4%; see **Table 4.1**). Cohen's kappa co-efficient was 0.60 (95% confidence interval 0.55 -0.65; $p<0.001$) indicating moderate agreement between the methods. With Scott's deprescribing algorithm representing the gold standard, the sensitivity of STOPPFrail (i.e. the proportion of *inappropriate* medications correctly identified by STOPPFrail) was 70.2%. The specificity (i.e. the proportion of *important* medications that were correctly continued by the physicians using STOPPFrail) was 90.6%. The positive predictive value of STOPPFrail (i.e. the proportion of medications deemed *inappropriate* by the physicians using STOPPFrail that were actually inappropriate) was 89.3% while the negative predictive value (i.e. the proportion of medications deemed *important* by the physicians using STOPPFrail that were actually important) was 73.2%.

Table 4.1: Contingency table of frequencies for medications deprescribed using Scott's algorithm and STOPPFrail.

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Scott's algorithm</td><td rowspan="2">Total</td></tr>
<tr><td>Deprescribe</td><td>Continue</td></tr>
<tr><td rowspan="2">STOPPFrail</td><td>Deprescribe</td><td>368</td><td>44</td><td>412</td></tr>
<tr><td>Continue</td><td>156</td><td>426</td><td>582</td></tr>
<tr><td colspan="2">Total</td><td>524</td><td>470</td><td>994</td></tr>
<tr><td colspan="2">Sensitivity (368/524)</td><td colspan="3">70.2% (95% CI, 66.3% to 74.1%)</td></tr>
<tr><td colspan="2">Specificity (426/470)</td><td colspan="3">90.6% (95% CI, 88% to 93.2%)</td></tr>
<tr><td colspan="2">PPV (368/412)</td><td colspan="3">89.3% (95% CI, 86.4% to 92.2%)</td></tr>
<tr><td colspan="2">NPV (426/582)</td><td colspan="3">73.2% (95% CI, 69.6% to 76.8%)</td></tr>
</table>

Legend: CI = Confidence interval; PPV = Positive predictive value; NPV = Negative predictive value.

The primary reasons for the deprescribing decisions are summarized in **Table 4.2**. 'No valid indication' was the primary reason for 50% of the deprescribing decisions made by the physicians using Scott's deprescribing algorithm and in 42.7% of the decisions made by the physicians using STOPPFrail. Lipid lowering agents, proton pump inhibitors, calcium and anti-resorptive drugs for osteoporosis accounted for 33% of the medications deprescribed using STOPPFrail.

Table 4.2: Primary reasons for deprescribing decisions by each method.

Scott's deprescribing algorithm (N=524)	N	(%)	STOPPFrail (N=412)	N	(%)
1. **No benefit:**			A2: No valid indication	176	(42.7%)
			B1: Lipid lowering medications	26	(6.3%)
NI	262	(50%)	C1: Antiplatelets for primary prevention	9	(2.2%)
ST	23	(4.4%)	D1: Neuroleptic antipsychotics	9	(2.2%)
CI	2	(0.4%)	D2: Memantine	10	(2.4%)
CP	22	(4.2%)			
2. **Harm outweighs benefit**	77	(14.7%)	E1: Proton pump inhibitors at full therapeutic dose	51	(12.4%)
			E2: H2 receptor blocker at full therapeutic dose	1	(0.2%)
			F1: Theophylline	3	(0.7%)
			F2: Leukotriene antagonists	3	(0.7%)
3. **Symptom or disease drugs**	48	(9.2%)	G1: Calcium supplements	43	(10.4%)
			G2: Anti-resorptive/ bone anabolics	16	(3.9%)
			G5: Long-term oral corticosteroids	18	(4.4%)
			H2: Alpha blockers for prostatism when urethral catheter in place	2	(0.5%)
4. **Preventive drugs**	90	(17.2%)	I1: Diabetic oral agents	11	(2.7%)
			J1: Multivitamin supplements	4	(1%)
			J2: Nutritional supplements	24	(5.8%)
			J3: Prophylactic antibiotics	6	(1.5%)

Legend: NI = no indication; ST = significant toxicity; CI = contraindicated; CP = cascade prescribing.

4.3.3 Discrepancies between methods

The physicians using STOPPFrail did not identify 156 medications (29.7%) that were potentially eligible for deprescribing according to Scott's deprescribing algorithm (**Table 4.4**). Antihypertensive agents, vitamin D supplements and laxatives (prescribed as part of a prescribing cascade) accounted for the majority (54.4%) of the potentially inappropriate medications that were not identified by the physicians using STOPPFrail. The physicians using STOPPFrail deprescribed calcium supplements and continued vitamin D preparations in all cases while the physicians guided by Scott's algorithm were more selective and generally continued these medications when a history of osteoporosis, fractures or recurrent falls was included in the patients' medical history.

Table 4.3: Discrepancies between the deprescribing methods: STOPPFrail guided deprescribing evaluated against 'gold standard' deprescribing

Potentially inappropriate or unnecessary drugs which were <u>not</u> identified by STOPPFrail (N=156)	**N (%)**	**Drugs <u>incorrectly</u> identified for deprescribing using STOPPFrail criteria (N=44)**	**N (%)**
Antihypertensive agents	32 (20.5%)	Calcium supplements	11(25%)
Vitamin D supplements	31(19.8%)	Anti-resorptive/ bone anabolic drugs	12(27.3%)
Laxatives (as part of prescribing cascade)	22(14.1%)	Memantine	6(13.6%)
Harm outweighs benefit	16(10.2%)	Prednisolone	3(6.8%)
Antiplatelets in patients with advanced frailty/ remote history of vascular events	16(10.2%)	Miscellaneous	12(27.3%)
Cholinesterase inhibitors in patients with advanced dementia	4(2.6%) 35(22.4%)		
Miscellaneous			

4.4 DISCUSSION

In this study, application of STOPPFrail -a novel, concise explicit deprescribing tool designed for all physicians who commonly provide care for older adults approaching end of life -demonstrated moderate agreement with gold-standard specialist geriatrician-led deprescribing. A major barrier to deprescribing is the difficulty associated with balancing risk and benefit of a specific medication for a particular patient. STOPPFrail addresses this difficulty by explicitly highlighting circumstances where commonly used medications can be reasonably discontinued. There is good evidence that people are much more likely to follow through on tasks that they see value in *when* those tasks are made easier for them.[217-219] It is therefore likely that providing explicit criteria will make the task of deprescribing more feasible for non-specialist physicians who care for older, adults approaching end of life.

The physicians using the STOPPFrail criteria identified 70.2% of medications that were potentially eligible for deprescribing according to gold standard assessment. When medications for deprescribing were identified by the physicians using STOPPFrail, these medications were *actually* inappropriate in 89.3% of cases. While the use of STOPPFrail does not 'catch all' potentially inappropriate medications, it is very reassuring that the great majority of the deprescribing decisions aligned with gold standard care.

For both methods, the most common reason for deprescribing was 'no valid indication'. This emphasizes the importance, during a medication review, of ensuring that each drug is linked to a diagnosis or active symptom. While STOPPFrail explicit criteria largely address step 2 (harm outweighs benefit) and step 4 (preventive drugs –benefit unlikely to be realized) of Scott's deprescribing algorithm, future iterations may need to go further to address aspects of step 3 (symptom or disease control drugs). For example, STOPPFrail does not prompt the physician to review symptoms such as pain which may be over-treated with potentially problematic medications. Furthermore, symptoms such as poor appetite, nausea, altered bowel habit, sedation and gait disturbance, which may represent the adverse effects of drugs, are not targeted. Finally, antihypertensive therapies and vitamin D supplements were the most common potentially inappropriate or unnecessary medications that were not identified by the physicians using STOPPFrail. These drugs are commonly prescribed yet evidence of clear benefit, as well as specific guidance for use in people with advanced frailty, is lacking.[220 - 223] In the absence of high quality clinical trial evidence, explicit criteria based on expert consensus opinion may enable physicians to make clinically sound decisions about the use of these medications in this particular expanding patient population.

All structured clinical cases in this study were derived from data collected from a cohort of hospitalized patients who died within 1 year of their hospital admission. A CFS score ≥6 was used to select frail patients from this cohort which would ensure that the deprescribing task was credible and that a short-term risk of death was not unforeseeable. It is important to emphasize that, in everyday clinical practice, it is not recommended that a CFS score ≥6 be used to select patients for STOPPFrail –guided deprescribing. STOPPFrail is intended for older people approaching end of life for whom the goal of care is to enhance quality of life and minimize the risk of drug-related morbidity. As discussed in previous chapters, the identification of older people who are approaching end of life is likely to depend largely on physician experience and judgement.

This study has some potential limitations. Firstly, it was a theoretical exercise using structured clinical cases. While derived from real patient data, the structured clinical cases do not reflect all of the complexities and nuances of real clinical care. However, we contend that standardization was necessary because external sources of variability (e.g. inequality of information) could have invalidated the primary aim of the study which was to compare the two methods of deprescribing.[215] Secondly, two physicians trained in geriatric medicine, arriving at deprescribing decisions through consensus, using Scott's deprescribing algorithm, represented 'gold standard' deprescribing in this study. It is important to emphasize that 'gold standard' does not necessarily mean 'perfect' but rather 'best available'.[224] We believe the method used in this study is likely to be very close to the 'best available' deprescribing for this population of patients in most hospitals.

In summary, the results of this study indicate that the STOPPFrail criteria can assist physicians in making appropriate deprescribing decisions and that, reassuringly, these decisions align closely with gold standard deprescribing. Before STOPPFrail can be recommended for use in everyday clinical practice, a randomized controlled trial evaluating the feasibility of applying STOPPFrail, and its effect on clinical outcomes, is required. This will be described in the next chapter.

CHAPTER 5

Deprescribing in frail older people approaching end-of-life: a randomized controlled trial using STOPPFrail criteria

5.1 INTRODUCTION

The majority of older people transferring to a nursing home for long-term care are frail and have high levels of dependency. In the United States, the median length of stay in a nursing home before death is 5 months, while in the United Kingdom, the median length of stay is 15 months.[169, 169] Despite limited life expectancy, these patients are amongst the greatest consumers of prescription medications.[225] Most patients who transfer to nursing homes come from the acute hospital setting.[226] Therefore, there is an opportunity, prior to this transition, to conduct a formal medication review while the patient is under medical supervision in the hospital environment.

The primary aim of the present study was to examine whether STOPPFrail-guided deprescribing could reduce the number of medications prescribed for frail older people undergoing transition from hospital to nursing home care. Secondary aims were to determine the effect of this intervention on unscheduled hospital admissions, falls, fractures, antipsychotic prescribing, monthly medication costs, quality of life and mortality.

5.2 METHODS

5.2.1 Design

This study was a parallel-group, unblinded, randomized pragmatic clinical trial conducted in two acute hospitals in Cork city (Cork University Hospital and Mercy University Hospital). Participants were randomized to receive STOPPFrail-guided deprescribing plus usual pharmaceutical care or usual pharmaceutical care alone at the time of enrolment. The local Clinical Research Ethics Committee approved the trial protocol. The trial was registered with ClinicalTrials.gov (NCT03501108).

5.2.1 Participants

Eligible participants were hospitalized older adults (aged ≥ 75 years), admitted from the community with acute unselected medical or surgical illness, who, following treatment were unable to return to home to independent living and consequently required long-term nursing home care. Eligible participants were prescribed ≥ 5 long-term medications and were severely frail. In this study, severe frailty was defined by (i) a Clinical Frailty Scale[139] score ≥ 7, and (ii) the treating physician indicating that he or she "would not be surprised if the patient died in the next 12 months".[119] Patients were excluded if they, or, in the case of cognitively impaired individuals, a proxy were unwilling or unable to provide informed consent.

Comprehensive multidisciplinary long-term nursing home care applications are reviewed fortnightly at a local placement panel meeting chaired by a consultant geriatrician. These applications, which include details about diagnoses, medications, functional and cognitive status, were used to screen for potentially eligible participants (see **Appendix 4** for copy of application form). Patients with a Mini-Mental State Examination (MMSE) ≥ 24 were considered competent to provide written informed consent.[227] For patients with a diagnosis of dementia or those with a MMSE < 24, a nominated proxy was required to co-sign the consent form.

5.2.2 Data collection

A trained research physician (the author) conducted patient and/or caregiver interviews and medical record reviews in order to collect the following baseline data before randomization: (i) current and past diagnoses; (ii) long-term regular medications and *pro re nata* (PRN) medications (PRN medications recorded if used ≥ 3 times in the previous week); (iii) functional status (modified Barthel Index[228]); (iv) co-morbidity status (Charlson Comorbidity Index[211]); (v) quality of life (QUALIDEM[229] and ICECAP-O[230]) . In addition, current or recent symptoms such as pain, sleep disturbance, and gastrointestinal symptoms were explored in an unstructured manner by the research physician. After baseline data collection was completed, the research physician used the STOPPFrail criteria to target medications for deprescribing. Medications targeted for deprescribing were recorded in the case report form.

Quality of life (QoL) was measured using two methods. Anticipating that a large proportion of participants would have advanced dementia and, therefore, could have difficulty completing self-reported questionnaires, the QUALIDEM instrument was selected.[229] The QUALIDEM is completed by nursing staff or health-care assistants and assesses QoL across multiple domains for people at all stages of dementia.[230] In addition, participants, where possible, or a proxy, were requested to complete the ICECAP-O questionnaire, which is a broad measure of quality of life (i.e. beyond health) and was developed for use in the economic evaluation of health and social care interventions in older adults.[229] Both the QUALIDEM and ICECAP-O questionnaires have previously been used to measure QoL in institutional care settings[231, 232] and can be viewed in **Appendix 5**.

5.2.3 Randomization

Participants were randomized to study arms in a 1:1 ratio using block randomization. Block sizes of 4 and 6 were generated using the website randomization.com (http://www.randomization.com) by an administrator external to the study. Randomization was not stratified by hospital site. The allocation sequence was concealed in sequentially numbered, opaque envelopes until the research physician had enrolled participants, completed baseline data collection, and identified deprescribing targets using the STOPPFrail criteria.

5.2.4 Intervention

For participants randomized to the intervention arm, a medication withdrawal plan was devised by the research physician. The recommended medication withdrawal plan was communicated directly to one of the participant's attending physicians and also documented in the participant's medical records. Medications associated with an increased risk of an adverse withdrawal reaction were recommended to be withdrawn slowly according to a standardized trial withdrawal protocol (**Table 5.1**). The attending physician judged whether or not to accept the drug withdrawal plan and implement the recommended changes. Because of the nature of the intervention, the research physician, attending physicians, and participating patients could not be blinded to group assignment after randomization. The intervention was applied at a single time point during the patients' hospital admission, but before transition to long term nursing home care.

Table 5.1: Protocol for withdrawal and re-instatement of drugs associated with the potential for acute drug withdrawal events

Drug	Withdrawal protocol	Re-instate drug if:
Alpha blockers for hypertension	Taper medication at intervals of 5 days	Increase in blood pressure above 160 mmHg systolic or 90 mmHg diastolic
Neuroleptic antipsychotics	Taper medication at intervals of 2 weeks[234]	Emergence of behavioural or psychological symptoms of dementia (BPSD), placing the patient or others at risk of harm
Proton pump inhibitors	Half dose initially. Stop altogether in 1 month if no symptoms of dyspepsia[235]	Recurrence of dyspepsia.
H2-receptor antagonists	Half dose initially. Stop altogether in 1 month if no symptoms of dyspepsia	Recurrence of dyspepsia
Gastrointestinal antispasmodics	Taper medication at intervals of 5 days	Recurrence of abdominal cramps
Theophylline	Taper medication at intervals of 5 days	Recurrence of wheeze or dyspnea
Long-term oral steroids	Tapering regimen will be individualized and will be based on underlying illness, stability of symptoms and duration of steroid use. Will be guided by consultant geriatrician.	Symptoms indicating possible adrenal insufficiency –anorexia, nausea, vomiting, weakness, confusion, hypotension.
Diabetic oral agents	Taper medication at intervals of 2 weeks	Polyuria, fasting capillary blood glucose >15 or HbA1C >10% at 6 weeks after withdrawal
Angiotensin Converting Enzyme (ACE) inhibitors /angiotensin receptor blockers for diabetes	Taper medication at intervals of 5 days	Increase in blood pressure above 160 mmHg systolic or 90 mmHg diastolic
Systemic oestrogens for menopausal symptoms	Taper medication at intervals of 2 weeks	Recurrence of menopausal symptoms
Nutritional supplements		5% total body weight loss over period of 2-4 weeks

5.2.5 Outcome measures

The primary outcome was the mean change in the number of long-term regularly prescribed medicines consumed by participants at 3 months post-randomisation. Short-term medicines (e.g. antibiotics, topical anti-fungal agents, topical corticosteroids etc.) were not included. For combination products, each ingredient was included as one drug as long as that ingredient was available as a single medicine in the contemporaneous British National Formulary (74th edition).[233] Secondary outcomes were measured at 3 months and included the following:

i. Unscheduled medical reviews and emergency transfers after discharge from the acute hospital.
ii. Falls and non-vertebral fractures after discharge from the acute hospital.
iii. Changes in prescriptions of neuroleptic anti-psychotic medications.
iv. Changes in 28-day cost of participants' prescription medications.
v. Changes in participants' quality of life (measured by the QUALIDEM instrument and the ICECAP-O questionnaire).
vi. Mortality.

Outcome data were collected by three trained research physicians (Dr. Emma Jennings, Dr. Ruth Daunt, Dr. Mary Randles) who were blinded to the group allocation of participants. Directors of nursing in the relevant nursing homes were contacted by telephone and requested to complete a case report form populated with the relevant data fields. It was requested that a nurse or care assistant, familiar with the participant, complete the QUALIDEM instrument while, where possible, the ICECAP-O was to be completed by the same person who completed the questionnaire at baseline. In some instances, the research physicians contacted the relevant person by telephone to complete the ICECAP-O. Twenty-eight-day cost of participants' prescription drugs was calculated using a 2018 Irish pharmaceutical wholesaler price list, produced by Clanwilliam Health®. For each specific medication dose and formulation, the lowest cost option was chosen.

5.2.6 Sample size calculation and statistical analysis

The trial was powered to detect a difference of 2.0 in the mean number of medications between the intervention and control groups ($\alpha = 0.5$, $1\text{-}\beta = 0.8$, population variance = 14 [taken from the study described in Chapter 3]) at 3 months. Allowing for an estimated attrition rate (deaths and drop-outs) of 30%, it was estimated that a sample size of 160 participants (80 in each group) would be required.

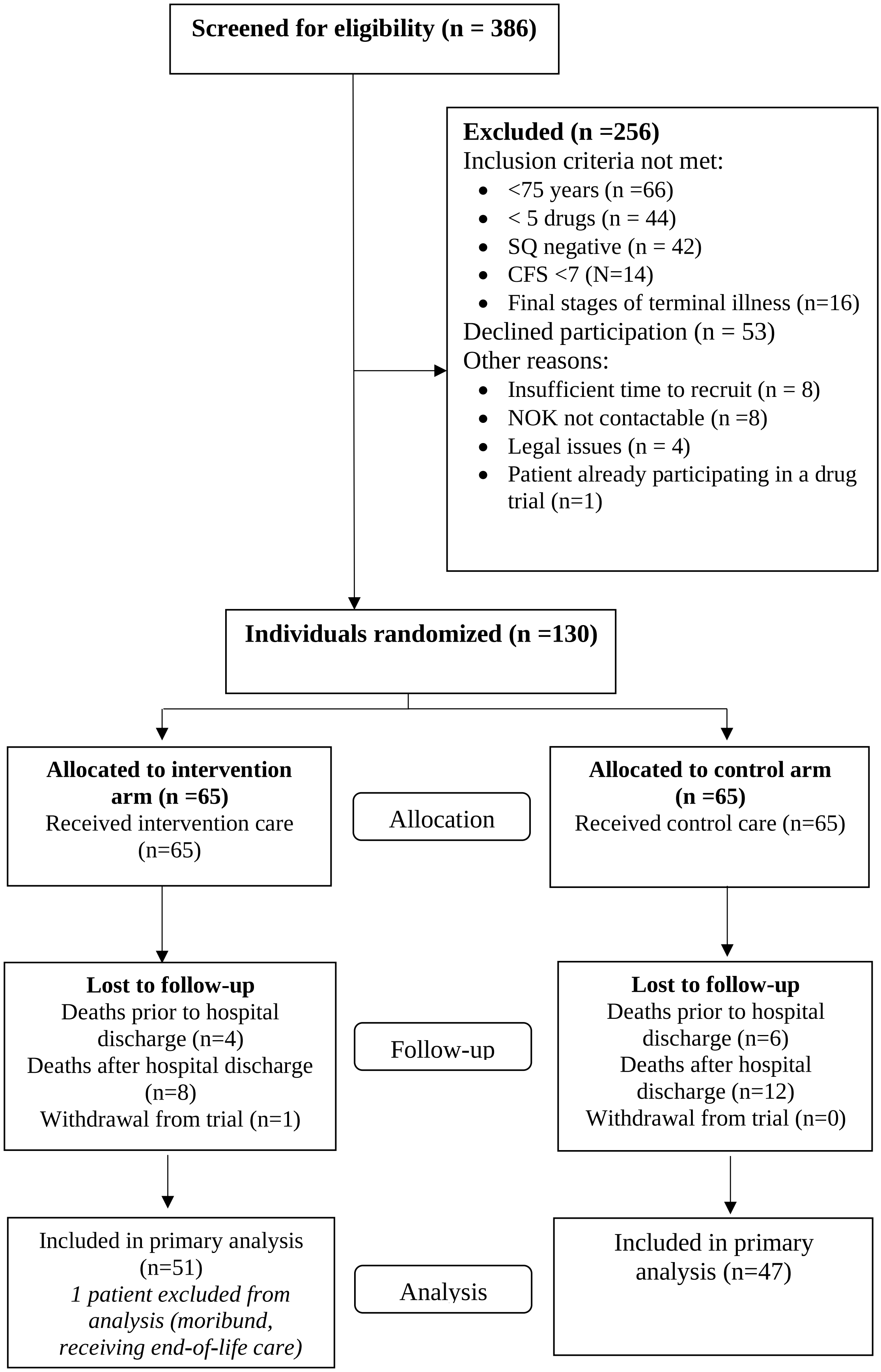
In the analysis of the primary outcome, we included only participants who completed follow-up. Because medications regimens frequently change in the final stages of terminal illness, we excluded deceased participants due to difficulties in determining final valid, verifiable medication lists. Emergency department presentations, hospital admissions, and mortality were determined on all randomized participants. We used standard descriptive statistics with study groups compared using $\chi 2$ or Fisher's exact tests for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Wilcoxon rank-sum test for nonparametric variables. All statistical analysis was performed using SPSS® version 25.

5.3 RESULTS

5.3.1 Baseline characteristics

Between March 27th 2018 and April 3rd 2019, 130 participants were randomized to receive either usual pharmaceutical care or usual pharmaceutical care supplemented by individualized STOPPFrail-guided deprescribing advice. Recruitment ended before the sample size goal of 160 was reached because of a requirement, due to resource constraints, to complete follow-up before the planned trial closure date of June 30th. Ten patients died prior to discharge from hospital, 20 patients died prior to follow-up at 3 months, while one patient withdrew from the trial after enrolment (**Figure 5.1**). At baseline, there were no significant differences between the intervention (n = 65) and control (n = 65) groups in terms of age, sex or measures of cognitive, functional and co-morbidity status (**Table 5.2**). The mean ± standard deviation (SD) number of daily medications prescribed at baseline was 11.5 ± 3.0 in the intervention group and 10.9 ± 3.5 in the control group (p = 0.28). Significantly more participants in the intervention group, relative to the control group, were prescribed analgesic medications at baseline (75% versus 49.2%, p = 0.03).

