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**Detection & Avoidance of Adverse Medication Outcomes
in Older Adults Living with Multimorbidity and Polypharmacy**

Thesis presented by

Dr. Ruth Daunt

MB BCh BAO MRCPI

[0000-0003-0464-3057]

For the degree of

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University College Cork

Department of Medicine

Head of Department: Prof. Subrata Ghosh

Supervisors: Prof. Denis O'Mahony and Dr. Denis Curtin

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Dedicated to my husband, John

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Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and Intellectual Property.

Digital signature of the candidate: Ruth Daunt

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List of Abbreviations

ACEi	Angiotensin Converting Enzyme inhibitor
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
A&E	Accident and Emergency
BCW	Behaviour Change Wheel
BNF	British National Formulary
BST	Basic Specialist Training
CCB	Calcium Channel Blocker
CCI	Charlson Co-morbidity Index
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CFS	Clinical Frailty Scale
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COREQ	CONsolidated criteria for REporting Qualitative research
CS	Corticosteroid
DDI	Drug-Drug Interaction
DOAC	Direct Oral Anticoagulant
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	EuroQol 5-Dimension 5- Level Questionnaire
GI	Gastrointestinal

GP	General Practitioner
GRIPP2	Guidance for Reporting Involvement of Patients and the Public 2
HCP	Healthcare Professional
IBM SPSS	International Business Machines Corporation Statistical Package for the Social Sciences
ICC	intra-class correlation coefficient
ICU	Intensive Care Unit
IMS	Intercontinental Medical Statistics
IT	Information Technology
IQR	Interquartile Range
LMQ	Living with Medicines Questionnaire
LUTS	Lower Urinary Tract Symptoms
MDT	Multidisciplinary Team
MRB-QoL	Medication-related Burden Quality of Life
mNGT	Modified Nominal Group Technique
mMRB-QoL	Modified Medication-related Burden Quality of Life
MR-QoL-LSV1	Medication-Related QoL-Life Scale Version 1
MTBQ	Multimorbidity Treatment Burden Questionnaire
NGT	Nominal Group Technique
NHS	National Health Service
NH	Nursing Home
NSAID	Non-Steroidal Anti-Inflammatory Drug
OAB	Over-active Bladder
OPD	Outpatient Department
PD	Parkinson's Disease

PIM	Potentially Inappropriate Medication
PIPC	Potentially Inappropriate Prescribing Cascades
PPI	Proton Pump Inhibitor
PPI	Patient/Public Involvement
PROM	Patient Reported Outcome Measure
PSSA	Prescription Sequence Symmetry Analysis
QoL	Quality Of Life
RMSEA	Root Mean Square Error Approximation
SD	Standard Deviation
SF 36	Medical Outcomes Short Form- 36
SGLT2	Sodium-Glucose coTransporter-2
SHO	Senior House Officer
SmPC	Summary of Product Characteristics
SMART	Specific, Measurable, Acceptable, Realistic, and Time-framed
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SpR	Specialist Registrar
SSRI	Selective Serotonin Reuptake Inhibitor
START	Screening Tool to Alert doctors to Right Treatments
STOPP	Screening Tool of Older Peoples Prescriptions
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAT	Think Aloud Task
TDF	Theoretical Domains Framework
TLI	Tucker Lewis Index
UTI	Urinary Tract Infection

WHO	World Health Organisation
WHO-UMC	World Health Organisation-Uppsala Monitoring Centre
4-AT	Arousal, Attention, Abbreviated Mental Test – 4, and Acute change

List of Statistical Symbols

α	Cronbach's alpha
CI	Confidence Interval
N	Population size
n	Sample size
p	Statistical Probability value
t	Test statistic for independent t-test
U	Test statistic for Mann-Whitney U test
Z	Statistic for level of confidence

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THESIS OVERVIEW

Therapeutic advances have undoubtedly transformed modern healthcare. Effective and curative treatments are now available for many previously life-limiting and fatal diseases conditions such as cardiovascular disease, infectious diseases and certain malignancies. These advances have contributed to increased longevity worldwide, and a marked shift in population demographics, with a population of adults now living to older age in much greater numbers than ever before. However, the pharmaceutical advances of the last 50 years have also contributed to an increasing number of adults - particularly older, frailer adults - living longer with multimorbidity and associated polypharmacy. Multimorbidity and polypharmacy are both strongly associated with adverse medication effects. Previous research has examined multiple aspects of adverse medication outcomes, including inappropriate prescribing and interventions aimed at optimising problematic prescribing. However, two key components remain relatively under-researched: (i) prescribing cascades and (ii) the impact of medication-related burden on patients' lived experiences and quality of life.

This thesis examines adverse medication outcomes in older adults living with multimorbidity and polypharmacy with a particular focus on prescribing cascades and medication-related burden. Firstly, it investigates the prevalence of prescribing cascades in hospitalised older adults and examines factors influencing their recognition by hospital physicians. Secondly, it addresses the measurement of medication-related burden through the evaluation and modification of a patient-reported outcome measure designed specifically for use in older adults living with multimorbidity and polypharmacy.

The thesis consists of five chapters. The first chapter is an introduction, divided into three sections: (i) medications; (ii) prescribing cascades; (iii) patient reported outcome

measures and medication related burden. Chapter 2 examines the prevalence of prescribing cascades in hospitalised older adults living with multimorbidity and polypharmacy. Chapter 3 investigates the facilitators and barriers to hospital physicians' recognition of prescribing cascades. Chapter 4 develops the modified medication-related burden quality of life (MRB-QoL) tool for older adults living with multimorbidity and polypharmacy. A mixed-methods design is used, including examining the original MRB-QoL in the target population and Modified Nominal Group Technique (mNGT) to achieve consensus. Finally, Chapter 5 synthesises the finding of this thesis and suggest priorities for future research.

This thesis is presented in the form of a Publication-based Thesis. Chapters 2 and 3 of this thesis have been published in peer-reviewed journals. The 'Methods' and 'Results' sections of these chapters are presented largely as published, while the 'Introduction' and 'Discussion' sections have been modified where necessary to enhance the coherence of the thesis. PDF versions of published articles are provided in Appendix 1.

CHAPTER 1

Introduction

1.1 Medications

1.1.1 Evolution of pharmacotherapy and therapeutic advances

The past century has witnessed unprecedented expansion in the development and availability of pharmaceutical therapies. In the mid-1970s, the British National Formulary (BNF), a pharmaceutical reference book containing prescribing information about drugs available in the United Kingdom's National Health Service (NHS), listed approximately 650 medicinal products [1]. By 1981, this had increased to approximately 4500 products, a figure that has increased several fold with successive editions [2]. This proliferation of pharmaceutical products, described as “the pharmaceutical revolution”, has influenced the approach to treating and managing diseases and symptoms, reshaping not only the medical therapeutic framework but also society's expectations of pharmacological solutions for all conditions [3].

This expansion of pharmaceutical products has contributed to major improvements, providing prescribers and patients with an ever-broader range of treatment options. The discovery and steady development of anti-infective drugs revolutionised the treatment of previously fatal infectious diseases [4]. Cytotoxic chemotherapy and hormonal therapies have improved cancer survival rates [5], while disease modifying treatments have changed the trajectory of several chronic and neurodegenerative conditions such as multiple sclerosis [6], rheumatoid arthritis [7] and, most recently, Alzheimer's dementia [8].

These advances have contributed to reductions in mortality, enhanced longevity, and consequently accelerated population ageing. However, the rapid growth in therapeutic options has fostered what Busfield (2010) termed a ‘pill for every ill’ culture, creating

a health system where both patients and physicians turn to prescription medicines for every clinical problem [3]. This has resulted in a therapeutic climate in many countries that promotes over-use of medication, particularly among older adults living with multiple long-term co-morbidities.

1.1.2 Population ageing and multimorbidity

Population ageing is one of the most significant demographic shifts of recent decades. Globally, life expectancy has risen steadily, with a major demographic shift in the world's population towards old age, an unprecedented modern sociological phenomenon. The World Health Organisation (WHO) projects that the global number of people over 80 years will treble between 2020 and 2050 reaching an estimated 426 million people, with a parallel increase in the number of people living with multimorbidity and polypharmacy [9].

As people age, they are more likely to accumulate more chronic medical conditions, this phenomenon is referred to as multimorbidity i.e. when two or more medical conditions coexist [10,11]. Multimorbidity is currently the norm rather than the exception in older adults. Two large systematic reviews in recent years have demonstrated similar results. Ho *et al.* analysed 193 studies and found that the prevalence of multimorbidity in people aged over 74 years was 67% compared to 47% in those aged 60-74 years and 28% in those aged under 60 years [12]. A systematic review by Hai Nguyen *et al.* found that more than 50% of adults aged over 65 years have multimorbidity [13].

Multimorbidity is associated with poorer functional status, increased mortality, reduced quality of life and increased healthcare utilisation [11,14–16]. Within the context of expanding therapeutic options, multimorbidity is also associated with

polypharmacy and increasingly complex medication regimens, which puts challenges on healthcare systems that were largely designed around the management of single diseases [17].

1.1.3 Organisation of modern healthcare

Modern health systems are predominantly organised according to an individual disease framework. Clinical guidelines, quality standards, and professional training remain largely single-disease specific, with each chronic condition typically linked to its own specialty clinic, management guideline, and recommended pharmacological regimen. Adherence to these evidence-based management guidelines in common conditions such as hypertension, COPD and coronary artery disease has been shown to improve clinical outcomes in those individual conditions [18–20]. However, this framework is poorly suited to the complexity of multimorbidity and interlinked pathophysiological processes in older adults. Healthcare professionals are encouraged to optimise each individual co-morbidity but in doing so often fail to recognise the cumulative impact of multimorbidity on older patients' overall health and treatment burden [21]. Consequently, application of multiple single-disease treatment guidelines to individual patients can result in multiple prescriptions, some of which may be ineffective, costly, contradictory and harmful [22].

Fragmentation of care further compounds these challenges. Older patients with multimorbidity frequently attend several specialists, each contributing additional treatments with poorly established communication and coordination structures [23]. Schoen *et al.* reported on patient care in six countries and found that patients who attended four or more prescribing doctors were significantly more likely to experience serious medication errors than those who attended fewer doctors [23].

Together, the limitations of the individual disease framework and fragmented care structures create conditions in which prescribing becomes increasingly complex, particularly for older adults living with multimorbidity.

1.1.4 Evidence-based pharmacotherapy

These challenges are further compounded by the limitations of evidence-based pharmacotherapy that is individual-disease focused rather than individual-patient focused. Most clinical guidelines are derived from clinical trials, that commonly exclude older multimorbid people [24]. Researchers seek to isolate the effect of a new treatment on a single disease, and therefore the presence of co-morbidities and heterogeneity in health status risks disrupting the statistical power of the study [25]. The WHO, has identified seven groups of patients who are at highest risk of ADRs, many of whom are those most often excluded from trials, see **Table 1.1** [26]. Consequently, many treatment guidelines, validated in homogenous trial populations, may be problematic when applied to patients with a wide variety of comorbidities and an even wider diversity of symptom constellations commonly encountered in clinical practice [25,27,28].

Other contributing factors include faulty clinical trial methodology [29,30], exclusion of older ('real-world') patients [24], ambiguity in aspects of trial design [30,31], publication bias [31], translation challenges from population-based results to individual patients, and bridging the gap between statistical significance and clinical relevance [32]. Collectively, these factors combined with pharmaceutical advances, increasing multimorbidity, and healthcare organisation are inextricably linked to the development of polypharmacy, problematic prescribing and increasing medication burden in older adults.

Table 1.1: Patients at risk from medication-related harm [26].

Group No.	Patients at risk from medication-related harm
1	Residents in a care home setting
2	Patients on high-risk medications (e.g. anticoagulants, immunosuppressive agents)
3	Patients with hyperpolypharmacy (≥ 10 daily medications)
4	Patients with multimorbidity
5	Patients with measurable frailty
6	Patients with dementia
7	Patients receiving palliative care

1.1.5 Polypharmacy: Definition, prevalence and determinants

Polypharmacy is most commonly defined as the concurrent and continuous use of five or more different medications [33]. Using data from over 32,000 participants aged ≥ 65 years across 17 European countries, Midão et al. reported that almost one third (32.1%) of older adults in Europe take 5 or more daily medications [34]. In the US, Charlesworth et al. found a threefold increase in polypharmacy prevalence among adults aged ≥ 65 years between 1988 and 2010, rising to 39% [35]. Trends are similar in Asian countries, where a recent study reported a prevalence of 38.8% and 46.6% in older adults in Taiwan and South Korea respectively [36]. Other studies have reported varying levels of polypharmacy, ranging from 2.6% to 86.6%. This variation reflects heterogeneity in the definitions of polypharmacy used and the settings, for example, some studies include over-the-counter medications and non-regular medication when assessing whether a patient has polypharmacy.

Polypharmacy is not exclusive to older individuals, many younger individuals with multimorbidity also experience polypharmacy. However, older people are most vulnerable to polypharmacy and medication-related harm arising as a result of age-associated physiological changes that commonly alter their pharmacokinetic and pharmacodynamic response to drug therapies compared to younger people; these age-related changes are summarized in **Table 1.2** [37]. Polypharmacy, in turn, is the principal risk factor for inappropriate prescribing in older people [38]. This phenomenon is more evident in older women, due to intrinsic differences in drug pharmacodynamics and pharmacokinetics compared to older men [37,39–41]. These differences included lower lean body mass, which can result in a higher concentration of lipophilic drugs such as diazepam [40]. In addition, sex-based differences in hepatic metabolism have been described, such that clearance of temazepam and paracetamol is greater in men, and clearance of erythromycin and verapamil is greater in women [41]. Moreover, beyond the age of 75 years, women outnumber men by approximately 2:1 in most developed countries, a survival difference that becomes more accentuated the older the age cohort [42].

Table 1.2: Age-associated pharmacokinetic and pharmacodynamic changes [37].

Pharmacokinetic changes			
	Physiological changes	Impact on medication	Drug examples
Absorption	Slight reduction in gastric acid secretion	Reduced absorption *rarely clinically significant	Calcium Iron supplements
Distribution	↓lean body mass ↓ total body water Relative ↑ total body fat ↓Total body albumin ↑ Permeability of blood brain barrier	↑ plasma concentration of hydrophilic drugs Prolonged drug effect of lipophilic drugs	Digoxin Lithium Benzodiazepines Morphine
Metabolism	<u>Liver</u> ↓mass ↓perfusion ↓first pass metabolism ↓ hepatic enzyme activity (variable)	↑ systemic bioavailability ↑plasma drug concentration	Antihypertensives Antianginals Warfarin Opiates Statins
Excretion	<u>Kidney</u> ↓mass ↓ perfusion ↓glomerular filtration rate	Drug accumulation and toxicity	Metformin Bisphosphonates Colchicine NSAIDs
Pharmacodynamic changes			
Changes in: - receptor activity, density and affinity - membrane environment or binding		Increased effect	Warfarin Neuroleptics Benzodiazepines Anticholinergics
		Decreased effect	Propranolol Furosemide Scopolamine Isoprenaline

Abbreviation: NSAIDs: Non-steroidal anti-inflammatory drugs.

1.1.6 Problematic polypharmacy & inappropriate prescribing

Polypharmacy is not inherently problematic. When drugs have a clear clinical indication and are regularly reviewed, the prescription of five or more medications for individuals with multimorbidity may be entirely appropriate to manage their chronic health conditions [33]. However, as the number of prescribed medications increases, there is a proportional increase in the risk of patients experiencing medication-related harm because of problematic polypharmacy [38,43]. Problematic polypharmacy encompasses a wide range of phenomena, including: inappropriately prescribed or omitted medications, avoidable drug-drug interactions or drug-disease interactions, inappropriate prescribing cascades, and a failure to align the goals of treatment with the individual's goals of care [38,44–46]. Inappropriate prescribing, as defined by the most widely published criteria, has been shown to be highly prevalent in older people across various clinical settings, see **Table 1.3**.

Table 1.3: Prevalence of potentially inappropriate medications in independent living older people, older people in hospital and older people living in the long-term nursing home setting.

Criteria	Community-dwelling adults	Hospitalised patients	Nursing Home residents
STOPP Version 2	66.8% [47]	68.5%-86.1% [48,49]	66%-85% [50,51]
Beers criteria 2015	54% [47]	21.6%- 71% [52,53,48]	51.5%-96% [54,55]

Abbreviation: STOPP: Screening Tool of Older Persons' Prescriptions.

1.1.7 Consequences of problematic polypharmacy

Problematic polypharmacy is associated with a range of adverse consequences for individual patients including increased risk of adverse drug reactions (ADR), increased risk of hospitalization, reduced health-related quality of life (QoL) and ultimately, increased mortality [38,43–45,56,57]. A UK prospective, observational study reviewed all patients admitted via the medical assessment unit over a one-month period [57]. The authors reported that ADRs were the main reason for, or a contributing factor in, 18.4% of hospital admissions, and that those patients admitted with an ADR were older, had more co-morbidities and were more likely to have polypharmacy than patients admitted for reasons other than ADRs [57]. Similar results were demonstrated by Cosgrave et al in a recent systematic review. Falls, delirium and bleeding were the most frequent drug-related problems requiring hospital admission [58].

Several studies have also demonstrated a significant association between polypharmacy and mortality. A systematic review and meta-analysis by Leelakanok et al. identified a dose-response relationship, with increasing numbers of medications being significantly associated with increased mortality ($P<0.05$) [43].

Additionally, problematic polypharmacy also places a considerable economic burden on healthcare systems through increased drug expenditure and expenses related to treating medication-induced harm. Research conducted by the Intercontinental Medical Statistics (IMS) Institute for Healthcare Informatics, entitled ‘Advancing the Responsible Use of Medicines: Applying Levers for Change’ reported that approximately 4% of the world’s avoidable healthcare expenditure can be attributed to mismanaged or suboptimal prescribing [59]. A Canadian study by Morgan et al.

reported that the use of potentially inappropriate medications (PIMs) can increase the annual per-patient costs of care by approximately \$2000, resulting in an estimated \$419 million in avoidable excess national healthcare cost [60]. Similarly, a Japanese study by Akazawa et al. reported a significant financial impact from PIM prescribing, with older adults prescribed PIMs incurring 33% higher average medical costs than those not exposed to PIMs [61]. In the UK, it is estimated that the NHS spends approximately £2.21 billion annually as a result of ADR-related hospital admissions, most of which occur in multimorbid older people on long-term polypharmacy [57].

Medication-related harm also has a significant impact on prescribers [62]. Psychological distress, reduced professional confidence, and burnout are commonly reported when prescribers are involved in cases of serious iatrogenic harm [63]. Despite adverse events experienced by their patients, doctors often hide their mistakes from their colleagues and their patients due to feelings of guilt and shame, fear of criticism or legal action, leading to missed opportunities to strengthen the safety climate within a healthcare environment [64].

1.1.8 Recognition and prevalence of problematic polypharmacy

Multiple tools have been developed to help prescribers identify potentially inappropriate prescribing. Explicit screening tools such as STOPP/START criteria [65], STOPPFrail criteria [66], Beers criteria [67], and EURO-FORTA criteria [68] provide clearly defined statements that highlight instances of potentially inappropriate prescribing in specific clinical circumstances. Through such explicit criteria, the prescriber is alerted to inappropriate medication use. These tools have been deployed to investigate the prevalence of inappropriate polypharmacy in multiple settings worldwide, including acute hospital, community settings and in long term residential

care settings. In a large, representative sample of community dwelling adults in Spain, Blanco-Reina investigated the prevalence of PIMs using STOPP/START version 2 criteria and Beers 2015 criteria and found that 66.8% and 54% of participants, respectively, were prescribed at least one PIM [47]. However, most explicit criteria focus on inappropriate prescribing and do not systematically capture other problematic prescribing phenomena such as inappropriate drug dosage and prescribing cascades.

Implicit approaches have also been identified as means for assessing medication appropriateness. These include the Medication Appropriateness Index, the SMART tool, and the 10-Step Discontinuation Guide [69–71]. The user must apply clinical judgement, contextual information, and enquire about patient preferences when evaluating medication appropriateness. Due to these variances, there is limited research investigating these tools in large-scale settings.

1.1.9 The WHO Global Patient Safety Challenge ‘Medication without Harm’

Given the scale of the clinical, economic and professional consequences associated with problematic polypharmacy, safer prescribing has become a major international patient safety priority. Recognising this, the WHO launched the third WHO patient safety challenge, ‘Medication without Harm’, in 2017 [72]. Through this initiative, the WHO strove to raise awareness about the importance of medication safety and to seek new and specific commitment from global leaders in healthcare to make policy changes to support safer medication practices. The specified target was to reduce severe and avoidable harm from medication by 50% within five years. The WHO challenge aimed to improve medication safety at each stage of the medication process, from prescribing, to dispensing, to administering, to monitoring and utilisation of drug therapy. It specifically targeted three contexts where patients face a particularly high

risk of experiencing medication related harm. These contexts were to be the basis for change implementation and included high risk situations, polypharmacy and transitions of care. High risk situations encompass scenarios which pose a significant risk of medication-related harm to patients, such as the use of higher-risk medications like insulin and warfarin, and interruptions during critical processes such as prescribing and administration of medication. Transitions of care from community to hospital and later from hospital to home are also commonly associated with unintentional medication discrepancies that can be potentially harmful [73]. Older individuals with multimorbidity frequently encounter all three contexts (high risk situations, polypharmacy and transitions of care) simultaneously, compounding the risk of adverse drug events (ADEs) in this cohort.

The challenges of optimising medications in the heterogenous population of multimorbid older adults are demonstrated by the fact that over five years since this ambitious WHO goal was set, there still is no published evidence to indicate that the initiative has significantly reduced medication-related harm, as expressly intended by the WHO. To emphasize the persistent necessity of achieving this goal, the WHO Safety Action Plan 2021-2030 prioritizes the ‘Medication without Harm’ challenge (3.2). The WHO Safety Action Plan outlines key actions for governments, healthcare stakeholders and the WHO secretariat, including establishing expert groups and leadership teams, appointing medication officers/ teams in healthcare, promoting patient involvement and medication literacy, recognizing and reporting ADRs, and monitoring of progress.

1.2 Prescribing Cascades

1.2.1 Overview and definition

Prescribing cascades, a component of problematic prescribing, were first described over 30 years ago by Rochon and Gurwitz. They defined prescribing cascades as occurring when an ADR to an initial drug (index drug) is misinterpreted as a new medical condition, resulting in the inappropriate prescription on an additional medication (so-called marker drug) to treat the drug-induced symptom rather than discontinuing or adjusting the causative drug [74]. This original conceptualisation emphasised misinterpretation, misdiagnosis and subsequent use of inappropriate therapeutic treatments, effectively framing prescribing cascades as avoidable medication errors.

Since then, there has been significant variability in how prescribing cascades have been described in the literature [75,76]. It is now generally recognised that prescribing a second medication to effectively manage the side-effect of a previously prescribed drug may be intentional and clinically appropriate, particularly where the benefit of continuing the index drugs outweighs the potential harm. Reflecting this heterogeneity, a recent scoping review proposed a more encompassing definition: a prescribing cascade is where at least one drug is prescribed to manage at least one side effect of at least one other drug [75]. A schematic overview of how prescribing cascades develop is presented in **Figure 1.1**.

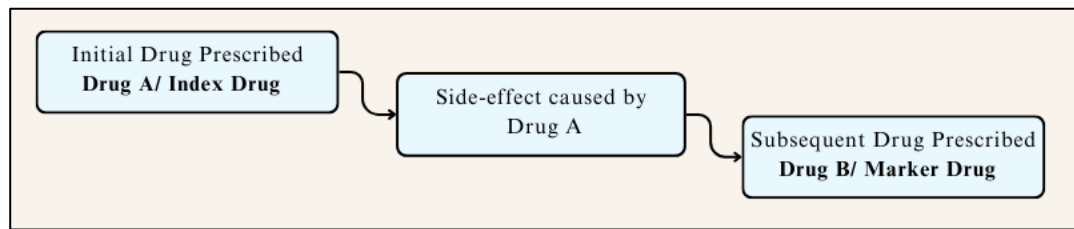


Figure 1.1: Schematic overview of how prescribing cascades develop.

1.2.2 Classifications of prescribing Cascades

As well as multiple definitions, several cascade classification systems have also been proposed, capturing different dimensions of prescriber decision-making, attribution of symptoms, and clinical reasoning [75]. These classifications include:

- appropriate vs. inappropriate
- intentional vs. unintentional
- recognised vs. unrecognised
- prophylactic vs. therapeutic.

Appropriate prescribing cascades occur when a new medication is prescribed to manage a well-recognized drug side-effect, with the benefits of initiation outweighing the risk, such as laxatives to counteract the common and predictable problem of constipation arising from opioid treatment [77].

In contrast, inappropriate prescribing cascades occur when drug side-effects are misdiagnosed as new conditions, leading to the inappropriate prescription of an unnecessary or potentially dangerous secondary medications to treat the misdiagnosed new condition or symptom, thereby increasing the risk of medication-related harm [77,78]. One well-known example is the prescription of diuretics to treat lower limb oedema arising as a side-effect from prior treatment with dihydropyridine calcium

channel blockers (CCB). In this case oedema is misdiagnosed as a sign of heart failure rather than as a side-effect of the CCB.

The intentional/ unintentional classification reflects whether the prescription of the marker drug was deliberate to manage a known ADR or side-effect, whereas recognised/ unrecognised refers to whether a prescribing cascade is identified or not by the healthcare professional. Prophylactic cascades involve prescribing medication to prevent an anticipated side-effect, such as co-prescribing proton pump inhibitors with NSAIDs. Therapeutic cascades involve treating an already manifest adverse effect of an initial drug, such as introduction of bisphosphonates in patients who develop corticosteroid-related osteoporosis where there is an ongoing indication for systemic corticosteroid therapy.

Furthermore, sequential prescribing cascades have also been described, in which a marker drug in turn causes a side-effect or ADR triggering the prescription of another medication, for example, CCB-associated peripheral oedema prompting the prescription of a diuretic, which later leads to the prescription of a medication for over-active bladder.

1.2.3 How prescribing cascades are determined

Much of the published research has concentrated on identifying, validating and reporting various prescribing cascades. Numerous examples of prescribing cascades have been reported in the literature through case reports, case series, case-control studies, cross-sectional studies and original research [79,80]. The likelihood that a concurrent drug pair represents a prescribing cascade may be investigated through so-called prescription sequence symmetry analysis (PSSA) methodology [79,81,82]. In essence, PSSA compares the number of patients prescribed the index drug before

introduction of the marker drug, to those who were prescribed the marker drug before the index drug (so-called crude sequence ratio). PSSA may be affected by prescribing trends such that many studies also report an adjusted sequence ratio, which is the crude sequence ratio divided by the null-effect sequence ratio. The null-effect sequence ratio represents the expected sequence ratio in the absence of a causal association and reflects underlying prescribing trends.

Although PSSA is an effective and validated method of establishing whether a drug pair constitutes a potential prescribing cascade, it cannot determine the actual clinical relevance of a suspected inappropriate prescribing cascade, nor can it establish clear causality [81]. Additionally, certain PSSA studies are hypothesis-free studies screening large datasets, generating potential prescribing cascades even where ADR/side-effect evidence is weak. This is demonstrated by examples such as direct oral anticoagulants (DOACs) leading to antidepressant prescribing, despite depression not being a recognised side-effect of DOACs in the Summary of Product Characteristics (SmPC) [83]. The key point here is that PSSA may identify potential prescribing cascades but for such potential cascades to be relevant to prescribing practice, they should also be clinically plausible. Savage et al, in large cohort study, used administrative prescription data to evaluate the CCB-diuretic prescribing cascade [84]. New CCB users were monitored for subsequent initiation of diuretics. While this method allowed for the examination of a large data set, it was limited by its inability to prove a cause-and-effect relationship between the two drugs. These varying approaches have generated many potential cascades in the literature, prompting the creation of formal prescribing cascade lists to help clinicians identify and prioritise clinically relevant examples.

1.2.4 Explicit lists of Prescribing Cascades

One such list was developed through a systematic review by Doherty et al. (**Table 2.5**) [79]. This study, which examined 101 published studies, was designed to identify published prescribing cascades in community-dwelling adults aged 18 years and older. From their systematic analysis of the literature, the authors generated a list of the 25 most identified prescribing cascades in community dwelling adults. However, given that most prescribing cascades were identified by studies that utilised PSSA methodology, including those where the ADR evidence is limited, this list may be of limited clinical utility. Several of the prescribing cascades listed are of questionable validity and clinical relevance such as: lower urinary tract symptoms arising from statins leading to drugs for urinary frequency/incontinence, and; depression arising from direct oral anticoagulants (DOACs) leading to antidepressant drug prescription. These examples highlight the limitations of relying heavily on statistical methods such as PSSA to define cascades without clinical data, expert endorsement and clinical plausibility to validate proposed prescribing cascades. Nevertheless, a recent follow-up study evaluating the strength of the evidence supporting the prescribing cascades identified by Doherty et al. found that 84% of these prescribing cascades were supported by moderate evidence i.e. single high-quality study or strong evidence i.e. multiple high-quality studies [85].

Another prescribing cascades list has also been created through formal consensus methods. The iKASKADE consortium published a consensus list (called “ThinkCascades”) of nine clinically relevant prescribing cascades validated by the Delphi consensus method involving international experts in geriatric pharmacotherapy (**Table 2.4**) [86]. Although there is some overlap with the Doherty list, the

ThinkCascade is of greater utility to healthcare providers as each prescribing cascade listed has undergone explicit expert panel Delphi validation. Nonetheless, given that only nine prescribing cascades met consensus criteria, this list very likely underrepresents the true number of clinically relevant prescribing cascades.

1.2.5 Clinical Relevance of Prescribing Cascades

Prescribing cascades, in particular those classified as inappropriate, are clinically important as they represent an avoidable component of problematic prescribing and are associated with increased risk of hospitalisation, drug-related harm, functional decline and mortality [87,88]. Inappropriate prescribing of cascades may result in prolonged symptom burden arising from ADEs, avoidable treatment escalation, and further inappropriate use of medications [87,89,90]. Additionally, prescribing cascades can place considerable psychological and practical burden to patients and caregivers, as well as unnecessary cost burden [88,91,92].

Older adults are particularly vulnerable to inappropriate prescribing cascades due to multimorbidity and associated polypharmacy, both of which increase the risk of inappropriate prescribing [17,38]. The cumulative effect of multiple medications also increases the risk of ADEs which can result in the prescription of additional medications to manage these ADEs, thus initiating a prescribing cascade [93,94]. Age-related physiological change and altered pharmacokinetics/pharmacodynamics further heighten susceptibility to ADEs. Preventing, recognising and resolving prescribing cascades is therefore an essential element for improving medication safety, quality of care and patient outcomes.

1.2.6 Recognition of prescribing cascades

Recognition of prescribing cascades in older adults is particularly challenging as ADEs often present with non-specific symptoms such as confusion, dizziness, or malaise [87,95,96]. These symptoms can be misattributed to known concurrent comorbidities, natural disease progression or misdiagnosed as new conditions, potentially perpetuating ADEs and resulting in further inappropriate prescribing.

In addition to diagnostic uncertainty, fragmentation of care further compounds the challenge of recognising prescribing cascades. In a healthcare system organised around single-disease management, specialist physicians might overlook prescribing cascades originating outside their specialty. Even when identified, physicians may be reluctant to deprescribe medications initiated by other physicians [97] or lack sufficient knowledge and experience to make confident decisions. For example, routine medication reviews rarely capture initiation dates, hindering any effort to establish the temporal relationship between medications and symptoms [92].

Awareness of prescribing cascades among both physicians and patients appears limited [92,98]. Multiple studies report that many primary care physicians are unfamiliar with the term and may struggle to recognise specific cascades in practice, while patients can have difficulty understanding the concept even when explained to them [92,99,100]. Although several tools have been developed to support cascade recognition [86,89], healthcare professionals continue to report uncertainty regarding identification and management of cascades [98,99]. Notably, no study to date has examined recognition among hospital physicians, despite their central role in medication assessment during acute illness and at points of care transition.

Prescribing cascades can be prevented by early recognition of the ADR and can be reversed by either dose reduction, discontinuing the index medication, or switching to safer alternatives. McCarthy et al. proposed three considerations for clinicians: (i) determining the optimal management of the ADE; (ii) evaluating whether the therapeutic benefit of adding a medication outweighs the harm; and (iii) ensuring ongoing assessment [78]. Piggott et al. suggested using a process map for improving cascade detection as well as simply asking the question “Could my patient’s new symptom be caused by a drug they are taking rather than a new medical condition?” [89]. However, in older patients with multimorbidity and complex polypharmacy, clinicians describe that even when a prescribing cascade is identified, the subsequent decision-making around medication adjustment can become highly challenging [99]. Due to the clinical ambiguity and delicate risk/benefit balance involved in such cases, classifying a prescribing cascade as appropriate or inappropriate has previously been described as ‘*unfeasible*’ [99]. As a result, the dynamic and complex nature of prescribing cascades makes them relatively difficult to detect and challenging to classify. This diagnostic uncertainty in combination with limited awareness and methodological challenges contribute to the paucity of real-world prescribing cascade prevalence data.

1.2.7 Prevalence of prescribing cascades

Despite being described for over 30 years, the prevalence of prescribing cascades remains unclear. Inconsistent terminology and challenges in detection have resulted in minimal population-level data compared to other aspects of problematic prescribing. Although multiple drug pairs have been described as potential prescribing cascades, only a small subset have been examined in terms of prevalence and incidence (**Table**

1.4). No published study has evaluated the overall prevalence of prescribing cascades using a comprehensive list or applied a standardised identification approach.

Table 1.4: Prevalence and incidence of specific sample prescribing cascades.

Study and setting	Population	Key findings
Calcium channel blocker → diuretic		
Retrospective cohort [84]	≥66 years >40,000 adults newly dispensed a CCB	3.5% initiated a loop or thiazide diuretic within 12 months after starting a CCB, after excluding heart failure and renal causes.
Cross-sectional observational study[101]	≥18 years 47.5 million patient visits	Potential CCB–loop diuretic cascade present in 4.6% - 11.8% of visits depending on definition used.
Retrospective cross-sectional analysis [102]	Adults ≥55 years 5.5 million CCB users	3.4% of CCB users started a loop diuretic after exclusions for heart failure/chronic kidney disease/cirrhosis.
Antipsychotic → Parkinson’s Medication		
Retrospective Cohort Study [103]	Adults ≥50 years with Alzheimer’s disease >4,500 patients	0.8% incidence of a potential cascade
Cross-sectional study [104]	Adults >65 years. 11.5 million	0.2% were prescribed an antipsychotic and Parkinson’s medication concurrently
NSAID → Proton Pump Inhibitor		
Retrospective Cohort Study [105]	Adults ≥40 years >16,000 community-dwelling adults	40% chronic NSAID users are co-prescribed PPIs.
Cholinesterase Inhibitor →Anticholinergic (for urinary symptoms)		
Retrospective Cohort Study [106]	≥65 years >117,000 patients with dementia	The prescribing cascade was identified in 0.2% of this cohort.
Retrospective cross-sectional observational study [107]	≥65 years >37,000 nursing home residents with dementia	15% co-prescribed cholinesterase inhibitor and anticholinergic.

Abbreviations: CCB: Calcium channel blockers; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor.

1.3 Patient Reported Outcomes and Medication related burden

1.3.1 What are PROMs and why are they important

Despite extensive research on medication-related harm, comparatively little attention has been directed to patient-reported outcomes, specifically the impact of medication burden on QoL [108,109]. Patient-reported outcome measures (PROMs) are standardised instruments, most often questionnaires, that capture patients' perceptions of their symptoms, functioning, health status, and quality of life, as well as more specific dimensions such as the impact of a condition and its treatment on wellbeing [110,111]. PROMS were initially developed for research to ensure that the patient perspective was incorporated into evaluations of treatment effectiveness, cost-effectiveness and equity of care [112]. Over time, their application has broadened such that PROMs are now also recognised as tools that can enhance healthcare quality and support system-level quality improvement and policy initiatives [113].

Modern healthcare is predominately shaped by evidence-based medicine, with clinical practice guided by research-derived guidelines, population-level data and expert consensus. Although, evidence-based medicine is essential for delivering high-quality, safe and effective care, this approach may inadvertently overshadow the other central paradigm of contemporary healthcare i.e. patient-centred care [25]. Integrating PROMs into trial design and routine clinical care provides a mechanism for ensuring that the patient perspective is at the centre of care delivery by measuring humanistic outcomes and effectively bridging the gap between evidence-based medicine and patient-centred care (**Figure 1.2**). Without PROMs, outcomes risk remaining predominantly clinician-centred, shaped by professional interpretation rather than the lived realities of those receiving treatment.

When used in clinical practice, PROMs can help healthcare professionals (HCPs) identify patient concerns, guide clinical decision-making about treatment and to encourage greater patient engagement in their own care [114]. This is particularly relevant within the time-constrained physician–patient consultation, where competing demands can limit the time available for discussion and influence what is raised or omitted between the physician, the patient and, often, their carer [115]. Integrating PROMs into these encounters offers a structured means through which patients’ concerns can be communicated more effectively. Across long-term conditions, systematic reviews show that incorporating PROMs into consultations typically prompts greater discussion of symptoms and facilitates clinicians’ recognition of patients’ lived experiences and quality of life [116,117].

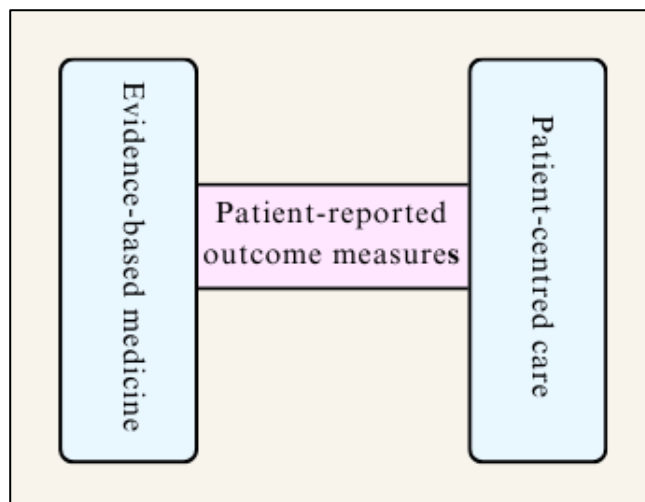


Figure 1.2: Schematic depiction of patient-reported outcome measures bridging the gap [25].

1.3.2 Patients-reported experiences and medication related burden

PROMs provide a structured means of capturing the entire spectrum of perspectives, burdens and non-objective outcomes that patients associate with their medication. These lived experiences arise from the biomedical, psychological, social, functional and economic impact of medications [109,118,119]. They may be positive or negative and can influence beliefs about medicines, influence compliance with medications and impact health outcomes and quality of life.

A core burden related to medication arises from the practical challenges patients face in managing their routine medication regimes [120,121]. This includes tasks such as scheduling, organising and administering medications [122,123]. Older adults describe the need to educate themselves and to seek assistance from HCPs, such as community pharmacists, to provide dispensed medications in various daily pill organisers [121–123]. Medication administration can also be burdensome, with difficulties related to swallowing, taste, dosing frequency or managing particular formulations [122]. For some people, these tasks and routines can be readily incorporated into daily life; for others, they are interruptive, time-consuming and burdensome [121,123]. Many older, frailer patients rely on family or carers for assistance, particularly when the medication regimes become increasingly complex in the setting of increasing multimorbidity-driven polypharmacy [123,124].

ADEs and medication side-effects further contribute to medication-related burden [121,122]. Beyond the physical objective effects, certain medications can cause psychological distress, such as fear relating to prescription recurrence and change in beliefs relating to medication efficacy [122,125,126]. Anxiety can arise from embarrassment due to the physical effects of medications such as diuretics, as well as

other specific medication effects such as impact on sexual wellbeing and cognitive function [126]. Even when patients do not experience the physical side-effects of medications, they often report other psychological effects such as reduced confidence, and loss of lifestyle control if they have observed medication-induced changes in others and fear their occurrence in themselves [127]. Cumulatively, this can erode trust in pharmacotherapy and affect medication adherence, leading patients to reduce doses, skip medications or stop treatment altogether [121].

As well as anxiety related to actual or potential ADEs, medication can also have other significant social implications. Treatment regimens can interfere with social routines, travel, holidays or the ability to leave home, sometimes leading to social withdrawal and isolation [128]. Concerns about stigma or being perceived as frail or dependent may further shape how patients manage medicines in social contexts [128]. Conversely, strong social support—from family, friends or community networks—can promote adherence and reduce perceived burden by providing practical and emotional assistance [123,124].

System-level factors can further impact patients' quality of life. Fragmented healthcare, attending multiple HCPs, irregular follow-up appointments and poor communication structures can all contribute to the burden of medications [119]. Additionally, patients face the logistical challenges such as organising transport to and from clinic appointments, long waiting times for appointments and undergoing regular monitoring [129,130]. Depending on the healthcare system in question, the financial cost of medications and associated care can further impact quality of life [129,130].

Collectively, these experiences highlight the multidimensional nature of medication-related burden and the extent to which medicines can affect functional, social, physical

and psychological quality of life and wellbeing. When clinicians better understand patients' lived experiences with medications, this could enable them to optimise treatment plans, address adherence concerns, and improve patient outcomes [25,114]. A therapeutic relationship that is not informed by patients' experience of their medication burden can lead to patients struggling to self-manage their medications potentially leading to unsafe and harmful medication use. Recognising patients' experiences of medication is essential for fostering good therapeutic relationships, improving treatment quality and patient outcomes [109]. PROMs provide a structured means of eliciting these non-objective, patient-centred experiences, many of which are difficult to capture through traditional clinical measures.

1.3.3 PROMs used to assess pharmacotherapy interventions

Studies that have used patient-reported outcomes to measure the impact of pharmacotherapy interventions, have frequently been statistically underpowered, and have relied on tools that lack specificity for medication-related burden [97,109,131]. Traditional QoL assessment instruments often fail to detect QoL improvements following medication optimisation interventions, possibly because they do not measure domains (factors) specifically related to medication-related burden [108,109,132]. This results in inconclusive outcomes and missed opportunities to capture meaningful improvements in patients' lived experiences as they pertain to long-term medication burden [132]. Widely used QoL measures such as Medical Outcomes Short Form- 36 (SF-36) and (EuroQol 5-Dimension 5- Level Questionnaire) EQ-5D-5L capture related but distinct constructs and are not sensitive to medication burden [133,134]. Other tools, such as the Medication-Related QoL-Life Scale version 1 (MR-QoL-LS v1), are considered unsuitable for measuring

medication-related QoL in older adults [108,135]. The Multimorbidity Treatment Burden Questionnaire (MTBQ) measures treatment burden, with the focus on the workload imposed by managing multiple chronic conditions—including appointments, monitoring and lifestyle demands—rather than the specific physical, psychological and social impacts of medications [136]. The Medication-Related Burden-Quality of Life (MRB-QoL) was the first validated PROM specifically designed to measure the impact of medication-related burden on functioning and well-being from the patients' perspective [137]. Developed through a multi-phase process, the MRB-QoL underwent psychometric and construct validation resulting in a 31-item scale organised into five subscales: *Routine and Regimen Complexity* (11 items), *Psychological Burden* (6 items), *Functional and Role Limitation* (7 items), *Therapeutic Relationship* (3 items), and *Social Burden* (4 items). It demonstrated good internal consistency and reliability and has been translated and culturally adapted for Arabic populations [137,138]. The PolyPrime pilot randomised controlled trial in Ireland showed that it can be used to reliably measure medication-related burden QoL in older adults with polypharmacy [139]. Nonetheless, the MRB-QoL tool has important limitations that restrict its use in older adults. The original validation study included individuals aged ≥ 18 years, who were community dwelling, computer literate and taking ≥ 3 prescription medications for at least one chronic medical condition [137]. The average age was 64 years and the median number of comorbidities was three. Older, frailer adults with multimorbidity and polypharmacy were underrepresented despite being the cohort most likely impacted by medication-related burden. Additionally, practical challenges such as its length, relative complexity, and relevance of certain items make it less applicable in older, frailer populations, with higher levels of multimorbidity. The PolyPrime study further highlighted some of

these challenges, reporting higher rates of missing data for the MRB-QoL compared to the EQ-5D-5L, possibly related to higher respondent burden [139]. An overview of the more commonly used PROMs, designed to measure the impact of medications on quality of life, are displayed in **Table 1.5** below.

Table 1.5: Comparison of patient reported outcome measures relevant to medication-related burden.

Instrument	No. of items	Target population	What it measures	Limitations
EuroQol 5-Dimension 5- Level Questionnaire (EQ-5D-5L) [134]	5 items and visual analogue scale	Adults ≥ 18 years	Generic health-related quality of life across 5 domains, mobility; self-care; usual activities; pain/discomfort; anxiety/depression.	Ceiling effects; lacks sensitivity to medication-related problems; limited psychosocial detail.
Medication- related - quality of life (MRQOL) [135]	14 items	Adults ≥ 18 years, taking ≥ 5 medications	Overall effect of polypharmacy on QoL across 3 domains, role limitations due to medication; self-control; vitality.	Considered unsuitable for measuring medication-related QoL in older adults [108]. Does not capture cultural, societal and psychological factors.
Living with Medicine questionnaire version 3 (LMQ) [140]	41 items	Adults ≥ 18 years using long-term medications	Burden of living with medicines across 8 domains, relationships with health professionals; practicalities; interferences; effectiveness; side effects; concerns; cost; and autonomy.	Lengthy; high respondent burden; not QoL-focused; frail adults may have inadvertently been excluded.

Medication- related Burden- quality of life (MRB-QoL) [137]	31 items	Adults $\geq$ 18 years taking $\geq$ 3 medications	Medication-related burden across 5 domains: routine and regimen complexity, psychological burden, functional and role limitation, therapeutic relationship, social burden.	Lengthy; high respondent burden; not developed specifically for older adults, frail adults may have inadvertently been excluded.
Medical Outcomes Short Form- 36 (SF-36) [133]	36 items	Adults $\geq$ 18 years and	Generic measure of health concepts across 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, mental health, reported health transition.	Lengthy; high respondent burden; not medication-specific; limited sensitivity to polypharmacy-related impacts.
Treatment Burden Questionnaire (TBQ) [141]	13 items	Adults $\geq$ 18 years and $\geq$ 1 comorbidity requiring follow-up	Global treatment burden (drug intake, appointments, monitoring, lifestyle changes).	Not medication-specific; does not assess medication-related psychosocial impacts, not developed specifically for older adults.
Multimorbidity Treatment Burden Questionnaire (MTBQ) [136]	10 items and 3 optional items	Adults $\geq$ 18 years and $\geq$ 3 comorbidity	Effort required to self-manage medical conditions and the associated impact on general well-being.	Not medication-focused; high floor effect, does not assess psychological impact.

Abbreviation: QoL: quality of life.

1.4 Conclusion

Advances in modern medicine and therapeutics have enabled people to live longer, healthier lives. However, older adults living with multimorbidity and polypharmacy whose longevity is directly related to these therapeutic advances are also those at greatest risk of medication-related harm and problematic polypharmacy. Problematic polypharmacy has emerged as a major healthcare and patient safety concern worldwide, driven by multiple factors including ageing populations, multimorbidity, fragmented healthcare systems, over-emphasis on evidence-based pharmacotherapy, and the organisation of healthcare around an individual disease treatment framework. Older adults are particularly vulnerable to adverse medication outcomes, encompassing both clinically measurable effects and the broader impact of medicines on their lived experiences. The challenge for all prescribers currently is how to make prescribing safer while navigating the gap between evidence-based medicine and the older, frailer patient typically encountered in clinical practice.

Reducing adverse medication outcomes in this high-risk population requires a multifaceted, personalised approach and a comprehensive understanding of all aspects of problematic prescribing. One such aspect, prescribing cascades, has been conceptualised for over 30 years, yet remains under-investigated. Research to date has focused on identifying and validating drug combinations that may represent cascades, with limited research investigating real-world prevalence in older patients living with polypharmacy and multimorbidity. It is clear that prescribing cascades are generally under-recognized and a deeper exploration of the factors that influence their recognition is required. These factors are likely to be most important in the acute

hospital setting where older patients are frequently exposed to new medication combinations.

Older adults with multimorbidity and polypharmacy represent a heterogeneous patient cohort that also require patient-centred, personalised clinical care that aligns with their individual preferences and lived-experiences. PROMs can capture these experiences and other difficult-to-measure constructs such as QoL. Medication-related burden represents an additional yet poorly measured dimension of medication safety that can impact patients' QoL. Existing PROMs either measure related but distinct domains or have limited applicability to older adults with polypharmacy and multimorbidity. Given that this population is the most highly susceptible to medication-related burden, a practical, reliable, and valid tool to assess the impact of medication-related burden on QoL is required. Such a tool could support a more personalised, patient-centred application of evidence-based medicine.

In subsequent chapters of this thesis, I will address these interconnected gaps through original and interconnected research studies. First, I will determine the prevalence of prescribing cascades in hospitalised older adults with multimorbidity and polypharmacy. Second, I will identify factors influencing hospital physicians' recognition of prescribing cascades. Third, I will develop a modified, short-form of the original MRB-QoL, designing it specifically to improve the usability and relevance for older adults with multimorbidity and polypharmacy.

CHAPTER 2

Detection of Potential Prescribing Cascades in Multimorbid Older Patients Hospitalised with Acute Illness—An Observational Prospective Prevalence Study

2.1 Introduction

Prescribing cascades occur when a new drug is prescribed to treat a side-effect or an adverse drug event (ADE) caused by an existing medication, potentially resulting in unnecessary, or hazardous additional drugs [76,78]. As outlined in Chapter 1, prescribing cascades are clinically relevant as they can result in prolonged symptom burden and accumulation of unnecessary medication, thereby increasing the risk of medication-related harm [87,89,90].

Although it is over 30 years since the original concept of prescribing cascades was described by Rochon and Gurwitz, there are currently no studies measuring the real-world prevalence of prescribing cascades in older people living with multimorbidity and exposed to polypharmacy i.e. the population at highest risk of inappropriate prescribing cascades [74]. This gap in the prescribing cascades literature has been driven largely by the lack of validated explicit prescribing cascades lists prior to 2022. As described in Chapter 1, two validated lists have subsequently been published, the ThinkCascade list and list compiled by Doherty et al. (henceforward referred to as the ‘Doherty list’) [79,86]. The availability of these explicit lists now enables the identification and prevalence estimation of multiple prescribing cascades rather than individual cascades.

In addition, no standardised approach exists to determine whether the co-prescription of a potential drug pair represents a true prescribing cascade or appropriate treatment for co-existing comorbidities. For example, concurrent prescription of a calcium channel blocker (CCB) and a diuretic may be clinically indicated in a patient with hypertension and congestive cardiac failure and does not necessarily constitute a

Older people with multimorbidity and polypharmacy who are hospitalised because of acute illness represent a key population in whom prescribing cascades may occur [38].

Accordingly, the aims of this study were:

1. To investigate the prevalence of prescribing cascades in hospitalized older adults living with multimorbidity and polypharmacy using the Doherty and ThinkCascades explicit prescribing cascades lists in combination.
2. To develop a classification system to determine the probability that identified drug pairs represent prescribing cascades.
3. To compare the prevalence of prescribing cascades prehospital admission and at discharge.

2.2 Methods

2.2.1 Study design, setting and recruitment

This study was a single-centre observational prospective prevalence study conducted in a major tertiary referral medical centre in Cork, Ireland. The local Clinical Research Ethics Committee approved this research study. Participants were recruited between October 2022 and July 2024. This study is reported according to STROBE guidelines (**Appendix 2**) [142].

Eligible participants were adults aged ≥ 65 years admitted through the emergency department with acute medical or acute surgical illness, with preadmission multimorbidity (i.e. ≥ 3 chronic co-morbidities diagnosed prior to admission) and associated polypharmacy (i.e. taking ≥ 5 long-term i.e. > 3 months daily prescription

medications). Exclusion criteria were: acute psychiatric illness (not including delirium), patients at end of life or admitted directly to the intensive care unit (ICU). Patients were also excluded if they or (if they lacked capacity) their legally authorised representative were unable or unwilling to give consent to study participation. Apart from their high prevalence of multimorbidity and polypharmacy, hospitalised older patients were selected as the focus of this study because hospital admission provides a unique opportunity to perform a comprehensive medication review, facilitating the identification of prescribing cascades [143].

2.2.2 Sample size

To achieve a statistically valid detection of prescribing cascades, using Cochran's formula a sample size of 384 was determined. Based on a margin of error of 5% at 95% confidence, this sample size was calculated using an assumed prevalence of 50%, an estimate that requires the largest sample size ensuring adequate power regardless of the true prevalence within the population. Furthermore, the sample size was calculated under the assumption of a large at-risk population (more than 5000) [144,145].

Sample size was calculated using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2} \qquad 384 = \frac{1.96^2 0.5(1-0.5)}{0.05^2}$$

n = sample size, Z = Z statistic for level of confidence (1.96 for 95% CI), P = expected prevalence (0.5), d = precision (margin of error) (0.05) [144,146].

2.2.3 Data collection

Patients' data were collected at two timepoints i.e. at recruitment, which was within 72 hours of admission, and at discharge. At recruitment, I and two research assistants

conducted patient and/or carer interviews, contacted patients' community pharmacists and reviewed medical records to obtain the following patient information: age, sex, admitting speciality, long-term regular medications, admitting diagnosis, specific diagnoses and cumulative co-morbidity as quantified by the Charlson Co-morbidity Index score (CCI), number of reported falls in the preceding 12 months, number of admissions in the preceding 12 months, delirium status on admission based on the 4AT screening test, and Clinical Frailty Scale (CFS) score. At discharge, we obtained the following information: length of hospital stay (days), discharge destination (home or long-term care facility), and updated list of regular medications.