Figure 5.1: Recruitment and participation



Legend: CFS = Clinical Frailty Scale; NOK = next of kin; SQ = Surprise Question

Table 5.2: Baseline characteristics of study participants

Variable	Control (n=65)	Intervention (n=65)	P value
Female (%)	38 (58.46%)	42 (64.61%)	0.59
Age (SD)	85.68 (5.87)	84.49 (5.60)	0.24
Hospital			
Cork University Hospital	50 (76.9%)	52 (80%)	0.83
Mercy University Hospital	15 (23.1%)	13 (20%)	-
MMSE (SD)	14.25 (7.52)	14.8 (7.37)	0.67
Modified Barthel Index (SD)	6.83 (4.04)	7.17 (3.87)	0.63
CCI (SD)	6.33 (1.86)	6.8 (2.31)	0.21
Diagnoses			
Dementia (%)	48 (73.8%)	49 (75.4%)	1.0
Heart failure (%)	10 (15.4%)	16 (24.6%)	0.27
Atrial fibrillation (%)	27 (41.5%)	24 (36.9%)	0.72
Chronic kidney disease (%)	15 (23.1%)	16 (24.6%)	1.0
Active cancer (%)	6 (9.2%)	5 (7.7%)	1.0
Osteoporosis (%)	18 (27.7%)	19 (29.2%)	1.0
Medication use			
No. of regular medications (SD)	10.89 (3.56)	11.52 (3.03)	0.28
No. of PRN medications (SD)	0.25 (0.47)	0.28 (0.6)	0.74
No. of patients with ≥10 regular medications (%)	39 (60%)	46 (70.8%)	0.27
STOPPFrail-defined PIMs (SD)	2.41 (1.27)	2.40 (1.4)	0.948
Medications eligible for dose reduction (SD)	0.71 (0.7)	0.75 (0.73)	0.71
Medication type			
Anti-thrombotic	47 (72.3%)	42 (64.6%)	0.45
Antipsychotic (%)	16 (24.6%)	13 (20%)	0.67
Lipid lowering agents	17 (26.1%)	12 (18.5%)	0.4
Calcium	23 (35.4%)	15 (23.1%)	0.18
Analgesics	32 (49.2%)	45 (75%)	0.03
Anti-resorptive	9 (13.8%)	7 (10.8%)	0.79
Nutritional supplement	37 (56.9%)	33 (50.8%)	0.59
Gastric acid suppression therapy	42 (64.6%)	39 (60%)	0.72
Medications for constipation	48 (73.8%)	55 (84.6%)	0.19

Legend: CCI = Charlson Co-morbidity Index; MMSE = Mini-mental State Exam; PIMs = potentially inappropriate medications; PRN = pro ne rata; SD = standard deviation.

5.3.2 STOPPFrail deprescribing recommendations

At least one deprescribing recommendation was made for 90.8% of participants in the intervention group. A mean of 2.4 ± 1.4 medications per patient were targeted for discontinuation while 0.75 ± 0.73 medications per patient were targeted for dose reduction. Overall, 87.8% of deprescribing recommendations were accepted and implemented by the attending physicians. STOPPFrail criterion A2 (i.e. Stop any drug without a clear clinical indication) was the most common recommendation triggered (44.4% of all recommendations). Lipid lowering therapies (criterion B1), neuroleptic antipsychotics (criterion D1), proton pump inhibitors (PPIs; criterion E1), anti-resorptive therapies (criterion G2), calcium supplements (criterion G1) and vitamin supplements (criterion J1) accounted for a further 40% of the deprescribing recommendations. The frequency of the individual STOPPFrail criteria is shown in **Table 5.3**.

5.3.3 Primary outcome

Data from 98 randomized participants were available for analysis for the primary outcome (**Figure 5.1**). Intervention arm patients (n = 51) and control arm patients (n = 47) were prescribed a mean (SD) of 11.5 (± 2.7) and 10.9 (± 3.6) regular prescription medications, respectively, at baseline. The mean (SD) change in the number of prescribed regular medications at 3 months was -2.61 (± 2.73) in the intervention group and -0.36 (± 2.60) in the control group (mean difference 2.25 ± 0.54, 95% confidence interval 1.18 -3.32, p<0.001). Of 141 medications that were discontinued in the intervention group, only 3 had been restarted at the 3-month follow-up timepoint.

Table 5.3: Frequency of STOPPFrail-defined potentially inappropriate medications in the control and intervention groups

Criterion	Control N (%)	Intervention N (%)
A1: Any drug that the patient persistently fails to take or tolerate	3 (1.5%)	7 (3.4%)
A2: Any drug without clear clinical indication	75 (37.1%)	91 (44.4%)
B1: Lipid lowering therapies	20 (9.9%)	11 (5.4%)
B2: Alpha-blockers for hypertension	0	0
C1: Anti-platelets for primary cardiovascular prevention	7 (3.5%)	4 (2%)
D1: Neuroleptic antipsychotics	7 (3.5%)	9 (4.4%)
D2: Memantine	5 (2.5%)	4 (2%)
E1: Proton Pump inhibitors	31 (15.3%)	26 (12.7)
E2: H2 receptor antagonists	0	0
E3: Gastrointestinal antispasmodics	1 (0.5%)	0
F1: Theophylline	0	0
F2: Leukotriene antagonists	1 (0.5%)	2 (1%)
G1: Calcium supplements	23 (11.4%)	14 (6.8%)
G2: Anti-resorptive/ bone anabolic drugs	9 (4.5%)	6 (2.9%)
G3: Selective oestrogen receptor modulators for osteoporosis	0	0
G4: Long-term oral nonsteroidal anti-inflammatory drugs	0	0
G5: Long-term oral steroids	2 (1%)	0
H1: 5-alpha reductase inhibitors with long-term bladder catheterisation	0	0
H2: Alpha blockers with long-term bladder catheterisation	1 (0.5%)	1 (0.5%)
H3: Muscarinic antagonists with long-term bladder catheterisation	0	0
I1: Diabetic oral agents	2 (1%)	3 (1.5%)
I2: Angiotensin converting enzyme-inhibitors for diabetes	0	1 (0.5%)
I3: Angiotensin receptor blockers	0	0
I4: Systemic oestrogens for menopausal symptoms	0	0
J1: Multivitamin combination supplements	9 (4.5%)	18 (8.7%)
J2: Nutritional supplements (other than vitamins)	4 (2.5%)	8 (3.9%)
J3: Prophylactic antibiotics	1 (0.5%)	0

5.3.4 Secondary outcomes

There were no statistically significant differences between the intervention and control groups for patient-related outcomes such as unscheduled hospital presentations, falls, fractures or mortality (see **Table 5.4**). QoL deteriorated significantly in both the intervention and control groups from baseline to three-month follow up but there were no statistically significant differences in the mean change in QUALIDEM or ICECAP-O scores between groups from baseline to follow-up (see **Table 5.5**).

Antipsychotic drugs were reduced or discontinued more often in intervention patients relative to control patients but, again, the differences did not reach statistical significance (see **Table 5.6**). At baseline, there were no statistically significant differences in the extrapolated mean (SD) monthly medication costs between the intervention and control groups (€240.53 ±105.57 and €225.68 ±126.68, respectively, p =0.53). However, at 3 months follow-up, the mean change in monthly medication cost was significantly greater in the intervention group i.e. –€67.51 ±133.56 compared to the control group i.e. –€11.90 ±99.42 (mean difference €55.60 ±23.95, 95% CI 8.06 -103.14, p =0.02).

Table 5.4: Effect of STOPPFrail-guided deprescribing on secondary outcomes

	Intervention (n=65)		**Control (n=65)**			
Outcome	Proportion (95% CI)	Number of participants (number of events)	Proportion (95% CI)	Number of participants (number of events)	Relative risk (95% CI)	p
ED presentation (not admitted)	0.05 (0.01, 0.13)	3 (5)	0.08 (0.03, 0.17)	5 (8)	0.60 (0.15, 2.41)	0.72
Unplanned hospital admission	0.14 (0.07, 0.24)	9 (10)	0.08 (0.03, 0.17)	5 (6)	1.80 (0.64, 5.08)	0.27
Deaths	0.18 (0.11, 0.3)	12	0.28 (0.18, 0.4)	18	0.67 (0.35, 1.27)	0.22
Unscheduled medical reviews by GP*	0.61 (0.47, 0.73)	31 (68)	0.57 (0.43, 0.70)	27 (52)	1.04 (0.74, 1.45)	0.82
Falls*	0.27 (0.17, 0.40)	14 (24)	0.30 (0.19, 0.44)	14 (32)	0.90 (0.48, 1.69)	0.75
Non-vertebral fractures*	0.02 (0, 0.11)	1 (1)	0.09 (0.03, 0.20)	4 (5)	0.23 (0.03, 1.95)	0.18

Legend: *measured in final analytical sample (intervention [n=52]; control [n=47]); CI = confidence interval; ED = emergency department; GP = general practitioner.

Table 5.5: Self-reported and proxy-measured quality of life outcomes at baseline and 3-month follow-up

	Baseline				**3 months**			
	Intervention	Control	*p*	95% CI	Intervention	Control	*p*	95% CI
ICECAP-O								
N	63	64	-	-	21	29	-	-
Mean (SD)	0.60 (0.22)	0.60 (0.20)	0.93	-0.07, 0.08	0.21 (0.33)	0.30 (0.35)	0.14	-0.03, 0.21
Mean change baseline to 3-months (SD)	-	-	-	-	-0.39 (0.36)	-0.30 (0.35)	0.17	-0.04, 0.21
QUALIDEM								
N	61	64	-	-	37	38	-	-
Mean (SD)	6.96 (2.58)	7.58 (1.94)	0.12	-0.17, 1.42	4.53 (4.23)	4.73 (4.30)	0.79	-1.28 to 1.68
Mean change baseline to 3-months (SD)	-	-	-	-	-2.43 (4.65)	-2.85 (4.64)	0.60	-2.03, 1.19

Legend: N = number completed; CI = confidence interval; SD = standard deviation

Table 5.6: Effect of STOPPFrail-guided deprescribing on antipsychotic prescribing

Outcome	Intervention (n=9)	Control (n=11)	Treatment difference (95% CI)	p
Participants who had successful discontinuation of an antipsychotic drug, n (%)	5 (55.6%)	1 (9%)	4.29 (0.57, 31.79)	0.15
Participants who had successful dose reduction of an antipsychotic drug, n (%)	2 (22.2%)	2 (18.2%)	1.18 (0.20, 7.06)	0.85

Legend: CI = confidence interval

5.4 DISCUSSION

In this study of very frail older hospitalized patients with limited life expectancy, application of STOPPFrail criteria at a single time point resulted in a sustained and significant reduction in the level of polypharmacy and average aggregate monthly medication costs compared with usual pharmaceutical care. We found that almost one-in-four medications were discontinued in frail older people with polypharmacy using this method resulting in a 28% average reduction in monthly medication costs. There were no significant differences between the intervention and control arms in terms of important health-related outcomes including unplanned hospital admissions, falls, fractures, quality of life and mortality although it must be acknowledged that the trial was likely to have been underpowered to detect significant differences in these secondary outcomes.

Other structured deprescribing methods have recently been evaluated in very frail older people using a randomized controlled trial design and have also reported a statistically significant reductions in potentially inappropriate prescriptions. Potter *et al.*[174] used an implicit (Scott's deprescribing algorithm) approach that required the user to answer a series of questions about each drug in the patient's regimen, while Wouters *et al.*[236] evaluated the Multidisciplinary Multistep Medication Review (3MR). Both methods are patient-centred and comprehensive but are limited by a requirement for resource-intensive processes. This may hinder their integration into widespread clinical practice. STOPPFrail overcomes these limitations by virtue of its conciseness and high inter-rater reliability between users of different disciplines and professional grades.[148]

The most common reason for deprescribing in this trial was when a drug had no clear valid clinical indication (STOPPFrail criterion A2). We contend that routinely clarifying whether a drug is *actually* indicated is fundamental to any formal medication review in older multi-morbid patients exposed to polypharmacy, particularly frailer patients with very limited survival prospects. The remaining criteria in STOPPFrail are predominantly explicit and target specific drugs that, under usual circumstances, may be clinically indicated but are likely to be associated with negligible benefits or net harm in the context of advanced irreversible frailty and limited life expectancy. During the conduct of the trial, it became clear that some of the explicit criteria in STOPPFrail lacked clinical relevance and were very seldom, if at all, applied (e.g. systemic oestrogens for menopausal symptoms, selective oestrogen receptor modulators for osteoporosis). Furthermore, just like the study described in Chapter 4, it was evident that some medications, commonly prescribed in frail older people but lacking a firm evidence base (e.g. vitamin D therapy), were absent from STOPPFrail. In the next chapter, the development of an updated version of STOPPFrail, that addresses these shortcomings, will be described.

This trial has some limitations. Firstly, participants were enrolled from just two acute hospitals in Ireland and this may limit the generalizability of our findings. STOPPFrail criteria were developed in the University affiliated with these hospitals and this may have influenced the readiness of some attending physicians to implement the deprescribing recommendations. Secondly, it is not possible to be certain of the effect of the intervention on important patient-related outcomes including mortality due to the relatively small sample size and short follow-up period. Thirdly, a cluster randomization design, which would diminish the possibility of contamination bias, was not used. Physicians may have simultaneously had both intervention and control patients under their care during the trial and, through a ‘training effect’, may have applied STOPPFrail criteria during medication reviews of control patients. However, any possible contamination of this kind would increase the chance of actual effects of the intervention *not* being detected (i.e. type II error). In spite of the possible presence of contamination, significantly different effects of the STOPPFrail intervention were still observed between the groups.

When frail older people approach end-of-life, the prescription of multiple medications may be burdensome or even futile in their clinical management. Our study provides evidence that STOPPFrail, an easily applied reliable deprescribing tool, substantially reduces polypharmacy and monthly medication costs in this patient cohort. The results, when combined with earlier studies, suggest that careful deprescribing can be accomplished in frail, older adults without compromising clinical outcomes or quality of life.

CHAPTER 6

STOPPFrail Version 2: Development and Validation

6.1 INTRODUCTION

Several important properties of STOPPFrail deprescribing criteria have now been demonstrated:

- The use of STOPPFrail criteria, as a method of deprescribing, has substantial inter-rater reliability between physicians of different disciplines and professional grades (kappa coefficient 0.76).[148]
- As demonstrated in Chapter 4, STOPPFrail-guided deprescribing decisions generally align with "gold standard" geriatrician-led deprescribing (positive predictive value 89.3% when methods compared using 100 standardized clinical cases).
- As shown in Chapter 5, implementation of STOPPFrail deprescribing recommendations significantly reduces medication numbers and costs for older people approaching end-of-life without clearly compromising well-being.

Despite these findings, it has become clear that STOPPFrail, as a deprescribing tool, has important limitations. Firstly, the method for identifying older people who are likely to be approaching end-of-life has limited application in a clinical setting (patients have to meet ALL the following criteria: end-stage irreversible pathology; poor 1-year survival prognosis; severe functional or cognitive impairment; symptom control is priority rather than prevention of disease progression).[147] Secondly, there is no reference to the role of the patient or family in the deprescribing decision-making process. Shared decision making is central to patient-centred care and clearly should be emphasized in any intervention involving vulnerable patients.[149] Thirdly, as discussed in earlier chapters, it is clear that there are several commonly prescribed medications, lacking firm evidence-based clinical utility for frail older people, that are absent from STOPPFrail version 1. Finally, as for all explicit criteria sets, an essential requirement is that they are regularly updated in line with emerging evidence and clinical guidelines.

Therefore, the aim of this study was to prepare and validate a new version of STOPPFrail criteria that would be more practical, patient-centred and complete.

6.2 METHODS

A review of the prognostic model and frailty literature was undertaken to devise a method for identifying older people approaching end-of-life. Key requirements were that any method would be easy-to-use and acceptable to practicing physicians. New deprescribing criteria were compiled by the author and his supervisors on the basis of experience garnered from using STOPPFrail in the randomized, observational, and method agreement analysis studies described in earlier chapters of this thesis. The proposed new criteria were then evaluated in terms of their clinical importance, accuracy and evidence base. Searches of PubMed, Google Scholar and Cochrane Library databases were undertaken. Searches included the drug in question along with key words including “frailty”, “limited life expectancy”, “end of life”, and “deprescribing”. The draft criteria, as well as the method for identifying older people approaching end-of-life, were then distributed to a panel of experts for consensus using the Delphi validation method, an established method of achieving consensus.[237]

The panel comprised eight members with expertise in geriatric medicine, clinical pharmacology, psychiatry of older age, general practice and palliative medicine (**Table 6.1**). All panel members were involved in the validation of the original STOPPFrail criteria.[147] Accompanying the draft criteria was a supporting document detailing the justification and evidence base for the new criteria (**Appendix 6**).

SurveyMonkey® software was used to facilitate the Delphi validation. Each draft criterion was accompanied by an explanatory statement. Panel members were required to choose their level of agreement for each criterion using a 5-item Likert scale: 1 = strongly agree; 2 = agree; 3 = neutral; 4 = disagree; 5 = strongly disagree. A median value of 1 or 2 and a 25th centile value of ≤ 2 (i.e. at least 75% of panel members agreed or strongly agreed) were required for the criterion to be included. Criteria with a median value of 1 or 2 but a 25th centile value of > 2 were to be rephrased according to the panel member suggestions and entered into the next Delphi validation round. Criteria with a median value of ≥ 3 were rejected. Panel members were encouraged to comment on criteria and provide suggestions. All panel member responses were anonymised and members were discouraged from communicating with each other during the consensus process. Repeat Delphi validation rounds were to be continued until agreement to include or reject was reached on all draft criteria.

Table 6.1 Expert panel members who participated in the validation of STOPPFrail version 2

Name	Discipline	Place of practice
Prof. Sean O'Keeffe	Geriatric medicine	University College Hospital, Galway
Prof. Joe Harbison	Geriatric medicine	St. James Hospital, Dublin
Dr. Suzanne Timmons	Geriatric medicine	Mercy Hospital, Cork
Prof. Stephen Byrne	Clinical pharmacy	University College Cork
Prof. David Williams	Clinical pharmacology	Beaumont Hospital, Dublin
Dr. Tony Foley	General practice	University College Cork
Prof. Brian Lawlor	Psychiatry of old age	St. James Hospital, Dublin
Prof. Tony O'Brien	Palliative medicine	Marymount Hospital, Cork

6.3 RESULTS

In Round 1 of the Delphi process, 8 new criteria, including a method for identifying patients approaching end-of-life, were submitted to the expert panel for evaluation. In addition, 7 of the original criteria, considered obsolete or less relevant, were submitted to the panel for re-evaluation. In these instances, panel members used the Likert scale to indicate their level of agreement for *removing* the potentially obsolete criteria from the new version of STOPPFrail.

Seven of the 8 new criteria in Round 1 had median Likert scores with 75th centile values of 1 or 2 and were retained as validated criteria. The remaining criterion, which related to the deprescribing of anti-anginal therapies (nitrates, nicorandil, ranolazine – "none of these anti-anginal drugs have been proven to reduce cardiovascular mortality or the rate of myocardial infarction. Aim to carefully reduce and discontinue these drugs in patients with a history of chest pain in the distant past [i.e. no chest pain in the previous 6 months]", had a median Likert score of 1.5 but three of the panel members were 'neutral' about its inclusion. This criterion was rephrased, based on suggestions from the panel members, and achieved validation for inclusion in Round 2 of the Delphi process. Consensus was reached on removing all 7 of the potentially obsolete criteria in Round 1 (see **Table 6.2** for details).

STOPPFrail version 2 is shown in **Table 6.3**. Included in STOPPFrail version 2 is a method for identifying patients who are likely approaching end-of-life as well as new criteria outlining circumstances when antihypertensive medications, vitamin D, folic acid, and diabetic agents can be reasonably deprescribed in this population.

Table 6.2 STOPPFrail version 1 criteria removed from the proposed version 2

Criterion	Rationale
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*	Obsolete. New criterion relating to anti-hypertensive therapies included in STOPPFrail Version 2
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*	Rarely applied. New criterion relating to symptomatic therapies included in STOPPFrail version 2.
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*	Rarely applied.
Angiotensin converting enzyme (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*	New criterion relating to anti-hypertensive therapies included in STOPPFrail Version 2
Angiotensin Receptor Blockers (ARBs) 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*	New criterion relating to anti-hypertensive therapies included in STOPPFrail Version 2
Systemic oestrogens for menopausal symptoms *Increases risk of stroke and venous thromboembolic disease. Discontinue and only consider recommencing if recurrence of symptoms*	Rarely applied.
Prophylactic Antibiotics *No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or urinary tract infections*	There is evidence that long-term antibiotic therapy has a role in the prevention of recurrent urinary tract infections in postmenopausal women[238]

Table 6.3: STOPPFrail Version 2

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with deprescribing decisions. It is intended for older people with limited life expectancy for whom the goal of care is to optimize quality of life and minimize the risk of drug-related morbidity. Goals of care should be clearly defined and, where possible, medication changes should be discussed and agreed with patient and/or family. Appropriate patients typically meet ALL of the following criteria: 1. ADL dependency (i.e. assistance with dressing, washing, transferring, walking) ± severe chronic disease ± terminal illness. 2. Severe irreversible frailty i.e. high risk of acute medical complications and clinical deterioration. 3. Physician overseeing care of patient would not be surprised if the patient died in the next 12 months.	
Section A: General	i. Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations. ii. Any drug without a clear clinical indication. iii. Any drug for symptoms which have now resolved (e.g. pain, nausea, vertigo, pruritis).
Section B: Cardiology system	i. **Lipid lowering therapies (statins, ezetimibe, bile acid sequestrants, fibrates, nicotinic acid, lomitapide, and acipimox).** ii. **Antihypertensive therapies:** Carefully reduce or discontinue these drugs in patients with systolic blood pressure (SBP) persistently <130mmHg. An appropriate SBP target in frail older people is 130 -160mmHg. Before stopping, consider whether the drug is treating additional conditions (e.g. beta-blocker for rate control in atrial fibrillation, diuretics for symptomatic heart failure). iii. **Anti-anginal therapy (specifically: nitrates, nicorandil, ranolazine):** None of these anti-anginal drugs have been proven to reduce cardiovascular mortality or the rate of myocardial infraction. Aim to carefully reduce and discontinue these drugs in patients who have had no reported anginal symptoms in the previous 12 months AND who have no proven or objective evidence of coronary artery disease.
Section C: Coagulation system	i. **Anti-platelets:** No evidence of benefit for primary (as distinct from secondary) cardiovascular prevention. ii. **Aspirin for stroke prevention in atrial fibrillation:** Aspirin has little or no role for stroke prevention in frail older people who are not candidates for anticoagulation therapy and may significantly increase bleeding risk.
Section D: Central Nervous System	i. **Neuroleptic antipsychotics in patients with dementia:** 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). ii. **Memantine:** Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD.
Section E: Gastrointestinal System	i. **Proton Pump Inhibitors:** Reduce dose of Proton Pump Inhibitors when used at full therapeutic dose ≥ 8 weeks, unless persistent dyspeptic symptoms at lower maintenance dose. ii. **H2 receptor antagonist:** Reduce dose of H2 receptor antagonists when used at full therapeutic dose for ≥ 8 weeks, unless persistent dyspeptic symptoms at lower maintenance dose.
Section F: Respiratory System	i. **Theophylline and aminophylline:** These drugs have a narrow therapeutic index, have doubtful therapeutic benefit and require monitoring of serum levels and interact with other commonly prescribed drugs putting patients at an increased risk of ADEs. ii. **Leukotriene antagonists (Montelukast, Zafirlukast):** These drugs have no proven role in COPD, they are indicated only in asthma.
Section G: Musculoskeletal System	i. **Calcium supplements:** Unlikely to be of any benefit in short-term unless proven, symptomatic hypocalcaemia. ii. **Vitamin D (ergocalciferol and colecalciferol):** Lack of clear evidence to support the use of vitamin D to prevent falls and fractures, cardiovascular events, or cancer. iii. **Anti-resorptive/bone anabolic drugs** *FOR OSTEOPOROSIS* (**bisphosphonates, strontium, teriparatide, denosumab)** iv. **Long-term oral NSAIDs:** Increased risk of side effects (e.g. peptic ulcer disease, bleeding, worsening heart failure) when taken regularly for ≥ 2 months. v. **Long-term oral corticosteroids:** Increased risk of major side effects (e.g. fragility fractures, proximal myopathy, peptic ulcer disease) when taken regularly for ≥ 2 months. Consider careful dose reduction and discontinuation.
Section H: Urogenital System	i. **Drugs for benign prostatic hyperplasia (5-alpha reductase inhibitors and alpha-blockers) in catheterized male patients:** No benefit with long term bladder catheterisation. ii. **Drugs for overactive bladder (muscarinic antagonists and mirabegron):** No benefit in patients with persistent, irreversible urinary incontinence unless clear history of painful detrusor hyperactivity.
Section I: Endocrine System	i. **Anti-diabetic drugs:** De-intensify therapy. Avoid HbA1c targets (HbA1C <7.5% [58 mmol/mol] associated with net harm in this population). Goal of care is to minimize

	symptoms related to hyperglycaemia (e.g. excessive thirst, polyuria).
Section J: Miscellaneous	i. **Multi-vitamin combination supplements:** Discontinue when prescribed for prophylaxis rather than treatment of hypovitaminosis. ii. **Folic acid:** Discontinue when treatment course completed. Usual treatment duration 1-4 months unless malabsorption, malnutrition or concomitant methotrexate use. iii. **Nutritional supplements:** Discontinue when prescribed for prophylaxis rather than treatment of malnutrition.
Disclaimer (STOPPFrail): Whilst every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence-based, it is emphasized that the final decision to deprescribe any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that deprescribing decisions should take account of current published evidence in support of or against the use of drugs or drug classes described in STOPPFrail.	

Legend: ADL = activities of daily living; NSAIDs = nonsteroidal anti-inflammatory drugs

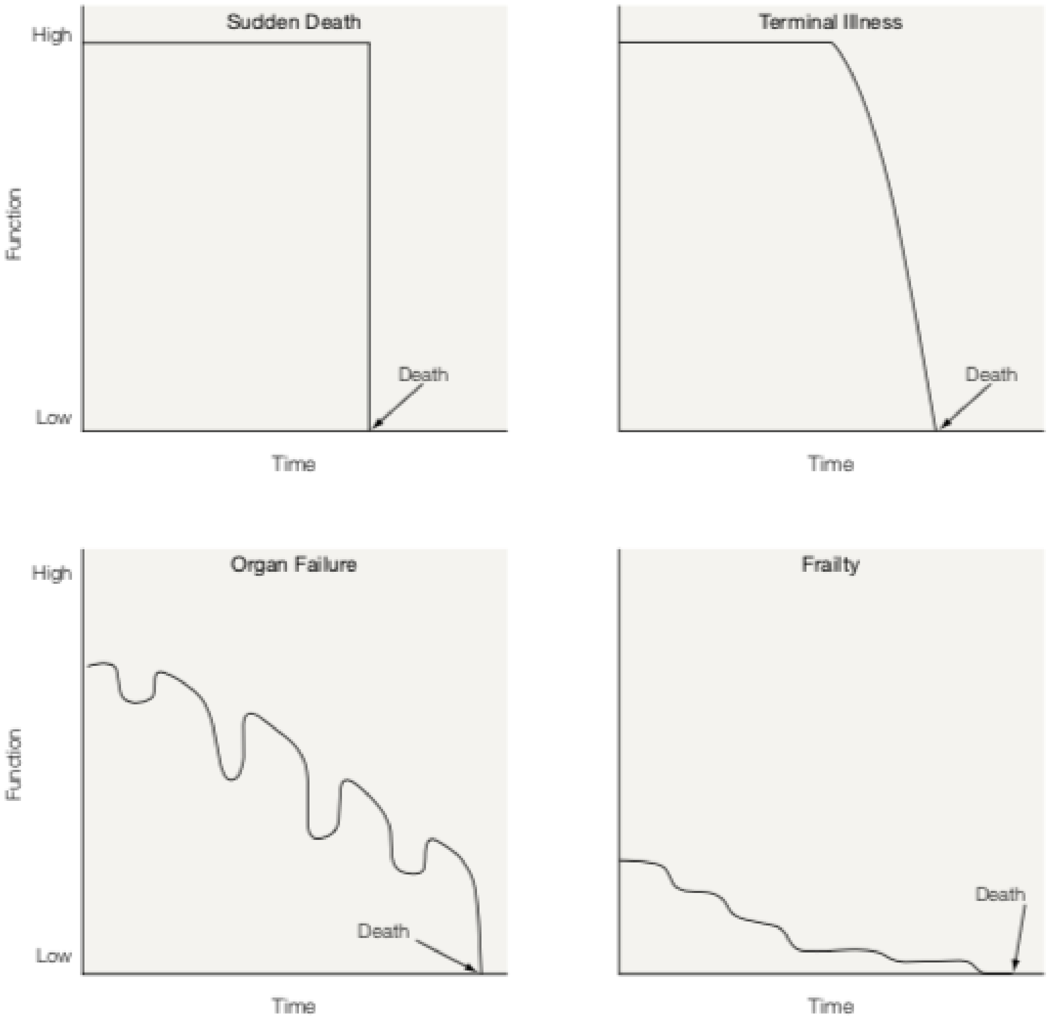
6.4 DISCUSSION

In this study, I have described the development and validation of version 2 of STOPPFrail. The goal of STOPPFrail version 2 is to provide clinicians with a practical, patient-centred and, where possible, up-to-date evidence-based approach to deprescribing decisions in older people approaching end-of-life. Central to this goal is the recognition that clinicians have duties beyond the restoration and maintenance of health. When the limits of medical care have been reached and continued decline is inevitable, it may be a relief to some older people to be taking fewer medications.

Recognizing when an older person is approaching end-of-life is a key challenge for physicians. Prognostic models, which are generally derived from large population-based databases, synthesize patient- and disease-related information to produce prognostic estimates. These estimates indicate the mortality risk for an *average* patient with a given set of risk factors under *average* circumstances. Relevant, specific information, related to the individual patient, may not be included in the prognostic model and, therefore, it is questionable whether prognostic models should be used to influence important decisions at an individual patient level. Regardless, there are no published non-disease-specific prognostic models that, to date, are validated and recommended for use in older adults.[124]

In STOPPFrail version 2, I suggest using three criteria to identify patients who are approaching end-of-life and are, therefore, appropriate for STOPPFrail-guided deprescribing. The first criterion essentially describes the profile of an older people who may be approaching end-of-life. The validity of this criterion is supported by an important longitudinal study by Lunney *et al.* that analyzed patterns of functional decline in older American decedents in the last years of life.[105] While perhaps oversimplified, the study nevertheless indicated that most older people experience functional decline prior to death and that the pattern of that functional decline tended to follow one of three trajectories depending on the profile of the older person (i.e. severe functional impairment, organ failure or terminal illness; see **Figure 6.1**).

Figure 6.1: Patterns of functional decline in older people approaching end-of-life[105]



Reproduced with permission[105]

The second criterion is severe, irreversible, frailty. While a single operational definition has yet to gain widespread acceptance among experts, it is generally accepted that frailty is characterized by a late life vulnerability to adverse health outcomes, including death.[128, 131, 133] Furthermore, it is generally accepted that frailty is a clinically recognizable state i.e. experienced physicians know it when they see it.[239, 240] For this reason, rather than recommend a specific frailty measurement tool, we recommend that attending physicians identify severe frailty using clinical judgement (is this older person at high risk of acute medical complications and clinical deterioration?), or if preferred, a frailty measurement tool of their choice. The final criterion features the 'surprise question' which has been widely adopted in frameworks for assessing end of life needs.[119-121] As discussed in Chapter 1, the 'surprise question' functions as a method of separating those with an intermediate-to-high probability of dying (the clinician answers that he/she would *not* be surprised if the patient died within 1 year i.e. surprise question positive [SQ+]) from those with a low probability of dying (the clinician *would be* surprised i.e. surprise question negative [SQ-]). Two recent systematic reviews evaluating use of the 'surprise question' showed that, while, as expected, the surprise question led to the detection of many 'false positives', the method seemed to be very effective at excluding patients with longer survival times (negative predictive value >90% in both reviews).[122, 123] Therefore, as part of this wider prognostic assessment, the 'surprise question' may serve as a safety net for patients who are *not* necessarily approaching end-of-life.

Version 2 of STOPPFrail includes new deprescribing criteria relating to antihypertensive therapies and vitamin D preparations. The guidance relating to antihypertensive therapies is influenced by European[241] and Canadian[242] position statements as well as findings from several longitudinal studies suggesting a possible association between intensive blood pressure control and poorer outcomes in older, frailer people.[243, 244] While the Hypertension in the Very Elderly Trial (HYVET)[245] and the Systolic Blood Pressure Intervention Trial (SPRINT)[246] showed that the prescription of antihypertensive therapies to lower blood pressure resulted in reduced mortality and cardiovascular events in robust older people, it is important to note that institutionalized patients and those with an estimated life expectancy of less than one year were excluded from these trials. The deprescribing statement relating to vitamin D therapies is informed by new evidence emphasizing the negligible role of vitamin D in the prevention of falls, fractures, cardiovascular events and cancer in older people. [247-249]

Shared decision making is highlighted as an integral part of the deprescribing process in Version 2 of STOPPFrail. When patients engage in shared decision making, they feel better informed and clearer about their values.[150] Clearly, some patients (or a surrogate) may indicate a preference to continue a potentially inappropriate medication. In this context, while it may be helpful to try to understand the reasons underlying this preference, we recommend avoiding decisional conflict unless the drug in question is causing significant overt harm. It seems, however, that the great majority of older people, according to recent studies, would be willing to discontinue one or more medications if their physician indicated it was possible.[154] This suggests that physicians can be reassured about discussing the option of deprescribing with their patients.

In conclusion, STOPPFrail version 2 has several important updates, including a method for identifying older people approaching end-of-life and several new criteria. The new iteration is more practical, patient-centred and comprehensive, and careful application of the criteria, I expect, will reduce medication burden for older people approaching end-of-life.

CHAPTER 7

Conclusion

7.1 SUMMARY OF RESEARCH FINDINGS

From the outset, the goal of this thesis was to address two important issues. The first relates to the question as to whether or not there is a reliable method for identifying older frailer people who are likely approaching end-of-life. When end-of-life is near apparent despite best medical efforts, directing attention towards the personal goals of the patient is likely to yield greater benefits than a futile, uncritical pursuit of chronic disease targets. These patients may benefit from a personalized approach that includes the deprescribing of long-term medications that no longer serve a useful purpose. Deprescribing involves carefully balancing the risks and benefits of specific medications for a particular patient and, therefore, has the potential to be highly challenging. This may be a barrier to deprescribing and opportunities to meaningfully intervene may be lost if physicians are uncomfortable with this practice. The second important issue, therefore, relates to operationalizing deprescribing i.e. how to enable physicians to deprescribe safely in older people approaching end-of-life.

In Chapter 2, the HOMR model was tested in a population of older hospitalized patients. The exceptionally high predictive performance of the HOMR model, reported in earlier validation studies in North America, was substantially attenuated in our patient group. The results were not very surprising: the accuracy of prediction models is often substantially lower in new patients compared to that found in patients of the development population.[192-194] Further refinement and validation may improve the predictive accuracy of the HOMR model in older hospitalized patients but, until then, it cannot be recommended for use in routine clinical practice. For now, at least, clinical judgement remains the physician’s best tool for determining the likely prognosis of his/ her patients. In Chapter 6, I suggested a heuristic approach to determining whether a patient is likely to be approaching end-of-life. Firstly, the physician determines if the patient has the profile of someone who is likely to be approaching end of life (i.e. terminal diagnosis, severe chronic disease or severe disability). Then, the physician decides whether the patient is at high risk of adverse health outcomes, either through clinical judgement or through the application of a validated frailty measurement tool. Finally, the physician asks 'would I be surprised if this patient were to die in the next 12 months'? This approach is by no means perfect but rather is a set of intuitive mental shortcuts to the ease the cognitive load of making a prognostic assessment.

The last year of life for the majority of older people is a period of high symptom burden with frequent and prolonged hospital admissions. In Chapter 3, I showed that patients in their final year consumed an average of 24 different medications while in hospital. When discharged, patients were prescribed an average of 2 long-term medications that were potentially inappropriate. This study showed that medication burden is high in the last year of life and that there could be an opportunity to intervene when older people are admitted to hospital.

In Chapter 4, STOPPFrail-guided deprescribing was compared with gold standard geriatrician-led deprescribing using 100 standardized clinical cases. Of the medications that were categorized as inappropriate by the gold standard method, 70.2% were also identified through the use of STOPPFrail. Reassuringly, the great majority of STOPPFrail-guided deprescribing decisions aligned with the gold standard. The results were important and showed that, while STOPPFrail as an explicit deprescribing tool has limitations, it could serve as a reasonable alternative to 'gold standard' deprescribing when this is not available. Deprescribing at end-of-life, therefore, need not be the sole preserve of the medication expert but rather would be accessible to all physicians who regularly deliver care to older, frailer people. Equally important, the results showed that, with the addition of new deprescribing criteria, STOPPFrail could be improved significantly.

In Chapter 5, STOPPFrail-guided deprescribing was compared with usual pharmaceutical care using a randomized controlled trial design. Among older frail hospitalized patients, application of STOPPFrail resulted in a sustained and significant reduction in polypharmacy and medication costs compared with usual pharmaceutical care. There was no significant difference between the intervention and control arms with regard to the secondary outcome measures i.e. mortality, hospital admissions, falls or fractures although the trial was likely underpowered to detect changes in these outcomes.

Arising from the results of studies described in Chapter 4 and 5, it was clear that STOPPFrail required updating to make it more practical, relevant and complete. Chapter 6 describes the preparation and validation of STOPPFrail version 2. Like its predecessor, STOPPFrail version 2 is concise, easy-to-use and evidence-based but now includes a new method, described above, for identifying older patients who approaching end-of-life as well several new deprescribing criteria.

Overall, the research presented in this thesis provides a strong evidence base to support STOPPFrail-guided deprescribing for older people approaching end-of-life. Indeed, the evidence base for STOPPFrail now compares very favorably to other deprescribing tools for very frail older people that were described in a recent systematic review by Thompson *et al.*[250] More importantly, the research has enhanced clarity on issues that are important to both patients and healthcare providers and has implications for how clinicians practice medicine and manage uncertainty relating to prescribing in an ageing society.

7.2 DIRECTIONS FOR FUTURE RESEARCH

Larger, multicentre, randomized trials with longer follow-up times are required to provide further clarification on the impact of deprescribing interventions on outcomes such as hospital admissions, quality of life and mortality. While demonstrating that STOPPFrail-guided deprescribing resulted in less polypharmacy and reduced costs of medications was important, practicing physicians are likely to need further reassurance that this does not occur at the expense of patient safety and quality of life. As patients approach end-of-life, these outcomes may be more important than longevity. In the STOPPFrail trial, I measured quality of life using short quantitative questionnaires which may not have been sensitive enough to detect more subtle but relevant changes. More creative methods, including the use of qualitative methods with, perhaps, greater involvement of caregivers and family, are likely to be required in future studies.

Some physicians, patients, and surrogates may prefer more information about the relative risks and benefits of discontinuing particular medications. The information contained within STOPPFrail Version 2 may not be enough. For this reason, future iterations of STOPPFrail may be improved with the addition of decision aids that enable stakeholders to manage uncertainty associated with deprescribing of certain medications. Decision aids promote shared decision making and enable patients to be clearer about their priorities when confronted with difficult choices.[150]

Table 7.1 outlines the categories and costs of medications consumed by the frail older people who participated in the STOPPFrail randomized trial. Interestingly, 'preventives' and 'nutrition/ vitamin supplements' (the categories of medications predominantly targeted by STOPPFrail) accounted for just 32% of the total number of medications but 50% of the total costs. The majority of prescribed drugs at baseline were in the 'symptom/ disease control' category. Clearly, it would not be appropriate to provide explicit deprescribing guidance for symptom/ disease control drugs: a clinical evaluation of the patient is required. Symptom burden is high in the last year of life and multiple medications may be necessary to achieve good symptom control. A reduction in the total number of regular medications may be a by-product of the formal medication review but the primary goal must be to ensure that patients are receiving the *right* medications to keep them well. Future iterations of STOPPFrail, therefore, may also be improved by including guidance on the pharmacological management of common problems experienced by older people approaching end-of-life such as pain, nausea, anxiety, and constipation.

Table 7.1: Categories and costs of medications consumed by participants enrolled in the randomized controlled trial described in Chapter 5

Preventives (217 drugs; 14.9% of total number; 14.7% of total cost)	**Symptom/ disease control** (990 drugs; 67.8% of total; 50.7% of total cost)	**Nutrition/ vitamins**** 253 items; 17.3% of total; 34.6% of the total cost***)
Antithrombotics (6.6%) Antihypertensive therapies (2.3%) * Lipid-lowering agents (2.3%) Calcium (2.6%) Antiresorptive therapies (1%)	Laxatives (13.1%) Analgesics (8.1%) Gastric acid suppressants (5.6%) Haematinic agents (2.7%) Psychiatric/hypnotic (8.3%) Inhaled medications (3.2%) Other (26.8%)	Oral nutritional supplements (9.2%) Vitamins (8.1%)

Legend: *Diuretics and b-blockers included in 'symptom/ disease control' category; **Vitamin B12 preparations included in 'symptom/ disease control' category; ***nutritional supplements alone accounted for 32.9% of the total cost of medications in the STOPPFrail trial

At the time of trial enrolment, oral nutritional supplements accounted for 9.2% of prescribed items but 32.9% of the total costs. This finding is surprising and warrants further investigation. Substantial weight loss is a core component of frailty[131, 132] and is highly predictive of future mortality.[251] Malnutrition is common in older hospitalized patients[251] and, therefore, the prescription of oral nutritional supplements for this patient cohort makes sense. However, while oral nutritional supplements produce small but consistent weight gain for older people, there is little evidence that they improve functional outcomes or quality of life.[252, 253] In fact, the literature indicates that compliance with oral nutritional supplements is low in long-stay wards due to poor palatability.[254] Future studies, therefore, should examine the effect of prescribing oral nutritional supplements on outcomes such as mealtime satisfaction, quality of life, function and mortality in older people with advanced frailty.

7.3 FINAL THOUGHTS

During the writing of this thesis, I have become somewhat sceptical about mortality prediction models, especially if they are to be used to influence important clinical decisions in individual frail older people. Prediction models, even when very accurate, tell us how an average patient with a given set of characteristics is likely to behave under average conditions. The danger is that the evaluation of a patient's clinical status is reduced to an aggregate score of measured risk factors. This would be a mistake since prediction models tell us nothing about individual patients' values. Everything that makes a patient an individual, the important things that define that individual's life, are outside the realm of prediction models. While risk scores and prediction models may be useful to identify *groups* of patients with shared characteristics who may benefit from a particular care pathway, I am rather doubtful that they should be used to influence important decisions about *individual* care.

Prognostic certainty, for an individual patient, is unattainable. However, when physicians maintain very frail older people on lengthy, problematic medication regimens, without consideration for prognosis and goals of care, they may be causing undue harm. The clinical reality is that these patients inch towards death with steady losses of function over time. Once frailty is established, it is perverse to think that medication can reverse or arrest this natural process of coming closer to death. While it may not be possible to accurately predict remaining life expectancy for frail older patients, I think it is important to at least consider whether they may be approaching end-of-life. In Chapter 6, I suggested a 3-step method for identifying patients who are approaching end-of-life. It may suffice to simply ask “is the older person so irreversibly fragile that a relatively minor stressor could spell end of life?” If the answer is ‘Yes’, then I think it is less important whether the patient dies imminently or lives for a few years in a very frail state: the same interventions –assistance for daily activities, advance care planning, palliation and, perhaps, deprescribing –are likely to be required.

This thesis does not intend to promote a nihilistic view of therapeutics in frailer older people. Rather, the intent is to emphasize the limits of certain medications when an older patient is approaching end-of-life. As I have shown, many patients approaching end-of-life are prescribed medicines for conditions or risk factors that do not cause symptoms but may result in adverse health outcomes later on – such as hypertension, hyperlipidaemia and osteoporosis. Most people treated with these medications do not benefit. The population-based approach of treating many to help the few need not apply to older people approaching end-of-life. Instead, these patients need their prescribers to focus on personalized care, prioritizing symptom relief rather than long-term prevention. It should be explained to frailer older patients and their families that the deprescribing of long-term medications is an option in these circumstances.

Some investigators have suggested that large scale trials are required to precisely examine the impact of deprescribing on mortality, quality of life and other patient related outcomes. While this of course is pertinent, an expectation that deprescribing will *improve* these outcomes may be over-reaching. Deprescribing involves the *withdrawal of a medical intervention* and, therefore, demonstrating that patents are no worse off in terms of symptoms and quality of life will justify the process.

Discussions about deprescribing often, appropriately, form part of a wider discussion around goals of care. These discussions are likely to be sensitive. It may be beneficial if they are initiated by a physician who knows the patient's case very well, ideally the physician who will support the patient in their final illness. This doctor/patient familiarity and trust may be more important than the application of nuanced, evidence-based geriatric pharmacotherapy. My contention is that the real value of a tool like STOPPFrail is that it enables the general practitioner, the oncologist, the geriatrician -in other words, the *patient's doctor* -to make clinically-sound deprescribing decisions.

Physicians need to remember that they have duties beyond that of restoring and maintaining patients in pristine health. Disability and death do not represent a failure of medical care but are, rather, natural processes for which science has no remedy. The fundamental obligation of physicians is to relieve the suffering of their patients – "to cure sometimes, to relieve often, to comfort always" as the aphorism goes. Deprescribing for older people approaching end-of-life is the withdrawal of medicines but *not* of care; patients, families and physicians must understand this concept. Care in these circumstances encompasses a demonstration of humane concern, palliative treatment for troublesome symptoms, helping the patient cope with his or her final illness and above all, understanding what is important to the patient. Peabody, in 1927, summarized this point as follows: "One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring *for* the patient".[255] This is the art of medicine.

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APPENDIX 1

Published articles arising from research described in this thesis

BRIEF REPORT

Predicting 1-Year Mortality in Older Hospitalized Patients: External Validation of the HOMR Model

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OBJECTIVES: Accurate prognostic information can enable patients and physicians to make better healthcare decisions. The Hospital-patient One-year Mortality Risk (HOMR) model accurately predicted mortality risk (concordance [C] statistic = .92) in adult hospitalized patients in a recent study in North America. We evaluated the performance of the HOMR model in a population of older inpatients in a large teaching hospital in Ireland.

DESIGN: Retrospective cohort study.

SETTING: Acute hospital.

PARTICIPANTS: Patients aged 65 years or older cared for by inpatient geriatric medicine services from January 1, 2013, to March 6, 2015 (n = 1654). After excluding those who died during the index hospitalization (n = 206) and those with missing data (n = 39), the analytical sample included 1409 patients.

MEASUREMENTS: Administrative data and information abstracted from hospital discharge reports were used to determine covariate values for each patient. One-year mortality was determined from the hospital information system, local registries, or by contacting the patient's general practitioner. The linear predictor for each patient was calculated, and performance of the model was evaluated in terms of its overall performance, discrimination, and calibration. Recalibrated and revised models were also estimated and evaluated.

RESULTS: One-year mortality rate after hospital discharge in this patient cohort was 18.6%. The unadjusted HOMR model had good discrimination (C statistic = .78; 95% confidence interval = .76-.81) but was poorly calibrated and consistently overestimated mortality prediction. The model's performance was modestly improved by recalibration and revision (optimism corrected C statistic = .8).

CONCLUSION: The superior discriminative performance of the HOMR model reported previously was substantially attenuated in its application to our cohort of older hospitalized patients, who represent a specific subset of the original derivation cohort. Updating methods improved its performance in our cohort, but further validation, refinement, and clinical impact studies are required before use in routine clinical practice. **J Am Geriatr Soc 00:1-6, 2019.**

Key words: prediction model; prognostic estimates; end-of-life care; HOMR model; prognosis in older people

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An important principle when caring for an older person with frailty and multimorbidity is to align interventions to the patient's condition, preferences, and prognosis.[1] When life expectancy is limited, strategies to optimize quality of life may be prioritized over invasive or futile interventions. Discussions about goals of care, however, are often deferred in frailer older patients because of the uncertainty associated with prognostic estimates.[2] An accurate method of assessing prognosis could inform and motivate discussions between physicians and their patients about values, priorities, and therapeutic goals.