2.2.4 Prescribing cascade ascertainment and classification

Potential prescribing cascades were identified at the point of recruitment using the ThinkCascades list and the Doherty list. Patients' long-term daily medications were screened for potential prescribing cascades using the two explicit cascades lists separately and in combination. When potential cascades were identified, the temporal relationship between Drug A and Drug B was determined, where ascertainable, through discussions with the community pharmacist and review of patients' medical records. Establishing the temporal relationship involved firstly determining whether Drug A was initiated before Drug B and, where possible, assessing the timeframe between initiation of both drugs. If Drug B was initiated after Drug A, further investigation was conducted to determine whether an ADE was implicated as the potential indication for Drug B. Patients were interviewed and their medical records carefully scrutinized, including correspondence letters and inpatient progress notes, to determine whether Drug B was initiated to treat a known ADE caused by or relating to Drug A. In this assessment, only ADEs documented on the ThinkCascades list and

the Doherty list, were considered as indicating potential cascades. Potential ADE's were only included if the ADE was documented in the patients' medical records. The likelihood of a prescribing cascade being present was categorized as 'definite', 'probable', 'possible', 'uncertain,' or 'indeterminate' according to pre-defined criteria (**Table 2.1**).

This classification system was developed in alignment with the WHO-UMC (World Health Organisation-Uppsala Monitoring Centre) system for standardised case causality assessment and was informed by elements of the prescribing cascade clinical process map described earlier [147]. Like the WHO-UMC's adverse drug reaction (ADR) causality assessment, this system cannot provide an accurate quantitative measurement of the Drug A/Drug B cascade relationship likelihood. However, it helps reduce assessor disagreement and improve the overall evaluation of potential prescribing cascades. The standardized process to ascertain prescribing cascade likelihood is illustrated in **Figure 2.2**.

Table 2.1: Prescribing Cascade likelihood criteria.

	Cascade Likelihood	Assessment Criteria
1	Definite	• Drug B follows Drug A • Drug B initiated to treat ADE caused by Drug A • Initiation of Drug B cannot be explained by other disease/ indication • Withdrawal challenge of Drug A results in improvement/ cessation of the side-effect
2	Probable	• Drug B follows Drug A • Drug B initiated to treat ADE caused by Drug A • Initiation of Drug B unlikely explained by another disease or symptom
3	Possible	• Drug B follows Drug A • Drug B possibly initiated to treat ADE caused by Drug A (Documentation of ADE in medical records after drug A prescribed and before drug B prescribed) • Initiation of Drug B could be explained by other disease/ indication
4	Uncertain	• Drug B follows Drug A • Unclear if Drug B initiated to treat ADE caused by Drug A (no documentation of ADE in medical chart) • Initiation of Drug B could be explained by other disease/ indication
5	Indeterminate	• Drug A and Drug B co-prescribed • Cannot determine temporal relationship between Drug A and Drug B • Data cannot be supplemented or verified

Abbreviation: ADE: Adverse drug event.

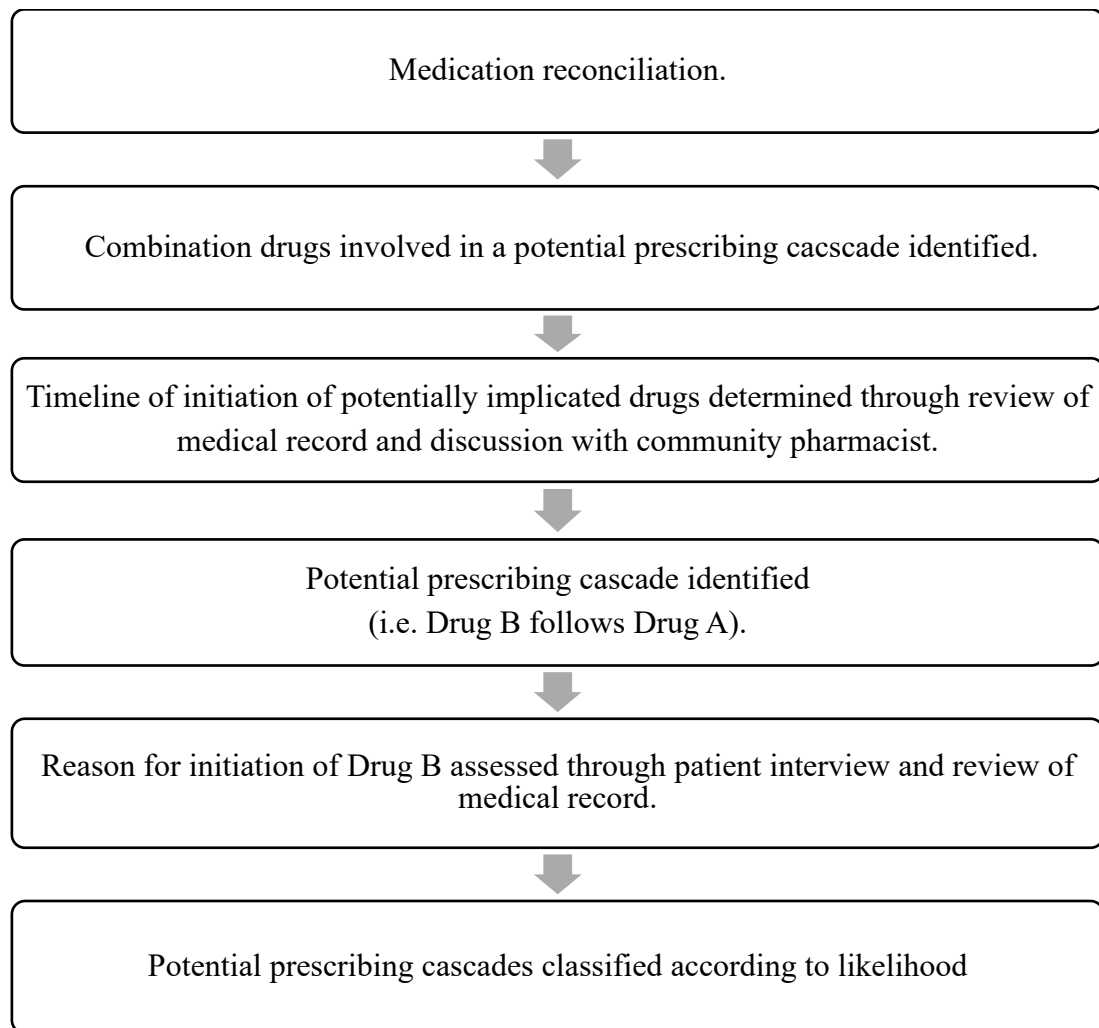


Figure 2.2: Standardised process to ascertain prescribing cascade likelihood.

2.2.5 Prescribing cascade prevalence estimation

Prescribing cascade prevalence, the primary outcome of interest, was determined as the proportion of patients identified with a potential prescribing cascade, categorised as definite, probable, possible or uncertain. Patients were then classified into two groups – (i) those with a potential prescribing cascade and (ii) those without a potential prescribing cascade - to evaluate statistical difference in demographic and clinical characteristics. The selected covariates were chosen based on review of the relevant literature of related studies on inappropriate prescribing in older multimorbid adults [44,53,94].

At discharge, patients' medications were reviewed to determine whether any potential prescribing cascades identified at recruitment were still included in their regular prescriptions.

2.2.6 Data quality assurance

To ensure accuracy and minimise data entry errors, a structured data quality assurance process was undertaken. All data were entered manually into a secure study database by 3 trained research physicians. Following data entry, a data quality check was performed to identify potential errors and inconsistencies. A random sample of records was cross-checked against original source data to confirm accuracy of data entry prior to statistical analysis.

2.2.7 Statistical analysis

Statistical analysis was conducted using SPSS® version 28.0 software. Descriptive statistics included the mean and standard deviation (SD) for normally distributed variables and the median and inter-quartile range (IQR) for non-parametric variables. Deceased patients were excluded from the analysis of medication prescriptions at discharge. Differences in the distribution of categorical variables were compared using Pearson's chi-squared test and continuous variables using the independent *t* test. The Mann-Whitney *U* test was used to determine independence of two nonparametric variables. A probability value of <0.05 was considered statistically significant. The probability values were selected to show the differences between the two groups- those with potential prescribing cascades and those without potential prescribing cascades - to test the null hypothesis, which assumes no difference between the groups. To ensure strong reliability in the classification of potential prescribing cascades and ADE's

among the three researchers, inter-rater reliability was calculated using the intra-class correlation coefficient, a two-way mixed model, assessing for absolute agreement.

2.3 Results

2.3.1 Patient Characteristics

In total, 385 patients were enrolled in this study, of whom 212 patients (55.1%) were female with a mean (SD) age of 80.2 (7.3) years. Baseline patient characteristics are presented in **Table 2.2**. The median (IQR) number of comorbid chronic conditions in patients with a potential prescribing cascade was 8 (6-10) versus 7 (5-9) in patients without a potential prescribing cascade ($p=0.003$). The three most common diagnoses were hypertension (72.7%), dyslipidaemia (50.6%) and atrial fibrillation (34.2%). A total of 3950 daily medications were prescribed to the 385 patients i.e. an average of 10.3 daily drugs per patient.

2.3.2 Prevalence of Potential Prescribing Cascades

Using both the ThinkCascades list and the Doherty list in combination, a total of 281 individual potential prescribing cascades were identified in 152 patients i.e. 39.4% prevalence, with 63 patients (16.3%) classified as having possible cascades and 7 patients (1.8%) classified as having probable cascades (**Table 2.3**). No patient was identified as having experienced a definite cascade. Due to overlap between the Doherty list and the ThinkCascades list, the total number of unique patients and prescribing cascades in the combined analysis was lower than the sum of the individual lists. Each patient and prescribing cascade was counted only once. Cascades categorized as 'indeterminate' were excluded from overall prevalence calculations.

The ratio of drug pairs prescribed Drug A followed by Drug B to those prescribed Drug B followed by Drug A was 1.57 (104/66) using the ThinkCascade list and 2.47 (210/85) using the Doherty list.

Table 2.2: Baseline characteristics and univariate analysis of association.

Variable		No Cascade Group (n= 233 (60.6%))	Cascade Group (n= 152 (39.4%))	P value
Female (%)		131 (55.9)	80 (52.6)	0.438
Age (years), median (IQR)		80.5 (74.75-86)	80 (75-85)	0.95
Living arrangements pre-admission	Home, number of patients (%)	218 (93.6)	139 (91.4)	0.435
	Long-term care facility, number of patients (%)	15 (6.4)	13 (8.6)	
Charlson Comorbidity Index, mean (SD)		5.57 (1.68)	6.13 (2.06)	0.006
Number of daily medications, median (IQR)		9 (7-11)	12 (9-14)	<0.001
Hyperpolypharmacy, number of patients (%)		87 (37.3)	107 (70.3)	<0.001
Clinical Frailty Scale score, median (IQR)		5 (4-6)	5 (4-6)	0.476
Number of comorbidities, median (IQR)		7 (5-9)	8 (6-10)	0.003
Fall in last 12 months, number of patients (%)		123 (52.7)	79 (52.0)	0.875
Admitted in last 12 months, number of patients (%)		128 (55.0)	88 (57.9)	0.567
4AT score at admission, median (IQR)		1 (0-2)	0 (0-2)	0.886
Number of patients admitted under Geriatric Medicine (%)		42 (18)	18 (11.8)	0.102
Admission service	Medical speciality, number of patients (%)	218 (93.6)	141 (92.8)	0.760
	Surgical speciality, number of patients (%)	15 (6.4)	11 (7.2)	
Five most common admission primary diagnoses (ICD Code)	Fall (W19) (%)	50 (21.5)	29 (19.1)	0.572
	Acute lower respiratory infection (J22) (%)	22 (9.4)	25 (16.4)	0.040
	Urinary tract infection (N39.0) (%)	17 (7.3)	8 (5.3)	0.429
	Syncopal (R55) (%)	14 (6)	4 (2.6)	0.125
	Decompensated congestive heart failure (I50.0) (%)	13 (5.6)	5 (3.3)	0.298
Length of hospital stay, days (IQR)		9 (4-17)	11 (5-21)	0.276
Survival Outcome (death), number of patients (%)		21 (9)	10 (7)	0.391
Discharge destination	Home, number of patients (%)	183 (78.5)	113 (74.3)	0.93
	Long-term care facility, number of patients (%)	50 (21.5)	39 (25.7)	

Abbreviation: 4AT : Arousal, Attention, Abbreviated Mental Test – 4, and Acute change.

Table 2.3: Prevalence of potential prescribing cascades.

		Potential prescribing cascades (includes probable, possible and uncertain)	Probable prescribing cascades	Possible prescribing cascades	Uncertain prescribing cascades	Remains prescribed at discharge	Indeterminate (sequence Drug A → Drug B unknown)	Prescribed in the sequence Drug B → Drug A
Combined Lists	Individual Patients Number (%)	152 (39.4%)	7 (1.8%)	63 (16.3%)	101 (26.2%)	110 (28.6%)	25 (6.5%)	80 (20.7%)
	No. Individual prescribing cascades	281	7	98	176	215	30	142
Doherty List	Individual Patients Number(%)	135 (35.1%)	2 (0.5%)	46 (11.9%)	95 (24.7%)	107 (27.8%)	15 (3.9%)	64 (16.6%)
	No. Individual prescribing cascades	210	2	61	147	159	17	85
Think Cascades list	Individual Patients Number(%)	75 (19.4%)	6 (1.5%)	39 (10.1%)	39 (10.1%)	46 (11.9%)	11 (2.9%)	46 (11.9%)
	No. Individual prescribing cascades	104	6	50	48	66	14	66

The four most common probable or possible prescribing cascades according to the Doherty list were:

- statin → drugs for urinary frequency and incontinence (n=17)
- dihydropyridine calcium channel blocker → loop diuretic (n=10)
- statin → antidepressant (n=10)
- selective serotonin reuptake inhibitor → drugs for urinary frequency and incontinence (or incontinence products) (n=10).

By comparison, the four most common probable or possible prescribing cascades according to the ThinkCascades list were:

- diuretic → overactive bladder medication (n=21)
- calcium channel blocker → diuretic (n=17)
- selective serotonin reuptake inhibitor/ serotonin-norepinephrine reuptake inhibitor → sleep agent (e.g., benzodiazepine, benzodiazepine receptor agonist, sedating anti-depressant, melatonin) (n=8)
- antipsychotic → antiparkinsonian agent (n=3).

The prevalence of each classification of prescribing cascade according to the ThinkCascade list and the Doherty list are displayed in **Table 2.4** and **Table 2.5** respectively.

Table 2.4: Prevalence of specific prescribing cascades according to the ThinkCascades list.

No.	Drug A	Suspected ADE	Drug B	Total (probable/ possible/ uncertain)	Probable cascade	Possible cascade	Uncertain cascade	Remains prescribed at discharge	Indeter- -minate cascade	Prescribed in the sequence Drug B → Drug A
1	Calcium channel blocker	Peripheral oedema	Diuretic	39	0	17	22	25	3	13
2	Diuretic	Urinary incontinence	OAB medication	30	4	17	9	19	2	16
3	Antipsychotic	extrapyramidal symptoms	Antiparkinsonian agent	3	1	2	0	3	0	2
4	Benzodiazepine	Cognitive impairment	Cholinesterase inhibitor or memantine	1	0	1	0	0	0	1
5	Benzodiazepine	Paradoxical agitation or agitation secondary to withdrawal	Antipsychotic	11	0	2	9	7	1	2
6	SSRI/ SNRI	Insomnia	Sleep agent (e.g., Benzodiazepine, Benzodiazepine receptor agonist, sedating anti-depressant, melatonin)	16	1	7	8	10	8	31

7	NSAID	Hypertension	Antihypertensive	2	0	2	0	1	0	1
8	Urinary Anticholinergics	Cognitive impairment	Cholinesterase inhibitor or memantine	2	0	2	0	1	0	0
9	Alpha-1 Receptor Blocker	Orthostatic hypotension, dizziness	Vestibular sedative (e.g., betahistine, Antihistamines, Benzodiazepines)	0	0	0	0	0	0	0
Total				104	6	50	48	66	14	66

Abbreviations: SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; NSAID: nonsteroidal anti-inflammatory drug; OAB: overactive bladder.

Table 2.5: Prevalence of specific prescribing cascades according to the Doherty list.

No.	Drug A	Suspected ADE	Drug B	Total (probable/ possible/ uncertain)	Probable cascade	Possible cascade	Uncertain cascade	Remains prescribed at discharge	Indeter- minate cascade	Prescribed in the sequence Drug B → Drug A
1	DH-CCB	Oedema	Loop diuretic	29	0	10	19	20	1	6
2	Amiodarone	Hypothyroidism	Thyroxine	2	1	1	0	2	0	1
3	Inhaled CS	Oral candidiasis	Topical antifungals	2	0	2	0	2	0	0
4	Neuroleptics/ Antipsychotics	Parkinsonian symptoms/ extrapyramidal symptoms	Anti- Parkinson's meds/ PD diagnosis	3	1	2	0	3	0	2
5	Acetylcholineste- rase inhibitors	Urinary incontinence	Drugs for urinary frequency and incontinence/ LUTS symptoms	3	0	2	1	2	0	4
6	Metoclopramide	Parkinsonian symptoms	Levodopa	0	0	0	0	0	0	0

7	ACEi	Cough	Antitussive	0	0	0	0	0	0	0
8	NSAID	GI symptoms	Anti-ulcer med	0	0	0	0	0	0	3
9	Ranitidine	Heart failure	Furosemide	0	0	0	0	0	0	0
10	Rosiglitazone	‘failure’	Furosemide	0	0	0	0	0	0	0
11	SGLT2	Genital infections	Antifungal	0	0	0	0	0	0	0
12	DOAC	Depression	Antidepressant	21	0	2	19	16	1	28
13	High ceiling diuretics (Loop diuretics)	Hypokalaemia	Potassium	0	0	0	0	0	0	0
14	Statins	LUTS	Drugs for urinary frequency and incontinence	59	0	17	42	40	9	11
15	Statins	Skin Soft tissue infection	Antibiotics- dicloxacillin/ Flucloxacillin	2	0	1	1	2	0	0
16	Statins	Depression	Antidepressant	70	0	10	60	60	5	21
17	Statins	Muscle cramps	Quinine	1	0	0	1	1	0	2
18	Brinzolamide	Heart failure	Furosemide	0	0	0	0	0	1	0

19	Latanoprost	Heart Failure	Furosemide	3	0	1	2	2	0	1
20	Carbamazepine	Hypothyroidism	Levothyroxine	1	0	1	0	1	0	1
21	Valproate	Hypothyroidism	Levothyroxine	1	0	1	0	1	0	0
22	Lithium	Drug induced tremor/ parkinsonism	Anti-Parkinson drug	0	0	0	0	0	0	0
23	Lithium	Hypothyroidism	Thyroxine	0	0	0	0	0	0	0
24	Benzodiazepine	Dementia	Anti-dementia drug	1	0	1	0	0	0	1
25	SSRI	Urinary incontinence	Drugs for urinary frequency and incontinence (or incontinence products)	12	0	10	2	7	0	4
Total				210	2	61	147	159	17	85

Abbreviations: DH-CCB: dihydropyridine calcium channel blocker; CS: corticosteroid; PD: Parkinson's disease; LUTS: lower urinary tract infections; ACEi: angiotensin-converting enzyme inhibitors; NSAID: nonsteroidal anti-inflammatory drug; GI: gastro-intestinal; SGLT2: sodium-glucose cotransporter-2; DOAC: direct oral anticoagulant; SSRI: selective serotonin reuptake inhibitor.

Potential prescribing cascades were more common in patients with hyperpolypharmacy (i.e. taking ≥ 10 daily long-term medications) compared to patients taking ≤ 9 daily medications (70.3% vs 37.3%, $p = <0.001$). In addition, patients exposed to potential cascades had higher mean Charlson Comorbidity Index (CCI) scores compared to patients not exposed to potential cascades (mean 6.13 [SD 2.06] vs 5.57 [SD 1.68]), $p = 0.006$). When comparing patients with a prescribing cascade categorised as ‘probable’ or ‘possible’ in combination to patients in the ‘uncertain’ cascades group, no significant differences were observed except for length of hospital stay (median: 7 days [IQR 3-13] vs 6 days [IQR 6.25-22], $p = 0.018$) (**Table 2.6**).

Hospital discharge prescriptions were reviewed to determine whether potential prescribing cascades identified at recruitment remained in patients’ regular ongoing prescriptions i.e. whether both Drug A and Drug B were still co-prescribed. Using both cascades lists in combination, 76.5% ($n=215$) of the identified potential prescribing cascades remained at discharge. In isolation, 75.7% ($n= 159$) of the Doherty list cascades and 63.4% ($n=66$) of the ThinkCascades cascades remained unchanged at discharge.

2.3.4 Inter-rater reliability

Inter-rater reliability for prescribing cascade detection and ADE classification was also evaluated to ensure acceptable reliability among the three researchers. Thirty-nine cases (10%) were selected at random for evaluation by the researchers. The intra-class correlation coefficient (ICC), a two-way mixed model, assessing for absolute agreement was calculated. For prescribing cascade classification, the ICC for the consistency of ratings was 0.935 (95% CI [0.884, 0.964]) and for consistency of

ratings of ADE classification, ICC was 0.896 (95% CI [0.813, 0.943]), indicating excellent inter-rater reliability for detection and classification of potential cascades and ADE's.

Table 2.6: Characteristics and univariate analysis of association according to cascade likelihood classification.

Variable		Probable & Possible Cascade (n=70 (46.1%))	Uncertain Cascade (n=82 (53.9%))	P value
Female (%)		34 (48.6)	45 (54.9)	0.438
Age (years), median (IQR)		80 (74- 84)	80 (76.75- 86)	0.238
Living arrangements pre-admission	Home, number of patients (%)	64 (91.4)	75 (91.5)	0.994
	Long-term care facility, number of patients (%)	6 (8.6)	7 (8.5)	
Charlson Comorbidity Index, median (IQR)		6 (5-8)	6 (5-7)	0.689
Number of daily medications, median (IQR)		12 (9-15)	11 (8-14)	0.267
Hyperpolypharmacy, number of patients (%)		52 (74.3)	55 (67.1)	0.332
Clinical Frailty Scale score, median (IQR)		5 (4-6)	5 (4-6)	0.342
Number of comorbidities, median (IQR)		7 (5-9)	8 (6-10)	0.829
Fall in last 12 months, number of patients (%)		38 (54.3)	39 (47.6)	0.408
Admitted in last 12 months, number of patients (%)		46 (65.7)	41 (50.0)	0.051
Admission service	Medical speciality, number of patients (%)	64 (91.4)	77 (93.9)	0.557
	Surgical speciality, number of patients (%)	6 (8.6)	5 (6.1)	
Length of hospital stay, days median (IQR)		7 (3-18)	6 (6.25- 22)	0.018
Survival Outcome (death), number of patients (%)		4 (5.7)	6 (7.3)	0.691
Discharge destination	Home, number of patients (%)	53 (80.3)	60 (78.9)	0.842
	Long-term care facility, number of patients (%)	13 (19.7)	16 (21.1)	

2.4 Discussion

This is the first prospective prevalence study of potential prescribing cascades in hospitalised older adults living with multimorbidity and polypharmacy. It demonstrates that prescribing cascades are substantially prevalent in this population to a clinically significant degree, particularly among those who experience hyperpolypharmacy. The analysis of drug pairs where Drug A was prescribed followed by Drug B compared to the reverse order suggests that the suspected prescribing cascades identified in this study are likely to be clinically valid. Although the more frequent prescribing in the sequence Drug A → Drug B does not definitively confirm the occurrence of prescribing cascades, it supports the hypothesis that the potential prescribing cascades identified in this study are more likely to represent true prescribing cascades. This is important, as true prescribing cascades can have serious adverse consequences for patient safety and healthcare outcomes [89].

In this study, prescribing cascades were associated with a higher number of prescribed medications, consistent with observed trends that increasing levels of polypharmacy and hyperpolypharmacy are associated with a greater risk of inappropriate prescribing [38,46,148].

While the management of patients with complex multimorbidity and associated polypharmacy has traditionally been the remit of general practitioners and geriatricians, the responsibility for medication management increasingly extends to all physicians dealing with older people in their own areas of clinical practice. In the present study, 84% (n=326) of the hospitalised patients were under the care of physicians who were not geriatricians i.e. specialists without specific training in age-

related multimorbidity and associated complex polypharmacy. Without sufficient training and experience in geriatric medicine, these physicians may struggle to recognise prescribing cascades, as was evident in the present study where very little curtailment of potential cascades was evident between admission and discharge, possibly related to lack of recognition of potential cascades. This challenge is compounded by the fact that ADEs in older adults with multimorbidity are more challenging to recognise and can often present with non-specific symptoms, such as new-onset confusion, gastrointestinal upset and dizziness [87,95,96].

A recent systematic review by Adrien et al. examined potential interventions for addressing prescribing cascades [82]. Fewer than half of the studies included in the review provided specific guidance on reversing inappropriate prescribing cascades. Among those that did, recommendations for dose reductions were often made without confirmation of a dose-dependent association, with most studies recommending the discontinuation of the index drug but not specifying an alternative medication. The persistence of potentially problematic drug combinations at hospital discharge identified in this study highlights the challenge physicians face in recognising and addressing prescribing cascades. It also points to the need for expert medication review at admission and particularly at discharge for older patients with multimorbidity and associated polypharmacy.

The identification and management of prescribing cascades are further complicated by the limitations of existing assessment tools. As discussed in Chapter 1, the ThinkCascades list contains a limited number of prescribing cascades and the Doherty List includes some clinically questionable prescribing cascades [79,86]. Nevertheless,

both lists were utilised as they represent the only published explicit prescribing cascades lists in the literature up to the initiation of the study and the use of the ThinkCascade list alone would likely significantly underestimate the true prevalence of prescribing cascades.

Most prescribing cascades in the present study were categorized as “possible” or “uncertain”. Accurate identification of the prevalence of probable or definite prescribing cascades using the criteria applied in this study is likely to be challenging, especially when used retrospectively. Categorisation of any clinical event as “probable” or “certain” in relation to multimorbid older patients requires rigorous assessment and therefore, as we have demonstrated, reliance on patient recall and physician or pharmacist documentation in patients’ medical records may not be sufficient. A prospective study design involving contemporaneous assessment of patients’ symptoms, as well as prescriber interviews, at the onset of possible prescribing cascades would be required for greater clarity. The feasibility of conducting such a labour-intensive study, likely with major recruitment challenges and resource implications, was beyond the scope of the present study.

A more comprehensive validated explicit list of clinically relevant prescribing cascades is likely required to enhance identification during routine medication review. In a recent commentary, O’Mahony and Rochon pointed out that the number of inappropriate prescribing cascades is potentially enormous, but that more clinically relevant and common cascades can be identified more readily using a systems-based structured explicit cascades list approach that can be applied readily in a manner that is more suitable for routine medication review [149]. Such a structured, systems-based

list of prescribing cascades could also be valuable as an educational tool in this important area of geriatric pharmacotherapy. Heightened awareness of potential cascades is likely to facilitate their prevention. Since the completion of the present study, a more comprehensive Delphi-validated explicit list of cascades, organized by physiological system, has been published [150]. It is likely that this larger list will help identify potentially inappropriate prescribing cascades more readily than the ThinkCascades tool or Doherty list.