The Hospital-patient One-year Mortality Risk (HOMR) model was shown recently to accurately predict 1-year mortality risk in hospitalized patients.[3,4] It is composed of covariates that include demographics, comorbidities, severity of acute illness, and recent acute hospital care utilization (Appendix S1). These covariates are determined at the time of hospital admission using routinely collected

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health administrative data. More than 3 million patients aged 18 years or older were included in the validation studies in Ontario and Alberta (Canada), and Boston (United States).[3,4] The HOMR model had a very high discriminative performance (concordance [C] statistic = .89-.92), and there was a less than a 1% difference between the observed and expected percentages of deceased patients at 1 year.

To our knowledge, the HOMR model's performance exceeds that of other similar prognostic models. However, it has not been validated in an exclusively older (≥65 y) hospitalized patient population. The aim of this study was to evaluate the performance of the HOMR model in a population of older hospitalized patients in a large teaching hospital in Ireland.

METHODS

Data Collection

The HOMR model was applied retrospectively to all hospitalized patients aged 65 years or older that were under the care of the specialist geriatric medicine service at Cork University Hospital from January 1, 2013, to March 6, 2015. When patients were admitted more than once during that period, a single hospital admission was chosen at random as the index hospitalization. Most of the information required to calculate the HOMR model was obtained using administrative data from the Hospital In-Patient Enquiry (HIPE) system, a national database of coded discharge summaries. The *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification;* Australian Classification of Health Interventions; and *Australian Coding Standards* apply to all activity coded in HIPE in Ireland.[5] Details about home supports before admission as well as provision of home oxygen therapy, which are not routinely collected by administration staff in Ireland, were obtained from the consultant geriatrician discharge reports. When information was missing from these sources, the patients' medical records were reviewed. Covariate values were determined independently by two researchers with discrepancies resolved through consensus.

Deaths within 1 year of hospital admission were determined by accessing the hospital clinical information system, an online death notification system (https://www.RIP.ie), the Births, Deaths and Marriages Registry Office in Cork City, and, if required, by contacting the patient's general practitioner. Unlike the initial HOMR derivation and validation studies, patients who died during the index hospital admission were not included. There were two reasons for this. First, geriatrician discharge reports were used to obtain information about home supports for the HOMR model, and these details were generally not included when the patient died during hospitalization. Second, the value of the predictive model, for the present project, is to calculate 1-year mortality risk after the acute hospital episode. Predicting in-hospital deaths largely depends on specific clinical factors.

Statistical Analysis

A sample size that results in at least 100 events, and preferably 200 or more events, is recommended to externally validate a prognostic model.[6] We estimated that 1-year mortality *after* hospital discharge would very likely exceed 15%,[7,8] and on that basis we calculated that a sample size of 1400 patients would be required.

To validate the HOMR model, the linear predictor for each patient was calculated based on the coefficient values provided in Appendix E of the original HOMR model development study.[3] The HOMR model was then evaluated in terms of its overall performance, discrimination, and calibration. The model's overall performance was evaluated using the Brier score, rescaled to range from 0 to 1, with higher values indicating better performance.[9] Discrimination, which refers to how well the model distinguishes those with the outcome from those without the outcome (ie, death in this case), was measured using the C statistic. Calibration refers to the agreement between observed outcomes and predicted outcomes and is usually displayed using a calibration plot. In addition to calibration plots, we also report the maximum and average difference in predicted vs loess-calibrated probabilities (Emax and Eavg).[10] Finally, we report bootstrapped 95% confidence intervals for these metrics, based on 500 resampled replicates.[11]

To recalibrate the HOMR model, three additional logistic regression models were estimated.[12] The first additional model included the HOMR linear predictor, with its coefficient set to equal 1, and a freely estimated intercept (Recalibration in the Large). The second model then allowed the coefficient on the HOMR linear predictor to be freely estimated (Logistic Recalibration). The third model included the complete set of variables used in the HOMR model, including the same transformations and interactions, and allowed their respective coefficients to be freely estimated (Model Revision). The performance of each of these models was assessed using the same metrics as those used to validate the original HOMR model. In addition, the optimism corrected C statistic and shrinkage factor were estimated for the Model Revision using bootstrapping (with 500 resampled replicates).

All analyses were conducted using R language for statistical computing software,[13] v.3.4.3 (November 30, 2017). All data and the code used to analyze it and generate outputs can be found on the Open Science Framework (https://osf.io/tv26k/).

RESULTS

Baseline Characteristics of Study Population

Between January 1, 2013, and March 6, 2015, 1654 individual patients aged 65 years or older were hospitalized under the care of the specialist geriatric service. Of these, 206 patients (12.4%) died during the index hospitalization and therefore were not included in the analysis. After removing 39 patients with missing outcome data (2.7%), a final sample of 1409 patients was analyzed. Of these, 259 (18.4%) died within 1 year of admission to the hospital. The median age of the study patients was 80 years (interquartile range = 74-85 y), two-thirds were living independently before their hospital admission, and 94.5% were admitted through the emergency department. The baseline characteristics of the study participants are summarized in Table 1.

Table 1. Baseline Characteristics of Study Participants (and How They Compare with Original Derivation Cohort)

Variable	Mean SD	Median (IQR)	(Min, max)	HOMR derivation cohort
Sex				
Female	800 (56.8%)			61.8%
Male	609 (43.2%)			38.2%
Age	79.3 ± 7.4	80 (74-85)	(65, 101)	59 (IQR = 37-75)
Living status[a]				
Independent	933 (66.2%)			83%
Rehabilitation unit	33 (2.3%)			.2%
Home care	295 (20.9%)			12.1%
Nursing home	148 (10.5%)			4.5%
Urgency of admission				
Elective	78 (5.5%)			47.4%
ED without ambulance	498 (35.3%)			25.7%
ED with ambulance	833 (59.1%)			26.9%
No. of ambulance transfers[b]	.3 ± .7	0 (.0)	(.5)	NA
Admitting service[c]				
General medicine (including geriatric medicine)	1365 (96.9%)			31.4%
General surgery	3 (.2%)			11%
Cardiology	17 (1.2%)			6.4%
Orthopedics	8 (.6%)			8.4%
Gastroenterology/Nephrology/Neurology	16 (1.1%)			4.9%
ICU admission directly from ED	3 (.2%)			7.4%
Home O_2[a]	0			2.3%
ED visits[b]				
0	828 (58.8%)			55.1%
≥1	581 (41.2%)			44.9%
Urgent readmission within 30 d	131 (9.3%)			4.5%
DRS	−1.9 ± 4.8	0 (−1 to 0)	(−22, 9)	NA
CCI[d]				
0	23.3%			57.8%
1-2	34.2%			21.7%
≥3	42.5%			20.5%

Abbreviations: CCI, Charlson Comorbidity Index; DRS, diagnostic risk score; ED, emergency department; HOMR, Hospital-patient One-year Mortality Risk; ICU, intensive care unit; IQR, interquartile range; NA, not available; SD, standard deviation.
[a]Prior toBefore index hospitalization.
[b]In 12 months before index hospitalization.
[c]All patients, after hospital admission, were under the care of the specialist geriatric medicine service.
[d]Not adjusted for patient age.

HOMR Model External Validation

When the HOMR model was applied directly to the sample of 1409 older patients, it showed good discrimination (C statistic = .78). Calibration, however, was poor (Figure 1 shows the calibration plot) with the model consistently overestimating mortality at all but the lowest levels of risk (Table 2 lists the performance metrics).

Performance of Updated HOMR Model

All three updating methods improved calibration over the original model. Recalibration in the Large resulted in a lower intercept (−0.42; Table 2) and a significant improvement in model fit over the HOMR model (likelihood ratio test [LRT] χ^2 *P* value = <.001). Logistic Recalibration did not lead to additional improvements in model fit (LRT χ^2 *P* value = .85), with a recalibration slope of .99 (ie, close to 1). The Brier score and Eavg were improved by recalibration (Table 2). The calibration plot for Recalibration in the Large (which is virtually identical to the plot for Logistic Recalibration) is shown in Figure 1. In addition to improving calibration, Model Revision also improved discrimination (C statistic = .82). The optimism corrected C statistic for the Model Revision was .8, and the shrinkage factor was .91, indicating some overfit. The reestimated HOMR model, with regression coefficients, is shown in Appendix **S2**.

DISCUSSION

This study provides information about the performance of the HOMR model in new patients, in a different geographic region, when validated by investigators who were not involved in the model's development. The high discriminative performance reported in the initial validation studies was substantially attenuated in our older hospitalized cohort, and calibration was found to be poor with the model consistently overestimating mortality risk. The results illustrate the importance of testing seemingly

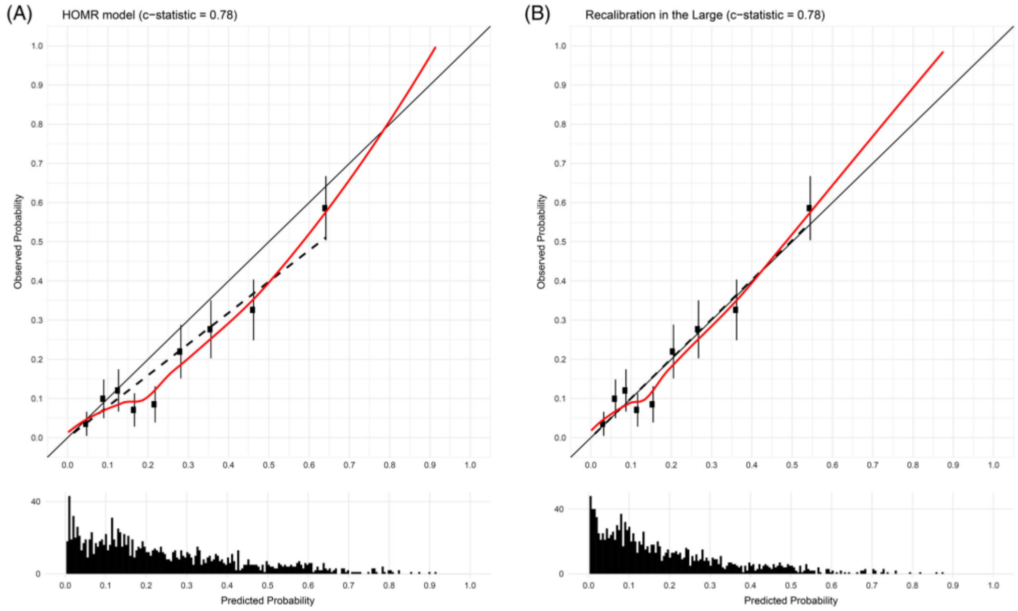

Figure 1. Calibration plots of the unadjusted and updated Hospital-patient 1 year mortality risk (HOMR) models. A, Original HOMR model. B, Recalibrated model (Recalibration in the Large).

accurate prediction models in target populations before applying them in routine practice.

There are plausible reasons for the reduced predictive performance in this external validation study. First, the patients in the present cohort were substantially older (median age was 80 y vs 59 y in the HOMR derivation cohort; Table 1) and less likely to be living independently (66.3% vs 83%).[3] Second, unlike the initial validation studies, patients who died during their index hospital admission were excluded. This is likely to be significant because one of the HOMR covariates, the diagnostic risk score, quantifies risk of death based on specific admission diagnoses. High scores associated with diagnoses such as intracerebral hemorrhage and sepsis reflect high risk of death during hospitalization. This risk may diminish significantly when patients survive the initial days of their acute hospital episode. Third, it is unclear whether the diagnostic risk scores, which were derived from a large population of adult patients of all ages, are weighted appropriately for older hospitalized patients. An admission diagnosis of syncope, for example, is assigned a diagnostic risk score of −9 that perhaps reflects its usually benign prognosis in younger adults. Syncope in older adults, however, is associated with reduced survival.[14] Finally, differences in access and organization of primary care between North America and Ireland may have had an important impact on covariates relating to recent acute hospital care utilization (ie, ambulance transfers, emergency department visits, readmissions).[15,16]

Table 2. Performance of the Unadjusted and Updated Hospital-Patient 1-Year Mortality Risk Models

	HOMR model	Calibration in the Large	Logistic Recalibration	Model Revision
Intercept	0	−0.42	−.43	…
Slope	1	1	.99	…
Residual deviance	1139.96	1107.76	1107.73	1046.55
df	1409	1408	1407	1389
LRT χ^2 *P* value	…	<.00	.85	…
Brier score, rescaled	.15 (.1 -.21)[a]	.19 (.13-.25)	.19 (.13-.26)	.23 (.18-.31)
Emax	.10 (.08-.14)	.11 (.03-.22)	.121 (.03-.23)	.01 (.01-.09)
Eavg	.05 (.04-.07)	.01 (.01-.02)	.01 (.00-.02)	.00 (.00-.01)
C statistic	.78 (.76-.81)	.78 (.75-.81)	.78 (.76-.81)	.82 (.8-.85)

Abbreviations: df, degrees of freedom; Eavg, average absolute difference in predicted and calibrated probabilities; Emax, maximum absolute difference in predicted and calibrated probabilities; LRT, likelihood ratio test.
[a]Bootstrapped 95% confidence intervals.

Our findings are not surprising: the accuracy of predictive models is often substantially lower in new patients compared with the accuracy found in patients of the development population.[17,18] Rather than simply reject the model, updating methods were used to improve performance in our older patient cohort. In this study, Recalibration in the Large (the simplest updating method where just one parameter of the original model [ie, the intercept] is adjusted) substantially improved performance. Although Model Revision resulted in further improvements, this more extensive updating method is less ideal because parameter estimates are redeveloped on the data of the validation set (a much smaller sample), and prior information from the larger derivation sample is disregarded.[19]

The performance of the recalibrated HOMR model compares favorably with other validated prognostic models for older hospitalized patients (Appendix S3).[8,18,20-28] However, it is important to emphasize that an updated HOMR model, just like a newly developed model, would require testing of its generalizability, as well as its impact on clinician behavior and patient outcomes, before it could be recommended for use in routine clinical practice.[29] Even then, because of inherent unwieldiness, it would need to be integrated into hospital information systems to ensure usability for practicing physicians.

The present study has some limitations. First, the HOMR model was applied and updated in a single medical center where patients were cared for by specialist geriatricians. As discussed, this limits the generalizability of our findings, and further validation in other centers is now required. Second, we used the model differently to how it was originally designed by excluding patients who died during their index admission. However, we contend that the primary purpose of an accurate 1-year mortality prediction in a hospitalized patient is to help guide decision making and care planning *after* the index acute episode when the patient's condition has stabilized.

In conclusion, the exceptional performance of the HOMR model, reported in the North American validation studies, was substantially attenuated in a cohort of older hospitalized patients in a large teaching hospital in Ireland. Nevertheless, the performance of the HOMR model in our older patient cohort was demonstrably good and compares favorably with other validated non–disease-specific mortality prediction tools for older people. Updating methods improved performance of the HOMR model, but further refinement, validation, as well as clinical impact studies, will be required before the model could be applied confidently in routine practice.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. The original Hospital-patient One-year Mortality Risk (HOMR) model. Covariates used to calculate a patient's HOMR score. ED, emergency department; ICU, intensive care unit.

Appendix S2. Reestimated Hospital-patient One-year Mortality Risk (HOMR) model with regression coefficients. CCI, Charlson Comorbidity Index; ED, emergency department; ICU, intensive care unit.

Appendix S3. Summary of prognostic models used to predict mortality in hospitalized older patients.

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Drug consumption and futile medication prescribing in the last year of life: an observational study

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Abstract

Background: the last year of life for many older people is associated with high symptom burden and frequent hospitalizations. Hospital physicians have an opportunity to prioritize essential medications and deprescribe potentially futile medications.
Objective: to measure medication consumption during hospitalization in the last year of life and the prevalence of potentially inappropriate medications (PIMs) at hospital discharge.
Design: retrospective chart review.
Setting: acute hospital.
Subjects: ≥65 years, hospitalized in the last year of life.
Methods: medication consumption was determined by examining hospital Medication Administration Records. PIMs were defined using STOPPFrail deprescribing criteria.
Results: the study included 410 patients. The mean age of participants was 80.8, 49.3% were female, and 63.7% were severely frail. The median number of days spent in hospital in the last year of life was 32 (interquartile range 15−59). During all hospitalizations, the mean number of individual medications consumed was 23.8 (standard deviation 10.1). One-in-six patients consumed 35 or more medications in their last year. Over 80% of patients were prescribed at least one PIM at discharge and 33% had ≥3 PIMs. Lipid-lowering medications, proton pump inhibitors, anti-psychotics and calcium supplements accounted for 59% of all PIMs. Full implementation of STOPPFrail recommendations would have resulted in one-in-four long-term medications being discontinued.
Conclusion: high levels of medication consumption in the last year of life not only reflect high symptom burden experienced by patients but also continued prescribing of futile medications. Physicians assisted by the STOPPFrail tool can reduce medication burden for older people approaching end of life.

Keywords: *deprescribing, frailty, medications, elderly, STOPPFrail*

Background

A hospital admission in an older person with end-stage chronic disease or progressive frailty is an appropriate time to review medications and goals of care [1–3]. Large observational studies have shown that hospitalizations are frequent in the last year of life due to high symptom and illness burden [4, 5]. Hospital physicians, therefore, have an opportunity to tailor medication regimens to the condition and prognosis of their patients and deprescribe potentially harmful or futile drugs.

The STOPPFrail criteria (Table 1) are an explicit list of 27 indicators to assist physicians with deprescribing decisions in frail older individuals with poor 1-year survival prognosis [6]. The STOPPFrail criteria were developed by Delphi consensus of an expert panel comprising academic geriatricians, clinical pharmacologists, palliative care physicians, old age psychiatrists, general practitioners and clinical pharmacists. The tool is concise, has good inter-rater reliability [7], and is designed to be used by clinicians who commonly provide care for older people. The relevance and applicability of the STOPPFrail criteria

Table 1. The STOPPFrail criteria

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:
(1) End-stage irreversible pathology
(2) Poor 1-year survival prognosis
(3) Severe functional or severe cognitive impairment or both
(4) Symptom control is the priority rather than prevention of disease progression

Section A: general
A1: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations
A2: Any drug without clear clinical indication

Section B: cardiology system
B1. Lipid lowering therapies (statins, ezetimibe, bile acid sequestrans, 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 ADEs outweighs the potential benefits
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

Section C: coagulation system
C1: Anti-platelets
Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit)

Section D: Central nervous system
D1. 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)
D2: Memantine
Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD (specifically in frail patients who meet the criteria above)

Section E: gastrointestinal system
E1. Proton pump inhibitors
Proton pump inhibitors at full therapeutic dose ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
E2: H2 receptor antagonist
H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
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

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
F2. Leukotriene antagonists (Montelukast, Zafirlukast)
These drugs have no proven role in COPD, they are indicated only in asthma (50)

The decision to prescribe/not prescribe medications to the patient, should also be influenced by the following issues:
(1) Drug adherence/compliance is difficult
(2) Administration of the medication is challenging
(3) Monitoring of the medication effect is challenging
(4) Drug adherence/ compliance is difficult

Section G: musculoskeletal system
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)**
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
G4. Long-term oral NSAIDs
Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months
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

Section H: urogenital system
H1. 5-alpha reductase inhibitors
No benefit with long term urinary bladder catheterisation
H2. Alpha blockers
No benefit with long term urinary bladder catheterisation
H3. Muscarinic antagonists
No benefit with long-term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity

Section I: endocrine system
I1. Diabetic oral agents
Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary
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
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
I4. Systemic oestrogens for menopausal symptoms
Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms

Section J: Miscellaneous
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
J3: Prophylactic antibiotics
No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs

Disclaimer (STOPPFrail)
While every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence-based, it is emphasized that the final decision to avoid or initiate any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that prescribing decisions should take account of current published evidence in support of or **against the use of drugs or drug classes described in STOPPFrail.**

Table 2. Baseline characteristics and results

	Total (n = 410)
Mean age (SD) at time of index hospitalization	80.8 (7.9)
Female (%)	202 (49.3)
Discharge health/functional status	
Mean (SD) CCI score	6.2 (2.3)
CFS ≥7	261 (63.7%)
Mean number (SD) of admission medications at index hospitalization	8.4 (4.3)
Mean number (SD) of discharge medications at index hospitalization	8.7 (4.2)
Median number (IQR) of days between index hospital discharge and death	124 (47–225.5)
At index hospital discharge	
Mean no. of PIMs per patient (SD)	1.9 (1.4)
≥1 PIM	81.5%
≥3 PIMs	34.0%
In the last year of life	
Median bed days (IQR)	32 (15–59)
Median hospital admissions (IQR)	2 (1.25–3)
Median emergency department episodes (IQR)	2 (1–3)
≥30 Bed days	53.4%
≥3 Hospital admissions	43.4%
≥3 Emergency department episodes	34.0%
Medications consumed during all hospitalizations in last year of life	
Mean	23.8 (10.1)
≥25 Medications	43.6%
≥35 Medications	17.3%
Medication-types consumed during all hospitalizations in last year of life	
Disease/symptom control	87.3%
Long-term preventive	9.5%
Short-term preventive	3.2%

to older people hospitalized in the last year of life has not yet been studied.

The aims of this study were:

- To determine the prevalence of potentially inappropriate medications (PIMs), as defined by the STOPPfrail tool, in the discharge prescription lists of older adults hospitalized in the last year of life.
- To measure medication consumption by older people while in hospital in the last year of life.

Methods

Study population

We included people aged ≥65 years who were hospitalized for ≥2 days under general medical services in our institution in the year prior to death. The Hospital In-Patient Enquiry system (a national database of coded discharge summaries) was used to identify patients discharged between January 2013 to December 2014. When patients were admitted more than once during this period, a single hospitalization was randomly chosen as the index hospitalization. Patients who died during their index hospital admission and those discharged to a hospice, presumably in the final stages of a terminal illness, were excluded because the primary end point was to measure the prevalence of STOPPFrail-defined PIMs at the time of discharge. Deaths within 1 year of hospitalization were determined by accessing the Hospital Information System and an online death notification system (www.RIP.ie). In total, 603 patients were eligible for inclusion. We estimated that 50% of patients would be prescribed PIMs at discharge. Using a precision of 5% and a 95% level of confidence, we calculated that a minimum sample of 384 patients would be required for this study. To ensure an adequate final sample size, a random sample of 434 was generated using a randomization (RAND) function in Microsoft Excel©. The local Clinical Research Ethics Committee approved the study protocol.

Data collection

A retrospective chart review was conducted on all study patients by a Geriatric Medicine trained physician using a standardized data collection pro-forma. The prevalence of STOPPfrail-defined PIMs was measured by accessing the discharge prescriptions from the patients' index hospitalization. Disease burden and performance status at the time of hospital discharge were determined using the Charlson Comorbidity Index (CCI) [8, 9] and the Clinical Frailty Scale (CFS) [10], respectively. The CFS is a 9-item scale and, in this study, we categorized patients into two groups: (i) those with scores of ≥7 (indicating severe frailty and/or terminal illness and therefore potentially eligible for the STOPPFrail tool) and (ii) those with scores <7 (indicating full independence, mild or moderate frailty). Medication consumption was determined by reviewing in-patient medication administration records from all hospitalizations in the last year of life. Medications that were prescribed but not consumed were not included, nor were nutritional products, blood products or intravenous fluids. A single ingredient constituted one medicine. For combination products, each ingredient was included as one drug as long as that ingredient was available as a medicine in the British National Formulary.

Results

Patient characteristics

In total, 410 patients were included (24 patients were excluded because of missing data or because they were discharged to the care of community palliative services). The principal characteristics of the decedents are summarized in Table 2. The mean age of patients was 80.8 (standard deviation [SD] 7.9) and males and females were evenly represented. Polypharmacy was highly prevalent and the mean number of medications per patient at the time of hospital admission was 8.4 (SD 4.3). At the time of hospital discharge, 63.7% of patients were either severely frail or had an advanced terminal diagnosis (CFS ≥ 7).

Prevalence of STOPPfrail PIMs at hospital discharge

The mean number of medications prescribed per patient did not change significantly from index hospital admission to discharge (8.4 [SD 4.3] versus 8.7 [SD 4.2], $P = 0.275$). More than 80% of patients were prescribed at least one STOPPfrail-defined PIM in their discharge prescription and 34% had ≥3 PIMs prescribed (Table 2). The mean number of PIMs did not differ significantly between patients' potentially eligible for STOPPFrail-guided deprescribing (CFS ≥ 7) and those with less advanced stages of frailty (2.0 [SD 1.5] versus 1.8 [SD 1.4], $P = 0.053$). Full implementation of the STOPPFrail recommendations for those with polypharmacy (defined here as ≥5 long-term medications) would have resulted in, on average, a 23% reduction in total medication burden. Lipid-lowering medications, proton pump inhibitors, anti-psychotics and calcium supplements accounted for 59% of all STOPPfrail-defined PIMs (Supplementary Appendix 1).

Medication consumption while in hospital in the last year of life

In the year prior to death, the median number of days in hospital was 32 (interquartile range [IQR] 15–58). One-third of people had three or more emergency department presentations. During all hospital stays in the last year of life, the mean number of individual medications consumed per patient was 23.8 (SD 10.1). One-in-six patients consumed ≥35 different medications (Table 2). Long-term preventive medications accounted for 9.5% of all medications consumed during hospitalization but 24.9% of medications prescribed at the time of hospital discharge.

Discussion

This is the first study of its kind using recently validated explicit deprescribing criteria designed for application in the frailest older people. Our data show that older people in their last year of life receive high levels of polypharmacy, a quarter of which includes long-term preventive therapies which are likely futile. Hospital physicians need to (i) be able to recognize frailer older patients in their last year of life, and (ii) be prepared to deprescribe thoughtfully where appropriate, particularly long-term preventive drugs where benefit is unlikely to be realized.

Symptoms at end of life are often complex. A large nationally representative longitudinal survey of adults in the USA reported that symptoms such as depression, confusion, dyspnea, incontinence, fatigue, anorexia and vomiting were all common in the last year of life [11]. While improvements can usually be made regarding prescribing quality, high levels of medication consumption may be inevitable. This is important because the number of medications prescribed is the most important predictor of iatrogenic harm [12]. The challenge for the prescribing physician is to strike a balance between controlling multiple symptoms and minimizing the inherent risks of polypharmacy.

Full implementation of STOPFrail recommendations for hospitalized patients would have resulted in almost one-in-four long-term medications being discontinued. The process of deprescribing, of course, must be individualized and patients' preferences, clinical contextual factors and the potential for adverse drug withdrawal events given due consideration. Other deprescribing tools (e.g. CEASE [13], Good Palliative-Geriatric Practice [14]) are 'implicit' and demand that the prescriber balance risk and benefit of each medication. The real-world applicability of these methods to all but expert prescribers is doubtful. The value of STOPPFrail is that it is explicit, concise, easy-to-use, and, as we have shown, highly relevant to the practice of hospital physicians.

Recognizing when people are in the final phase of life is key to operationalizing deprescribing. A 2012 systematic review by Yourman *et al.* [15] concluded that there was insufficient evidence to recommend application of any of the available prognostic models for older adults. Some degree of uncertainty when predicting prognosis seems inevitable. In this study, the majority of patients were severely frail and functional status has been shown to be a strong predictor of mortality in older people [1, 15]. In addition, functional decline following hospitalization is associated with a poor survival prognosis [16]. Perhaps then, it is patients who are severely frail at the time of hospital admission, and those who decline to a new frailer baseline despite adequate rehabilitation, that should be considered appropriate candidates for deprescribing.

Our study has some limitations. Firstly, the experience described does not apply to the 18–29% of older people who are not hospitalized in the last year of life [1, 4]. However, symptom, disease and medication burden are presumably less marked in this cohort. Secondly, we may have underestimated medication exposure and acute hospital care utilization because information about hospitalizations outside of our institution was not captured.

In summary, hospitalizations are common and drug burden is high in the last year of life and people are frequently discharged home with prescriptions for potentially futile medications. The STOPPFrail criteria are highly relevant and may assist physicians with deprescribing decisions.

Key points

- The last year of life is associated with frequent and prolonged hospital admissions.
- Medication consumption is high in the last year of life and many patients consume medications that are potentially futile.
- Hospital physicians can reduce medication burden for older people approaching end of life using the STOPPFrail tool.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of interest

D.OM. and P.G. were involved in the development of the STOPPFrail Criteria which were used to define 'futile medications'.

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Deprescribing in multi-morbid older people with polypharmacy: agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases

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Abstract

Purpose Older people with advanced frailty are among the highest consumers of medications. When life expectancy is limited, some of these medications are likely to be inappropriate. The aim of this study was to compare STOPPFrail, a concise, easy-to-use, deprescribing tool based on explicit criteria, with gold standard, systematic geriatrician-led deprescribing.

Methods One hundred standardized clinical cases involving 1024 medications were prepared. Clinical cases were based on anonymized hospitalized patients aged ≥ 65 years, with advanced frailty (Clinical Frailty Scale ≥ 6), receiving ≥ 5 regular medications, who were selected from a recent observational study. Level of agreement between deprescribing methods was measured by Cohen's kappa coefficient. Sensitivity and positive predictive value of STOPPFrail-guided deprescribing relative to gold standard deprescribing was also measured.

Results Overall, 524 medications (51.2%) of medications prescribed to this frail, elderly cohort were potentially inappropriate by gold standard criteria. STOPPFrail-guided deprescribing led to the identification of 70.2% of the potentially inappropriate medications. Cohen's kappa was 0.60 (95% confidence interval 0.55–0.65; $p < 0.001$) indicating moderate agreement between STOPPFrail-guided and gold standard deprescribing. The positive predictive value of STOPPFrail was 89.3% indicating that the great majority of deprescribing decisions aligned with gold standard care.

Conclusions STOPPFrail removes an important barrier to deprescribing by explicitly highlighting circumstances where commonly used medications can be safely deprescribed in older people with advanced frailty. Our results suggest that in multi-morbid older patients with advanced frailty, the use of STOPPFrail criteria to address inappropriate polypharmacy may be reasonable alternative to specialist medication review.

Keywords STOPPFrail · Deprescribing · Frailty · Polypharmacy · Multi-morbidity

Introduction

An important principle when caring for older people with multi-morbidity is to carefully align the medication regimen to the condition and goals of care of the individual patient [1]. This is particularly important for patients approaching end of life where symptom management usually takes priority over stringent chronic disease control. Polypharmacy is common in this cohort and many of these patients are prescribed medications that are probably futile [2]. Yet, physicians commonly forego the opportunity to deprescribe because of fear of negative consequences (i.e., symptom relapse, clinical deterioration) [3, 4]. This is despite evidence indicating that deprescribing can be achieved without compromising patient safety or wellbeing [5–7].

The complexity associated with frailty, multi-morbidity, and polypharmacy necessitates a systematic approach to deprescribing. Scott and colleagues have recently proposed a 5-step deprescribing protocol (CEASE—confirm current medications, estimate risk of drug-related harm, assess each medication for discontinuation, sort/prioritize medications for

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discontinuation, eliminate medications according to agreed deprescribing plan). The third step—assessing each medication for discontinuation—requires the user to answer a series of questions about each medication in the patient's regimen (Fig. 1) [8]. While comprehensive and patient-centered, the outcome of this step will depend on the knowledge, attitudes, and experience of the user. Implicit approaches, such as CEASE, are usually time-consuming, thereby greatly limiting their integration into routine clinical practice [9]. More recently, the STOPPFrail criteria (Table 1), a list of 27 indicators to assist physicians with deprescribing decisions in frail older individuals with poor 1-year survival prognosis, have been validated [11]. Of the 27 indicators, 26 are explicit (i.e., clearly defined statements highlighting the potentially inappropriate use of particular drug/drug classes in a particular clinical situation) and one is implicit (i.e., A2: stop any drug without a clear clinical indication). STOPPFrail criteria, which are organized according to physiological system, are concise, have substantial inter-rater reliability [12], and are designed to be used by physicians of all disciplines who provide care for frailer older people on a routine basis.

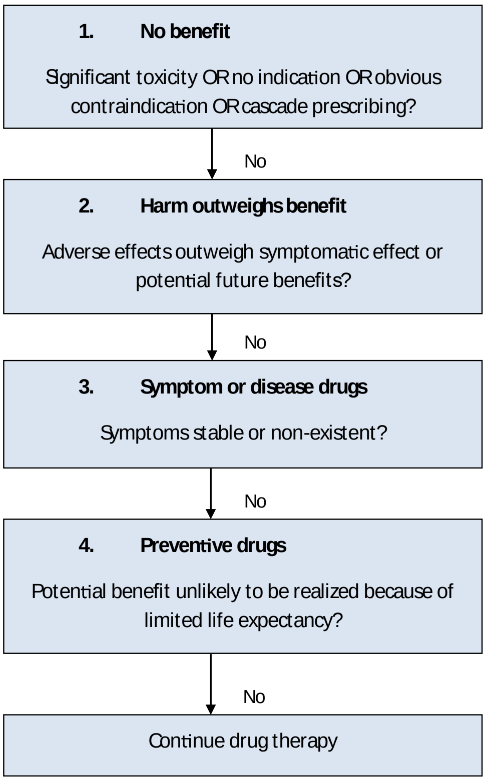

Fig. 1 Step 3 of the CEASE protocol: Scott's deprescribing algorithm

The primary aim of the present study is to compare the utility of the structured predominantly explicit STOPPFrail criteria with a gold standard comparator in frail older people with poor 1-year survival prognosis. Of the available published deprescribing guides, the CEASE protocol has the strongest evidence of efficacy and physician acceptability [10], and therefore, its use by a physician with expertise in clinical pharmacotherapy is an appropriate gold standard for deprescribing. If STOPPFrail reproduces the results of this gold standard, then its brevity and easy usability may make it a more appropriate method of deprescribing in routine clinical practice for this particular population of older people. The secondary aim was to determine which inappropriate or unnecessary medications are not identified by STOPPFrail. This information could inform future iterations of the STOPPFrail criteria.

Methodology

Clinical cases

To ensure that the comparison between the two deprescribing methods was valid, it was important to minimize external sources of variability [13]. For this reason, structured clinical cases were prepared to ensure timely and equal access to information relevant to the deprescribing decision (Supplementary appendix 1). These clinical cases were based on anonymized patients included in a recent observational study that examined the prevalence of potentially inappropriate medications in the discharge prescriptions of older people hospitalized in the year prior to their death [2]. Each structured clinical case included a list of diagnoses, regular medications, functional and cognitive status, and routine blood tests results prior to hospital discharge. All clinical cases were based on patients aged ≥ 65 years, prescribed ≥ 5 regular medications with moderate to severe frailty (Clinical Frailty Score ≥ 6 [14]). For each of the clinical cases, it was assumed as follows:

i. The patient was medically stable
ii. The patient had a poor 1-year survival prognosis
iii. The list of diagnoses was complete and correct
iv. Laxatives (unless potentially part of a prescribing cascade) and paracetamol were appropriate
v. There were no difficulties with medication administration (e.g., dysphagia, poor inhaler technique) unless explicitly stated
vi. The patient's nutritional status was satisfactory unless otherwise stated
vii. Behavioral and psychological symptoms of dementia were present only if explicitly stated

Table 1 The STOPPFrail criteria [10]

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:

1) End-stage irreversible pathology
2) Poor one year survival prognosis
3) Severe functional or severe cognitive impairment or both
4) 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:

1) Drug adherence/compliance is difficult
2) Administration of the medication is challenging
3) Monitoring of the medication effect is challenging
4) Drug adherence/ compliance is difficult

Section A: General

A1: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations.
A2: Any drug without clear clinical indication.

Section B: Cardiology system

B1. Lipid lowering therapies (statins, ezetimibe, bile acid sequestrans, 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
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

Section C: Coagulation system

C1: Anti-platelets
Avoid anti-platelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit)

Section D: Central Nervous System

D1. 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)
D2: Memantine
Discontinue and monitor in patients with moderate to severe dementia, unless
memantine has clearly improved BPSD (specifically in frail patients who meet the criteria above)

Section E: Gastrointestinal System

E1. Proton Pump Inhibitors
Proton Pump Inhibitors at full therapeutic dose ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
E2: H2 receptor antagonist
H2 receptor antagonist at full therapeutic dose for ≥ 8/52, unless persistent dyspeptic symptoms at lower maintenance dose
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

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
F2. Leukotriene antagonists (Montelukast, Zafirlukast)
These drugs have no proven role in COPD, they are indicated only in asthma (50)

Section G: Musculoskeletal System

G1: Calcium supplementation
Unlikely to be of any benefit in the short term
G2: Anti-resorptive/bone anabolic drugs [illegible] (bisphosphonates, strontium, teriparatide, denosumab)
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
G4. Long-term oral NSAIDs
Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure etc.) when taken regularly for ≥ 2 months
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

Section H: Urogenital System

H1. 5-alpha reductase inhibitors
No benefit with long term urinary bladder catheterisation
H2. Alpha blockers
No benefit with long term urinary bladder catheterisation
H3. Muscarinic antagonists
No benefit with long term urinary bladder catheterisation, unless clear history of painful detrusor hyperactivity

Section I: Endocrine System

I1. Diabetic oral agents
Aim for monotherapy. Target of HbA1c <8%/64mmol/mol. Stringent glycaemic control is unnecessary
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
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
I4. Systemic oestrogens for menopausal symptoms
Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms

Section J: Miscellaneous

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
J3: Prophylactic Antibiotics
No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs

Disclaimer (STOPPFrail)
Whilst every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence-based, it is emphasized that the final decision to avoid or initiate any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that prescribing decisions should take account of current published evidence in support of or against the use of drugs or drug classes described in STOPPFrail.

Application of deprescribing methods

Four physicians, all trained in geriatric medicine, reviewed the clinical cases and identified medications that were potentially eligible for deprescribing. Two physicians (DC and DOD) rigidly applied STOPPFrail criteria while the other physicians (KJ and TD), who were not familiar with STOPPFrail criteria, identified drugs to be deprescribed using step 3 of the CEASE protocol (hereafter referred to as Scott's deprescribing algorithm; Fig. 1). The physicians were instructed to document the primary reason for each deprescribing decision. Drugs that were not eligible for deprescribing were classified as BImportant.^ The physicians initially worked independently and then resolved any discrepancies in pairs to produce a final consensus list for each deprescribing method.

Sample size calculation and statistical analysis

A sample size of 100 was chosen to detect with 80% probability a Cohen's kappa coefficient of 0.70 under the alternative hypothesis when Cohen's kappa under the null hypothesis was 0.6. This sample size would also allow for more than 500 medications to be evaluated. Cohen's kappa coefficient 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 almost perfect if 0.81–1.00 [15]. Statistical analysis was performed using SPSS® version 21.

Results

Clinical cases

The mean number of medications per clinical case was 10.2 (standard deviation 3.3). The total number of medications to be evaluated (when paracetamol was excluded) was 994. Most medications were taken orally (88.7%), while the remainder were administered by inhaled (5.1%), transdermal (3%), topical (2%), or subcutaneous/intramuscular (1.3%) routes.

Agreement between methods

The physicians using Scott's deprescribing algorithm identified 524 medications (52.7% of the total) as potentially eligible for deprescribing; the physicians using STOPPFrail criteria identified 412 medications for deprescribing (41.4%; see Supplementary appendix 2). Cohen's kappa coefficient was 0.60 (95% confidence interval 0.55–0.65; $p < 0.001$) indicating moderate agreement between the methods. With Scott's deprescribing algorithm representing the gold standard, the sensitivity of STOPPFrail (i.e., the proportion of inappropriate medications correctly identified by STOPPFrail) was 70.2%. The specificity (i.e., the proportion of important medications that were correctly continued by the physicians using STOPPFrail) was 90.6%. The positive predictive value of STOPPFrail (i.e., the proportion of medications deemed inappropriate by the physicians using STOPPFrail that were actually inappropriate) was 89.3% while the negative predictive value (i.e., the proportion of medications deemed important by the physicians using STOPPFrail that were actually important) was 73.2%.

The primary reasons for the deprescribing decisions are summarized in Supplementary appendix 3. BNo valid indication^ was the primary reason for 50% of the deprescribing decisions made by the physicians using Scott's deprescribing algorithm and in 42.7% of the decisions made by the physicians using STOPPFrail. Lipid-lowering agents, proton pump inhibitors, calcium, and anti-resorptive drugs for osteoporosis accounted for 33% of the medications deprescribed using STOPPFrail.

Discrepancies between methods

The physicians using STOPPFrail did not identify 156 medications (29.7%) that were potentially eligible for deprescribing (Table 2). Antihypertensive agents, vitamin D supplements, and laxatives (prescribed as part of a prescribing cascade) accounted for 54.4% of the potentially inappropriate medications that were not identified by the physicians using STOPPFrail. The physicians using STOPPFrail deprescribed calcium supplements and continued vitamin D preparations in all cases while the physicians guided by Scott's algorithm were more selective and generally continued these medications when a history of osteoporosis, fractures, or recurrent falls was included in the patients' medical history.

Discussion

This study is important because it shows that approximately half of all the medications prescribed to older people approaching end of life may be unnecessary or inappropriate. Many people with advanced frailty and polypharmacy will not have the benefit of a comprehensive specialist medication review. In this study, application of STOPPFrail—a novel, concise explicit deprescribing tool designed for all physicians who commonly provide care for older adults approaching end of life—demonstrated moderate agreement with gold standard specialist geriatrician-led deprescribing.

A major barrier to deprescribing is the difficulty associated with balancing risk and benefit of a specific medication for a particular patient. STOPPFrail addresses this difficulty by explicitly highlighting circumstances where commonly used medications can be safely discontinued. There is good evidence that people are much more likely to follow through on tasks that they see value in when those tasks are made easier

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Table 2 Discrepancies between the deprescribing methods. STOPPFrail-guided deprescribing evaluated against Bgold standard^ deprescribing

Potentially inappropriate or unnecessary drugs which were not identified by STOPPFrail (N = 156)	N	%	Drugs inappropriately identified for deprescribing using STOPPFrail criteria (N = 44)	N	%
Antihypertensive agents	32	20.5	Calcium supplements	11	25
Vitamin D supplements	31	19.8	Anti-resorptive/bone anabolic drugs	12	27.3
Laxatives (as part of prescribing cascade)	22	14.1	Memantine	6	13.6
Harm outweighs benefit	16	10.2	Prednisolone	3	6.8
Antiplatelets in patients with advanced frailty/remote history of vascular events	16	10.2	Miscellaneous	12	27.3
Cholinesterase inhibitors in patients with advanced dementia	4	2.6			
Miscellaneous	35	22.4			

for them [16–18]. It is therefore likely that providing explicit criteria will make the task of deprescribing more accessible to non-specialist physicians who care for older adults approaching end of life.

The physicians using the STOPPFrail criteria identified 70.2% of medications that were potentially eligible for deprescribing according to gold standard assessment. When medications for deprescribing were identified by the physicians using STOPPFrail, these medications were actually inappropriate in 89.3% of cases. While the use of STOPPFrail does not Bcatch all^ potentially inappropriate medications, it is very reassuring that the great majority of the deprescribing decisions appear to align with gold standard care.

For both methods, the most common reason for deprescribing was Bno valid indication.^ This emphasizes the importance, during a medication review, of ensuring that each drug is linked to a diagnosis or active symptom. While STOPPFrail explicit criteria largely address step 2 (harm outweighs benefit) and step 4 (preventive drugs—benefit unlikely to be realized) of Scott's deprescribing algorithm, future iterations may need to go further to address aspects of step 3 (symptom or disease control drugs). For example, STOPPFrail does not prompt the physician to review symptoms such as pain which may be over-treated with potentially problematic medications. Furthermore, symptoms such as poor appetite, nausea, altered bowel habit, sedation, and gait disturbance, which may represent the adverse effects of drugs, are not targeted. Finally, antihypertensive therapies and vitamin D supplements were the most common inappropriate or unnecessary medications that were not identified by the physicians using STOPPFrail. These drugs are commonly prescribed yet evidence of clear benefit, as well as specific guidance for use in people with advanced frailty, is lacking [19–22]. In the absence of high-quality clinical trial evidence, explicit criteria based on expert consensus opinion may enable physicians to make clinically sound decisions about the use of these medications in this particular expanding patient population.

All structured clinical cases in this study were derived from data collected from a cohort of hospitalized patients who died within 1 year of their hospital admission. A CFS score ≥ 6 was used to select frail patients from this cohort which would ensure that the deprescribing task was credible and that a short-term risk of death was not unforeseeable. It is important to emphasize that, in everyday clinical practice, we do not recommend using a CFS score ≥ 6 to select patients for STOPPFrail-guided deprescribing. STOPPFrail is intended for older people approaching end of life for whom the goal of care is to enhance quality of life and minimize the risk of drug-related complications. In the absence of sensitive and reliable prediction models [23], identifying older people who are approaching end of life will depend largely on physician experience and judgment [11].

Our study has some potential limitations. Firstly, it was a theoretical exercise using structured clinical cases. While derived from real patient data, the structured clinical cases do not reflect the complexities and nuances of real clinical care. However, we contend that standardization was necessary because external sources of variability (e.g., inequality of information) could have invalidated the primary aim of the study which was to compare the two methods of deprescribing [13]. Secondly, two physicians trained in geriatric medicine, arriving at deprescribing decisions through consensus, using Scott's deprescribing algorithm, represented Bgold standard^ deprescribing in this study. It is important to emphasize that Bgold standard^ does not necessarily mean Bperfect^ but rather Bbest available^ [24]. We believe the method used in this study is likely to be very close to the Bbest available^ deprescribing for this population of patients in most hospitals.

In summary, the results of this study indicate that the STOPPFrail criteria can assist physicians in making appropriate deprescribing decisions and that, reassuringly, these decisions align closely with gold standard deprescribing. In everyday clinical practice, where frail older people approaching end of life are commonly encountered by attending physicians with variable expertise, STOPPFrail-guided deprescribing may be a reasonable alternative to specialist medication review. Future iterations of STOPPFrail should include guidance on antihypertensive therapy discontinuation as well as prompts to the physician to explore particular symptoms which may represent adverse drug events.

Author contributions Curtin, O'Mahony, Gallagher: study concept and design. Curtin, Dukelow, James, O'Donnell: application of deprescribing methods. Curtin, O'Mahony, Gallagher: preparation of manuscript. All authors: critical revision and final approval of manuscript.

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Compliance with ethical standards

Conflict of interest O'Mahony and Gallagher were involved in the development of the STOPPFrail criteria.

Disclaimer The European Union's Horizon 2020 research and innovation programme had no role in the design, conduct, or reporting of this study.

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CLINICAL INVESTIGATION

Deprescribing in Older People Approaching End of Life: A Randomized Controlled Trial Using STOPPFrail Criteria

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OBJECTIVES: Older people approaching end of life are commonly prescribed multiple medications, many of which may be inappropriate or futile. Our objective was to examine the effect of applying the STOPPFrail, a recently developed deprescribing tool, to the medication regimens of older patients with advanced frailty.

DESIGN: Randomized controlled trial.

SETTING: Two acute hospitals in Ireland.

PARTICIPANTS: Adults 75 years or older (n = 130) with advanced frailty and polypharmacy (five or more drugs), transferring to long-term nursing home care.

INTERVENTION: A STOPPFrail-guided deprescribing plan was presented to attending physicians who judged whether or not to implement recommended medication changes.

MEASUREMENTS: The primary outcome was the change in the number of regular medications at 3 months. Secondary outcomes included unscheduled hospital presentations, falls, quality of life, monthly medication costs, and mortality.

RESULTS: Intervention (n = 65) and control group (n = 65) participants were prescribed a mean (plus or minus standard deviation [SD]) of 11.5 (±3.0) and 10.9 (±3.5) medications, respectively, at baseline. The mean (SD) change in the number of medications at 3 months was −2.6 (±2.73) in the intervention group and −.36 (±2.60) in the control group (mean difference = 2.25 ± .54; 95% confidence interval [CI] = 1.18-3.32; $P < .001$). The mean change in monthly medication cost was −\$74.97 (±\$148.32) in the intervention group and −\$13.22 (±\$110.40) in the control group (mean difference \$61.74 ± \$26.60; 95% CI = 8.95-114.53; $P = .02$). No significant differences were found between groups for any of the other secondary outcomes.