2.4.1 Study limitations

This study has some limitations. First, the absence of a national electronic healthcare system in most public hospitals in Ireland, coupled with frequent transitions of care and missing medication initiation dates made reconstruction of the chronology of potential prescribing cascades challenging and at times wholly uncertain. This limited our ability to establish clear timelines between Drug A and Drug B initiation in some cases. However, there is no consensus in the literature on the appropriate timeframe for defining prescribing cascades, which can range from a short number of weeks to several years. The timeframe can also vary according to the onset of ADE symptoms, which may vary between medications, as well as the recognition of ADEs which may depend on the timing of patients' presentation to healthcare settings. For example, it may take many months to some years before antipsychotic medication leads to drug-induced parkinsonism leading to the addition of antiparkinsonian medication. In contrast, gastrointestinal upsets induced by acetylcholinesterase inhibitor therapy may lead to inappropriate proton pump inhibitor or antidiarrheal or antiemetic prescription within days. Second, as mentioned, patients' medical records in the Irish public hospital system are still predominantly paper-based, with no widespread integrated

electronic platform between community healthcare settings and hospital settings. This resulted in incomplete access to clinical data, particularly that relating to general practitioner assessments. Third, this study was conducted in a single hospital, which may limit the generalizability of the finding to other hospitals or healthcare settings. Finally, as this was an observational (i.e. non-interventional) study, we were unable to apply the definitive test for prescribing cascades i.e. observation for resolution of ADE symptoms by discontinuing Drug A.

2.5 Conclusion

This study, the first of its kind to report the prevalence of prescribing cascades in older people living with multimorbidity and polypharmacy in the acute hospital setting, indicates that potentially inappropriate prescribing cascades are both highly prevalent and poorly recognised in hospitalized older adults in Ireland. Explicit prescribing cascade lists can facilitate prescribers and medication reviewers with identification and intervention towards curtailment of this under-reported element of inappropriate prescribing in older people. In the next chapter, I will examine factors influencing clinicians' recognition of prescribing cascades in the hospital setting.

CHAPTER THREE

Factors Influencing Hospital Physicians' Recognition of Prescribing Cascades: A Qualitative Interview Study

3.1 Introduction

Interventions to reduce inappropriate prescribing cascades should be a priority for all healthcare providers, especially those caring for older people experiencing multimorbidity and associated polypharmacy. In Chapter 2, *potential* prescribing cascades were identified in 39.4% of patients, with the majority persisting in patients' discharge prescriptions, although just 1.8% had probable cascades and 16.3% had possible cascades. These findings suggest that prescribing cascades are under-recognised by clinicians and that opportunities to appropriately manage them are missed.

A qualitative study was identified as the next step to investigate the factors (facilitators and barriers) influencing recognition and curtailment of prescribing cascades during hospital admission. Understanding the behavioural determinants underpinning recognition of prescribing cascades is required to inform future, evidence-based interventions. The Theoretical Domains Framework (TDF), a validated theory-informed framework often used in qualitative research, allows an effective method for exploring facilitators and barriers [151]. The TDF has been extensively used to guide data collection on factors influencing prescribing behaviours in various healthcare settings, including qualitative research on prescribing cascades [152]. It provides a valuable framework for systematically identifying barriers and facilitators, which can then be targeted in behaviour change interventions to improve clinical practice.

As outlined in Chapter 1, no study of prescribing cascades to date has focused specifically on hospital physicians. We identified this as an important gap, as

hospitalisation presents a unique and underutilised opportunity for medication reviews and recognition of prescribing cascades.

Therefore, the aim of this study was to apply the TDF to identify the key behavioural factors influencing hospital physicians' recognition of prescribing cascades, including an evaluation of their knowledge and understanding of this aspect of inappropriate prescribing.

3.2 Methods

3.2.1 Study approval and reporting

Ethical approval for this study was granted by the Social Research Ethics Committee, University College Cork (Reference: 2024-048). Study reporting was guided by the COREQ checklist for reporting qualitative research findings (**Appendix 2**).

3.2.2 Study design, setting, and recruitment

Semi-structured interviews were undertaken as the preferred method of data collection because they are well suited to generating detailed, nuanced descriptions of participants' experiences and perspectives, especially with an under-researched phenomenon [153].

One-to-one semi-structured interviews were conducted with hospital physicians working in a large university teaching hospital in Ireland. At the time of the interviews, all physicians had active and ongoing clinical responsibility for patients admitted either electively or non-electively through the hospital emergency department.

The hospital medical records were primarily paper-based, including patients' prescribed medication lists, which were recorded both in ward-based Kardex® prescription sheets and in discharge reports.

To obtain a range of physicians' perspectives, a sampling matrix was used to ensure that the interviews were conducted with at least three participants from each grade of non-consultant physician (intern [house officer], senior house officer [SHO or junior resident], registrar/specialist registrar [SpR or senior resident], and consultant or senior attending physician) and that at least one male and at least one female were represented within each grade. This reflects the highly organised social context and well-established hierarchical structure of clinical medicine within the Irish public hospital system [154]. In addition, previous research suggests that prescribing practices differ between grades of physician and that junior doctors often defer complex prescribing decisions to senior colleagues [155,156]. While prescribing patterns do not differ significantly according to physician sex, it can influence patient interactions and outcomes and was therefore included in the sampling matrix [99,157]. The inclusion criteria required that participants were registered with the Irish Medical Council and working in a recognised medical specialty in the university teaching hospital at the time of the interview. Doctors working at any grade in a surgical specialty, psychiatry, paediatrics, or obstetrics/gynaecology were not included in the study, as comprehensive medication review involving larger medication lists is less of a routine task in their usual care delivery. Physicians were also excluded from the study if they worked in geriatric medicine at consultant or SpR grade, or if they held an additional degree in pharmacy. Participants were recruited via convenience and snowball sampling. Potential participants were identified through the professional

network of the research team and were invited to participate via email, which included an information sheet and consent form.

3.2.3 Application of the TDF

The TDF provides an accessible and structured means of identifying factors that impact practice across a comprehensive range of potential behavioural determinants [152]. Compared to conducting qualitative research without theory-based approaches, using the TDF allows the generation of a broader range of responses, partially due to its ability to mitigate against cognitive bias [158,159].

In the context of the present study, the recognition of prescribing cascades was conceptualised as a behaviour. To acquire a thorough understanding of the facilitators and barriers influencing this behaviour, the development of the topic guide was informed by the 14 TDF domains and their constructs, and these domains were used as pre-determined codes during directed content analysis.

3.2.4 Data collection

Immediately prior to their interviews, participants completed a short questionnaire collecting demographic information (gender, grade, years of post-qualification experience, specialty, university in which their medical degree was obtained, and whether they received any prior education on prescribing cascades, either formally or informally) and whether they recalled having ever identified a prescribing cascade or witnessed a colleague recognise one. A topic guide was developed based on reviewing the relevant literature [92,98,160], by application of the TDF version 2 [161], and drawing from the research group's knowledge of prescribing cascades. At least one question was included for each of the 14 TDF domains. The topic guide (**Appendix 3**) aimed to elicit factors affecting recognition of prescribing cascades based on

interviewees' knowledge and experience, as well as barriers to and recommendations for improving the recognition of prescribing cascades. The topic guide was pilot tested with one physician not affiliated with the research team; this interview was not included in the data analysis (as planned *a priori*).

All interviews were conducted by the principal investigator of this study, Dr Ruth Daunt (RD). All interviews were conducted in person in a private room within the hospital between May and July 2024. All participants provided written consent prior to interview and verbal consent immediately prior to the interview. Field notes were recorded by the interviewer after each interview. All interviews were audio-recorded and transcribed *verbatim*, with transcripts subsequently deidentified.

It was decided *a priori* that interviews would continue until there were at least two additional interviews in which no new major themes appeared, as this would help ensure that the topic has been adequately explored [162].

3.2.5 Data analysis

NVivo® software version 14 was used to facilitate analysis. Data were analysed in four phases. In the first phase, transcripts were read and re-read to ensure familiarity. In the second phase, the principal investigator conducted conventional content analysis, which involved open coding to create non-hierarchical codes that were then grouped into initial themes [163]. The third phase involved directed content analysis, using constructs and domains from the TDF as predetermined codes [163]. To enhance the reliability of coding, a second researcher (Dr Kieran Dalton (KD), pharmacist) independently identified themes and TDF domains across all transcripts. Factors considered when identifying predominant TDF domains included the frequency of beliefs, the presence of conflicting beliefs, and the strength of beliefs expressed [164].

Finally, in the fourth phase, themes identified through conventional coding were categorised under the TDF domains that best reflected the themes and their associated codes [151].

3.2.6 Reflexivity

Research team background and professional experience

Reflexivity, defined as the active, ongoing process of critically examining how a researcher's own subjectivities, biases, and positionality influence the research process and outcomes, was an important element of the present study [165]. The research team included a research physician with specialist training in geriatric medicine (RD), a senior academic pharmacist with experience in qualitative methods (KD), and two consultant geriatricians (Prof. Denis O'Mahony (DOM) and Dr Denis Curtin (DC)). Three of the interviewees had previously worked clinically with RD. All participants were aware that DOM and DC were consultant colleagues working in the same hospital. KD had no contact with study participants. Acknowledging the influence of the research team's background on the study design and methods, the following steps were taken to leverage the advantages of the team's background and mitigate biases [166].

Topic guide development

The topic guide was developed using the research team's experience in prescribing cascades, alongside the TDF and review of relevant literature. This approach had the advantage of creating a well-rounded guide based on current evidence and suited to the clinical context of the study.

Insider positionality

As a physician with higher specialist training in geriatric medicine, RD recognised her '*insider position*' and was aware of the need to set aside her own perspectives and retain a neutral position when interviewing physician colleagues as a researcher [167,168]. Potential study participants were aware that RD had specialist training in geriatric medicine; this knowledge was beneficial in accessing potential participants within the hospital. Creating a pre-planned sampling matrix ensured diversity in participant characteristics, thus minimising the risk of selecting participants with potentially similar perspectives. During the interviews, the insider position meant that RD had the advantage of a shared clinical language and contextual understanding, facilitating rapport and easing the flow of interviews. One potential challenge of a shared language is the so-called '*deadening effect*', where shared understanding is assumed and participants do not elaborate on their own individual views [169]. To overcome this, RD encouraged participants to elaborate and clarify their answers where needed.

Data interpretation

It is almost inevitable that the researchers' own professional background will influence data interpretation, with views most congruent with the team's own most easily received [165]. Consequently, RD debriefed the team regularly throughout the analytical process to maintain openness and critical reflection within the research team. Prior to finalising the TDF codes, RD and KD met to discuss the data findings and code development.

3.3 Results

3.3.1 Participant Characteristics

Fifteen potential hospital physician participants were contacted, of whom 14 were interviewed. These physicians had varying levels of training and experience aligned with the sampling matrix (**Table 3.1**). One physician agreed to participate but was unable to schedule an interview within the study timeframe due to other commitments. Seven participants were male and seven were female, with a mean of 6 years' postgraduate experience (range: 10 months to 23 years). The mean interview duration was 18 minutes (range: 14-35 minutes). At the time of the interviews, participants were practising in the following specialties: respiratory medicine ($n=4$), rheumatology ($n=3$), acute internal medicine ($n=2$), and one each in cardiology, geriatric medicine (below SpR grade), endocrinology, stroke medicine, and infectious diseases.

Table 3.1: Sampling matrix details of physician participants.

Physician Characteristic	Number of interviewees	Minimum number required as part of sampling strategy
Gender		
Male	7	4
Female	7	4
Grade		
Intern/House officer ^a	4	3
Senior House Officer ^b	3	3
Registrar/Specialist Registrar ^c	4	3
Consultant	3	3

a <1 year post-qualification experience

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

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

All 14 TDF domains were identified in the transcripts, with corresponding quotations shown in **Table 3.2**, noting that some quotations are aligned to more than one TDF domain. All TDF domains are presented below, whereby the first four were identified as predominant in influencing hospital physicians' recognition of prescribing cascades: environmental context and resources, knowledge, skills, and social/professional role and identity.

3.3.2 TDF Domains

(i) Environmental context and resources

(a) Lack of access to up-to-date medications

Interviewees highlighted difficulties accessing up-to-date lists of patients' medications, as well as information relating to indications for medications, initiation dates, and intended duration, as significant barriers to recognising prescribing cascades. This challenge was particularly evident in the emergency department outside routine working hours, when it is often impossible to access patients' full medical records or communicate with community healthcare providers.

(b) Staffing

Perceived chronic staff shortages, among both medical and pharmacy teams, contribute negatively to the recognition of prescribing cascades because they reduce the time available for comprehensive medication reviews.

(c) Excessive workload

Many participants identified excessive workload, specifically the responsibility for reviewing large numbers of patients within a limited daily timeframe as a key factor limiting their ability to devote time to recognising prescribing cascades. Time

constraints leading to “*fast-paced*” ward rounds limit the opportunity for thorough medication reviews.

(d) Information technology

Participants highlighted deficiencies in healthcare information technology (IT), including inadequate infrastructure and limited online resources. Ireland’s predominantly paper-based medical records system was seen as a significant hindrance, with participants expressing a desire for electronic records systems capable of providing alerts for potential prescribing cascades.

Online resources, such as the Summary of Product Characteristics, were commonly cited as resources used to check drug side effects. Access to other resources, such as the online British National Formulary (BNF), was inconsistent and challenging for some participants. Some interviewees proposed ideas for enhancing IT resources, including the development of smartphone applications for healthcare professionals to check for common prescribing cascades and for patients as a method for maintaining up-to-date medication records.

(ii) Knowledge

(a) Recognising the term ‘prescribing cascade’ and its conceptual understanding

Familiarity with the term ‘prescribing cascade’ varied across professional grade. Consultant physicians generally seemed unfamiliar with the term; however, they identified with the concept once provided with the definition. In contrast, all interns were able to define the term ‘prescribing cascades’ but admitted limited knowledge about specific prescribing cascades. During the interviews, some participants had difficulties explaining precisely what a prescribing cascade entailed and mistakenly described them as drug-drug interactions and non-specific prescribing errors.

(b) Knowing examples of prescribing cascades

When asked, most participants had difficulty providing examples of specific prescribing cascades. When examples were provided, they were mostly ‘appropriate’ prescribing cascades (e.g. anti-emetic for nausea caused by an antibiotic) with very few examples of inappropriate prescribing cascades provided (e.g. anti-tussive for cough caused by an angiotensin-converting enzyme [ACE] inhibitor).

(c) Education and training deficiencies

All participants reported limited education on prescribing cascades. Few recalled undergraduate teaching on the topic, and none had received formal postgraduate teaching on cascades. Interviewees emphasised the need for targeted education, particularly for the most junior physicians (e.g. interns and SHOs), to improve recognition of prescribing cascades in clinical settings.

(iii) Skills

(a) Experiential learning

Several participants noted that most of their knowledge about prescribing and deprescribing – including prescribing cascades – developed informally during postgraduate training, often through experiential learning while working with geriatric medicine consultants.

(b) Improvement with training

Participants reported that their ability to recognise prescribing cascades improved with experience. Intern physicians, in particular, reported challenges with recognising cascades due to limited exposure. Participants suggested that case-based learning and early-career training (during intern/SHO years) could enhance skills.

(iv) Social/professional role and identity

(a) Physicians' responsibility in prescribing cascade recognition

All interviewees stated that recognising prescribing cascades is primarily the responsibility of the prescriber, with ultimate accountability resting with the most senior attending physicians in the hospital system i.e. consultants. Some junior physicians felt less responsible, as they reported prescribing most medications under the direction of more senior colleagues. This perspective contrasted with that of senior physicians, who noted that junior physicians can sometimes prescribe without complete understanding of the clinical context, increasing the risk of prescribing cascades.

(b) Pharmacists' roles

Pharmacists were identified as crucial for recognising prescribing cascades through routinely performing an accurate medication reconciliation and review, identifying side effects, and highlighting potentially inappropriate medications to the attending physicians. Some participants also suggested that a combined pharmacist-physician ward round would be an effective method to monitor and review patients' medications for potential prescribing cascades.

(c) Specialty role

Geriatricians were frequently mentioned for their expertise in deprescribing inappropriate medications and greater capacity to recognise prescribing cascades. Some participants indicated that they were more confident recognising prescribing cascades within their own specialty.

(v) Social Influences

(a) Hierarchy and modelling within medical teams

Junior physicians, particularly interns and SHOs, described hesitancy with discussing medications with senior colleagues, influenced by relationships and team culture. They also reported that they tended to imitate the prescribing and deprescribing practices of their senior colleagues and would hesitate to question their prescribing decisions. In contrast, consultants indicated that they welcomed junior physician input on patients' medications e.g. if they were to highlight potential adverse effects and/or potential prescribing cascades.

(b) Support from patients

Participants expressed mixed views on patients' roles in supporting physicians to recognise prescribing cascades. Some expected patients to maintain an accurate medication list and to report any suspected adverse symptoms to their doctor, while others perceived that it was "*unfair*" to expect patients to do this, particularly older adults and those with limited knowledge about their medications.

(c) Support from other healthcare professionals

Many interviewees emphasised the possibly beneficial supportive role of other healthcare professionals (i.e. other than pharmacists) in recognising prescribing cascades, including nurses, occupational therapists, and physiotherapists. Nursing staff, in particular, were noted to be well positioned to identify adverse effects following medication changes. One participant commented that all healthcare professionals should be "*empowered*" to speak up regarding any medication-related concerns, which could help prescribing cascade recognition.

(d) Reluctance to change medications prescribed by others

Participants reported reluctance to discontinue medications initiated by other physicians, particularly when the physician had expertise in the relevant area, even when they suspected a prescribing cascade had occurred.

(vi) Goals

Interviewees reported that the focus during hospital admissions tends to be primarily on the treatment of presenting acute problems rather than reviewing longstanding medications which may be contributing to prescribing cascades. Even when a patient presents with a new symptom or change of clinical status, the goal is usually to address the acute problem by prescribing symptom-relieving medication rather than a more comprehensive medication review of all drugs taken by patients that might help to identify potential side-effects.

(vii) Memory, Attention and Decision Processes

Interviewees noted challenges with distinguishing between side-effects and new medical conditions, highlighting that a “*fresh set of eyes*” can help to identify side-effects and potential prescribing cascades.

Participants noted that the focus in the acute hospitalisation context is primarily on the acute problem that led to admission. Therefore, less attention is given to reviewing medications (especially long-term medications), limiting the opportunity to recognise pre-existing prescribing cascades.

(viii) Beliefs about Consequences

(a) Prescribing cascades leading to patient harm

Participants commented on the potential for harm associated with unrecognised prescribing cascades (polypharmacy, pill burden, increased hospitalisation). However,

some participants appeared to downplay the consequences, viewing certain prescribing cascades as “*benign*”, and had an acceptance that side-effects and associated prescribing mistakes happen frequently.

(b) Personal impact on physicians and patient disclosure

Interviewees perceived few personal consequences for failing to recognise prescribing cascades. Some indicated they would only inform the patient if severe adverse effects arising from prescribing cascades occurred.

(ix) Beliefs about capabilities

Junior physicians, particularly interns/SHOs, expressed low confidence in recognising prescribing cascades, despite familiarity with the term. In contrast, other participants, particularly consultants, expressed confidence in recognising prescribing cascades even if they were not familiar with the term prior to the interview.

(x) Intentions

When new symptoms appear, hospital physicians’ primary motivations are centred on symptom management, and were not actively inclined to identify potential prescribing cascades i.e. to search for cascades proactively.

(xi) Emotion

Some participants highlighted that they would avoid asking questions of senior colleagues regarding potential prescribing cascades for fear of appearing “*silly*” or “*unintelligent*”.

In the theoretical setting of recognising that they had caused an inappropriate prescribing cascade, some participants described that they would feel “*horrible*”, whereas others described that they would feel “*okay*” about this.

(xii) Behavioural regulation

Participants expressed a desire for external mechanisms, either through feedback from colleagues or from alert systems, to learn from prescribing errors and recognise prescribing cascades more easily in the future.

(xiii) Optimism

Some participants seemed less concerned about the consequences of prescribing cascades, describing them as “*benign*” consequences.

Additionally, participants were generally pessimistic regarding the frequency of inappropriate prescribing cascade recognition, stating that “*most are not recognised*” and opportunities to recognise prescribing cascades are frequently missed.

(xiv) Reinforcement

One interviewee noted that the rapport they developed with patients reinforced their response to patients reporting side effects (e.g. they were less likely to recognise if lower rapport or high level of complaints in general).

Some participants suggested that junior doctors could be incentivised to report errors related to suspected prescribing cascades, by framing it as a learning opportunity and reassuring them that reporting would not result in punitive consequences.

Table 3.2: Illustrative quotations.

Descriptor	Quotations
Environmental context and resources	
Lack of access to up-to-date medications	<i>“...if everybody just starts writing what this medication is indicated for and we kept it in the patient's medical records, that would be really helpful.” [SHO 1]</i> <i>“...you don't know what medications they're on...significant problem with then trying to manage their medication when they come in, because maybe you have a prescribing cascade that happens because they're on something you just don't realize they are on...” [Consultant 3]</i> <i>“...often, we don't know what drugs patients are on... if they come into the emergency department, you don't know what they're on, so you might start instigating some treatment, for example... you might start a diuretic but unbeknownst to you they're actually on a calcium channel blocker that was started by the GP a couple of weeks ago.” [Consultant 2]</i> <i>“If [patients] write down their medications and the dates of things were changed... can be helpful because we don't have a unified prescribing log between GPs and pharmacies and hospitals...” [SHO 2]</i>

Staffing	<i>“...they [patients] come in and they're not sure what medications they are on and they don't have a list... you're looking at their last list... hoping this is right.” [Registrar 4]</i> <i>“...in general, when patients are in hospital, (they) don't tend to know what they're on...” [Intern 1]</i> <i>“Like the hospital's understaffed simple as. I think if we have more staff, more time to think about things, we are more likely to identify [prescribing cascades].” [Intern 1]</i> <i>“...there's lack of staff members in the hospital because if we have more staff, we will reduce clinical workload and then hospital doctors can spend the time looking through the Kardex® and making decisions...” [SHO 1]</i>
Excessive workload	<i>“...with a busy inpatient list, you're running around the ward, you're often dealing with one or two key aspects of the patient care... we do try and look at the Kardex® each time ... you have to try and keep it all in your head, where you remember the background medical history of the patient, what drugs they're on... sometimes, I think due to time constraints, you don't realise that maybe the side effect of the drug is contributing to the symptom that you're now looking at...” [Consultant 2]</i> <i>“...we just couldn't find a time to dedicate ourselves to work on that [identifying prescribing cascades] on top of our already massive clinical workload.” [SHO 3]</i> <i>“...a busy inpatient service... ideally it would be great to have a proper sit down with every patients' Kardex ® to go through the medications. But the reality is, if you have 30 odd patients on an inpatient list, and you have to see all of them every day, you might overlook some of the Kardex's®...” [Registrar 2]</i>

Information technology	<i>“The number one barrier that jumps out to me would be time pressure... the speed at which ward rounds happen...” [SHO 3]</i> <i>“In an ideal world, if we were doing electronic prescribing, you could probably have something say, ‘is this medication warranted?’ or ‘what is your reason for starting it?’” [Registrar 1]</i> <i>“We're living in a very archaic system that doesn't help with flagging when prescribing cascade might be happening... a simple intervention would be having an electronic health record prescribing system, but it's a very complex intervention to put in place unfortunately.” [Consultant 3]</i> <i>“I would just type in the name of the medication and look at the SPC and then look at the information of what side effects are common. On the computers in the hospital, they have medicines.ie, I can get information on it as well.” [Intern 3]</i> <i>“I know that there's new ways to access it [the BNF], but it's always, in the last few years, been tricky.” [Consultant 1]</i> <i>“...if you had an app-based system where you have common prescribing cascades, for example, you click in opiates and then common co-prescribers, and then you could have a list of inappropriate common prescribing cascades.” [Consultant 2]</i> <i>“I think it'd be brilliant if everyone [patients] had...an app or something that would have their medications on it, so that ... if they had swelling in their legs, you'd know they were on amlodipine or...” [Registrar 4]</i>
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Knowledge	
Recognising the term 'prescribing cascades' and its conceptual understanding	<i>"I didn't know what they [prescribing cascades] were before coming here today. And I certainly don't think a lot of the doctors in training would be familiar with the concept". [Consultant 2]</i> <i>"I think people would recognise what happened ... the laxative for constipation in the opioid patient ... but they wouldn't group it together as 'oh look at this interesting prescribing cascade'..." [Consultant 1]</i> <i>"People are paralysed by lack of knowledge in regard to deprescribing, so they do nothing..." [Consultant 3]</i> <i>"...oftentimes opioids can have side effects ... nausea and then people need an anti-emetic to manage that ... it's not something I've thought about much..." [Intern 3]</i>
Knowing examples of prescribing cascades	<i>"... ACE inhibitor →cough, opioid → constipation → laxative. Antihypertensive and then hypotension and then, I don't know adding in something to raise the heart rate or something...uh, inotrope, or vasopressor...other barriers, just not being aware of them... I only know the ones I mentioned and that's not very many." [Intern 4]</i> <i>"...if somebody is on a PPI like lansoprazole, and they get put on clopidogrel, or they are on omeprazole and get put onto clopidogrel and then you have to change the omeprazole to something else." [Registrar 1]</i> <i>"So I'm trying to come up with examples, but I keep thinking of contraindications as opposed to prescribing cascades..." [Registrar 2]</i>

Education and training deficiencies	<i>"I don't really remember being taught anything about it in college or ... BST teaching [formal post-graduation teaching for SHOs] or anything..." [SHO 2]</i> <i>"I think it's very important to have like the foundation level of education as an undergraduate, but also have constant reminders post-grad..." [Registrar 2]</i> <i>"...general education about 'the most common inappropriate prescribing cascades', 'can you screen for them'." [Consultant 1]</i> <i>"... a medication alert system ... just to highlight that these were the inappropriate prescribing errors that have occurred... builds your awareness of it... always comes back to education, education, re-education and reminders..." [Consultant 2]</i>
Skills	
Experiential learning	<i>"...at an intern level, just a lack of experience and the lack of seeing these patterns from before and... anticipating these treatments." [Consultant 3]</i> <i>"I think as time goes on, maybe when you become a reg ... you try and to take more of that in perspective and look at people's Kardex® before they go home and see do they need to be on everything." [Registrar 4]</i>

Improvement with training	<i>“In medical school, it's a bit theoretical at that point... if we had a prescribing safety course in... your first year as an intern... where you could refresh things and... talk about common drugs and common errors, that might be a bit more practical at that point. ...and as an SHO as well.” [Registrar 4]</i> <i>“You can start by training the young doctors, so when they become consultants to keep that in mind.” [SHO 1]</i>
Social/Professional Role and Identity	
Physicians' responsibility in prescribing cascade recognition	<i>“It's probably everyone's responsibility to recognise prescribing cascades to the best of their ability...senior staff would probably be much more used to it and probably better at it in general” [SHO 3]</i> <i>“...the medical team ... the buck stops with them ... you're the one prescribing, you're the one reviewing prescriptions on a regular basis...” [Consultant 1]</i> <i>“...the more junior, the less likely that they would be to pick it up and [more likely] to kind of give something a little bit more 'blindly'.” [Registrar 1]</i> <i>“Being an intern, I'm not the one deciding to start the new medication, it'd be someone more senior on my team saying, 'start this medication for this patient' ...” [Intern 3]</i> <i>“...if we really want to solve this problem... having a specific team that review medication would be good, without interfering with the normaL ward jobs...” [SHO 1]</i>