CONCLUSION: STOPPFrail-guided deprescribing significantly reduced polypharmacy and medication costs in frail older people. No significant differences between groups were observed with regard to falls, hospital presentations, quality of life, and mortality, although the trial was likely underpowered to detect differences in these outcomes. J Am Geriatr Soc 00:1-8, 2019.

Key words: deprescribing; frailty; STOPPFrail

Nursing home residents are among the greatest consumers of prescription medications.[1] This is important for several reasons. First, polypharmacy in this population is strongly associated with an increased risk of adverse drug events.[2,3] Second, many older people entering the nursing home environment have markedly reduced life expectancy. In the United States, the median length of stay in a nursing home before death is 5 months; in the United Kingdom, the median length of stay is 15 months.[4,5] In this context, patients frequently do not live long enough to realize the benefit of some of their prescribed medicines, and, indeed, the consumption of multiple pills may be physically and emotionally burdensome. Finally, there is an opportunity cost to prescribing inappropriate medications that could be measured as the health benefits that would have been achieved had the money been spent on alternative interventions or programs (eg, improving the social environment of the nursing home, specialist palliative care services).[6]

Functional decline during an acute hospital admission is often the trigger for admission to long-term care facilities. Indeed, most patients who transfer to nursing homes come from the hospital setting.[7] Therefore, there is an opportunity, before this transition, to conduct a formal medication review while the patient is under medical supervision in the hospital environment. When life expectancy is likely to be

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limited, an approach focused on enhancing quality of life should be prioritized over long-term preventive strategies or achieving strict chronic disease management targets. The term *deprescribing* refers to the process of withdrawing potentially inappropriate medications, supervised by healthcare professionals, with the goal of managing polypharmacy and improving patient outcomes.[8] A 2018 systematic review by Thillainadesan et al that evaluated randomized controlled trials of deprescribing interventions in hospitalized older adults found that potentially inappropriate medications could be successfully withdrawn without compromising patient safety or well-being.[9]

Many of the deprescribing interventions included in the review by Thillainadesan et al involved a pharmacist and/or a physician conducting a formal medication review. Identifying deprescribing targets in frail multimorbid older people is clearly complex, and healthcare professionals are likely to vary in their assessment of the importance and appropriateness of medications.[10,11] Evidence indicates that hospital physicians commonly forgo the opportunity to deprescribe because of fear of negative consequences such as symptom relapse, clinical deterioration, litigation, or increased workload.[12] Therefore, structured interventions, which can be reproduced in different settings by clinicians of different specialties, may be preferable.[13]

STOPPFrail criteria were recently developed to assist clinicians with deprescribing decisions in older people approaching end of life (Table 1).[14] The criteria consist of 27 indicators that highlight instances of potentially inappropriate prescribing in this particular population of older patients. STOPPFrail-guided deprescribing was shown to have substantial interrater reliability among clinicians of different specialities, and it may be a reasonable and potentially efficient alternative to a specialist medication review where this is unavailable.[15,16]

The primary aim of the present study was to examine whether STOPPFrail-guided deprescribing could reduce the number of medications taken by frail older people transferring from the hospital to nursing home care compared with usual pharmaceutical care alone. Secondary aims were to determine the effect of this intervention on unscheduled hospital admissions, falls, fractures, antipsychotic prescribing, monthly medication costs, quality of life, and mortality.

METHODS

Design

This study was a parallel-group unblinded randomized pragmatic clinical trial conducted in two acute hospitals in Cork City, Ireland. Participants were randomized to receive usual pharmaceutical care (ie, hospital physician and pharmacist care) or usual pharmaceutical care supplemented by individualized STOPPFrail-guided deprescribing. The local Clinical Research Ethics Committee approved the trial protocol. The trial was registered with ClinicalTrials.gov (NCT03501108).

Participants

Eligible participants were hospitalized older adults (aged ≥75 y), admitted from the community with acute unselected medical or surgical illness, who following treatment were unable to return home to independent living and consequently required long-term nursing home care. Eligible participants were prescribed five or more long-term medications and were severely frail as defined by (1) a Clinical Frailty Scale[17] score of 7 or higher, and (2) the treating physician indicating that he or she "would not be surprised if the patient died in the next 12 months."[18,19] Patients were excluded if they, or, in the case of cognitively impaired individuals, a proxy was unwilling or unable to provide informed consent.

Comprehensive multidisciplinary long-term nursing home care applications are reviewed every 2 weeks at a local placement panel meeting presided over by a consultant geriatrician. These applications, which include details about diagnoses, medications, and functional and cognitive status, were used to screen for potentially eligible participants. Patients with a Mini-Mental Status Examination (MMSE) score of 24 or higher were considered competent to provide written informed consent.[20] For patients with a diagnosis of dementia or those with an MMSE score lower than 24, a nominated proxy was required to cosign the consent form. The full trial protocol can be found in Supplemental Protocol S1.

Data Collection

A trained research physician (D.C.) conducted patient and/or caregiver interviews and medical record reviews to collect the following baseline data before randomization: (1) current and past diagnoses; (2) long-term regular medications and pro re nata (PRN; as needed) medications (PRN medications recorded if used three or more times in the previous week); (3) functional status (modified Barthel Index[21]); (4) comorbidity status (Charlson Comorbidity Index[22]); and (5) quality of life (QUALIDEM[23] and ICECAP-O[24]). In addition, symptoms such as pain, sleep disturbance, and gastrointestinal symptoms were explored in an unstructured manner by the research physician. After baseline data collection was completed, the research physician used the STOPPFrail criteria to identify deprescribing targets. Medications targeted for deprescribing were recorded in the case report form.

Quality of life (QoL) was measured using two validated assessment tools. Anticipating that a large proportion of participants would have advanced dementia and therefore could have difficulty completing self-reported questionnaires, the QUALIDEM instrument was selected.[23] It is completed by nursing staff or healthcare assistants and assesses QoL across multiple domains for people at all stages of dementia.[23] In addition, participants, where possible, or a proxy were requested to complete the ICECAP-O questionnaire, a broad measure of QoL (ie, beyond health) that was developed for use in the economic evaluation of health and social care interventions in older adults.[24] Both the QUALIDEM and ICECAP-O were previously used to measure QoL in institutional care settings.[25,26]

Randomization

Participants were randomized to study arms in a 1:1 ratio using block randomization. Block sizes of four and six were generated using the website randomization.com (http://www.randomization.com) by an administrator external to the study. Randomization was not stratified by hospital site. The allocation sequence was concealed in sequentially

Table 1. STOPPFrail Criteria

STOPPFrail is a list of potentially inappropriate prescribing indicators designed to assist physicians with stopping such medications in older patients (≥65 y) who meet *all* of the criteria listed here:	The decision to prescribe/not prescribe medications to the patient should also be influenced by the following issues:
1. End-stage irreversible pathology 2. Poor 1-year survival prognosis 3. Severe functional or severe cognitive impairment or both 4. Symptom control is the priority rather than prevention of disease progression	1. Drug adherence/compliance is difficult 2. Administration of the medication is challenging 3. Monitoring of the medication effect is challenging 4. Drug adherence/ compliance is difficult
Section A: General *A1*: Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations. *A2*: Any drug without a clear clinical indication. **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 ADEs outweighs the potential benefits *B2: α-Blockers for hypertension* Stringent blood pressure control is not required in very frail older people. α-Blockers in particular can cause marked vasodilatation that can result in marked postural hypotension, falls, and injuries **Section C: Coagulation System** *C1: Antiplatelets* Avoid antiplatelet agents for primary (as distinct from secondary) cardiovascular prevention (no evidence of benefit) **Section D: Central Nervous System** *D1: Neuroleptic antipsychotics* Aim to reduce dose and discontinue these drugs in patients taking them for > 12 wk if there are no current clinical features of BPSD *D2: Memantine* Discontinue and monitor in patients with moderate to severe dementia, unless memantine has clearly improved BPSD (specifically in frail patients who meet the criteria above) **Section E: Gastrointestinal System** *E1: Proton pump Inhibitors* Proton pump Inhibitors at full therapeutic dose ≥8/52, unless persistent dyspeptic symptoms at lower maintenance dose *E2: H_2 receptor antagonist* H_2 receptor antagonist at full therapeutic dose for ≥8/52, unless persistent dyspeptic symptoms at lower maintenance dose *E3: Gastrointestinal antispasmodics* Regular daily prescription of gastrointestinal antispasmodics agents unless the patient has frequent relapse of colic symptoms because of high risk of anticholinergic side effects **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 *F2: Leukotriene antagonists (montelukast, zafirlukast)* These drugs have no proven role in COPD; they are indicated only in asthma	**Section G: Musculoskeletal System** *G1: Calcium supplementation* Unlikely to be of any benefit in the short term *G2: Antiresorptive/bone anabolic drugs FOR OSTEOPOROSIS (bisphosphonates, strontium, teriparatide, denosumab)* *G3: SERMs for osteoporosis* Benefits unlikely to be achieved within 1 year; increased short- to intermediate-term risk of associated ADEs, particularly venous thromboembolism and stroke *G4: Long-term oral NSAIDs* Increased risk of side effects (peptic ulcer disease, bleeding, worsening heart failure, etc) when taken regularly for ≥2 mo *G5: Long-term oral steroids* Increased risk of side effects (peptic ulcer disease, etc) when taken regularly for ≥2 mo. Consider careful dose reduction and discontinuation **Section H: Urogenital System** *H1: 5-α reductase inhibitors* No benefit with long-term urinary bladder catheterization *H2: α-Blockers* No benefit with long-term urinary bladder catheterization *H3: Muscarinic antagonists* No benefit with long-term urinary bladder catheterization, unless clear history of painful detrusor hyperactivity **Section I: Endocrine System** *I1: Diabetic oral agents* Aim for monotherapy. Target of hemoglobin A1c <8%/64 mmol/mol. Stringent glycemic control is unnecessary *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 *I3: 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 *I4: Systemic estrogens for menopausal symptoms* Increases risk of stroke and VTE disease. Discontinue and only consider recommencing if recurrence of symptoms **Section J: Miscellaneous** *J1: Multivitamin combination supplements* Discontinue when prescribed for prophylaxis rather than treatment *J2: Nutritional supplements (other than vitamins)* Discontinue when prescribed for prophylaxis rather than treatment *J3: Prophylactic antibiotics* No firm evidence for prophylactic antibiotics to prevent recurrent cellulitis or UTIs

Abbreviations: ACE, angiotensin-converting enzyme; ADE, adverse drug event; ARB, angiotensin receptor blockers; BPSD, behavioral and psychiatric symptoms of dementia; COPD, chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SERMS, selective estrogen receptor modulators; UTI, urinary tract infection; VTE, venous thromboembolism.

Disclaimer (STOPPFrail).

Although every effort has been made to ensure that the potentially inappropriate prescribing criteria listed in STOPPFrail are accurate and evidence based, it is emphasized that the final decision to avoid or initiate any drug referred to in these criteria rests entirely with the prescriber. It is also to be noted that the evidence base underlying certain criteria in STOPPFrail may change after the time of publication of these criteria. Therefore, it is advisable that prescribing decisions should consider current published evidence in support of or against the use of drugs or drug classes described in STOPPFrail.

numbered opaque envelopes until the research physician had enrolled participants, completed baseline data collection, and identified deprescribing targets using the STOPPFrail criteria.

Intervention

For participants randomized to the intervention arm, a medication withdrawal plan was devised by the research physician. The recommended medication withdrawal plan was communicated directly to one of the participant's attending physicians and also documented in the patient's medical record. Medications associated with an increased risk of an adverse withdrawal reaction were recommended to be withdrawn slowly according to a standardized trial withdrawal protocol (Supplemental Protocol S1). The attending physician judged whether or not to accept the drug withdrawal plan and implement the recommended changes. Because of the nature of the intervention, the research physician, attending physicians, and participating patients could not be blinded to the intervention or control group assignment after randomization. The intervention was applied at a single time point during the patients' hospital admission at the time of trial enrollment. Attending physicians and nursing staff were encouraged to report any potential adverse consequences of deprescribing (adverse drug withdrawal events or disease relapse) to the research team.

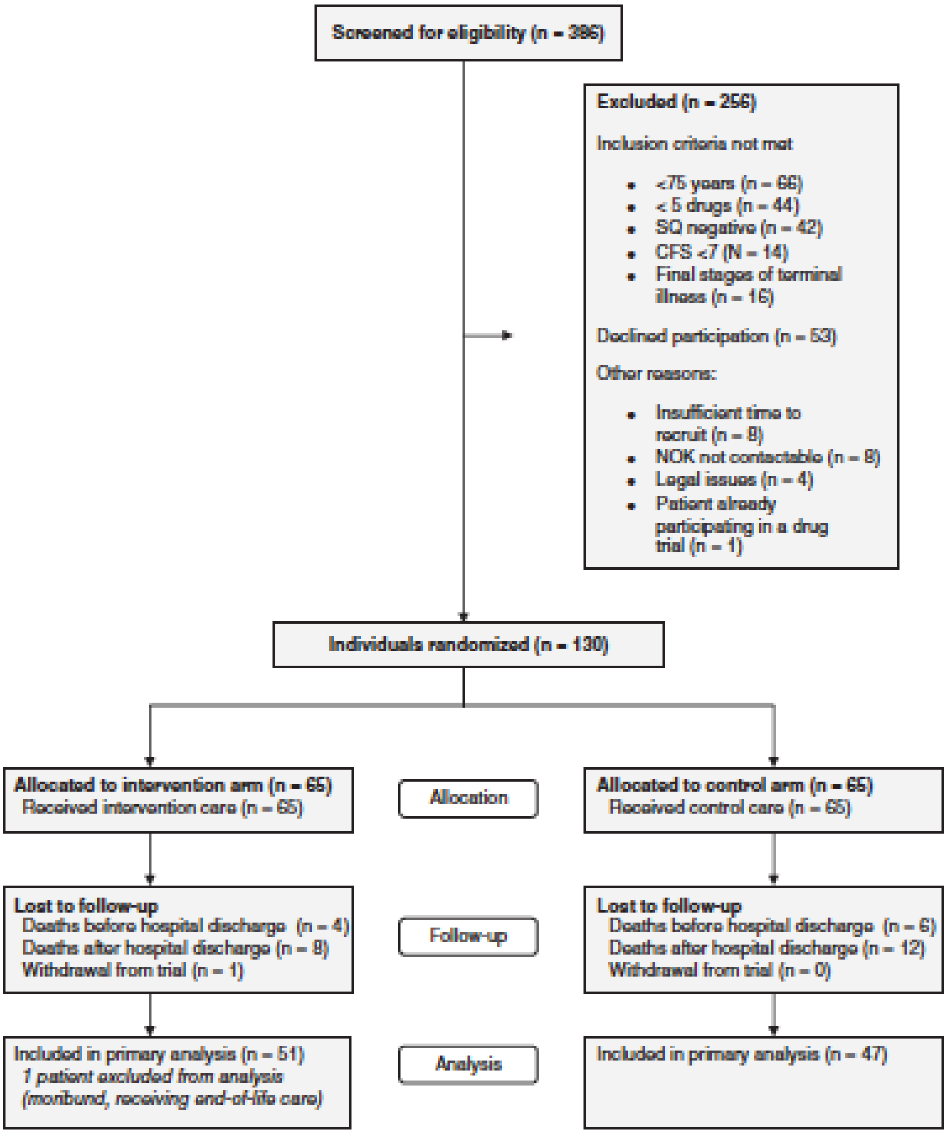

Figure 1. Recruitment and participation. CFS, Clinical Frailty Scale; NOK, next of kin; SQ, surprise question.

Outcome Measures

The primary outcome was the mean change in the number of long-term prescribed medicines consumed by participants at 3 months after randomization. Short-term medicines (eg, antibiotics, topical antifungal agents, topical corticosteroids) were not included. For combination products, each ingredient was included as one drug as long as that ingredient was available as a single medicine in the contemporaneous *British National Formulary*, 74th ed.[27]

Secondary outcomes were measured at 3 months and included the following:

1. Unscheduled medical reviews and emergency transfers after discharge from the acute hospital
2. Falls and nonvertebral fractures after discharge from the acute hospital
3. Changes in prescriptions of neuroleptic antipsychotic medications
4. Changes in 28-day cost of participants' prescription medications
5. Changes in participants' QoL (measured by the QUALIDEM instrument and the ICECAP-O questionnaire)
6. Mortality

Outcome data were collected by three research physicians (E.J., R.D., and M.R.) who were blinded to the group allocation of participants. We contacted directors of nursing in the relevant nursing homes by telephone and requested them to complete a case report form populated with the relevant data fields. We requested that a nurse or care assistant, familiar with the participant, complete the QUALIDEM instrument. Where possible, the ICECAP-O was to be completed by the same person who completed the questionnaire at baseline. In some instances, the research physicians contacted the relevant person by telephone to complete the ICECAP-O. We calculated the 28-day cost of participants' prescription drugs using a 2018 Irish pharmaceutical wholesaler price list, produced by Clanwilliam Health. For each specific medication dose and formulation, the lowest cost option was chosen.

Sample Size Calculation and Statistical Analysis

We calculated the statistical power of the trial to detect a difference of 2 in the mean number of medications between the intervention and control groups ($\alpha = .5$; $1\text{-}\beta = .8$; population variance = 14 [taken from a recent prevalence study[28]) at 3 months. Allowing for an estimated attrition rate (deaths and dropouts) of 30%, we estimated that a sample size of 160 participants (80 in each group) would be required.

In the analysis of the primary outcome, we included only participants who completed follow-up. Because medications regimens frequently change in the final stages of terminal illness, we excluded deceased participants due to difficulties in determining final valid, verifiable medication lists. Emergency department presentations, hospital admissions, and mortality were determined on all randomized participants. We used standard descriptive statistics with study groups compared using χ^2 or Fisher exact tests for categorical variables, the independent samples *t* test for normally distributed continuous variables, and the Wilcoxon rank-sum test for nonparametric variables. We performed statistical analyses using SPSS v.25.

RESULTS

Baseline Characteristics

Between March 27, 2018, and April 3, 2019, we randomized 130 participants to receive either usual pharmaceutical care or usual pharmaceutical care supplemented by individualized STOPPFrail-guided deprescribing advice. Recruitment ended before the sample size goal of 160 was reached because of a requirement, due to resource constraints, to complete follow-up before the planned trial closure date of June 30. Ten patients died before hospital discharge, 20 patients died before follow-up at 3 months, and one patient withdrew from the

Table 2. Baseline Characteristics of Study Participants

Variable	Control (n = 65)	Intervention (n = 65)	*P* value
Female (%)	38 (58.46)	42 (64.61)	.59
Age (SD)	85.68 (5.87)	84.49 (5.60)	.24
Hospital (%)			
Cork University Hospital	50 (76.9)	52 (80)	.83
Mercy University Hospital	15 (23.1)	13 (20)	...
MMSE (SD)	14.25 (7.52)	14.8 (7.37)	.67
Modified Barthel Index (SD)	6.83 (4.04)	7.17 (3.87)	.63
CCI (SD)	6.33 (1.86)	6.8 (2.31)	.21
Diagnoses (%)			
Dementia	48 (73.8)	49 (75.4)	1.0
Heart failure	10 (15.4)	16 (24.6)	.27
Atrial fibrillation	27 (41.5)	24 (36.9)	.72
Chronic kidney disease	15 (23.1)	16 (24.6)	1.0
Active cancer	6 (9.2)	5 (7.7)	1.0
Osteoporosis	18 (27.7)	19 (29.2)	1.0
Medication use			
No. of regular medications (SD)	10.89 (3.56)	11.52 (3.03)	.28
No. of PRN medications (SD)	.25 (.47)	.28 (.6)	.74
No. of patients with ≥10 regular medications, %	39 (60)	46 (70.8)	.27
Mean (SD) number of days between trial enrollment and hospital discharge	24.7 (18.1)	18.7 (16.5)	.07
STOPPFrail-defined PIMs (SD)	2.41 (1.27)	2.40 (1.4)	.948
Medications eligible for dose reduction (SD)	.71 (.7)	.75 (.73)	.71
Medication type (%)			
Antithrombotic	47 (72.3)	42 (64.6)	.45
Antipsychotic	16 (24.6)	13 (20)	.67
Lipid lowering agents	17 (26.1)	12 (18.5)	.4
Calcium	23 (35.4)	15 (23.1)	.18
Analgesics	32 (49.2)	45 (75)	.03
Antiresorptive	9 (13.8)	7 (10.8)	.79
Nutritional supplement	37 (56.9)	33 (50.8)	.59
Gastric acid suppression therapy	42 (64.6)	39 (60)	.72
Medications for constipation	48 (73.8)	55 (84.6)	.19

Abbreviations: CCI, Charlson Comorbidity Index; MMSE, Mini-Mental State Examination; PIMs, potentially inappropriate medications; PRN, pro re nata [as needed]; SD, standard deviation.

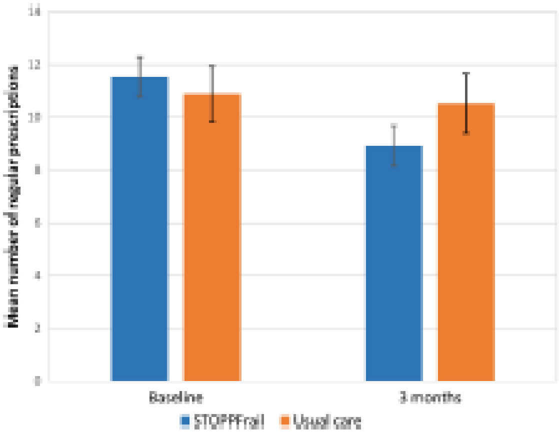

Figure 2. Change in number of regular prescriptions from baseline to 3-month follow-up. Mean (standard deviation) change in the number of regular prescriptions (for final analytic sample, n = 99) at 3 months was −2.61 (±2.73) in the intervention arm and −.36 (±2.60) in the control arm (mean difference = 2.25 ± .54; 95% confidence interval (CI) = 1.18-3.32; $P < .001$). Error bars are 95% CIs.

trial after enrollment (Figure 1). At baseline, no significant differences were found between the intervention (n = 65) and control (n = 65) groups in terms of age, sex, or measures of cognitive, functional, and comorbidity status (Table 2). The mean plus or minus standard deviation (SD) number of regular prescribed medications at baseline was 11.5 ± 3.0 in the intervention group and 10.9 ± 3.5 in the control group ($P = .28$). Significantly more participants in the intervention group, relative to the control group, were prescribed analgesic medications at baseline (75% vs 49.2%; $P = .03$).

STOPPFrail Deprescribing Recommendations

At least one deprescribing recommendation was made for 90.8% of participants in the intervention group. A mean ± SD of 2.4 ± 1.4 medications per patient was targeted for discontinuation while .75 ± .73 medications per patient were targeted for dose reduction. Overall, 87.8% of deprescribing recommendations were accepted and implemented by the attending physicians. STOPPFrail criterion A2 (ie, Stop any drug without a clear clinical indication) was the most common recommendation triggered (44.4% of all recommendations; Supplementary Table S1 lists the most common drugs deprescribed using this criterion). Lipid lowering therapies (criterion B1), neuroleptic antipsychotics (criterion D1), proton pump inhibitors (criterion E1), antiresorptive/bone anabolic drugs (criterion G2), calcium supplementation (criterion G1), and multivitamin combination supplements (criterion J1) accounted for a further 40% of the deprescribing recommendations. The frequency of the individual STOPPFrail criteria is shown in Table S2. No potential adverse effects of deprescribing were reported to the research team during the conduct of the trial.

Primary Outcome

Data from 98 randomized participants were available for analysis for the primary outcome (Figure 1). Intervention arm patients (n = 51) and control arm patients (n = 47) received a mean (SD) of 11.5 (±2.7) and 10.9 (±3.6) regular prescription medications, respectively, at baseline. The mean (SD) change in the number of regular prescriptions at 3 months was −2.61 (±2.73) in the intervention group and −.36 (±2.60) in the control group (mean difference = 2.25 ± .54; 95% confidence interval [CI] = 1.18-3.32; $P < .001$; Figure 2). In the final analytical sample at 3 months, three drugs that were discontinued as a result of the intervention had been restarted.

Secondary Outcomes

No statistically significant differences were found between the intervention and control groups for patient-related outcomes such as unscheduled hospital presentations, falls, fractures, or mortality (Table 3). QoL deteriorated

Table 3. Effect of STOPPFrail-guided deprescribing on secondary outcomes

	Intervention (n=65)		Control (n=65)			
Outcome	Proportion (95% CI)	Number of participants (number of events)	Proportion (95% CI)	Number of participants (number of events)	Relative risk (95% CI)	P
ED presentation (not admitted)	0.05 (0.01, 0.13)	3 (5)	0.08 (0.03, 0.17)	5 (8)	0.60 (0.15, 2.41)	0.72
Unplanned hospital admission	0.14 (0.07, 0.24)	9 (10)	0.08 (0.03, 0.17)	5 (6)	1.80 (0.64, 5.08)	0.27
Deaths	0.18 (0.11, 0.3)	12	0.28 (0.18, 0.4)	18	0.67 (0.35, 1.27)	0.22
Unscheduled medical reviews by GP*	0.61 (0.47, 0.73)	31 (68)	0.57 (0.43, 0.70)	27 (52)	1.04 (0.74, 1.45)	0.82
Falls*	0.27 (0.17, 0.40)	14 (24)	0.30 (0.19, 0.44)	14 (32)	0.90 (0.48, 1.69)	0.75
Non-vertebral fractures*	0.02 (0, 0.11)	1 (1)	0.09 (0.03, 0.20)	4 (5)	0.23 (0.03, 1.96)	0.18

CI = confidence interval; ED = emergency department; GP = general practitioner.
*measured in final analytical sample (intervention [n = 52]; control [n = 47]).

significantly in both the intervention and control groups from baseline to 3-month follow-up, but no statistically significant differences were found in the mean change in QUALIDEM or ICECAP-O scores between groups from baseline to follow-up (Table S3).

Antipsychotic drugs were reduced or discontinued more often in intervention patients relative to control patients, but, again, the differences did not reach statistical significance (Table S4). At baseline, there were no statistically significant differences in the extrapolated mean (SD) monthly medication costs between the intervention and control groups ($267.04 ± $117.21 and $250.56 ± $140.64, respectively; $P = .53$). However, at 3-month follow-up, the mean change in monthly medication cost was significantly lower in the intervention group (ie, −$74.97 ± 148.32) compared with the control group (ie, −$13.22 ± $110.40) (mean difference = $61.74 ± $26.60; 95% CI = 8.95-114.53; $P = .02$).

DISCUSSION

In this study of very frail older hospitalized patients with limited life expectancy, application of STOPPFrail criteria at a single time point resulted in a sustained and significant reduction in polypharmacy and average aggregate monthly medication costs at 3 months after randomization compared with usual pharmaceutical care. We found that almost 1 in 4 medications were discontinued in frail older people with polypharmacy using this method, resulting in a 28% average reduction in monthly medication costs. No significant differences were found between the intervention and control arms in terms of important health-related outcomes including unplanned hospital admissions, falls, fractures, QoL, and mortality, although it must be acknowledged that the trial was likely to have been underpowered to detect differences in these secondary outcomes.

Other structured deprescribing methods have recently been evaluated in very frail older people using a randomized controlled trial design, and they also reported statistically significant reductions in potentially inappropriate prescriptions. Potter et al[29] used an implicit (ie, judgment-based) algorithm that requires the user to answer a series of questions about each drug in the patient's regimen; Wouters et al[30] evaluated the Multidisciplinary Multistep Medication Review. Both methods are patient centered and comprehensive but limited by a requirement for resource-intensive processes that may hinder their integration into routine clinical practice. STOPPFrail overcomes these limitations by virtue of its conciseness and high interrater reliability between users of different disciplines and professional grades.[15,16]

The most common reason for deprescribing in this trial was when a drug had no clear valid clinical indication (STOPPFrail criterion A2). We contend that routinely clarifying whether a drug is linked to a verifiable diagnosis or an active or recurring symptom is fundamental to any formal medication review in older multimorbid patients exposed to polypharmacy, particularly frailer patients with very limited survival prospects. The remaining criteria in STOPPFrail are predominantly explicit and target specific drugs that, under the usual circumstances, may be clinically indicated but are likely to be associated with negligible benefits or net harm in the context of advanced irreversible frailty and limited life expectancy. During the conduct of the trial, it became clear that some of the explicit criteria in STOPPFrail lacked clinical relevance and were very seldom, if at all, applied (eg, systemic estrogens for menopausal symptoms, selective estrogen receptor modulators for osteoporosis). Likewise, it was evident that some medications, commonly prescribed in frail older people but lacking a firm evidence base (eg, vitamin D supplements), were absent from STOPPFrail. Future iterations of the criteria will aim to address these shortcomings.

Our study has several important limitations. First, we enrolled participants from just two acute hospitals in one city in Ireland which may limit the generalizability of our findings. STOPPFrail criteria were developed in the university affiliated with these hospitals, and this may have influenced the readiness of attending physicians to implement the deprescribing recommendations. Second, the attending physicians and participants were not blinded to intervention or control group allocation. Although this had the potential to introduce bias, we believed that, given the nature of the intervention, blinding would have been inappropriate. The research physician who identified deprescribing targets using STOPPFrail was also unblinded to the group allocation of participants, which, in theory, could have influenced the nature of the intervention. Furthermore, there were no quality control measures to assess the accuracy of the STOPPFrail-guided deprescribing recommendations. However, STOPPFrail criteria are predominantly explicit, and this, in effect, would be expected to limit variability in their deployment. Nonetheless, even though the trial was unblinded, the measured outcomes (apart from QoL assessments) were not subject to bias. Third, we were unable to determine the effect of the intervention on important patient-related outcomes including mortality due to the relatively small sample size. Fourth, because of resource restrictions, it was not possible to actively collect data on adverse drug withdrawal events or disease relapses due to the deprescribing intervention. Consequently, we may have missed these events if they were not reported to the study team. Finally, we did not use a cluster randomization design that would diminish the possibility of contamination bias. Physicians may have simultaneously had both intervention and control patients under their care during the trial and, through a "training effect," they may have applied STOPPFrail criteria during medication reviews of control patients. However, any possible contamination of this kind would increase the chance of actual effects of the intervention *not* being detected (ie, type II error). In spite of the possible presence of contamination, significantly different effects of the STOPPFrail intervention were still observed between the groups.

This study also has notable strengths. We included a representative sample of real-world highly frail, multimorbid older people, approximately 75% of whom had a known diagnosis of dementia. This patient group are commonly excluded from clinical trials despite being encountered with increasing frequency in clinical settings and having the highest levels of disease burden.[31] Deprescribing recommendations for this vulnerable population were implemented under medical supervision in the acute hospital and only after review and approval by participants' attending physicians. In addition, the deprescribing intervention in this trial was relatively straightforward and would be easy to replicate in other settings.

When very frail older people approach end of life, the prescription of multiple medications may be burdensome or even futile in their clinical management. This exploratory study provides evidence that STOPPFrail, an easily applied reliable and explicit deprescribing tool, substantially reduces polypharmacy and monthly medication costs in this patient cohort. Although there were no differences between groups for important clinical end points such as unscheduled hospital presentations, QoL, and mortality, the trial was very likely underpowered to detect significant changes in these outcomes. A larger scale multicenter trial with greater statistical power is required to reassure clinicians that STOPPFrail-guided deprescribing of long-term medications can be achieved in the frailest older people without compromising clinical outcomes.

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Author Contributions: *Study concept and design*: D. Curtin, Gallagher, and O'Mahony. *Data collection*: D. Curtin, Jennings, Daunt, and Randles. *Statistical analysis*: D. Curtin and S. Curtin. *Preparation of manuscript*: D. Curtin, Gallagher, and O'Mahony. *Critical revision and final approval of manuscript*: All authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Drugs recommended for deprescribing (ie, discontinuation or tapered dose reduction) in the intervention arm because of "no clear valid indication".

Supplementary Table S2: Frequency of triggered STOPPFrail criteria in the control and intervention groups.

Supplementary Table S3: Self-reported and proxy-measured quality of life outcomes at baseline and 3-month follow-up.

Supplementary Table S4: Effect of STOPPFrail-guided deprescribing on antipsychotic prescribing.

Supplementary Protocol S1: Original trial protocol.

APPENDIX 2

Diagnostic Risk Score (component of the HOMR model)

Appendix 1: Diagnostic Risk Score[1]

Diagnosis	Points	ICD10 code	ICD9 codes
Cardiac arrest	12	I46	427.5
Anoxic inju[illegible] bral disorders	11	G93	331.8, 348.0–348.5, 348.8, 348.9
Brain cancer	9	C71	191.0–191.9
Adult respiratory distress syndrome	9	J80	518.8
Pancreatic cancer	8	C25	157.0–157.4, 157.8, 157.9
Shock	8	R57	785.5
Esophageal cancer	7	C15	150.0–150.5, 150.8, 150.9
Gastric cancer	7	C16	151.0–151.6, 151.8, 151.9
Myeloid leukemias	7	C92	205.0–205.3
Acute endocarditis	7	I33	421.0, 421.9
Diffuse parenchymal lung disease	7	J84	516.0–516.6, 516.8, 516.9
Liver cancer	6	C22	155.0–155.2
Intestinal lesions	6	K63	211.3, 569.5, 569.8, 569.9
Alcoholic liver disease	6	K70	571.0–571.3
Bronchogenic carcinoma	5	C34	162.0, 162.2–162.5, 162.8, 162.9
Non-Hodgkins lymphoma	5	C85	200.7, 202.8
Intracerebral hemorrhage	5	I61	431
Aspiration pneumonitis	5	J69	507.0, 507.1, 507.8
Respiratory faillure	5	J96	518.5, 518.8
Biliary tract disease	5	K83	576.1, 576.2, 576.4, 577.8, 577.9
Ascites	5	R18	568.8, 789.5
Septicemia	4	A41	038.0, 038.1, 038.3, 038.4, 038.8, 038.9
Metastatic cancer	4	C78, C79	197.0–197.8, 198.0–198.8
Hepatic failure	4	K72	570.0, 572.2, 572.4, 572.8
Cirrhosis	4	K74	571.5, 571.6, 571.9
Bladder cancer	3	C67	188.0–188.9
Pleural effusion	3	J90	511.1, 511.8, 511.9
Head injury and consequences	3	S06	085.0, 851.0, 851.1, 852.0, 852.1, 853.0, 853.1, 854.0, 854.1
Oncological treatment and aftercare	2	Z51	V07.1, V58.0–V58.2, V58.8, V58.9
Hip or femoral fracture	1	S72	820.0–820.3, 821.0–821.3
Acute myocardial infarction	–1	I21	410.0–410.9
Unspecified dementia	–3	F03	290.1, 290.2, 290.4, 290.8, 290.9
Delirium	–3	F05	290.3, 293.0, 293.8
Atrial fibrillation or flutter	–3	I48	427.3
Chronic obstructive pulmonary disease	–3	J44	491.0–491.2, 491.8, 491.9, 492.8, 496.0
Lumbar or pelvic fracture	–3	S32	805.4–805.7, 808.0–808.5, 808.8, 808.9
Convalescence	–3	Z54	V66.0–V66.6, V66.9
Breast cancer	–4	C50	174.0–174.6, 174.8, 174.9
Type 2 diabetes mellitus	–4	E11	250.0–250.7
Cellulitis	–4	L03	681.0, 681.1, 682.0, 682.2, 682.3,

Appendix to: van Walraven C, McAlister FA, Bakal JA, et al. External validation of the Hospital Patient One-Year Mortality Risk (HOMR) model for predicting death within one year after hospital admission. *CMAJ* 2015. DOI:10.1503/cmaj.150209.

			682.5, 682.6, 682.8, 682.9
Abdominal pain	–4	R10	789.0
Diarrhea, presumed infectious	–5	A09	009.0–009.3
Prostate cancer	–5	C61	185.0
Conduction abnormalities	–5	I44	426.0–426.6, 426.8, 426.9
Diverticular disease	–5	K57	562.0, 562.1
Rehabilitation	–5	Z50	V57.1–V57.4, V57.8, V57.9
Tachycardia	–6	I47	427.0–427.2
Osteoarthritis of the hip	–6	M16	715.1–715.3
Type 1 diabetes mellitus	–7	E10	250.0–250.7
Coronary artery disease	–7	I25	412.0, 414.0, 414.1, 414.8, 414.9, 429.2
Inguinal hernia	–7	K40	550.0, 550.1, 550.9
Abnormalities of heart beat	–7	R00	427.8, 785.0, 785.1, 785.3
Signs of neurological/MSK system	–7	R29	719.6, 781.6, 781.7, 781.9, 796.1
Lower leg fracture	–7	S82	822.0, 822.1, 823.0–823.3, 824.0–824.9, 827.0, 827.1
Cholelithiasis	–8	K80	574.0–574.3, 574.5
Angina	–9	I20	411.0, 411.1, 411.8, 413.0, 413.1, 413.9
Intervertebral disc disorder	–9	M51	722.1, 722.3, 722.5, 722.7, 722.9
Syncope	–9	R55	780.2
Spondylopathy	–10	M48	721.0, 721.2, 721.3, 721.5–721.9, 723.0, 724.0
Hypertension	–11	I10	401.0, 401.1, 401.9
Osteoarthritis of the knee	–11	M17	715.1–715.3
Acute appendicitis	–12	K35	540.0, 540.1, 540.9
Neck or chest pain	–12	R07	784.1, 786.5
Cerebral ischemia	–13	G45	362.3, 435.X, 435.0, 436.X
Dizziness	–13	R42	780.4
Asthma	–15	J45	493.0–493.2, 493.9
Vertigo	–16	H81	386.0–386.5, 386.8, 386.9
Female genital prolapse	–20	N81	618.0, 618.2–618.4, 618.6, 618.8, 618.9
Thyroid cancer	–21	C73	193.0
Cerebral artery occlusion or stenosis	–22	I65	433.0–433.2, 433.8, 433.9

Details regarding the derivation and validity of the Diagnostic Risk Score are available elsewhere.[1]

Reference

1. van Walraven C. The Hospital-patient One-year Mortality Risk score accurately predicts long term death risk in hospitalized patients. *J Clin Epidemiol* 2014;67:1025-34.

Appendix to: van Walraven C, McAlister FA, Bakal JA, et al. External validation of the Hospital Patient One-Year Mortality Risk (HOMR) model for predicting death within one year after hospital admission. *CMAJ* 2015. DOI:10.1503/cmaj.150209.

APPENDIX 3

Sample standardized case used in Chapter 4

Clinical Cases

In the following clinical cases, it can be assumed that:

1. The patient is medically stable.
2. The patient has a poor 1-year survival prognosis.
3. The list of diagnoses is complete and correct.
4. Laxatives (unless potentially part of a prescribing cascade) and paracetamol are appropriate.
5. There are no difficulties with medication administration (e.g. dysphagia, poor inhaler technique etc.) unless explicitly stated.
6. The patient's nutritional status is satisfactory unless otherwise stated
7. Behavioural and psychological symptoms of dementia are not present unless explicitly stated.

Please identify the medications that are potentially eligible for deprescribing.

Laboratory Analytes

Analyte	**Symbol**	**Unit**	**Reference range**
Hemoglobin	Hb	g/dL	Males: 14.0 - 17.5 Females: 12.0 - 15.5
Mean Corpuscular volume	MCV	fL	80-100
Sodium	Na	mmol/L	135 -145
Potassium	K	mmol/L	3.4 -5.0
Urea	-	mmol/L	2.9 -8.2
Creatinine	-	µmol/L	50 -110
Haemoglobin A 1c (glycated haemoglobin)	HbA1c	mmol/mol	<42: normal 42-47: 'prediabetes' >47: diabetes

Case:

73-year-old female

Nursing Home resident

Past Medical History:
1. Dementia
2. Epilepsy
3. Type 2 diabetes mellitus
4. Diabetic retinopathy
5. Dyslipidaemia
6. Depression
7. Hypothyroidism

Medications:
1. Memantine 20mg od
2. Paroxetine 20mg od
3. Movicol 1 sachet od
4. Levetiracetam 500mg bd
5. Gliclazide Modified Release 30mg od
6. Ferrous fumarate 305mg od
7. Paracetamol 1g tds
8. Sitagliptin 100mg od
9. Metformin 1g bd
10. Aspirin 75mg od
11. Levothyroxine 50mcg od
12. Donepezil 10mg od
13. Forticreme 1 od
14. Calcium 500mg od
15. Colecalciferol 400units od

Function:

Incontinent x2
Standing hoist transfer

Cognition
"advanced dementia"

Measurements:

Average BP:	125/64
Hb:	11.7
MCV	80
Na	138
K	4.5
Urea	10.7
Creatinine	87
HbA1C	53

APPENDIX 4

Common Summary Assessment Report

(CSAR i.e. nursing home application form)

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** ____________
(Delete as appropriate)

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

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)

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)

8: ASSESSMENTS

8 (A): BARTHEL INDEX

8 (A): BARTHEL INDEX				Please insert Date(s) Undertaken	DATE	DATE
WEIGHTING SCORE	**3**	**2**	**1**	**0**	**SCORE**	**SCORE**
Bowel (Preceding week)		Continent	Occasional Accident	Incontinent (Or needs an enema)		
Bladder (Preceding 24-48 hours)		Continent	Occasional Accident	Incontinent (Or Catheterised & Unable to Manage)		
Grooming			Independent	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 sitting balance)		
Mobility	Independent	Walks with help of 1 person	Wheelchair Iindependent	Immobile		
Dressing		Independent (Buttons, zips and laces)	Needs Help (But can do half unaided)	Dependent		
Stairs		Independent (Up & down must carry walking aid)	Needs Help (Verbal or physical/carrying of aid)	Unable		
Bathing			Independent (Getting in & out unaided & wash self)	Dependent		
Findings	Independent (20)	Low Dependency (16-19)	Medium Dependency (11-15) High Dependency (6-10)	Maximum Dependency (0-5) **TOTAL**		

Completed by: NAME: ___________________________ Role: ______________ Date: _________ Signature: ______________
(PRINT)

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: ______________
(PRINT)

CSAR Applicant's Name ______________________________ *DOB* ____________

9: ADDITIONAL COMMENTS e.g. Employment, Recreational or Social Needs (Attach supporting documentation):

Completed by: NAME: ______________________ Role: ____________ Date: ________ Signature: ____________
(PRINT)

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.)

Geriatric Medicine	Completed		Date:		**Signature:**	
Old Age Psychiatry	Completed		Date:		**Signature:**	
Rehabilitation Consultant	Completed		Date:		**Signature:**	
Neurologist	Completed		Date:		**Signature:**	
Other(Specify)	Completed		Date:		**Signature:**	
Specialist Comment: (Or append report)						

Completed by: NAME: ______________________ Specialty: ____________ Date: ________ Signature: ____________
(PRINT)

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: ______________ Date: ________	Role: ______________ Date: ________
Signature: ______________________	Signature: ______________________

Name & Signature of Professional Co-ordinating completion of this CSAR Form

NAME: ______________________ Role: ____________ Date: ________ Signature: ____________
(PRINT)

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)	Additional Information
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: ________ Date: ________	Role: ________ Date: ________	Role: ________ Date: ________
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/CMHN ☐	Therapy or other discipline ☐	Day Hospital ☐	Other (Specify) ☐	Other (Specify) ☐	
Comment(s)						

APPENDIX 5

Quality of Life Questionnaires used in Chapter 5

(ICECAP-O and QUALIDEM)

The ICECAP -O

ABOUT YOUR QUALITY OF LIFE

By placing a tick (✓) in ONE box in EACH group below, please indicate which statement best describes your quality of life at the moment.

1. Love and Friendship	
I can have all of the love and friendship that I want	☐ 4
I can have a lot of the love and friendship that I want	☐ 3
I can have a little of the love and friendship that I want	☐ 2
I cannot have any of the love and friendship that I want	☐ 1

2. Thinking about the future	
I can think about the future without any concern	☐ 4
I can think about the future with only a little concern	☐ 3
I can only think about the future with some concern	☐ 2
I can only think about the future with a lot of concern	☐ 1

3. Doing things that make you feel valued	
I am able to do all of the things that make me feel valued	☐ 4
I am able to do many of the things that make me feel valued	☐ 3
I am able to do a few of the things that make me feel valued	☐ 2
I am unable to do any of the things that make me feel valued	☐ 1

4. Enjoyment and pleasure	
I can have all of the enjoyment and pleasure that I want	☐ 4
I can have a lot of the enjoyment and pleasure that I want	☐ 3
I can have a little of the enjoyment and pleasure that I want	☐ 2
I cannot have any of the enjoyment and pleasure that I want	☐ 1

5. Independence	
I am able to be completely independent	☐ 4
I am able to be independent in many things	☐ 3
I am able to be independent in a few things	☐ 2
I am unable to be at all independent	☐ 1

Tick one box only in each section

Table 3: QUALIDEM indicative and contra-indicative items

No.	Item	Response options					
1.	Is cheerful [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		B
2.	Makes restless movements [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		D
3.	Has contact with other residents [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		F
4.	Rejects help from nursing assistants [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0		A
5.	Radiates satisfaction [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		B
6.	Makes an anxious impression [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		C
7.	Is angry [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		A
8.	Is capable of enjoying things in daily life [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		B
9.	Does not want to eat [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA [3] 9	J
10.	Is in a good mood [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		B
11.	Is sad [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0		C
12.	Responds positively when approached [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		F
13.	Indicates that he or she is bored [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	H
14.	Has conflicts with nursing assistants [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		A
15.	Enjoys meals [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3	NA 9	J
16.	Is rejected by other residents [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		G
17.	Accuses others [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	A
18.	Takes care of other residents [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		F
19.	Is restless [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		D
20.	Openly rejects contact with others [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		G
21.	Has a smile around the mouth [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3	NA 9	B
22.	Has tense body language [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		D
23.	Cries [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		C
24.	Appreciates help he or she receives [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		A
25.	Cuts himself/herself off from environment [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0		F
26.	Finds things to do without help from others [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		I
27.	Indicates he or she would like more help [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	E
28.	Indicates feeling locked up [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	H
29.	Is on friendly terms with one or more residents [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		F
30.	Likes to lie down (in bed) [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	J
31.	Accepts help [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		A
32.	Calls out [1, 2]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	G
33.	Criticizes the daily routine [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0		A
34.	Feels at ease in the company of others [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		F
35.	Indicates not being able to do anything [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	E
36.	Feels at home on the ward [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		H
37.	Indicates feeling worthless [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0	NA 9	E
38.	Enjoys helping with chores on the ward [1]	Never 0	Rarely 1	Sometimes 2	Frequently 3		I
39.	Wants to get off the ward [1]	Never 3	Rarely 2	Sometimes 1	Frequently 0		H
40.	Mood can be influenced in positive sense [1, 2]	Never 0	Rarely 1	Sometimes 2	Frequently 3		B

Remarks:

[1] People with mild to severe dementia (GDS 2 - 6).
[2] People with very severe dementia (GDS = 7).
[3] NA = Not applicable

APPENDIX 6

STOPPFrail version 2 supplementary document for Delphi panel

STOPPFrail version 2

November, 2018

University College Cork, Ireland

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Introduction

- STOPPFrail Version 2 is a list of prescribing indicators that highlight medications/medication classes that are potentially inappropriate (risks likely outweigh benefits) or that have negligible benefit in the context of reduced life expectancy.

- It is recognized that physicians caring for older people approaching end of life will not always have expertise in geriatric pharmacotherapy; STOPPFrail Version 2 was developed to assist physicians with deprescribing medications in this particular patient population.

- New criteria are based on:
    - Focused literature review
    - Findings from observational studies
    - Findings from recent method agreement analysis which compared use of STOPPFrail with gold standard deprescribing
- Version 2 includes a practical method for identifying older people approaching end-of-life.

- Version 2 recognizes core ethical principle of *autonomy* and emphasizes *shared decision making*.

- Version 2 includes new criteria relating to antihypertensive therapy, anti-anginal therapy, vitamin D and folic acid.