Pharmacists' role	<i>"People tend to 'pass the buck' to someone else when it comes to deprescribing, especially if unsure why someone is on a medication, don't know who started it, don't know when it was started, don't know why it was started – in all that uncertainty some people just pass the buck."</i> [Consultant 3] <i>"In my own experience, the pharmacist has been my primary source of flagging 'this medication is inappropriate', 'this adverse effect might be due to a medication'..."</i> [SHO 1] <i>"...if there was if a prescribing cascade or unwanted side effects from medications, more often than not the pharmacists... flag them to us."</i> [Registrar 2] <i>"...if there was (a) joint ward round with the pharmacist ...(and) consultants... where you sit down and go through the medications and things like that, that might be more of a structured way..."</i> [SHO 2]
Specialty role	<i>"In my previous rotation, my consultant was really good at reviewing patients' Kardex®, but partly because he was the consultant geriatrician..."</i> [SHO 1] <i>"I previously worked in geriatrics ... [the consultant] was really big on stopping the extra medication."</i> [SHO 2] <i>"... what we see a lot is people come into hospital, with respiratory exacerbations, they're put on antibiotics, they're put on steroids... you can often end up with people who develop peripheral oedema. They end up developing volume overload... then you're into your prescribing cascade of giving them furosemide. Now they're hypokalaemic so you're giving them potassium ... that's a prescribing cascade that we'd see frequently and recognise very, very quickly ..."</i> [Consultant 3]

Social Influences

Hierarchy and
modelling within
medical teams

“... our consultants change every two weeks, if I don't know a consultant, I'm less likely to speak up. Whereas there are some consultants... I know them more... so I'd be more comfortable speaking up.” [Intern 4]

“...it depends on the team structure and how comfortable they feel in asking for help or asking for advice or, you know, I suppose even having things explained to them...” [Consultant 3]

“...you wouldn't want to challenge... someone more senior that has like prescribed... the team I'm working with at the moment, I would be very happy... to bring it up with someone. But I can't say that for every team that I've been on...it's difficult to challenge someone more senior... if you did feel that you were really challenging them... then you might not be as inclined.”
[Intern 2]

“... we all admire the SHO and intern who do speak up... I think we want people to be challenging us. And we want we want the status quo to be challenged all the time...Empower the nurses, empower the pharmacists, empower every level of doctor to do the same thing [speak up about medication concerns].” [Consultant 1]

“I think everyone has their preferences for the drugs they prescribe... if you're with a consultant who tends to prescribe a certain thing... you kind of copy that.” [SHO 2]

Support from patients

“The patients themselves can also say ‘I'm not feeling well since this has started. These are my symptoms’...” [Intern 3]

Support from other healthcare professionals	<i>“Patients need to take responsibility for... their own healthcare management. I think it is their responsibility to have an up-to-date medication list that they bring to each clinical appointment and... to the hospital. They also probably need to take a role in the prompt recognition of change to their prescription and the prompt delivery of that prescription to their GP practice or their pharmacy...”</i> [Consultant 2] <i>“...it’s unfair to ask them [patients] to read up on medications... that’s not their job, that’s not what they’re trained for...”</i> [Registrar 2] <i>“We should be empowering them to challenge us on all of these things... by giving them prompts, between printed prompts and things like that saying, ‘it would be in your best interest to prompt the doctors with these questions every time you see them’...”</i> [Consultant 1] <i>“...any senior clinician... any pharmacists... and any senior nursing staff should have a role in that [recognising prescribing cascades] it’s the whole MDT.”</i> [Consultant 3] <i>“...nurses... they’re exquisitely positioned to do it [recognise medication side effects/ prescribing cascades] because they’re giving the medicine to the patient... they have a huge amount of experience ... it’s more opportunistic... Although I understand that they might have less formal training in it, but they might have excellent experience... and we shouldn’t discount their experience...”</i> [Consultant 1]
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Reluctance to change medications prescribed by others	<i>"I think people are probably quite speciality focussed. And while I would be comfortable changing someone's diabetes medication and things like that, and I mightn't necessarily be comfortable..., you'd write to the rheumatologist and say, 'does this person need to be on steroids?' ... but I wouldn't necessarily stop if it's been prescribed by another specialist." [Registrar 4]</i>
Goals	
Focus tends to be on treating the acute issue and often a 'quick fix'	<i>"...as a hospital doctor reviewing inpatients... we often just focus on the primary issue and try to get the patient out of hospital as soon as possible. We don't often go and review the medication, although I believe a lot of patients probably have polypharmacy issues that are caused by prescribing cascades." [SHO 1]</i> <i>"We're always quick to start someone on a medication and less quick to look at a medication we start and go 'is that maybe causing that?' ... we need to be looking more at deprescribing as opposed to increasing the number of drugs..." [Intern 1]</i> <i>"...it sounds really bad, that we don't care. We, people would rather have a quick fix 'oh their overloaded give them diuretics' than going back and reviewing the medications if there's any reason for them having this rather than just fixing it easily..." [Registrar 3]</i>
Memory, attention and decision processes	
A 'fresh set of eyes' can help identify potential errors	<i>"...on call [doctors] would review them [patients] and question things and a fresh set of eyes is good... sometimes reviewing the Kardex® yourself as the reg [registrar] on the ward every second day that someone has not been prescribed something completely off the charts..." [Registrar 3]</i>

Less attention given to medication reviews	<i>"I don't even think it would cross my mind [prescribing cascades] ... "</i> [Intern 4] <i>"...if people have been put on medications, they [doctors] don't always wonder if they still need to be on them. Sometimes they just add rather than actually review... people are thinking more of the acute issue at hand rather than the long-term things..."</i> [Registrar 4]
Beliefs about Consequences	
Prescribing cascades leading to patient harm	<i>"...the risk of harm to the patient... that'd be readily avoidable if we had recognised it... longer length of stay, patient harm... more investigations, more anxiety for the patient..."</i> [Consultant 2] <i>"I think both short term and long term quite significant effects to it [prescribing cascades], maybe less so short term if it's something where it's just the symptom that you're trying to get under control... but you're not thinking about the long-term outcomes."</i> [Intern 1] <i>"...polypharmacy, more interactions, longer patient stay... confusion... probably leading to frustration amongst families and the patients and most GPs if things aren't made clear."</i> [Registrar 1]
Personal impact on physicians and patient disclosure	<i>"I'd probably wonder if I need to tell the patient [about a prescribing cascade] if I'm not 100% certain myself. I would do my best to prevent or stop this happening in future... I wouldn't be a 100% certain if I would... inform the patient exactly that this happened."</i> [SHO 3]

	<i>“Open disclosure is very important. It's key to making sure that patients feel safe... patients prefer open disclosure rather than finding out down the line... it's sometimes just as easy to be honest with the patient... ‘I made this mistake, now we've fixed it, and it's something that we can, you know, continue to improve upon’...” [Registrar 3]</i>
Beliefs about capabilities	
Confidence in capability to recognise prescribing cascades	<i>“I'd say that it has become maybe a bit more prominent, just as I have become more experienced. Maybe in my entire intern year, I would have been happy knowing what the drug was and knowing what a drug did... I probably wouldn't have known much else about a particular drug other than the more obvious side effects, but in terms of recognising a drug that might cause a certain side effect and then recognising the negative cascade, I would not have been able to do that in the intern year and maybe only slightly picking it up at this stage.” [SHO 3]</i> <i>“I don't know if I would be very confident about, for some obviously, the obvious ones that you hear about, but maybe other stuff I wouldn't really know. And then, I suppose, recognising... I'm not sure...” [Intern 2]</i> <i>“It's something intuitively that we see all the time, well recognised.” [Consultant 3]</i> <i>“I think people would recognise what happened [a prescribing cascade] ... but they wouldn't group it together as ‘oh look at this interesting prescribing cascade’...” [Consultant 1]</i>

Intentions	
Motivations are centred on symptom management	“[Prescribing cascades are] <i>probably not recognised enough... a lot of time on ward rounds, there's a reflex just to treat rather than to think...</i>” [Consultant 3] “...that's [prescribing cascades] <i>not something I would have consciously been thinking of, we look at their medication list and pharmacy would do their med rec [reconciliation]...but prescribing cascades isn't something I've actively been looking for...</i>” [Intern 3] “<i>On call I don't even think it [prescribing cascade] would cross my mind. I'd never change a medication on call. I'd maybe write it in the notes and say for team to review. But I'd never change it myself.</i>” [Intern 4]
Emotion	
Fear of asking questions Emotions after a mistake	“... <i>it's probably a knowledge and experience piece... but scared perhaps to ask questions.</i>” [Registrar 4] “<i>I know other staff members would have a fear of bringing up a question that they'd have and they would just choose not to bring it up... for fear of looking silly or inappropriate or unintelligent and fear of that being known...</i>” [SHO 3] “<i>If I was the one that made the mistake, I would feel terrible.</i>” [SHO 1] “<i>I'd feel reasonably okay if it was the first experience of it, making sure I actually made an effort to learn from it and not make the same mistake again.</i>” [SHO 3]

Behavioural regulation	
Desire to learn from errors	<i>“...if I didn’t recognise it, then I won’t recognise the next time if it hasn’t been pointed out, you know that sort of way. So that’s just like, uh, not learning from it then...”</i> [Intern 2] <i>“...in previous institutions where I’ve worked there used to be a medication alert system that went around maybe once a month, just to highlight that these were the inappropriate prescribing errors that have occurred... builds your awareness of it...”</i> [Consultant 2]
Optimism	
Potentially ‘benign’ consequences of prescribing cascades	<i>“Usually they would be benign [consequences of prescribing cascades] ...”</i> [Registrar 1] <i>“...we probably miss opportunities in clinic to do a reconciliation or something of someone’s drugs.”</i> [Registrar 4]
Pessimism about recognition	<i>“I’m not sure if they’re [prescribing cascades] recognised...”</i> [Intern 1] <i>“...in my limited experience, I have probably seen... less than five... think there’s a lot more of them [prescribing cascades] that go on, that are missed...”</i> [SHO 3]

Reinforcement	
Rapport with patients influences response	<i>“It depends on... prior interactions with the patient... they’re just some patients that seem to find an issue with everything, so when they say stuff, it’s like the boy who cried wolf, you’re less likely to take it on board... other patients it’s just the way they say things ...it’s the rapport you have with [them]...” [Intern 4]</i>
Learning opportunity is an incentive to report	<i>“...people are less likely to own up to errors that are made because ... [of] ... what would happen if they did own up. So, they need to be reassured that you’re not going to give out to them. No one’s going to lose their job over it, but it’s very important that we have discussed it, so we all learn from it.” [Consultant 2]</i>

Abbreviations: *ACE inhibitor*: angiotensin converting enzyme inhibitor; *app*: smartphone application; *BST*: basic specialist training; *GP*: general practitioner (primary care physician); *MDT*: multidisciplinary team; *PPI*: proton pump inhibitor; *SHO*: senior house officer; *SPC*: Summary of Product Characteristics.

Note: Kardex®: a type of medication prescription and administration record; BST: hospital-based training programme completed by senior house officers.

3.4 Discussion

This research has uniquely identified key factors that impact hospital physicians' recognition of prescribing cascades using the TDF, which served as the theoretical model to gain comprehensive insights into the clinical behaviour of recognising prescribing cascades [151].

In essence, our findings indicate that knowledge about prescribing cascades is very limited among hospital physicians. While more junior physicians recalled being taught about prescribing cascades during their medical education, senior physicians were generally unfamiliar with the term. This suggests that the topic of prescribing cascades has only relatively recently been incorporated into medical education and that as a therapeutics concept it has not yet been integrated into routine clinical practice. This is emphasised by the fact that no participant recalled hearing the term 'prescribing cascade' mentioned in the clinical setting. Although in the three decades since prescribing cascades were first described, considerable research has been conducted on the topic, further efforts are needed to ensure that all physicians are familiar with prescribing cascades as a clinical term and therapeutic concept in order to increase awareness and recognition in practice [149]. Participants in this study were generally unable to name more than a few examples of specific prescribing cascades, most of which are classified as appropriate (e.g. opioid → constipation → laxative) rather than inappropriate (e.g. ACE-inhibitor → cough → anti-tussive). A comprehensive, validated list could serve as a resource for physicians, improving awareness, which has been identified in previous research as a key priority to improve recognition of prescribing cascades [98,99].

In addition to limited knowledge of prescribing cascades, participants also demonstrated uncertainty distinguishing between polypharmacy, prescribing errors,

prescribing cascades, and drug-drug interactions during the interviews. For example, physicians sometimes provided examples of drug-drug interactions when asked for prescribing cascade examples. While previous research on deprescribing interventions has largely focused on reducing inappropriate or unnecessary medications, recognising prescribing cascades requires an additional layer of complexity i.e. identifying when a drug has been prescribed to treat a side-effect of another drug [170]. The conceptual overlap and confusion around the terminology is likely to further hinder efforts to recognise prescribing cascades.

Participants indicated that the primary responsibility for recognising prescribing cascades lies with them as prescribers. However, despite this acknowledgement, recognising cascades was seemingly not a priority. One possible explanation is that participants often perceived the consequences of failing to recognise prescribing cascades in hospital as “benign” or inconsequential to the patient’s acute hospitalisation episode. Previous research has highlighted that the absence of clear evidence of patient harm can result in ‘*deprescribing inertia*’ [99]. Similarly, the present study displays ‘*recognition inertia*’. Additionally, participants did not perceive any personal negative consequences for failing to recognise and correct inappropriate prescribing cascades, with some suggesting that medication side-effects and prescribing errors are an inherent and to some extent unavoidable part of clinical practice [99].

This attitude may reflect a broader view that failing to recognise prescribing cascades is an acceptable deficiency driven by systemic challenges and the day-to-day realities of busy clinical practice in hospitals. The lack of a well-established clinical focus on prescribing cascades, combined with the consensus from interviews that ‘*most are not*

recognised' emphasises the low priority placed on their detection and management. Furthermore, errors related to unrecognised prescribing cascades are rarely the sole responsibility of one physician [98]. More often, they result from a combination of systemic and environmental challenges within the healthcare environment that influence the decision-making process. These challenges, frequently highlighted by interviewees, contribute to a culture wherein the relative lack of concern may stem from an acceptance of working in an imperfect healthcare system.

Several prominent environmental challenges were repeatedly highlighted by participants. These included lack of accurate information regarding patients' medications, insufficient staffing, and time constraints. A key issue identified was the lack of basic information during medication reviews, such as accurate medication lists, the original prescribing indications, and medications' intended duration. The Irish public hospital system remains predominantly paper-based, with no widespread integrated electronic platform between community healthcare settings and hospital settings. This fragmentation often results in incomplete access to documentation, including medication changes made in other clinical settings.

A recent study by Jennings *et al.* reported that communication failures and a lack of prescribing stewardship during healthcare transitions added to the degree of risk for patients when making prescribing decisions in such settings [99]. In line with this finding, interviewees in the present study emphasised that this issue was particularly problematic in the emergency department, where they described medication decision-making as "*hoping it is right*". In addition, physicians often make prescribing decisions in the context of limited, or at times inaccurate, information due to what one

interviewee described as an “*archaic*” health record system. This lack of comprehensive transfer of accurate information is a significant barrier to recognising prescribing cascades and increases the risk of medication-related harm to patients. It is unsurprising, therefore, that medication safety in transitions of care has been identified as a priority in the World Health Organisation’s ‘*Medication Without Harm*’ challenge in 2017 [72].

Physicians in this study also stressed the need for improved documentation, noting that medications are very often prescribed without a clearly documented indication. This aligns with a similar finding from previous research which noted that patients’ health records often contain insufficient information to support decisions on prescribing and deprescribing [78,156]. Research on deprescribing has similarly reported that clearer documentation of drug indications and long-term plans of each medication, as well as records of previously prescribed medications, in tandem with the reasons for their discontinuation, could facilitate easier recognition of prescribing cascades [171].

To improve recognition of inappropriate prescribing cascades, participants in this study suggested implementation of integrated IT solutions, aligning with previous research on prescribing cascades [160]. Such systems could support screening for prescribing cascades by improving documentation around prescribing and ensuring that all healthcare providers have access to all current medication information. Some participants suggested software-based systems such as electronic alerts. For electronic alerts to be effective, they must capture users’ attention whilst minimising ‘alert fatigue’, a challenge highlighted in the present study and previous studies [160,172].

Other considerations for electronic alert systems include grading the priority of alerts, choosing appropriate timing, avoiding excessive numbers of alerts and cognitive overload, and ensuring they do not undermine clinical autonomy [172,173]. A critical factor highlighted in a previous study is the importance of accurate information in generating alerts without which alerts may be misleading [174]. In well-organised and fully resourced hospital systems, physicians could decide to refer patients with suspected potentially inappropriate prescribing cascades to polypharmacy clinics for assessment, if such clinics are available. However, in most hospitals, physicians will need to assess and decide on deprescribing when they receive electronic alerts to potential cascades, or to refer to specialists for advice. Furthermore, as suggested by participants, IT solutions could incorporate the development of smartphone applications both for patients and healthcare professionals. For patients, an application could help them maintain a personal record of their medication regimen and identify potential side-effects, empowering them to have an active role in medication management and prescribing cascade recognition [98,175]. For physicians, an application with a searchable database of common prescribing cascades could be clinically valuable.

During inpatient admissions and ward rounds, staffing shortages, time constraints and acute issue prioritisation were frequently cited as obstacles to comprehensive medication reviews, with the cumulative effect of these factors limiting opportunities for identifying prescribing cascades [92]. Routine tasks, such as rewriting medication charts, are often delegated to the most junior members on the team due to time constraints, possibly representing a missed opportunity for prescribing cascade recognition [156].

Interviewees highlighted several challenges related to recognising prescribing cascades in older adults particularly. Hospitalised patients are increasingly older, frailer people who live with polypharmacy relating to their multimorbidity, in line with global demographic trends [9]. Identifying and classifying a prescribing cascade as appropriate or inappropriate in this cohort of patients, often with complex polypharmacy, has previously been described as “*unfeasible*” [99]. One strategy proposed by the present study’s participants to address these challenges was the implementation of routine expert medication reviews through a collaborative, interdisciplinary model including pharmacists and physicians. Such a model aligns with existing pharmacotherapy optimisation recommendations and could be integrated within a polypharmacy stewardship programme. Effective management of prescribing cascades involves several key steps: identifying the cascade, determining the indication for the original medication, assessing whether this indication remains, and deprescribing the original and/or subsequent medications where appropriate [143]. This model is likely to be more effective than simply increasing staff without ensuring that the additional staff have the required training and skills to effectively recognise and manage prescribing cascades.

In the present study, participants also commented that many older adults had difficulty managing their medications, identifying side-effects, and communicating concerns regarding side-effects to their physician, making the detection of prescribing cascades more challenging. These challenges are exacerbated by the organisation of modern medicine around a single-disease framework, in which each condition is, in general, treated in isolation [23]. This framework is evident in hospital settings, where patients’

assessments focus primarily on immediate presenting problems. Interviewees generally agreed with this, commenting that hospitalisation is usually focused on the acute presenting problem. Many participants also discussed the reluctance among doctors to modify or discontinue long-standing medications, especially those prescribed by other specialists expressing concerns about overstepping professional boundaries, even when they suspected that an inappropriate prescribing cascade had occurred.

The present study highlighted that the hierarchical structure in hospital medical teams influences both the initiation and discontinuation of inappropriate prescribing cascades. More senior physicians commonly direct prescribing adjustments, with more junior physicians unlikely to question instructions from their senior colleagues [155]. This reduces the opportunity to scrutinise whether a prescription might cause an inappropriate prescribing cascade [149]. More junior physicians also reported lower self-confidence in identification of prescribing cascades, often perceiving their prescribing patterns as lower risk. These findings highlight the need for targeted education to enhance junior physicians' knowledge and confidence in recognising medication side-effects and prescribing cascades. While formal educational programmes are essential, informal learning remains invaluable [155]. Many physicians in this study reported that they gained much of their knowledge on prescribing and deprescribing through working with consultants, especially geriatricians, because of their expertise with routine management of multimorbid patients who experience polypharmacy. They also suggested that leveraging teachable moments when prescribing cascades are identified and using these cases as direct learning opportunities may be valuable.

Ultimately, the integration of IT resources, a collaborative approach with specialists in pharmacotherapy (both physicians and pharmacists), and medication educational initiatives for both healthcare providers and patients would likely empower all parties to recognise and address prescribing cascades effectively, improving medication safety across healthcare settings.

3.4.1 Strengths and limitations

All interviews in this study were conducted by the same interviewer, ensuring consistency in data collection and data analysis. Reflexivity was considered throughout, enhancing the study's rigour by accounting for potential biases in data interpretation. The TDF was utilised both in topic guide development and content analysis. This framework was beneficial to the study as it provides a structured approach to exploring behaviours and has been shown to reveal additional themes that may not be generated through other approaches [158,159]. Furthermore, TDF domains can be mapped to the Behaviour Change Wheel (BCW), which can be utilised to identify and design suitable interventions to address the barriers identified [176].

The main limitation of the present study was the potentially low degree of transferability of the results, as this study was conducted in a single hospital in Ireland. This hospital operates within a particular social and environmental context, where health records are predominantly paper based. Consequently, the findings may be less generalisable to other healthcare settings, particularly those with different systems, resources, and cultures.

3.5 Conclusion

This study highlights the barriers that hospital physicians encounter in recognising inappropriate prescribing cascades, including gaps in knowledge, systemic and

environmental challenges, and cultural attitudes. Limited awareness of prescribing cascades, combined with fragmented healthcare information systems and often inadequate documentation of medication indication and duration, contribute to unrecognised prescribing cascades, increasing the risk of harm to patients, particularly multimorbid older adults with polypharmacy in the Irish hospital setting. Addressing these challenges requires targeted behaviour change interventions informed by these findings. These interventions could include integrated IT solutions, improved documentation of diagnoses and medications prescribed, interdisciplinary expert medication reviews, and enhanced education and training opportunities. Such interventions could empower physicians to recognise inappropriate prescribing cascades more effectively, thus facilitating their minimisation, ultimately reducing medication-related harm and improving patient safety.

CHAPTER FOUR

Development of a modified Medication-Related Burden Quality of Life (mMRB-QoL) short form tool for older people with multimorbidity and polypharmacy: a mixed-methods study.

4.1 Introduction

Despite extensive research on prescribing safety, no patient-related outcome measure (PROM) has been designed to specifically measure medication-related burden in older adults living with multimorbidity and polypharmacy [108,109]. As outlined in Chapter One, capturing patients' perspectives using PROMs is recommended in clinical practice and clinical research as a component of treatment evaluation, helping to bridge the gap between evidence-based medicine and patient-centred care and ultimately improve healthcare quality.

The original 31-item Medication-Related Burden-Quality of Life (MRB-QoL) was designed to measure the impact of medication-related burden on functioning and well-being from the patients' perspective. It provides a robust foundation for modification, due to its conceptual development from a meta-synthesis of 34 qualitative studies (encompassing 966 participant quotes), strong psychometric validity, and good internal consistency and reliability [137]. However, the original MRB-QoL's application to older adults is limited and there are practical challenges such as length, linguistic complexity, and potentially excessive respondent burden. Other PROMs exist, such as the EQ-5D-5L, the Multimorbidity Treatment Burden Questionnaire (MTBQ) and the Medication-Related Quality of Life (MR-QoL) tool; however, as discussed in Chapter One, these tools measure related but conceptually distinct constructs such as general health-related quality of life.

Given that older adults with multimorbidity and polypharmacy are often the focus of deprescribing and medication optimisation interventions, a practical, reliable, and valid PROM to assess the impact of medication-related burden on QoL in this population is required [97,108,177]. Accordingly, this study aimed to develop a

modified short-form MRB-QoL (mMRB-QoL) specifically designed for older adults living with multimorbidity and polypharmacy that can measure the impact of medication-related burden on overall QoL in both clinical and research settings.

4.2 Methods

4.2.1 Study ethical approval, study design, and target population

Ethical approval for this study was granted by the Clinical Research Ethics Committee, University College Cork. This study utilised a mixed-methods approach guided by the Goetz *et al.* framework for shortening composite measurement scales and the quality criteria proposed by Terwee *et al.* for health status questionnaires [178,179]. The process ensured the conceptual model was maintained, content validity was preserved, and the psychometric properties of the MRB-QoL were retained. A schematic process map for the development of the mMRB-QoL is presented in **Figure 4.1**. The study involved five phases:

- i. Prospective assessment of the original MRB-QoL in older adults living with multimorbidity and polypharmacy.
- ii. Qualitative research with potential end-users.
 - a. Exploring perspectives on the MRB-QoL through semi-structured interviews with older adults attending the geriatric medicine out-patient department (OPD).
 - b. Exploring perspectives on the MRB-QoL through a focus group with experts in geriatric medicine.
- iii. Clinical, multidisciplinary expert analysis of the MRB-QoL: evaluating for overlap, relevance, and wording.

- iv. Consensus panel for developing the mMRB-QoL for use in older adults living with multimorbidity and polypharmacy
- v. Patient and public involvement for design and final modifications.

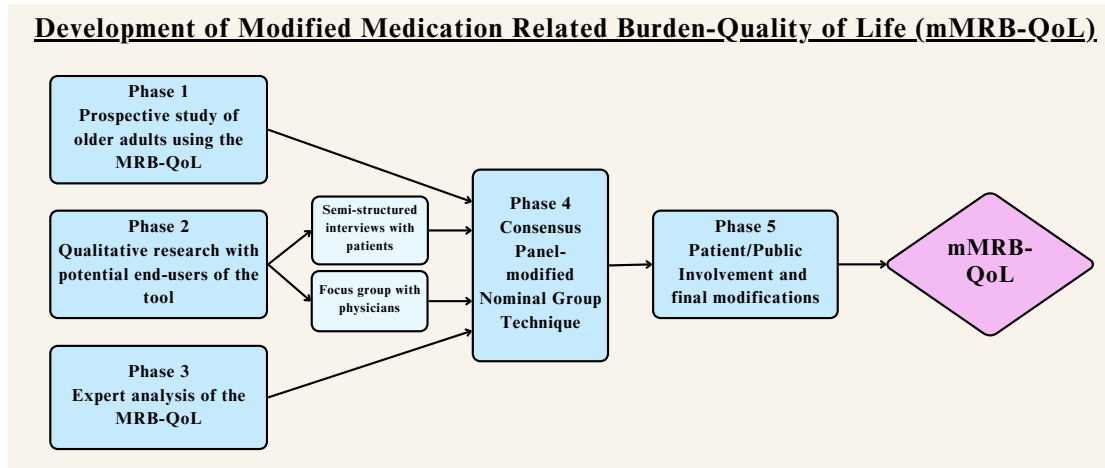


Figure 4.1: Process map of development of Modified MRB-QoL.

4.2.2 Phase 1. Prospective assessment of the original MRB-QoL in older adults living with multimorbidity and polypharmacy

4.2.2.1 Study design, setting, and participants

This phase was a single-centre observational prospective study conducted in the Cork University Hospital OPD in Cork, Ireland. A cohort of older adults attending the geriatric medicine OPD between August 2024 and November 2024 were consecutively approached by me, while awaiting their clinic appointment; each patient was recruited only once during the study period. I was not working in a clinical capacity within the OPD during the recruitment period. Eligible participants were adults aged ≥ 65 years, with multimorbidity (i.e. ≥ 3 chronic long-term health conditions concurrently) and associated polypharmacy (≥ 5 medications prescribed

daily long term, i.e. >3 months.). Patients were excluded if they were unable or unwilling to give consent to study participation or if they did not have sufficient English language proficiency to complete the questionnaire. Patients completed the MRB-QoL in a private room in the OPD. Clinical and demographic information was obtained through interview with the patient and review of their medical records including details of age, sex, long-term daily medications, medical diagnoses, clinical frailty score (CFS), living situation (i.e. independently, receiving home help, or living in a residential care facility), and whether their medications were blister packed.

4.2.2.2 Sample size

There is no universally agreed sample size calculation for shortening or adapting composite measure scales [180,181]. One commonly used sample size calculation is the 5:1 ratio, meaning that five participants are included for each item on a scale [179,182]. For this study, the estimated sample size ($n=155$) was calculated using the 5:1 ratio, ($31 \times 5=155$).

4.2.2.3 Scoring methods

The original MRB-QoL uses a formula to convert scores on the MRB-QoL to a scoring system ranging from 0 to 100, where 0 indicates best possible medication-related burden QoL and 100 indicates the worst possible medication-related burden QoL (**Appendix 4**). No established cut-off points have been determined to indicate clinically meaningful scores. The same scoring formula was applied to the modified version.

4.2.2.4 Data analysis

Statistical analysis was conducted using SPSS® version 28.0 software and IBM® SPSS® Amos version 26.0.0 software. Descriptive statistics included the mean and

standard deviation (SD) for normally distributed variables and the median and inter-quartile range (IQR) for non-parametric variables. Differences in MRB-QoL scores between dichotomous variables were compared using the independent *t* test. Associations between variables were assessed using Spearman's correlation for non-parametric variables and Pearson's correlation for normally distributed variables. A probability value of <0.05 was considered statistically significant.

Factor analysis and model fit

Model fit was evaluated using four commonly applied indices: root mean square error approximation (RMSEA), comparative fit index (CFI), Chi square, and Tucker Lewis Index (TLI). An increase in CFI indicates an improvement in goodness of fit, with a threshold of ≥ 0.95 considered acceptable [183]. Conversely, lower RMSEA values reflects a better fit, with a threshold of ≤ 0.07 considered acceptable [184].

Internal consistency and reliability

Internal consistency for each subscale was measured using Cronbach's alpha (α) coefficient ($0 \leq \alpha \leq 1$) to ensure that items within each dimension measured the same concept. A Cronbach's α value ≥ 0.70 was considered indicative of satisfactory reliability for each factor [179,185]

Items were further examined for response distribution, missing data, kurtosis, and skewness with corresponding z-scores. Item-level skewness and kurtosis values between -1 and $+1$ were considered acceptable [186]. Z-values < 1.96 were considered to indicate approximate normality ($p > 0.05$), while $z \geq 1.96$ indicated significant deviation ($p < 0.05$). [186] Items with $<15\%$ of missing values were considered acceptable in line with previous studies [179,185].

Floor and ceiling effects

Floor and ceiling effects were defined as the proportion of respondents scoring the highest (ceiling) or lowest (floor) possible score across any given item or factor. Significant floor and ceiling effects were defined as >15%, indicating reduced discriminatory power and limited sensitivity to change [179,185].

4.2.3 Phase 2. Qualitative research with potential end-users- Exploring perspectives on the MRB-QoL through semi-structured interviews with older adults attending the geriatric medicine OPD

4.2.3.1 Study design, setting and participants

One-to-one semi-structured interviews were conducted with a subset of participants who had completed the MRB-QoL as part of Phase 1. Semi-structured interviews were identified as the preferred method of data collection because they are well suited to generating detailed, nuanced descriptions of participants' experiences and perspectives [153]. To obtain a range of patients' perspectives, a stratified sampling matrix was used to ensure that the semi-structured interviews were conducted with ≥ 4 participants aged ≥ 80 years and ≥ 4 participants aged between 65 and 79 years, and with at least two males and two females represented in each age category. Participants were selected using stratified purposive sampling from those who had completed the MRB-QoL tool in Phase 1 [187].

4.2.3.2 Data collection

Immediately prior to their interviews, participants completed the MRB-QoL. An interview topic guide was developed based on reviewing relevant literature [179,188]. The topic guide was designed to elicit patients' perspectives on the accessibility,

relevance, completeness, and length of the original tool as well as probe for any recommendations to improve the MRB-QoL (**Appendix 3**).

All interviews were conducted in person by me (RD) between August and November 2024. All participants provided written and verbal consent immediately prior to their interview. Field notes were recorded after each interview. All interviews were audio-recorded and transcribed *verbatim*, with transcripts subsequently deidentified.

4.2.3.3 Sample size

It was decided *a priori* that two additional interviews would be conducted after the initial eight, and that interviews would continue until there were at least two contiguous interviews where no new major themes appeared, as this would help ensure that the topic has been adequately examined [162]. This approach was aligned with the principle of information power, whereby the richness and relevance of the data, rather than a predetermined sample size, determine the number of interviews required [189].

4.2.3.4 Data analysis

NVivo® software version 14 facilitated data analysis. The data were analysed according to the method of Braun and Clarke [190]. Firstly, the transcripts were read and re-read to ensure familiarity. Secondly, I conducted conventional content analysis, which involved open coding to create non-hierarchical codes that were then grouped into initial themes [163]. To enhance the reliability of coding, a second researcher, Dr Denis Curtin (DC) independently identified themes across all transcripts. Themes were then reviewed and discussed to define the themes and subthemes, followed by selection of supporting illustrative quotes. Factors considered when identifying key

themes included the frequency of beliefs, presence of conflicting beliefs, and the strength of beliefs expressed [164].

4.2.4 Phase 2. Qualitative research with potential end-users- exploring perspectives on the MRB-QoL through a focus group with experts in geriatric medicine.

4.2.4.1 Study design, setting and participants

One focus group was conducted with four physicians, as decided *a priori*. The inclusion criteria required that participants were working in geriatric medicine, at consultant or specialist registrar (i.e. senior resident) grade, in the participating university teaching hospital at the time of the interview. Potential participants were identified through the professional network of the research team, and were invited to participate via email, which included an information sheet and consent form.

4.2.4.2 Data collection and analysis

A topic guide was developed based on reviewing relevant literature encompassing similar domains to the patient interviews (**Appendix 3**) [179,191]. Immediately prior to the focus group, participants completed a short questionnaire collecting demographic information (gender, grade, years of post-qualification experience). The focus group was conducted in October 2024 by me and was audio-recorded, transcribed, and analysed using the same methodology described previously in Section 4.2.3.

4.2.5 Phase 3. Expert analysis of the MRB-QoL: evaluating for overlap, relevance and wording

4.2.5.1 Expert panel composition

The panel consisted of four participants (including representatives from pharmacy and geriatric medicine) with expertise in the care of older adults and pharmacotherapy in this population.

4.2.5.2 Review process

The panel was provided with the MRB-QoL for review prior to the meeting. During the meeting, each item was reviewed systematically for overlap with other items, relevance to the construct being measured, and clarity of wording. A consensus-based decision was made for each item, with the following possible outcomes: (i) retain item unchanged, (ii) propose revised wording, or (iii) recommend removal.

4.2.5.3 Data analysis

All decisions were documented, including justifications for retaining, revising, or removing items.

4.2.6 Phase 4. Consensus panel for developing the mMRB-QoL for older multimorbid adults living with polypharmacy

4.2.6.1 Consensus panel composition

The panel was identified through the inter-professional network of the research team. It was planned *a priori* to include at least two physicians and two pharmacists, with the prerequisite that the panel included one physician and one pharmacist who had not been involved in any other phase of the study.

4.2.6.2 Consensus method

A nominal group technique (NGT) was used to finalise the mMRB-QoL by integrating findings from the prospective study, qualitative research, and expert analysis [192,193]. This is a recognised approach used to achieve consensus between specialists in a particular field where expert opinion is important in shaping judgements, and where the literature may be limited [193,194]. A key advantage of NGT is that by including people with varied knowledge, expertise and skills, the results are likely to be of higher quality than those obtained through other methods [194]. The NGT method is typically modified to optimally suit the needs of the research study and therefore is generally referred as the modified NGT (mNGT).

4.2.6.3 Process of mNGT

The mNGT process was designed in accordance with the steps described by Dunham et. al (**Figure 4.2**) [194]. The results from the prospective study, the qualitative research and the expert panel's proposals were reviewed by me and summarised in a document which provided suggestions for each MRB-QoL item (**Appendix 4**). This document was distributed to the panel members in advance of the meeting to facilitate 'silent idea generation' and anonymous topic generation. By gathering written feedback prior to the meeting, each participant had the opportunity to share their ideas in an equal manner. Each participant reviewed all items in the document and provided an individual response regarding whether the specific item should be retained, revised, or removed. Participants were encouraged to base their feedback primarily on their expertise and if required to utilise the qualitative data and statistical results to support their decision. Participants were also invited to offer any additional comments, provide feedback on the Likert scale, and suggest any new items they believed should be included in the mMRB-QoL. Participants submitted their individual responses prior to

the consensus meeting. Feedback was consolidated and a revised document was prepared and shared with participants, summarising:

1. The number of participants that agreed with the suggestion for each item.
2. Feedback received on individual items.
3. Proposed actions for each item, describing potential revisions if required.
4. Summary of additional feedback from the panel.

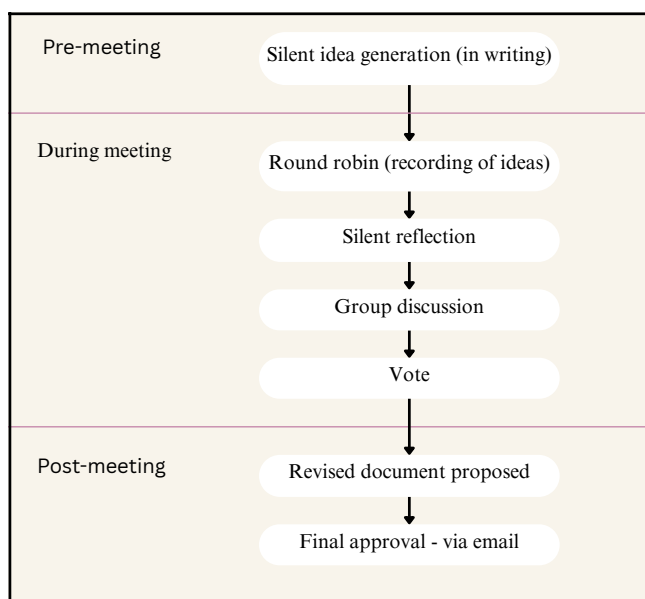


Figure 4.2: Standardised process to modified Nominal Group Technique

4.2.6.4 mNGT meeting

A structured, in-person meeting was convened to facilitate group discussion on the consolidated feedback. The meeting was led by the group facilitator (RD), who guided participants through the process. Following an introduction, the participants were asked to reflect on each subscale of the MRB-QoL. During the Round-Robin discussion, each participant was encouraged to verbalise their feedback. This was

followed by a group discussion where differing views were explored and justifications for retaining, revising, or removing items were discussed.

If consensus on a particular item was not initially reached, participants provided reasons for the lack of agreement. When necessary, items were revised based on feedback from the panel. Following the mNGT meeting, a draft mMRB-QoL was developed and shared with all participants for review, feedback, and re-voting on any items yet to reach consensus.

4.2.6.5 Final consensus

There is no agreed level of acceptable consensus for NGTs [195,196]. However, it was decided *a priori* that an 80% consensus level would be acceptable.

4.2.7 Phase 5. Final modifications and Patient / Public involvement (PPI)

4.2.7.1 Overview and rationale

PPI helps ensure patient-centred research, offering valuable insights through informal discussions with PPI contributors rather than formal, structured interviews [197]. In the context of questionnaire development, PPI contributes a greater understanding of end-users' experiences, ultimately enhancing the questionnaire's usefulness. It can reduce response error and response burden as well as improving questionnaire comprehensiveness and relevance while minimising item ambiguity [198,199]. The consensus-agreed draft of the mMRB-QoL for older adults with multimorbidity and polypharmacy was reviewed by a PPI group, consisting of three older adults who provided feedback.

4.2.7.1 Contributors

No formal selection procedures were applied. Eligibility criteria required contributors to be representative of the tool end-users, i.e. older adults living with multimorbidity taking multiple daily medications. The opportunity to be involved in this study was advertised to potential contributors through a panel within the School of Pharmacy, University College Cork and through the research team's social network.

4.2.7.2 Steps to PPI

A key enabler of effective PPI involves the development of strong rapport between the researcher and the contributor, which encourages more detailed feedback [198]. PPI input consisted of informal discussions to build rapport and the use of Think Aloud Task (TAT) methodology [200]. Contributors completed the questionnaire while verbalising their thought processes, providing insight as to how they interpreted, processed, and responded to individual items [198,200]. Issues identified during the TAT sessions were then further explored in an open-ended follow-up discussion. Contributors were encouraged to share additional feedback, and the researcher had an opportunity to ask open questions to probe any issues they detected during the TATs. Contributor feedback was incorporated into an updated version of the mMRB-QoL, ensuring that final refinements enhanced its clarity and usability. This process contributed to testing for face validity, confirming that the tool was comprehensive, relevant, and appropriately structured for the target population. PPI contribution is reported according to the GRIPP2 short form checklist (**Appendix 2**) [201].

4.2.8 Reflexivity

i. Research team background and professional experience

The research team included a research physician with specialist training in geriatric medicine (RD), and two consultant geriatricians (Prof. Denis O'Mahony, DOM and Dr Denis Curtin, DC). The team's clinical and research expertise informed the study design, data collection, and analysis. However, as in Chapter Three, the research team was aware of the potential for subjectivity in this study and that the team's background could influence the study design, methods, and conclusion. Therefore, the following steps were taken to leverage the advantages of the team's expertise and mitigate biases [166].

ii. Mixed-methods approach

A mixed-methods approach was adopted to ensure methodological triangulation, strengthening the findings' validity [202]. Triangulation was achieved through integrating multiple data sources (quantitative and qualitative) and involved a diverse range of perspectives on the mMRB-QoL through the consensus panel and PPI involvement. This approach supported the development of a valid and appropriate mMRB-QoL for older adults.

iii. Mitigating against response bias

The research team recognised how participants' awareness of the research objective might influence their responses. For example, patients might attempt to provide the 'right' answers that they believe align with the researchers' expectations, leading to response bias. To mitigate this, I implemented strategies such as emphasising the importance of honest feedback and designing questions that reduced the likelihood of participants providing responses to perceived expectations.

iv. Insider positionality

As a physician with higher specialist training in geriatric medicine, I recognised my '*insider position*' and was aware of the need to set aside my own perspectives and to remain neutral when interviewing physician colleagues [167,168]. Potential study participants were aware that I had specialist training in geriatric medicine; this knowledge was beneficial in accessing potential participants within the OPD.

v. Data interpretation of qualitative phases

It was recognised that the research team's own biases could influence the interpretation of perspectives during the analysis [165]. To challenge interpretive bias and to foster critical reflection, I debriefed the team regularly throughout the analytical process. Prior to finalising the thematic codes, the one of the consultant geriatricians (DC) and I met to discuss the data findings and code development.

vi. Framing of evidence

The final development phase of the mMRB-QoL included an expert consensus panel that comprised individuals who had not been involved in earlier study phases. These external perspectives challenged assumptions, enhanced objectivity, and supported the rigour of the final development phase of the mMRB-QoL. Additionally, PPI was incorporated to ensure that the modified tool would be relevant and accessible to end-users. The inclusion of PPI contributors helped maximise acceptability and real-world mMRB-QoL application.

4.3 Results

4.3.1 Phase 1. Prospective assessment of MRB-QoL in older adults with multimorbidity and polypharmacy

4.3.1.1 Patient characteristics

In total, 155 patients were enrolled in this study phase, of whom 87 (56.1%) were female and the remainder male, with a mean (SD) age of 80.3 (6.23) years. Baseline patient characteristics are presented in **Table 4.1**. The median (IQR) number of long-term chronic conditions was 5 (4-6). A total of 1350 daily medications were prescribed to 155 patients i.e. an average of 8.7 daily drugs per patient, and 52 (33.5%) patients were prescribed 10 or more medications. The median (IQR) burden score was 23 (13-34). A breakdown of the MRB-QoL score for each subscale is presented in **Table 4.2**. Of the 155 MRB-QoL questionnaires, five (3%) were incompletely filled. No participant left more than one statement blank. Items 18, 19, 23, and 29 were excluded from analysis due to high levels of “non applicable” responses.

Table 4.1: Baseline patient characteristics and their associations with MRB-QoL burden scores.

Variable	Values	P value
Number of medications [Median (IQR)]	8 (4-10)	0.942
Use of blister pack [Number of patients (%)]*	62 (41.9)	0.724
Co-morbidities [Median (IQR)]	5 (4-6)	0.569
Age [Mean (SD)]	80.3(6.23)	0.89
Sex [Female (%)]	87 (56.1)	0.65
Clinical Frailty Scale [Mean (SD)]	4.47 (0.9)	0.936

Abbreviations: MRB-QoL: medication-related burden quality of life; IQR: interquartile range; SD: standard deviation.

Notes: Statistical tests included Spearman’s correlation, Pearson’s correlation, and the independent t-test; *missing data for $n=7$ patients.

4.3.1.2 Scale internal consistency, reliability, skewness and kurtosis

All subscales demonstrated acceptable internal consistency, except for Subscale D which showed questionable internal consistency. Details of Cronbach's alpha values are presented in **Table 4.2**. Subscale means (SD), skewness, and kurtosis are also reported in **Table 4.2**. Z-tests indicated significant skewing for Subscales D and E. Significant floor effect was also observed in Subscales D and E, with a less pronounced floor effect in Subscales A and C.

Table 4.2: Scale Internal Consistency, Reliability, Skewness, and Kurtosis.

Factor/ Subscale	Number of items included in analysis	Cronbach's Alpha	Floor (%)	Ceiling (%)	Interpretation of Cronbach's	Total Mean Score and SD	Skewness	Kurtosis
A: Medicine Regimen and routines of taking medicines	11	0.851	20.6	0.6	Good	18.8 (14.9)	0.337 Z = 1.73	-0.767 Z=- 1.98
B: Psychological Wellbeing	6	0.834	7.7	1.9	Good	39.1 (24.4)	0.361 Z= 1.86	-0.0518 Z=-1.33
C: Physical Wellbeing	4	0.742	17.4	0.6	Acceptable	27.2 (20.3)	0.396 Z= 2.03	-0.467 Z= -1.21
D: Health Services	3	0.68	45.1	0.6	Questionable	15.1 (16.9)	1.01 Z 5.18	0.590 Z= 1.52
E: Social Wellbeing	3	0.766	42.2	0.6	Acceptable	17.6 (19.8)	1.116 Z= 5.9	0.778 Z=2.01

Note: Four items were excluded from analysis due to high levels of “non applicable” response

4.3.1.3 Factor analysis

Confirmatory Factor Analysis (CFA) was performed using the previously proposed five-factor model (Subscales A to E) from the original MRB-QoL study. Item numbers in **Figure 4.3** correspond to their number in the MRB-QoL, with factor loadings and latent factor correlations also presented. Model fit indices were as follows: Chi: 0.000, TLI = 0.797, CFI = 0.82, and RMSEA = 0.082, indicating suboptimal model fit.

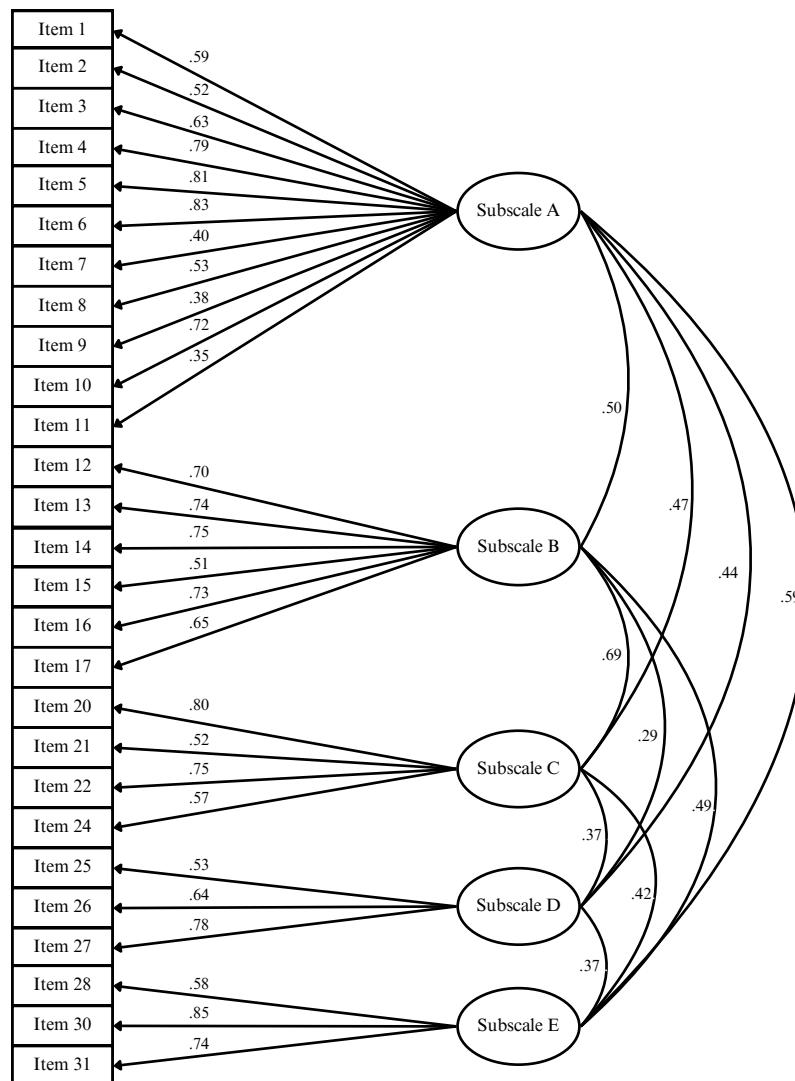


Figure 4.3: Factor Model for Confirmatory Factor Analysis.

Note: Subscales correspond to the various factors within the MRB-QoL: Subscale A: Medicine Regimen and routines of taking medicines; Subscale B: Psychological Wellbeing; Subscale C: Physical Wellbeing; Subscale D: Health Services; Subscale E: Social Wellbeing.

4.3.1.4 MRB-QoL associations

The total number of medications and co-morbidities were not significantly correlated with total MRB-QoL scores. In addition, age, gender, and CFS were not significantly associated with higher MRB-QoL scores (**Table 4.1**).

4.3.2 Phase 2. Qualitative research with potential end-users

4.3.2.1 Exploring older adults' views and perspectives on the MRB-QoL

Ten semi-structured interviews were completed with patients according to the sampling matrix (**Table 4.3**). The mean age was 81.0 years (SD 8.67). The mean interview duration was 6.24 minutes (SD 3.26), range: 3 – 14 minutes.

Table 4.3: Sampling matrix details of patient participants.

Patient Characteristic	Number of interviewees	Minimum number required as part of sampling strategy
Gender		
Male	4	4
Female	6	4
Age		
< 80 years	5	4
>80 years	5	4

Four key themes were identified from the interviews, as shown below, with corresponding quotations shown in **Table 4.4**.

i. Accessibility issues: wording clarity and font size

Several participants, particularly those over 80 years, reported difficulties in comprehending certain statements, describing longer statements as “*a bit confusing*”. The use of examples helped item understanding. While the font size was generally

acceptable, some participants suggested that increasing the font size could enhance accessibility for older adults.

ii. Manageable length, but preferably shorter with less repetition

Some participants found the length manageable, particularly as the MRB-QoL is divided into different sections. In contrast, others felt that a shorter version would be preferable, describing the current length as potentially “*daunting*” to complete. Many interviewees commented on repetitive items within the tool, particular within Subscales A and E.

iii. Likert scale complexity

Several interviewees highlighted challenges in using the Likert scale, such as distinguishing between response options such as ‘*strongly agree*’ and ‘*agree*’. A few participants suggested that a simpler response format, such as ‘*yes*’ and ‘*no*’, might improve usability for older adults. Others suggested that MRB-QoL users may need guidance on how to answer according to the Likert scale and assistance may facilitate accurate response selection.

iv. Questionable relevance and personal applicability of some items

Overall, participants felt that the MRB-QoL dealt with all key aspects of medication-related burden. While some statements were perceived as “*unnecessary*” or “*irrelevant*”, it was acknowledged that perceived relevance might vary between individuals, influenced by personal circumstances. This was particularly noted for sexual function-related statements. In contrast, statements related to stigma and social embarrassment were generally deemed to be less relevant to most older adults. Content gaps were also identified in relation to side effects.

Table 4.4: Themes and illustrative quotations from semi-structured interviews with older adults attending the geriatric medicine out-patient department.