Recognizing when older people are approaching end of life

Appropriate patients typically meet ALL of the following criteria:

1. *ADL dependency (i.e. assistance with dressing, washing, transferring, walking) ± severe chronic disease ± terminal illness.*
2. *Severe irreversible frailty i.e. high risk of acute medical complications and clinical deterioration.*
3. *Physician overseeing care of patient would not be surprised if the patient died in the next 12 months.*

Rationale:

- A 2012 systematic review by Yourman *et al*. concluded that there was insufficient evidence to recommend application of any of the available prognostic models for older adults.[1]

- Even if a very precise prognostic model was available, there would continue to be a high degree of uncertainty when that model was used at an individual patient level. For example, consider a patient with a high one-year mortality risk –say, a 60% risk of dying within 12 months –it will not be clear whether the patient will be 1 of the 60 out of 100 who will die or 1 of the 40 who will live.

- Recommending a change in goals of care solely on the basis of a prognostic model depersonalizes the doctor-patient interaction. It may be difficult for physician to justify, to the patient and his/her family, a change in goals of care on this basis.

- We suggest 3 criteria for identifying patients who are approaching end of life and are, therefore, appropriate for STOPPFrail-guided deprescribing. Patients suitable for STOPPFrail typically meet all 3 criteria.

- The second criterion - severe irreversible frailty – refers to patients who are very vulnerable for developing adverse outcomes such as functional decline and clinical deterioration. *Vulnerability to adverse outcomes* is central to the Fried, Rockwood and consensus definitions of frailty.[2-4]

- The first criterion describes the profile of an older person who may be approaching end-of-life.
    - Dependency in activities of daily living –person requires assistance with basic ADLs (i.e. dressing, washing, walking, transferring)
    - Severe chronic disease (i.e. recurrent exacerbations/ hospitalizations despite optimal medical therapy)
    - Terminal illness (e.g. cancer, motor neuron disease)

- The third criterion features the 'surprise question' which has been widely adopted in frameworks for assessing end of life needs.[5-7]

References:

1. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. JAMA 2012; 307: 182–92.
2. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Med Sci. 2001;56A:M146–M156.
3. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722–7.
4. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392–7.
5. Kersun L, Gyi L, Morrison WE. Training in difficult conversations: a national survey of paediatric haematology-oncology and paediatric critical care physicians. *J Palliat Med* 2009;12:525-30.
6. Gómez-Batiste X, Martínez-Muñoz M, Blay C, et al. Identifying patients with chronic conditions in need of palliative care in the general population: development of the NECPAL tool and preliminary prevalence rates in Catalonia. *BMJ Support Palliat Care* 2013;3:300-8.
7. Dyingmatters.org: a coalition of individual and organisational members across England and Wales within Hospice UK.

Autonomy and Shared Decision Making

(STOPPFrail) is intended for older people with limited life expectancy for whom the goal of care is to enhance quality of life and minimize the risk of drug-related morbidity. Goals of care should be clearly defined and, where possible, medication changes should be discussed and agreed with patient and/or family.

- Patient involvement in health care decision making is a central aspect of patient-centered care, and a majority of older adults report wanting to be involved in decision making about their health care.[1-3]

- Multiple recent studies indicate that the great majority of older patients are willing to have medications deprescribed. [4-7] This suggests that clinicians can be reassured about broaching the topic of deprescribing with their older patients.

- Broaching the topic of deprescribing may lead to a conversation about goals of care. This can be a positive step:
    - The patient and family can focus on what is important to them
    - The chances of the patient being subject to treatments of limited value may be reduced

- The deprescribing physician may not be the patient's primary physician and, therefore, may not feel that he/she is the appropriate person to initiate a conversation about goals of care. In addition, some patients may not wish to engage in a discussion about goals of care. In this context, indicating to the patient that some medications may no longer be necessary (i.e., that benefits and risks can change over time; what was good for the patient years ago may no longer be so) may be the best approach.

References:

1. Chi WC, Wolff J, Greer R, Dy S. Multimorbidity and decision-making preferences among older adults. Ann Fam Med. 2017;15(6):546-551. doi:10.1370/afm.2106
2. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. Patient Educ Couns. 2012;86(1):9-18. doi:10.1016/j.pec.2011.02.004
3. Wolff JL, Boyd CM. A look at person- and family-centered care among older adults: results from a national survey [corrected]. J Gen Intern Med. 2015; 30(10):1497-1504. doi:10.1007/s11606-015-3359-6.
4. Reeve E, Wolff JL, Skehan M, Bayliss EA, Hilmer SN, Boyd CM. Assessment of Attitudes Toward Deprescribing in Older Medicare Beneficiaries in the United States. JAMA Intern Med. doi:10.1001/jamainternmed.2018.4720.
5. Reeve E, Wiese MD, Hendrix I, Roberts MS, Shakib S. People’s attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. J AmGeriatr Soc. 2013; 61(9):1508-1514. doi:10.1111/jgs.12418
6. Qi K, Reeve E, Hilmer SN, Pearson S-A, Matthews S, Gnjidic D. Older peoples’ attitudes regarding polypharmacy, statin use and willingness to

have statins deprescribed in Australia. Int J Clin Pharm. 2015;37(5):949-957. doi:10.1007/s11096-015-0147-7

7. Galazzi A, Lusignani M, ChiarelliMT, et al. Attitudes towards polypharmacy and medication withdrawal among older inpatients in Italy. Int J Clin Pharm. 2016;38(2):454-461. doi:10.1007/s11096-016-0279-4.

Ethical Considerations

1. *Patient and/or a surrogate indicate a preference to continue a potentially inappropriate medication.*

   It is helpful to try to understand the reasons underlying the preference to continue an inappropriate medication. The patient or surrogate may be concerned about adverse withdrawal effects of stopping the medication. The medication may symbolize hope to the patient, and therefore the recommendation to deprescribe the medication may be perceived as a loss of hope, abandonment, and a concern that the physician is hastening death.[1]

   The physician should address the concerns of the patient/ surrogate and discuss the benefits and risks of continuing the medication. Ultimately, the patient has the right to refuse the recommendation. Decisional conflict should probably be avoided unless the medication is causing overt harm to the patient.

2. *The potentially inappropriate medication is very unlikely to be causing harm (e.g. vitamin D). Why not continue the medication?*

   It may be helpful to approach this question using the "four core ethical principles" framework. The four principles are autonomy, non-maleficence, beneficence, and justice.[2]

Non-maleficence refers to the principle that physicians must “first, do no harm”. In the context of prescribing, this involves ensuring that the risks of a medication do not outweigh the benefits. Regarding vitamin D, unless there are difficulties with drug administration, this medication is very unlikely to cause harm.

Beneficence refers to the principle that physicians should act in the best interests of the patient. In the context of prescribing, this involves determining whether a medication can fulfill its goal by providing benefit to the patient. Regarding vitamin D, there is a lack of firm evidence to support the use of vitamin D to prevent risk of falls and fractures, cardiovascular events, or cancer.[3-6] It is very unlikely that vitamin D provides meaningful benefit to patients approaching end of life.

The principle of justice is important to this question and refers to the fair and equitable distribution of burdens and benefits to participants in society. Healthcare is associated with limited resources. There is an opportunity cost when medications are used without a good indication (resources that could have been put to good use elsewhere, are lost). Physicians should, therefore, consider the wider implications of inappropriate medication use.

References:

1. Tija J, Givens J. Ethical framework for medication discontinuation in nursing home residents with limited life expectancy. Clinics in Geriatric

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2. Jonsen A, Siegler M, Winslade W. Clinical ethics. 6th edition New York: McGraw-Hill; 2006.
3. Autier P, Mullie P, Macacu A, Dragomir M, Boniol M, Coppens K, Pizot C, Boniol M. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol. 2017(12):986-1004.
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5. Khaw KT, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo CA Jr, Scragg R. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017(6):438-447.
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New Criteria

Antihypertensive Therapies

Antihypertensive therapies

Reduce and discontinue these drugs in patients with systolic blood pressure (SBP) persistently <130mmHg. An appropriate SBP target in frail older people is 130 - 160mmHg. Before stopping, consider whether drug is treating additional conditions (e.g. beta-blocker for rate control in atrial fibrillation, diuretic for symptomatic heart failure).

Rationale:

SECTION A: RCT evidence

SECTION B: Evidence form longitudinal/ cross-sectional studies

SECTION C: Position statements

SECTION A: RCT evidence

Two recent randomized controlled trials (RCT) have evaluated the benefits of antihypertensive therapy in older adults. Both trials excluded participants with dementia and advanced frailty.

1. **Hypertension in the Very Elderly Trial (HYVET –NEJM 2008[1])**
    - Double blind placebo-controlled trial, evaluated benefit of treating older patients (≥ 80 years) with sustained SBP ≥ 160mmHg.

- 3845 participants randomized within Europe, Asia, Tunisia (mean age 83; mean entry SBP 173mmHg in both groups.)
- Intervention patients received indapamide ± perinodpril. Target SBP <150mmgHg.
- Primary outcome: stroke (fatal or non-fatal). Secondary outcomes: all-cause mortality, deaths from cardiovascular causes.
- At 2 years, mean SBP in active group was 143mmHg versus 158mmHg in the control group.
- Median follow-up 1.8 years.
- Results:
    - Primary outcome: 51 events in the active group vs 69 events in control group
    - 30% reduction in rate of stroke (p=0.06; NNT for 2 years to prevent 1 stroke =94)
    - All-cause mortality: 196 deaths in active group vs 235 deaths in control group.
    - 21% reduction in all-cause mortality (P=0.02; NNT for 2 years to prevent 1 death =40)
    - 23% reduction in deaths from cardiovascular causes (p=0.06)

- Note: **Exclusion criteria** for HYVET study included dementia, residence in a nursing home, life expectancy ≤1-year, heart failure, creatinine value >150μmol/L.

2. The Systolic Blood Pressure Intervention Trial (SPRINT –JAMA 2016[2])

- Participants randomized to an intensive SBP target of <120 versus standard SBP target of <140mmHg.
- 2636 participants ≥75 years in the United States (mean age 80; mean entry SBP 142mmHg)
- Primary outcome: cardiovascular events (including stroke) and deaths from **cardiovascular** causes. Secondary outcomes: all-cause mortality.
- Median follow-up 3.14 years.
- At follow-up, mean SBP in intensive group was 123mmHg while mean SBP in standard group was 135mmHg.
- Results:
    - Primary outcome (fatal and non-fatal cardiovascular events): 102 events in intensive group and 148 events in standard group.
    - 34% reduction in rate of primary outcome (p=0.001, NNT for 3.14 years to prevent 1 primary outcome = 27)
    - Secondary outcome (all-cause mortality): 73 events in intensive group vs 107 in standard group.
    - 33% reduction in all-cause mortality (p=0.009; NNT for 3.14 years to prevent 1 death =41)
    - Serious adverse events were similar in each group.

- Amongst participants with frailty (characterized using a 37-item frailty index) and slow walking speed (<0.8m/s on a timed 4m walk test), there was no statistically significant difference in outcomes between those randomized to the intensive treatment group and the standard treatment group.
- Note: **Participants were excluded** if life expectancy <3 years, dementia diagnosis, residence in a nursing home, diabetes, stroke, EF<35%, weight loss >10% in previous 6 months.

3. A meta-analysis (**Journal of Hypertension, 2010**[3]) of all the randomized controlled trials evaluating the treatment of hypertension in patients ≥80 (included HYVET; did not include SPRINT) reported concluded that:
    a. Treating hypertension in very old patients reduces stroke and heart failure with no effect on total mortality
    b. Thiazides should be considered first-line drugs with a maximum of 2 drugs
    c. Frail elderly and institutionalized patients were generally excluded from these trials.

SECTION B: Evidence form longitudinal/ cross-sectional studies

Several longitudinal studies have examined the association of blood pressure levels and antihypertensive use in older patients with frailty and/or dementia:

1. **The Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population Study (PARTAGE –JAMA Int Med 2015[4])**
    - Evaluated association between BP and mortality risk in nursing home residents
    - Multi-centre (France & Italy), longitudinal study involving 1130 nursing home residents ≥80 years.
    - Participants excluded if MMSE <12 or very high levels of dependency.
    - At baseline, BP was measured (mean of 18 different recordings over 3 days)
    - All-cause mortality recorded at 2 years.
    - Results:
        - Patients with SBP<130mmHg who were prescribed ≥2 antihypertensive drugs had an 81% excess all-cause mortality risk (32.2% vs 19.7%)
        - Patients with SBP <130mmHg who were prescribed <2 antihypertensives did not have an excess mortality risk.

2. **Effects of Low Blood Pressure in Cognitively Impaired Elderly Patients Treated with Antihypertensive Drugs (JAMA Int Med 2015[5])**
    - Evaluated association between baseline blood pressure and subsequent cognitive decline in 172 patients with dementia (68%) or mild cognitive impairment (32%) attending 2 outpatient facilities in Italy

- Baseline BP measured with 24-hour ambulatory monitor.
- Median follow-up 9 months.
- Results:
    - Low mean daytime SBP (≤128mmHg) was associated with greater cognitive decline (mean decline -2.8 on MMSE versus -0.7 for those with higher mean SBP measurements. Note, findings were only significant for those with low mean daytime SBP who were treated with antihypertensive medications.

3. Leiden 85-plus Study (JAGS 2012[6])

- Evaluated association between SBP measures at age 85 and future decline in physical and cognitive function.
- Included 572 community dwelling 85-year olds in Leiden (no selection criteria in terms of demographic or health status: inhabitants of Leiden were contacted on the month of their 85th birthday and invited to participate.)
- Yearly follow-up to age 90. Mean follow-up 3.2 years.
- Results:
    - At baseline, higher BP measures were associated with less physical and cognitive disability at age 85.
    - Higher SBP at age 85 was associated with slower rates of physical and cognitive decline.
    - The relationship between higher BP and slower cognitive decline was most pronounced in participants with pre-existing physical disability

- Results were similar for those prescribed anti-hypertensive medications and those who were not prescribed antihypertensive medications.

- **Note:** This study had significant limitations. Participants were categorized into groups at baseline based on blood pressure. Participants in the ‘Low SBP’ group very likely had more patients with dementia (it could explain accelerated cognitive and functional decline in this group).

4. Milan Geriatrics 75+ Cohort Study (Age & Ageing 2015[7])

- Evaluated association between baseline blood pressure with all-cause mortality over a period of 10 years
- 1587 participants recruited from outpatient Geriatric clinic in Italy.
- Median age 82 (IQR 78 -86), median MMSE 25 (20-29).
- Results:
  - Participants with SBP<120mmHg and 120-139mmHg had a 1.64 (95% CI 1.21 -2.23) and 1.32 (95% CI 1.1 -1.6) fold increased mortality risk compared with participants with SBP 160 -179mmHg.
  - Higher SBP and reduced mortality risk was statistically significant in patients with impaired ADL functioning (p=0.001) and in those with MMSE<24 but not in patients with preserved ADL functioning (p=0.085) or those with MMSE ≥24 (P=0.07)

SECTION C: Position statements

1. An Expert Opinion from the European Society of Hypertension–European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects (**Hypertension. 2016;67:820-825**[8]):

"The 2013 ESH/ESC guidelines recommend treatment to lower SBP to <150 mm Hg in octogenarians in good physical and mental conditions We believe that this might be usefully complemented by mentioning that, while keeping <150 mm Hg SBP as the evidence-based target, for safety reasons antihypertensive drugs should be reduced or even stopped if SBP is lowered to <130 mm Hg, thus keeping the 150 to 130 mm Hg on-treatment SBP values as a safety range."

2. Canadian group consensus guideline promoting higher blood pressure targets for frail older adults (Dalhousie Academic Detailing Service and the Palliative and Therapeutic Harmonization program):

Cleveland Clinic Journal of Medicine 2014[9]

- *For frail elderly patients, consider starting treatment if the systolic blood pressure is 160 mm Hg or higher.*
- *An appropriate target in this population is a seated systolic pressure between 140- and 160-mm Hg, as long as there is no orthostatic drop to less than 140 mm Hg upon standing from a lying position and treatment does not adversely affect quality of life.*

- *The blood pressure target does not need to be lower if the patient has diabetes. If the patient is severely frail and has a short life expectancy, a systolic target of 160 to 190 mm Hg may be reasonable.*
- *If the systolic pressure is below 140 mm Hg, antihypertensive medications can be reduced as long as they are not indicated for other conditions.*
- *In general, one should prescribe no more than two antihypertensive medications.*

References:

1. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–98.

2. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT,Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT Jr, Pajewski NM, SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged 75 years: a randomized clinical trial. JAMA. 2016;315(24):2673–82.

3. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. J Hypertens. 2010 Jul;28(7):1366-72.

4. Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, Salvi P, Zamboni M, Manckoundia P, Hanon O, Gautier S. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: the PARTAGE Study. JAMA Intern Med. 2015;175(6):989–95.

5. Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, Tonon E, Cavallini MC, Baroncini C, Di Bari M, Baldasseroni S, Cantini C, Biagini CA, Marchionni N, Ungar A. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015;175(4):578–85.

6. Sabayan B, Oleksik AM, Maier AB, et al. High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. J AmGeriatr Soc. 2012;60(11):2014-2019.

7. Ogliari G, Westendorp RG, Muller M, Mari D, Torresani E, Felicetta I, Lucchi T, Rossi PD, Sabayan B, de Craen AJ. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional and cognitive status. Age Ageing. 2015;44:932–937.

8. Benetos A, Bulpitt CJ, Petrovic M, Ungar A, Agabiti Rosei E, Cherubini A, Redon J, Grodzicki T, Dominiczak A, Strandberg T, Mancia G. An expert opinion from the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the management of

hypertension in very old, frail subjects. Hypertension. 2016;67(5):820–5.

9. Mallery LH, AllenM, Fleming I, et al. Promoting higher blood pressure targets for frail older adults: a consensus guideline from Canada. Cleve Clin J Med. 2014;81(7):427-437.

Anti-Anginal Therapies

Anti-anginal therapies (specifically: nitrates, nicorandil, ranolazine)

None of these anti-anginal drugs have been proven to reduce cardiovascular mortality or the rate of myocardial infraction. Aim to carefully reduce and discontinue these drugs in patients with a history of chest pain in the distant past (i.e. no chest pain in previous 6 months).

Reference:

Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, Manolis AJ, Marzilli M, Rosano GMC, Lopez-Sendon JL. Expert consensus document: A 'diamond' approach to personalized treatment of angina. Nat Rev Cardiol. 2018;15(2):120-132.

Aspirin for Stroke Prevention in Atrial Fibrillation

Aspirin for stroke prevention in atrial fibrillation

Aspirin has little or no role for stroke prevention in frail older patients who are not candidates for anticoagulation therapy and may significantly increase bleeding risk.

1. Lip GYH. The role of aspirin for stroke prevention in atrial fibrillation. *Nat. Rev. Cardiol. 2011;* 8:602-606.
2. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet. 1989;1:175–179.

Vitamin D (Ergocalciferol and Colecalciferol)

Vitamin D (ergocalciferol and colecalciferol)

Low vitamin D status is likely to be a consequence of ill-health, rather than its cause.[1] *There is a lack of firm evidence to support the use of vitamin D to prevent risk of falls and fractures*[2, 3]*, cardiovascular events,*[1] *or cancer.*[3-4]

1. Autier P, Mullie P, Macacu A, Dragomir M, Boniol M, Coppens K, Pizot C, Boniol M. Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials. Lancet Diabetes Endocrinol. 2017(12):986-1004.
2. Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;(4):CD000227.
3. Khaw KT, Stewart AW, Waayer D, Lawes CMM, Toop L, Camargo CA Jr, Scragg R. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017(6):438-447.
4. Scragg R, Khaw KT, Toop L, Sluyter J, Lawes CMM, Waayer D, Giovannucci E, Camargo CA Jr. Monthly High-Dose Vitamin D Supplementation and Cancer Risk: A Post Hoc Analysis of the Vitamin D Assessment Randomized Clinical Trial. JAMA Oncol. 2018:e182178. doi: 10.1001/jamaoncol.2018.2178. [Epub ahead of print]

Drugs for Overactive Bladder (Muscarinic Antagonists and Mirabegron)

Drugs for overactive bladder (muscarinic antagonists and mirabegron):

No benefit in patients with persistent, irreversible urinary incontinence unless clear history of painful detrusor hyperactivity.

Diabetic Therapies (Change in Words Reflecting New Guidance)

Diabetic therapies:

De-intensify therapy. Avoid HbA1c targets (HbA1C <7.5% [58 mmol/mol] associated with net harm in this population). Goal of care is to minimize symptoms related to hyperglycaemia

Reference:

Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Ann Intern Med. 2018 Apr 17;168(8):569-576.

Folic Acid

Folic acid

There is no evidence that folic acid improves cognitive performance in older people. Discontinue when treatment course completed. Usual treatment duration 1-4 months unless malabsorption, malnutrition or concomitant methotrexate use.

Reference:

Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD004514.

Potentially Obsolete Criteria

1. **Alpha-blockers for hypertension**
    - New antihypertensive therapy guideline

2. **Gastrointestinal antispasmodics**
    - These medications are not prescribed very commonly. New recommendation (A3) to review symptoms which may have resolved.

3. **Selective Estrogen Receptor Modulators (SERMs) for osteoporosis**
    - These medications are seldom prescribed

4. **ACE-Inhibitors for diabetes**
    - New antihypertensive therapy guideline

5. **Angiotensin Receptor Blockers (ARBs) for diabetes**
    - New antihypertensive therapy guideline

6. **Systemic oestrogens for menopausal symptoms**
    - These medications are not very commonly prescribed

7. **Prophylactic Antibiotics**

- There is evidence that long-term antibiotic therapy has a role in the prevention of recurrent urinary tract infections in postmenopausal women

Reference:

Ahmed H, Davies F, Francis N, et al. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. BMJ Open. 2017; 7(5): e015233

APPENDIX 7

Ethical approval for research described in this thesis

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

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

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

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

ECM 4 (y) 15/08/17 & ECM 3 (bb) 17/10/17

CORK UNIVERSITY HOSPITAL

2017

[illegible] DEPT.

18th September 2017

Professor Denis O'Mahony
Consultant Physician in Geriatric Medicine
Cork University Hospital
Wilton
Cork

Re: Medication rationalisation for older people awaiting long-term nursing home care: a randomised controlled trial using the STOPPfrail criteria.

Dear Professor O'Mahony

The Chairman approved the following:

- Evidence of Insurance.

Full approval is now granted to carry out the above study.

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

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

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

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter)

2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study

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

4. Notify CREC of discontinuation of the study

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Clinical Research Ethics Committee

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6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

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

Yours sincerely

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

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

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Clinical Research Ethics Committee

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University College Cork, Ireland

ECM 4 (oo) 15/11/16

15th November 2016

Professor Denis O'Mahony
Consultant Physician General and Geriatric Medicine
Cork University Hospital
Wilton
Cork

Re: Validity of the hospital patient one year mortality risk (HOMR) model for predicting death amongst older adults one year after admission to Cork University Hospital.

Dear Professor O'Mahony

Approval is granted to carry out the above study at:

- Cork University Hospital.

The following documents have been approved:

- Cover letter dated 1 November 2016
- Application form signed 28 October 2016
- Data collection sheet.

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

- Dr Paul Gallagher, Consultant Geriatrician, Dr Denis Curtain, Specialist Registrar in Geriatric Medicine and Dr Des O'Donnell, Senior House Officer.

Yours sincerely

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

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

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University College Cork, Ireland

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Clinical Research Ethics Committee

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Cork,
Ireland.

ECM 4 (f) 10/01/17

22nd December 2016

Professor Denis O'Mahony
Consultant Geriatrician
Cork University Hospital
Wilton
Cork

Re: Medication burden and acute care utilisation in the final year of life.

Dear Dr O'Mahony

Approval is granted to carry out the above study at:

- Cork University Hospital.

The following documents have been approved:

- Application form signed 28th November 2016
- Data Collection Sheet.

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

- Dr Paul Gallagher, Consultant Geriatrician, Dr Denis Curtin, Specialist Registrar in Geriatric Medicine and Dr Des O'Donnell, Senior House Officer.

Yours sincerely

Professor Michael G Molloy
Chairman
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of the Cork Teaching Hospitals

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