Descriptor	Quotations
Theme 1 – Accessibility: wording clarity and font size	
Difficulty comprehending longer or complex items	<i>“...I could understand them all... I found it easy enough to read...”</i> [Patient 8 (<80)] <i>“...some of them were a bit long. And the long ones tended to be a bit confusing”.</i> [Patient 1 (≥80)] <i>“I could find no problem (with completing the MRB-QOL), and I thought it was grand.”</i> [Patient 2 (≥80)] <i>“...some of them (item statements) were long and others were okay...shorter was easier (to understand)”.</i> [Patient 6 (≥80)] <i>“[The wording is a]... small bit confusing, a couple of questions, such as number 25...”</i> [Patient 5 (<80)] <i>“But some of them (item statements), you know were a bit confusing...the wording... some words you don't understand, but if it is in a simpler language, it would be easier for people.... well for the likes of me and other older people, it would be more beneficial.”</i> [Patient 6 (≥80)] <i>“I thought it's (Subscale D) hard to make out... the way they were stated.”</i> [Patient 3 (<80)]
Visual readability and font size preferences	<i>“... if you had reading glasses, it would be very good, but if I took my time, I could manage it without my reading glasses.”</i> [Patient 10 (<80)] <i>“I find this is quite comfortable ... but I'd have to put my reading glasses on.”</i> [Patient 4 (<80)]
Examples help item understanding	<i>“...the writing (font) ... for older people, it could be larger.”</i> [Patient 6 (≥80)] <i>“... you're putting down examples as well - made that...made it easier (to understand) ...”</i> [Patient 3 (<80)]

Theme 2 – Manageable length, but preferably shorter with less repetition	
Shorter MRB-QoL preferable	<i>“I think making it shorter would make it easier...” [Patient 10 (<80)]</i> <i>“... if you need to ask all those questions then you need to, but I would prefer if there were less (items).” [Patient 1 (≥80)]</i> <i>“... it's nice that it's in segments...It may be a bit too long... it might be a bit daunting when you see it first and you know it's not just that page... there's more at the back... maybe a little bit shorter.” [Patient 4 (<80)]</i> <i>“It's a bit long... if you have less questions, and if it was more to the point of what you're trying to achieve it would be better.” [Patient 6 (≥80)]</i> <i>“... it's not too short or it's not too long.” [Patient 3 (<80)]</i>
Perceived overlap between items	<i>“... maybe 1 or 2 of the questions could have been ...and I remember thinking, ‘that could have gone in with that other one’. But maybe they just maybe want to be specific.” Patient 9 (≥80)]</i> <i>“... some repetition on ‘whether anybody cares’... I would say one answer would have done the lot.” [Patient 9 (≥80)]</i>
Theme 3 – Likert Scale Complexity	
Challenges distinguishing between response options	<i>“...to define between ‘strongly agree’ and ‘agree’ ... I found it difficult to distinguish ...” [Patient 1 (≥80)]</i> <i>“...it was a bit tricky to do it (Likert scale) but I worked it out in the end and it was okay...” [Patient 5 (<80)]</i>

Assistance may facilitate accurate response selection	<i>"...if you give me a range of answers, I'd rather just have yes or no. ... I can find these types of things ... a bit off-putting. I always feel unsure as to whether I've marked the right column ... it would be nice to have somebody there that could say 'yes, if that's how you feel, you put it in this column or that column'." [Patient 4 (<80)]</i>
Theme 4 – Questionable relevance and personal applicability of some items	
Personal circumstances influenced item relevance	<i>" It really applies differently to different people.... " [Patient 9 (≥80)]</i> <i>"I think it's important to let the doctor... know your feelings... I think they [the item statements] are important to ask." [Patient 8 (<80)]</i> <i>"I found it necessary otherwise you're not going to have any background." [Patient 9 (≥80)]</i>
Certain items not applicable to all	<i>"I found a lot of the questions unnecessarily... like 'you're embarrassed, people seeing how much medicine you take' ... " [Patient 6 (≥80)]</i> <i>"I found an awful lot of it irrelevant." [Patient 7 (≥80)]</i> <i>" 'I would rather not tell others I'm taking medicines regularly' ... That was true in the olden days but definitely not now." [Patient 1 (≥80)]</i> <i>"... sexually frustrated... everybody's built differently. I suppose that it would be necessary to some people." [Patient 9 (≥80)]</i>
Content gaps identified	<i>"I think there should be more questions on side effects." [Patient 5 (<80)]</i>

Abbreviations: MRB-QoL: Medication- related burden- quality of life.

4.3.2.2 Exploring geriatric medicine experts' views and perspectives on the MRB-QoL

The focus group consisted of two consultant physicians and two trainee physicians completing specialist training in geriatric medicine (meeting duration: 28 minutes). Two participants were female and two were male, with a median of 10 years' post-qualification experience (range: 5-13 years). Participants reached a consensus in ranking the items in each subscale from most important to least important in terms of content (**Appendix 5**). Two key themes were identified as shown below and corresponding quotations are presented in **Table 4.5**.

i. Repetition and redundancy between multiple items

The participants identified redundancy within the MRB-QoL, noting that several items address similar concepts with only minor differences in wording. This was particularly evident within subscales A and E. It was suggested that streamlining these sections could enhance usability, making the tool more accessible for older adults.

ii. Relevance and completeness of content

Overall, the tool was considered highly relevant to older adults, particularly in relation to Subscales B, C, and D. Certain items were perceived as less relevant to older people depending on clinical context and personal circumstances.

Additionally, participants highlighted two potential aspects of medication-related burden relevant to older adults which are not measured in the tool. These include the challenge of medication management in a fragmented healthcare system and the social impact of complex medication regimens, particularly when family/carers assist with medication management and organisation.

Table 4.5: Themes and illustrative quotations from focus group with experts in geriatric medicine

Descriptor	Quotation
Theme 1 – Repetition and redundancy between multiple items	
Many items address similar concepts with only minor differences in wording, resulting in perceived repetition.	<i>“They are all sorts of variations on a theme.”</i> [Physician 3] <i>“There is a bit of duplication ... (items) four, six and ten are similar, the ‘fitting medication routine into my schedule’ and ‘sometimes cancelling my schedule’ ... ”</i> [Physician 1] <i>“It might be ... simpler to administer to older people if it was ... streamlined or narrowed ... (Section A) could definitely be narrowed ... the physical act could be tied into one thing (item) ... the organisation of the medications, is it convenient opening the packages, difficult to organise There is a bit of repetition, but it is relevant, definitely.”</i> [Physician 3] <i>“...(items) 18 and 19 - similar theme and 21 and 22 - similar theme...”</i> [Physician 1]
Theme 2 – Relevance and completeness of content	
Limited relevance of some items to older people	<i>“... ‘reminded of one's health problems’ ... I don't know that that's a theme that I encounter much in clinic, people don't like polypharmacy, but they don't usually say to me, ‘this reminds me that I have heart failure’.”</i> [Physician 2] <i>“They're all [Subscale D] pretty relevant here.”</i> [Physician 3] <i>“...maybe for a younger person this is relevant (Subscale E), but for an older person, less so...”</i> [Physician 4] <i>“..it's [medication management] one of the things that interferes with people's independence at an early point, they can manage a lot ... but they mightn't be able to manage their medications and everybody gets very excited.”</i> [Physician 3]

Important content gaps	<i>"I think impact on your care system and needing assistance with medication, such as having to blister pack, supervise medications etc. I think that's relevant ... because, if you have a carer doing it and your medications are blister packed, you would score low burden in Section A."</i> [Physician 1] <i>"... patients have to bring medications to their appointments. We are relying on patients to relay what medications [they are using]. I think one of the things is that patients they end up coming to A&E, telling ED, telling the medical SHO, telling the team.... duplication of interactions with different doctors."</i> [Physician 1]
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Abbreviations: A&E: Accident and Emergency i.e. Emergency Department); ED: Emergency department; SHO: senior house officer i.e. junior resident.

4.3.3 Phase 3. Expert analysis of the MRB-QoL: evaluating for overlap, relevance, and wording

4.3.3.1 Expert panel composition

The panel consisted of four participants with expertise in the care of older adults and pharmacotherapy in this population. The panel consisted of three physicians (two consultants in geriatric medicine and one physician completing specialist training in geriatric medicine) and one academic pharmacist with expertise in geriatric pharmacotherapy.

4.3.3.2 Review outcomes

Expert analysis of the MRB-QoL produced recommendations for item refinement to enhance clarity, relevance, and alignment with the construct of medication-related burden in older people. Of the 31 items reviewed, four were recommended for retention in their original form. Revised wording was proposed for 13 items, and it was suggested that 14 items be removed from the mMRB-QoL, with their core concepts, in some cases, integrated into the revised items. The recommended modifications for each item are summarised in **Appendix 5**.

4.3.4 Phase 4. Consensus panel for developing the mMRB-QoL for older adults living with multimorbidity and polypharmacy

4.3.4.1 Panel composition

All invited panellists agreed to participate. The panel consisted of five experts in pharmacotherapy and clinical management of older adults, as well as the primary researcher acting as facilitator. The panel consisted of three physicians (two consultants in geriatric medicine and one senior academic general practitioner) and

two pharmacists with expertise in older adults with polypharmacy. The median post-qualification experience was 16 years (range 10 to 39 years). One physician and one pharmacist who had not been involved in earlier study phases provided an external perspective. All panellists completed the pre-mNGT meeting feedback document and attended the in-person meeting.

4.3.4.2 Pre-mNGT meeting feedback

The original MRB-QoL was considered conceptually relevant but requiring modifications to enhance applicability for the target population.

Proposals were based on results from the previous three stages. Each of the 33 items (31 items from the original MRB-QoL plus two newly proposed items) were independently evaluated for inclusion. Consensus agreement ($\geq 80\%$) was achieved for 30 items regarding inclusion. A complete summary of all 33 item outcomes is presented in **Table 4.6**.

Some panellists recommended using consistent terminology (e.g. “medication” rather than “medicines”) and standardising syntactic patterns (e.g. consistently phrasing items as “I find it difficult to...” rather than alternating with “I find it hard to...”).

The panel reviewed feedback from the qualitative research regarding the Likert scale. Some panellists emphasised that any modifications would need to preserve metric equivalence with the original format.

4.3.4.3 mNGT meeting

The meeting was attended in full by all panellists. All 33 items (31 from the original MRB-QoL plus two newly proposed items) were sequentially reviewed. Outcomes are displayed in **Figure 4.4**. For the items with consensus for inclusion pending wording

adjustments, revised phrasing was discussed and agreed upon, with an emphasis on maximising relevance to older people with multimorbidity and polypharmacy, improving clarity, reducing the length, and standardising terminology and syntax.

Discussion also led to the addition of two new items deemed highly relevant to the construct of medication-related burden in the target population: one focused on cognition-related medication side effects and one focused on the challenges of attending follow-up appointments for medication monitoring. These additions were supported by expert opinion and relevant literature, and consensus was reached on their inclusion [203].

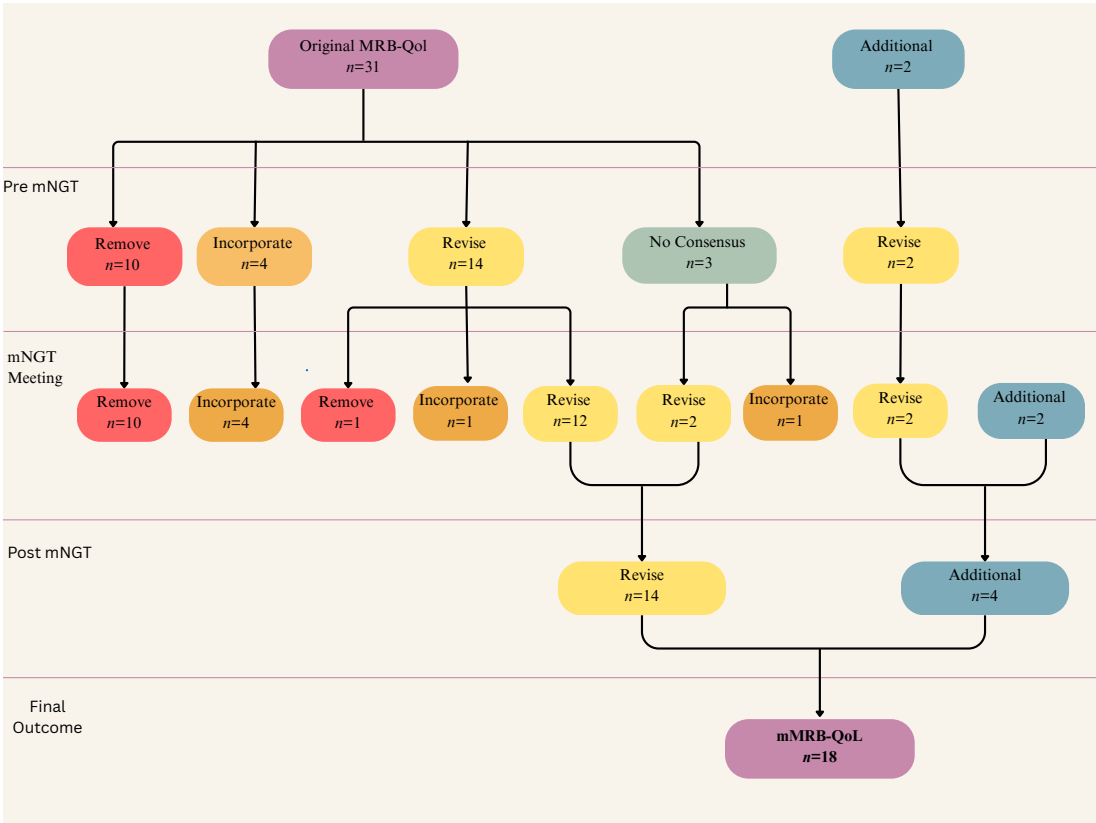


Figure 4.4: Item Outcomes from modified Nominal Group Technique

Abbreviations: MRB-QoL: medication-related burden quality of life; mNGT: modified Nominal Group Technique

The Likert scale format and wording was also reconsidered. While alternatives were explored, consensus was reached to retain the original format to ensure metric equivalence, supplemented by an optional explanatory sheet for end-users to support consistent interpretation [204].

The mNGT process achieved $\geq 80\%$ consensus on an 18-item modified MRB-QoL. Detailed item-level consensus outcomes and rationales are presented in **Table 4.6**.

4.3.4.4 Post mNGT meeting

Following the mNGT meeting, the 18-item mMRB-QoL was compiled and circulated via email to the panel for final feedback and approval, resulting in minor adjustments.

Table 4.6: Consensus outcomes and rationales

Item No.	Original statement	Initial Proposal and rational	Initial consensus agreement No. (%)	Feedback	Outcome of mNGT Meeting	Consensus agreement No. (%)	Final item from inclusion
Subscale A: The following statements are about the burden associated with the medicine regimen and routines of taking medicines.							
1	I find it difficult organising my medicines	Retain as is, 'I find it difficult organising and maintaining an up-to-date list of my medicines'	2 (40%)	Retain Items 1 & 2 as individual items. <i>"Organising and keeping an up-to-date list of meds are different issues...by incorporating both into the same question you risk losing relevant information"</i> .	Do not incorporate Item 2. Incorporate item 3.	5 (100%)	I find it difficult organising and/or managing my medication without help (carer/family).
2	I find it hard keeping my medicines record	Incorporate into Item 1 Overlap with Item 1 - amalgamate into one item	2 (40%)	Retain as individual item <i>"the patient may not maintain an up-to-date record/list... is it more about 'keeping track' of what medication they are on"</i> .	Retain as individual item. #	5 (100%)	I find it difficult keeping an up-to-date record of my medication.
3	It is difficult for me to manage my routines associated with my medicine taking	Reframe as new item to increase relevance to older adults with multimorbidity and polypharmacy 'I need help organising my medications (carer assistance / blister pack)'	2 (60%)	<i>"Is the burden offset by help?"</i>	Important concept. But does it capture 'transfer' of burden to carer/family. Incorporate the concept of 'managing medications' into Item 1.	5 (100%)	Not applicable

4	Fitting medicine routines into my other life schedules is a difficult task for me	Reword as, 'My medicine schedule restricts me in my daily routine'. This terminology better captures the impact of medicine routines on older adults Medicine routine→ medicine schedule Life schedule → daily routine	5 (100%)	Consensus agreement with proposal with minor wording adjustments	Retain *	5 (100%)	My medication schedule restricts me in my daily routine.
5	Taking medicine/s interferes with my physical activities	Remove, concept adequately covered in Item 4	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
6	It is difficult to balance my daily life schedules with taking medicines	Remove, concept adequately covered in Item 4	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
7	My current medication regimen is not simple for me to manage (e.g. injections, tablets, eye drops)	Reword as, 'Taking my medicines is challenging (e.g. injections, swallowing tablets, eye drops, inhalers, opening medicine containers)' This suggested phrasing improves comprehension	5 (100%)	Consensus agreement with proposal with minor wording adjustments	Retain *	5 (100%)	Taking my medication is challenging (e.g. injections, swallowing tablets, eye drops, inhalers, opening medication containers).

8	Understanding the instruction on my medicine/s is challenging at times	Reword as, 'Understanding the exact instruction on my medicine's label is challenging at times (e.g. timings in relation to other medications/ food etc) Examples added to improve clarity of statement	5 (100%)	Consensus agreement with proposal with wording adjustments “... the word exact...complicates the sentence”. “Instructions are not just on labels”.	Retain item with some wording changes -Remove 'exact' -Remove 'at times' *	5 (100%)	Understanding the instructions on my medication is challenging (e.g. timings in relation to other medication/food etc).
9	My current medicine/s are not in a convenient form for me to take (e.g. difficult to swallow, unpleasant taste/ smell)	Incorporated into Item 7, overlap and poor individual factor loading	5 (100%)	Consensus agreement with proposal -incorporated	No change to initial proposal	5 (100%)	Not applicable
10	Sometimes I have to cancel my daily schedules because of my medicines	Remove, less relevant to older adults and overlap with Item 4	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
11	Opening the package of my medicines is sometimes a difficult task for me (e.g. child-proof caps)	Incorporated into Item 7. Low factor loading and overlap with Item 7.	5 (100%)	Consensus agreement with proposal -incorporated	No change to initial proposal	5 (100%)	Not applicable

Subscale B: The following statements are about the impact of medicines associated burden on psychological wellbeing							
12	It bothers me that I have to take medications for the long term	Incorporate into Item 13, the number of long-term medications is often more significant to older adults	5 (100%)	Consensus agreement with proposal - incorporated	No change to initial proposal	5 (100%)	Not applicable
13	I am concerned about the number of medicines I am on	Reword as: 'I am concerned about the number of long-term medications I am on'	5 (100%)	Consensus agreement with proposal with wording adjustments <i>'I am bothered by the number of long-term medications I am on'</i>	Decision to retain the word 'concern'	5 (100%)	I am concerned about the number of long-term medications I am on.
14	I worry about the long-term effects of medicines on my health	Reword as, 'I worry about the long-term side- effects of medicines on my health' Some of the 'effects' may be positive and not a cause for worry	5 (100%)	Consensus agreement with proposal with wording adjustments <i>Add 'potential' side effects</i>	Retain with changes # -Change 'worry' to 'concern ' -Add the word 'possible' -Remove term 'on my health'	5 (100%)	I am concerned about the possible long-term side effects of my medication.
15	Taking medicines on a regular basis reminds me of my health problems	Remove, not deemed relevant. Low factor loading.	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable

16	I am concerned that my medicines may interact with each other	Retain as and reword, 'I am anxious that my medicines may interact with each other'	5 (100%)	Consensus agreement with proposal with wording adjustments <i>'I am concerned that my medications may be affected by other medicines, food, or drink'</i>	Retain with changes *# -Change 'anxious' to 'concerned' Discussion on whether to include interactions with food/ drink (incl. alcohol). Decision not to include to maintain consistency with original item	5 (100%)	I am concerned that my medication may interact with each other.
17	My medicines signify me as not being healthy	Remove, less relevant	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
Subscale C: The following statements are about the impact of medicines associated burden on physical wellbeing.							
18	I am sometimes sexually frustrated because of my medicine/s	Remove, concept adequately covered in item 19	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
19	I am unable to relax and enjoy sex because of my medicine/s	Reword as, 'Some of my medications negatively affect my sex life'	5 (100%)	Move this item to the end of Section C The use of 'some of' implies more than one	Retain with changes -Move to end of section -Remove term 'some of'	5 (100%)	My medication negatively affects my sex life.

20	Some of my medicines slow down my physical health	Retain and improve clarity 'Some of my medicines slow me down'.	5 (100%)	<i>"Add 'physically' (as distinct from mentally/psychologically)"</i> The use of 'some of' implies more than one	Retain and reword. Incorporate item 20 into this item. Decision made not to add 'physically' and to prioritise keeping statement short and clear.	5 (100%)	I have less energy for daily activities and/or feel 'slowed down' because of my medication.
21	I often have a bad night's sleep because of my medicine/s	Reword as, 'I often sleep poorly because of my medicine's' This suggested phrasing improves comprehension	5 (100%)	Consensus agreement with proposal with wording adjustments	Retain with changes * -Remove term 'often', frequency implied in Likert scale	5 (100%)	I sleep poorly because of my medication.
22	Because of my medicine/s I feel too tired to perform physical activities	Reword as 'Because of my medications I have less energy for daily activities'	5 (100%)	Consensus agreement with proposal with wording adjustments	Rediscussed at meeting, the decision was revised; due to conceptual overlap, it was incorporated into Item 20	5 (100%)	Not applicable
23	I work less than usual because of the effect of my medicine/s	Remove, low relevance to older adults	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
24	Some of my medicine make me feel uncomfortable due to side effects	Reword to improve clarity 'Some of my medications cause unpleasant side-effects'	5 (100%)	Consensus agreement with proposal with wording adjustments The use of 'some of' implies more than one	Retain with changes # -Remove term 'some of'	5 (100%)	My medication causes unpleasant side effects.

New item				Proposal to include a specific item on the side effects of medication on cognition	Consensus agreement with proposal- very relevant side effect, particularly in the target population	5 (100%)	My medication negatively affects my memory and concentration.
Subscale D: The following statements are about medication burden related to health services.							
25	I am not treated with respect and dignity as a patient	Reword as 'I am not treated with respect and dignity by healthcare professionals', to improve specificity related to health services	4 (80%)	Consensus agreement with proposal with wording adjustments	Discussion and decision made to remove item- vague statement, does not clearly relate to MRB and significant floor effect measured in Phase 1	5 (100%)	Not applicable
26	My doctor doesn't take into account the health of my body, mind and spirit	Reword as, 'My doctor doesn't consider my opinions and preferences regarding my medication' 'body, mind and spirit' is not common terminology used by older adults	5 (100%)	Proposed alternative option <i>'My doctor does not consider my physical health, mental health, and emotional well-being all together'</i>	Retain with change: -Change 'doesn't' to 'does not' to improve clarity	5 (100%)	My doctor does not consider my opinions and preferences regarding my medication.
27	My doctor/s talk about my medicine/s as if I'm not there	Incorporate into item 26, overlap between both items	5 (100%)	Consensus agreement with proposal to incorporate	No change to initial proposal	5 (100%)	Not applicable

	Additional Item	'Poor communication about my medications between healthcare services places a burden on me'. This item was added based on focus group feedback highlighting that healthcare services are poorly coordinated regarding medications, potentially placing a significant burden on patients.	5 (100%)	Suggestion to provide some examples of healthcare services (e.g. my GP, the hospital and the pharmacy) <i>'Suggest 'It is difficult for me when changes in my medicines are not clearly communicated between healthcare services (e.g. hospital and GP)'</i>	Term 'GP' not internationally recognised- family doctor better Examples added to statement	5 (100%)	I find it difficult when changes in my medication are not communicated between healthcare services (e.g. hospital and family doctor).
	Additional Item				Appointments and monitoring (i.e. phlebotomy, blood pressure monitoring) in relation to medications can place a significant burden on patients.	5 (100%)	I find it difficult to manage and/or attend appointments in relation to my medication (e.g. bloods, follow ups).
Subscale E: The following statements are about the impact of medicines associated burden on social wellbeing.							
28	I would rather not tell others I'm taking medicines regularly	Remove, conceptual overlap with Item 30	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
29	I get embarrassed using my medicines in public	Remove, not relevant to target cohort	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable

30	I feel stigmatized because of what people say about the medicine's I take	Reword as, 'I would feel embarrassed if people knew about the number and/or types of medicines I take regularly'. This suggested phrasing improves comprehension	5 (100%)	Consensus agreement with proposal with wording adjustments	Retain with change: -Remove term 'regularly'	5 (100%)	I would feel embarrassed if people knew about the number and/or types of medication I take.
31	If people found out I was on medicines, they would see me as weak	Remove, not relevant	5 (100%)	Consensus agreement with proposal to remove	No change to initial proposal	5 (100%)	Not applicable
	Additional Item	'It bothers me that someone else has to organise my medicines'. This item was added based on focus group feedback that needing assistance with medications may impact social wellbeing	5 (100%)	'Organise' is only one aspect of medication management Proposed alternative option: <i>'It bothers me that someone else helps me with my medications'</i>	Retain as proposed alternative option	5 (100%)	It bothers me that someone else helps me with my medication.

Note: * 'Medicine' was changed to 'medication' throughout for consistent wording across items.

Syntax was edited for consistent phrasing across items.

4.3.5 Phase 5. Final modifications and Patient & Public involvement

4.3.5.1 Contributors

Three PPI contributors participated (two males, one female), with an age range of 65 to 87 years. All contributors were living with multimorbidity and were taking ≥ 5 long-term medications daily. One PPI contributor had prior experience with PPI exercises. One-to-one meetings were arranged to take place in a location that suited the contributor.

4.3.5.2 Outcome

Contributors completed a Think Aloud Task (TAT) while reviewing the first mMRB-QoL draft. Overall, contributors reported that the mMRB-QoL was user-friendly and relevant to older adults. Minor modifications were suggested, including repetition of the Likert scale halfway down the page and minor wording adjustments. The resulting final version of the mMRB-QoL tool is displayed in **Figure 4.5**.

The modified Medication-Related Burden Quality of Life (mMRB-QoL) Tool		Name/ID:					
		Date:					
Based on the past two weeks, indicate how much you agree or disagree with each statement.							
Section A: The following statements are about the burden associated with your medication regimen.							
		Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Not applicable
1	I find it difficult organising and/or managing my medication without help (carer/family).						
2	I find it difficult keeping an up-to-date record of my medication.						
3	My medication schedule restricts me in my daily routine.						
4	Taking my medication is challenging (e.g. injections, swallowing tablets, eye drops, inhalers, opening medication containers).						
5	Understanding the instructions on my medication is challenging (e.g. timings in relation to other medication/food etc).						
Section B: The following statements are about the impact of medicines associated burden on psychological wellbeing.							
6	I am concerned about the number of long-term medications I am on.						
7	I am concerned about the possible long-term side effects of my medication.						
8	I am concerned that my medication may interact with each other.						
Section C: The following statements are about the impact of medication associated burden on physical wellbeing.							
		Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Not applicable
9	I sleep poorly because of my medication.						
10	I have less energy for daily activities and/or feel 'slowed down' because of my medication.						
11	My medication causes unpleasant side effects.						
12	My medication negatively affects my memory and concentration.						
13	My medication negatively affects my sex life.						
Section D: The following statements are about medication burden related to health services.							
14	My doctor does not consider my opinions and preferences regarding my medication.						
15	I find it difficult when changes in my medication are not communicated between healthcare services (e.g. hospital and family doctor).						
16	I find it difficult to manage and/or attend appointments in relation to my medication (e.g. bloods, follow ups).						
Section E: The following statements are about the impact of medications associated burden on social wellbeing.							
17	I would feel embarrassed if people knew about the number and/or types of medication I take.						
18	It bothers me that someone else helps me with my medication.						

Figure 4.5: Final version of the mMRB-QoL tool.

4.4 Discussion

This study describes the novel development of the first PROM specifically designed to evaluate medication-related burden in older adults with multimorbidity and polypharmacy.

Findings from Phase 1 highlighted the challenges in applying the original MRB-QoL in this cohort. CFA demonstrated a ‘poor’ model fit and while some degree of overlap between factors is expected, a stronger model fit would typically be anticipated [205]. Furthermore, several subscales demonstrated significant floor effects, indicating limited effectiveness at discriminating between respondents [179]. Overall MRB-QoL burden scores were relatively low, and no significant correlation was observed between the number of medications, and number of comorbidities with reported burden – findings consistent with previous research in similar cohorts [108,139,206]. Potential explanations include caregiving support, adaptation to long-term treatment, and difficulty distinguishing the impact of long-term health conditions from adverse or burdensome effects of medication [108,139]. Additionally, limitations in the relevance and sensitivity of the original MRB-QoL may have restricted its ability to accurately measure medication-related burden in this population [108,206]. These findings indicated that reducing item number would be insufficient and that modification was required to ensure relevance, clarity and appropriateness for the target population. Such adjustments would address both the practical challenges and deficiencies of the original tool and strengthen the reliability and validity of the mMRB-QoL in older adults with multimorbidity and polypharmacy.

Scale modification is commonly undertaken, and almost half (45.8%) of published assessment scales are reported as adapted from earlier versions [204]. However, scale

shortening and modification is often based on weak methodological processes that limit the validity and utility of the modified or abbreviated scale [178,207–209]. Where a gold standard exists, modification should be based on criterion validity; however, for constructs such as QoL, there is no gold-standard measurement. One commonly used but flawed method in such scenarios is to rely excessively and uncritically on statistical results such as Cronbach's alpha coefficient or factor analysis to select items. This can result in problems of component under- or over-extraction, resulting in a poor selection of items to retain and reduced construct validity [178,207]. To overcome this challenge, the present study followed a transparent mixed methods process that integrated psychometric analysis, qualitative insights, expert consensus, and PPI contribution. Notably, half of the participants in the qualitative phase were aged 80 years or older, a deliberate sampling strategy designed to ensure that the perspectives of the oldest population cohort informed scale modification and enhanced relevance and sensitivity of the mMRB-QoL for the target population. Item-level decisions were driven primarily by expert consensus, supported by questionnaire results [178,207]. The final PPI review ensured usability and appropriateness for older adults. This triangulation of data sources preserved the psychometric, construct and content validity of the original MRB-QoL while ensuring that the mMRB-QoL is firmly grounded in the lived experiences and preferences of end-users.

The mNGT process facilitated structured expert consensus, enhancing methodological transparency and supporting item refinement. Retaining the original conceptual model and Likert response format ensured continuity and comparability with the original MRB-QoL, while wording revisions were made to improve clarity and discrimination between respondents [204,210]. Although items relating to sexual function generated high levels of 'not applicable' responses during the prospective assessment of the

MRB-QoL, the panel concluded that omitting this aspect entirely would inappropriately exclude a less common yet important aspect of medication-related burden in older adults [209].

4.4.1 Comparison with existing literature

Concerns regarding scale sensitivity and relevance of existing PROMs are supported by a systematic review by Lesage et al. [211]. In this review, which examined studies measuring the impact of medical interventions on patient-reported burden of treatment, the authors suggest that the use of inappropriate outcome measures that lack specificity and relevance may explain the absence of change in patient-reported burden [211]. This highlights the need for a specific tool for older adults living with multimorbidity and polypharmacy.

Similar challenges have been reported with other treatment and medication-burden questionnaires. In a UK study evaluating the MTBQ in adults over 55 years, Morris et al. reported only modest psychometric performance and suggested that MTQB, in its current form, was not appropriate for use in routine clinical practice [212]. The study also demonstrated an inverse relationship between age and reported burden, a phenomenon also observed in other studies [141,213]. While this may be attributable to factors such as fewer competing demands following retirement, increased formal and informal support, and changing expectations regarding healthcare burden, it may also reflect reduced sensitivity of existing instruments when applied to older populations living with multi-morbidity.

Other medication-focused instruments also have limitations when applied to older adults with polypharmacy. For example, the Living with Medicines Questionnaire (LMQ) assesses aspects of medicine-related burden but comprises 41 items and was

developed primarily in younger adult populations [140]. In its development and validation study, over 90% of participants were aged under 65 years and more than half were taking fewer than five medications. These design characteristics may impose a high respondent burden and limit feasibility and relevance in frail older adults.

4.4.2 Strengths and limitations of study

The principal study strength was its mixed-methods design, integrating statistical analysis, qualitative input from end-users (both questionnaire administrators and respondents), expert consensus and PPI contribution. Compared to the original MRB-QoL, the modified version has the advantage of greater relevance and conciseness, providing a comprehensive yet user-friendly scale to measure older patients' medication-related quality-of-life burden.

Despite efforts to include the most important items and to maintain the holistic view over all areas important to QoL, shortening the MRB-QoL may have compromised the ability to address specific issues relevant to the respondent. Additionally, as with all patient-reported measures, further validation steps are required including confirmatory factor analysis, test-retest reliability, sensitivity and responsiveness of the mMRB-QoL in diverse populations and clinical settings.

4.5 Conclusion

The mMRB-QoL is the first patient-related outcome measure specifically designed to assess the individualised impact of medication-related burden in older adults with multimorbidity and polypharmacy. It represents a comprehensive and substantial modification of the original MRB-QoL. It has the potential to support healthcare professionals and researchers to recognise and understand the impact of polypharmacy

on the QoL of older people. However, further internal and external validation is required before the mMRB-QoL can be integrated into clinical practice or used as an outcome measure in pharmacotherapy research studies in older people.

CHAPTER FIVE

Summary and Conclusion

5.1 Summary of research findings

This thesis examined important aspects of adverse medication outcomes experienced by older adults living with multimorbidity and polypharmacy. While advances in pharmacotherapy over the past century have substantially improved health outcomes and longevity, they have also contributed to a polypharmacy culture and consequently patients can be subjected to complex and burdensome medication regimens. Prescribing in older patients with multimorbidity is also complicated by the organisation of modern healthcare, which remains largely structured around individual disease frameworks with limited integration between specialities and disconnected information systems across community and hospital settings. These factors, along with the practice of excluding representative older adults with multimorbidity and frailty from clinical trials, increases the risk of problematic prescribing and medication-related harm. This thesis has focused on prescribing cascades and medication-related burden, which despite their clinical relevance, remain under-investigated and under-recognised as adverse outcomes in clinical practice. Accordingly, this thesis aimed to contribute to the medical literature by expanding the understanding of prescribing cascades and by developing a patient-reported outcome measure (PROM) specifically designed to assess medication-related burden in older adults with multimorbidity and polypharmacy.

Older adults living with multimorbidity and polypharmacy were the primary focus of this thesis. This cohort is particularly vulnerable to medication-related harm due to increasing comorbidity burden, frailty, age-related physiological changes and frequent under-representation in clinical research. Across the studies described in Chapters 2 and 4, a total of 540 patient participants were included, with comparable clinical and pharmacotherapy characteristics in both studies. The cohort had a mean age of 80.2

years. Almost all (95%) were living independently with multimorbidity and polypharmacy in the community i.e. not in institutional care. Almost half (45.5%) had major polypharmacy i.e. ≥ 10 daily long-term medications and approximately one third (31.8%) were classified as moderately or severely frail according to Rockwood's Clinical Frailty Scale [214]. Half of the patient participants in the qualitative research study were aged 80 years or older, a deliberate sampling strategy. The patient participants included in this thesis therefore reflect 'real-world' older adults at high risk of adverse medication outcomes, commonly encountered in clinical practice.

In Chapter 2, I investigated the prevalence of potential prescribing cascades in hospitalised older adults with multimorbidity and polypharmacy. Prescribing cascades were identified according to two explicit lists that had been published shortly before the design and conduct of the data collection i.e. the ThinkCascade list and the Doherty list. A prescribing cascade assessment tool was developed to standardise classification in alignment with the WHO-UMC's ADR causality assessment tool [79,86,147]. The prescribing cascade assessment tool provides clear guidance on the likelihood of a prescribing cascade, is easy to apply, and has demonstrated excellent inter-rater reliability (ICC 0.935 (95% CI [0.884, 0.964])).

Using these sets of explicit prescribing cascade criteria, potential prescribing cascades were identified in approximately two-fifths (39.4%) of patients, of which 41.4% were classified as possible and 4.6% as probable. The most frequently identified probable or possible prescribing cascade was diuretic to overactive bladder medication. Patients with potential prescribing cascades experienced higher levels of polypharmacy and higher comorbidity burden compared to patients with no identified prescribing cascade. Notably, over three quarters of identified prescribing cascades remained in

place at the time of hospital discharge i.e. they were either not identified or were identified and not corrected. This study demonstrated that potential prescribing cascades are highly prevalent among hospitalised older adults and are under-recognised.

In Chapter 3, qualitative research was conducted to examine factors influencing recognition of prescribing cascades. Semi-structured interviews were conducted with hospital physicians across all grades, from intern to consultant. This is the first study to explicitly elucidate determinants affecting recognition of prescribing cascades by hospital-based physicians. The findings supported the hypothesis that prescribing cascades are under-recognised in clinical practice. Four TDF domains appeared as predominant, namely: *'Environmental context and resources'*, *'Knowledge'*, *'Social/professional role and identity'*, and *'Social Influences'*. Knowledge of prescribing cascades was limited among all interviewees. Some, particularly senior physicians, were unfamiliar with the term 'prescribing cascade'. Furthermore, no interviewee could recall hearing the term 'prescribing cascades' ever being explicitly mentioned in a clinical setting.

Chapter 4 addressed medication-related burden and its impact on quality of life (QoL) through the development of the mMRB-QoL, a modified short form of the original MRB-QoL [137]. The MRB-QoL was selected for adaptation due to its strong conceptual foundation and prior validation; however, limitations were identified when applied to older populations i.e. its length, complexity, and questionable relevance of some items. It is distinct from generic health-related quality of life tools as described in Chapter 1, which measure broader treatment burden or combine medication-burden

with other constructs such as morbidity, non-pharmacological treatments, limiting their specificity to pharmacotherapy-related outcomes.

The mixed-methods approach was designed to achieve two primary goals. First, it maintained the original MRB-QoL conceptual model while preserving content validity and psychometric properties. Second, it ensured that the modified tool reflected the lived experiences of those patients who are most vulnerable to medication-related burden, thereby enhancing its relevance and sensitivity for this population. Triangulation across five phases, including psychometric evaluation, qualitative research with end-users, multidisciplinary expert analysis, formal consensus methods (included expert representatives from geriatric medicine, pharmacy, and general practice) and PPI contribution, informed item reduction and modification. The resulting 18-item short form mMRB-QoL retained the original subscale structure while improving clarity, reducing respondent burden, and maximising accessibility. New items were added to reflect domains particularly relevant to older adults, including cognitive burden and management of healthcare. This tool may enable the measurement of meaningful patient-reported outcomes in a patient cohort for whom this has been difficult to achieve using pre-existing tools.

Improving the awareness of prescribing cascades and medication-related burden highlights the complexity of prescribing and deprescribing in this at-risk population. Optimising medications for these older adults requires a nuanced, multifaceted approach supported by expertise in geriatric pharmacotherapy. However, in this thesis the great majority (84%) of hospitalised older adults with multimorbidity and polypharmacy were under the care of specialists without expertise in geriatric pharmacotherapy. This pattern is likely to persist, as admission under the care of other

specialty services is often clinically appropriate (for example, admission under cardiology for an acute myocardial infarction) and, with an ageing population, is it not feasible for all older adults to be managed exclusively within specialist geriatric services. This emphasises the need for novel medication management frameworks and models of care to support older adults living with complex polypharmacy.

5.2 Strengths and limitations of these research findings

The specific strengths and limitations of each study have already been described in the individual research chapters (Chapters 2 – 4). However, the main overarching strengths and limitations of this thesis are outlined below.

A key strength was the complementary use of quantitative and qualitative research, in relation to both prescribing cascades and the development of the mMRB-QoL. The prescribing cascade work combined a prospective prevalence study with theory-informed qualitative research, allowing both measurement of prevalence and identification of determinants influencing prescribing cascades recognition in practice. The development of the mMRB-QoL similarly integrated qualitative with quantitative evidence to enhance validity, relevance and acceptability for older adults living with multimorbidity and polypharmacy. Where available, the studies in this thesis were reported in accordance with best practice guidelines. Reporting of the prescribing cascade prevalence study was guided by the STROBE checklist, the qualitative research in Chapters 3 and 4 was reported in accordance with the COREQ checklist and the GRIPP2 checklist guided reporting of patient/public involvement (PPI) in Chapter 4. Finally, all three research chapters in this thesis are novel and have either been published in peer-reviewed journals or are currently under review for publication.

Furthermore, the findings from this thesis have been presented at local, national, and international conferences – reflecting substantial interest in this body of work, the quality of the research conducted, and its relevance to clinical practice and research.

There are some limitations to consider. First, participants (both patients and HCP's) included in this thesis all were recruited from healthcare services affiliated with a single university hospital. Consequently, the findings may not be fully transferable to other clinical settings or healthcare systems.

Second, prescribing cascades often represent adverse medication outcomes; however, some prescribing cascades may be therapeutically and clinically appropriate and may not require deprescribing e.g. laxatives following opioid prescription. In this thesis, the persistence of prescribing cascades at hospital discharge was suggestive of poor recognition. However, it is possible that some of the identified prescribing cascades (a small minority) were clinically appropriate and therefore were appropriately continued at discharge. The explicit lists used to identify prescribing cascades included drug pairs that may be appropriate in some clinical contexts (for example Amiodarone followed by L-thyroxine). Determining the appropriateness of prescribing cascades was beyond the scope of this thesis. Nevertheless, this limitation is partly mitigated by the qualitative findings, which support the conclusion that prescribing cascades are poorly recognised in clinical practice in hospitals.

Finally, while the methodology of the study in Chapter 4 was designed to preserve the validity of the original MRB-QoL in the modified versions, prospective validation of the mMRB-QoL was not undertaken in this thesis. This was beyond the timeframe of

this body of work, and priority was placed on conducting a comprehensive development process to ensure relevance and sensitivity for the target population.

5.3 Directions for future research

This thesis has identified several areas that warrant investigation. First, further prevalence studies of potentially inappropriate prescribing cascades are required across wider healthcare settings to improve generalisability of findings. Since completion of the prevalence study reported in this thesis, a more comprehensive explicit prescribing cascade list has been published: the International Expert Panel's Potentially Inappropriate Prescribing Cascades (PIPC) list [150]. This list includes 65 potentially inappropriate prescribing cascades identified through a modified Delphi process and represents an advancement, both in terms of number and clinical relevance, of prescribing cascades. In addition, longitudinal and interventional studies are needed to better assess the prevalence of confirmed prescribing cascades by applying a more definitive test, for example, observation for resolution of ADR/ADE symptoms by discontinuing the index medication, where clinically appropriate.

Second, the findings from the study reported in Chapter 3 point to multiple opportunities for behaviour change interventions aimed at improving the recognition of prescribing cascades. The TDF is often applied with the Behaviour Change Wheel (BCW) to systematically design targeted, theory-based interventions [215]. Identification of all 14 TDF domains in this thesis allows for a multi-faceted intervention to be designed. For example, 'knowledge' was identified as a key domain influencing physicians' recognition of prescribing cascades. According to the BCW model, knowledge maps onto 'capability', which can be addressed through

intervention functions such as modelling, education, and enablement [215]. A potential intervention could involve interactive, case-based learning sessions for both junior and senior doctors, where prescribing cascade scenarios are discussed. In addition, while ‘beliefs about consequences’ was identified as a less influential domain, it could still be integrated into the intervention as ‘motivation’ and ‘education’ components. Incorporating discussions on the potential harm to patients and the clinical responsibility to recognise and deprescribe inappropriate prescribing cascades could enhance the effectiveness of the intervention. Future research should focus on the development and evaluation of multi-component interventions, such as the one described, to address the barriers to recognising prescribing cascades.

Third, as with all PROMs, further internal external validation steps are required before the mMRB-QoL can be integrated in clinical practice or used as an outcome measure in pharmacotherapy research. Future validation should include confirmatory factor analysis, test-retest reliability, sensitivity to change, and the responsiveness of the mMRB-QoL in diverse populations and clinical settings.

Finally, improved understanding of adverse medication outcomes, including prescribing cascades and the impact of medications on QoL, has the potential to improve the management of complex medication regimens, with the aim of reducing medication-related harm. Future studies are required to evaluate coordinated models of care designed to optimise pharmacotherapy for older adults with multimorbidity and polypharmacy. One potential framework is polypharmacy stewardship, a novel concept intended to promote the appropriate use of medication and minimise medication-related harm. The process model for polypharmacy stewardship is illustrated in **Figure 5.1** [143]. Implementation of a polypharmacy stewardship model

would vary depending on the healthcare setting, and well-designed clinical trials are required to evaluate the effectiveness of such a framework in older patients, both in hospital and in the community setting. This model could incorporate assessment for prescribing cascades, as well as the mMRB-QoL to help assess the burden that medication places on patients' lived experiences, allowing for personalised, patient-centred intervention.

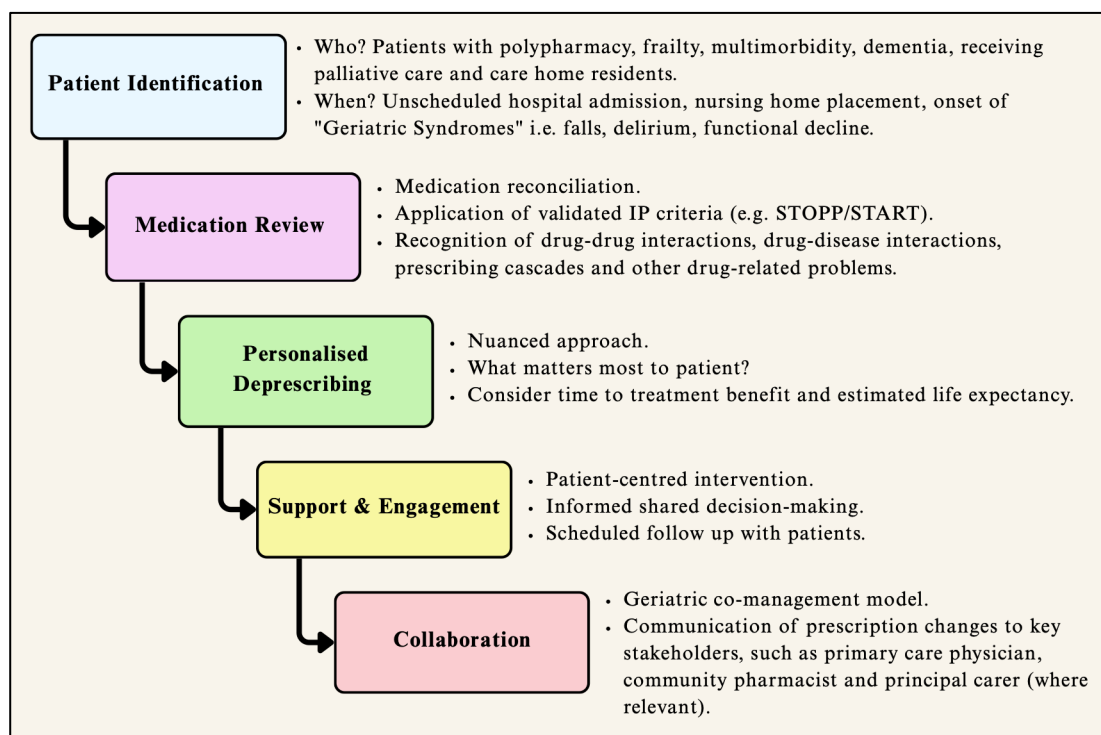


Figure 5.1: Process Model for Polypharmacy Stewardship [143].

5.4 Conclusion

Overall, the research presented in this thesis advances the medical literature on adverse medication outcomes in older adults living with multimorbidity and polypharmacy. Findings demonstrated that prescribing cascades are common in hospitalised older adults and provided insights into factors influencing their recognition. In addition, this work presented a practical tool to measure the impact of medication-related burden in

the population most at risk. Collectively, these findings highlight opportunities to improve recognition of prescribing cascades and the assessment of medication-related burden, with implications for clinical practice, undergraduate and postgraduate education, and future research.

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APPENDIX 1

Publications in peer-reviewed journals and presentation of work

CHAPTER ONE	
Publications	
• Daunt R, Curtin D, O'Mahony D. Polypharmacy stewardship: a novel approach to tackle a major public health crisis. <i>The Lancet Healthy Longevity</i>. 2023 May 1;4(5):e228-35. • Daunt R, Curtin D, O'Mahony D. Optimizing drug therapy for older adults: shifting away from problematic polypharmacy. <i>Expert Opinion on Pharmacotherapy</i>. 2024 Jun 12;25(9):1199-208.	
CHAPTER TWO	
Publication	
• Daunt R, McGettigan S, Kelly L, Curtin D, O'Mahony D. Detection of potential prescribing cascades in multimorbid older patients hospitalised with acute illness—an observational prospective prevalence study. <i>Drugs & aging</i>. 2025 Apr 4;42(6):535.	
Presentations	
• College of Medicine and Health Research Conference UCC, 2024. • Irish Geriatric Society Annual and Scientific Meeting, 2024. • European Geriatric Medicine Society Congress, 2024.	
CHAPTER THREE	
Publication	
• Daunt R, Dalton K, Curtin D, O'Mahony D. Factors Influencing Hospital Physicians' Recognition of Prescribing Cascades: A Qualitative Interview Study: R. Daunt et al. <i>Drugs & Aging</i>. 2025 Jul 4:1-6.	
Presentations	
• College of Medicine and Health Research Conference, UCC 2024. • Irish Geriatric Society Annual and Scientific Meeting, 2025.	

CHAPTER FOUR	
Submitted Manuscript	
• Development of a modified Medication-Related Burden Quality of Life (mMRB-QoL) short-form tool for older people with multimorbidity and polypharmacy: a mixed-methods study (<i>Research in Social and Administrative Pharmacy</i>).	
Presentation	
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Polypharmacy stewardship: a novel approach to tackle a major public health crisis

Ruth Daunt, Denis Curtin, Denis O'Mahony



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Department of Medicine,
School of Medicine, University
College Cork, and Department
of Geriatric Medicine, Cork
University Hospital, Wilton,
Cork, Ireland

(R Daunt MB MRCP,
D Curtin PhD MRCP,
Prof D O'Mahony MD FRCP)

Correspondence to:
Prof Denis O'Mahony,
Department of Geriatric
Medicine, Cork University
Hospital, Wilton, Cork T12 DC4A,
Ireland
denis.omahony@ucc.ie

With growing global concern regarding medication-related harm, WHO launched a global patient safety challenge, Medication Without Harm, in March, 2017. Multimorbidity, polypharmacy, and fragmented health care (ie, patients attending appointments with multiple physicians in various health-care settings) are key drivers of medication-related harm, which can result in negative functional outcomes, high rates of hospitalisation, and excess morbidity and mortality, particularly in patients with frailty older than 75 years. Some studies have examined the effect of medication stewardship interventions in older patient cohorts, but focused on a narrow spectrum of potentially adverse medication practices, with mixed results. In response to the WHO challenge, we propose the novel concept of broad-spectrum polypharmacy stewardship, a coordinated intervention designed to improve the management of multimorbidities, taking into account potentially inappropriate medications, potential prescribing omissions, drug–drug and drug–disease interactions, and prescribing cascades, aligning treatment regimens with the condition, prognosis, and preferences of the individual patient. Although the safety and efficacy of polypharmacy stewardship need to be tested with well designed clinical trials, we propose that this approach could minimise medication-related harm in older people with multimorbidities exposed to polypharmacy.

Introduction

In March, 2017, WHO launched a global patient safety challenge, called Medication Without Harm, as a response to a growing global concern regarding drug-related iatrogenic injury.¹ More drugs, vaccinations, procedures, and medical specialists exist today than at any other time in history. These advances in health care have enabled people to live better and longer lives by eradicating infectious diseases such as poliomyelitis, allowing some previously lethal illnesses to be cured, and providing effective management of highly prevalent chronic conditions such as hypertension, diabetes, and cardiovascular disease.^{2–5} However, these developments have also created a health-care system in which both patients and physicians expect prescription medicines to be available for every clinical problem, which results, in many countries, in a therapeutic climate that promotes the simultaneous use of multiple medications, a practice known as polypharmacy.⁶ The minimum number of medications used to define polypharmacy varies in the literature, but the term generally refers to five or more drugs taken daily.⁷ Hyperpolypharmacy, or excessive polypharmacy, refers to concurrent use of ten or more daily medications.⁷ Patients older than 65 years with multimorbidity are most vulnerable to the adverse effects of polypharmacy and inappropriate prescribing, and are consequently at a higher risk of medication-related harm.⁸ The 2017 WHO initiative challenged health-care leaders to drive change and reduce iatrogenic medication-related morbidity and mortality by 50% in the prospective 5 years to 2022.¹ Although the Medication Without Harm initiative was timely and appropriate, it had little specific detail about how health-care systems would actually implement and measure the impact of various interventions to decrease iatrogenic injury caused by potentially inappropriate medication.

Several large-scale, multicentre clinical trials have attempted to address this challenge by testing novel interventions to reduce medication-related harm in older people with multimorbidity exposed to polypharmacy.^{9–13} Given that none of these trials has yielded an intervention that is reproducibly effective in improving clinical outcomes for older patients, the need persists for a different—but practical—approach to managing polypharmacy in this section of the population. In this Personal View, we examine the concept of polypharmacy stewardship as a novel way of assessing and optimising polypharmacy in older people. We will also look at the potential of adapting the principles of antimicrobial stewardship to polypharmacy in late life (aged ≥70 years) and propose a framework for polypharmacy stewardship that could be applied to a variety of clinical settings. In doing so, we emphasise the large, diverse, and complex nature of polypharmacy in the heterogeneous population of older people with multimorbidity, as well as the need for polypharmacy stewardship to be interdisciplinary and highly integrated across health-care settings.

Diseases, drugs, and doctors

As individuals age, they tend to accumulate chronic medical conditions, a concept described as multimorbidity (ie, the coexistence of two or more chronic medical conditions in a patient).¹⁴ Multimorbidity is associated with reduced functional status, high mortality, lower quality of life, and increased use of health care.^{15–17} A consistent cause-and-effect relationship exists between ageing, multimorbidity, and polypharmacy.⁵ Two large systematic reviews of multimorbidity prevalence have shown similar results: the first analysed 193 studies and found a multimorbidity prevalence of 67% in people older than 74 years, compared with 47% in those aged 60–74 years and 28% in those younger than 60 years,¹⁸ and the second found that more than 50% of adults older

	Community-dwelling adults	Hospitalised patients	Nursing home residents
STOPP/START, version 2, 2015	66·8% ²¹	68·5–86·1% ²²	64·8–86·5% ²³
Beers Criteria, American Geriatrics Society, 2015	54·0% ²¹	21·6–71·5% ^{24,25}	51·1–52·4% ²⁶

STOPP=Screening Tool of Older Persons' Prescriptions; START=Screening Tool to Alert to Right Treatment.

Table. Estimated prevalence of potentially inappropriate prescribing in older people in different care settings, by criteria

than 65 years have multimorbidity.¹⁹ WHO predicts that the global population of people older than 65 years will double between 2015 and 2050, which will result in a subsequent large increase in the number of people living with multimorbidity and polypharmacy.²⁰

Reducing medication-related harm is particularly challenging in the context of multimorbidity and polypharmacy, which might be appropriate and beneficial when treating complex comorbidities in older patients, particularly when individual drugs are carefully considered in the context of the overall condition and prognosis of the patient. However, polypharmacy can beget a cluster of interconnected problems, increasing the risk of inappropriate prescribing, adverse drug reactions and adverse drug events, prescribing cascades, drug–drug interactions, unscheduled hospitalisation, and drug-related mortality.^{21–23} The prevalence of polypharmacy is growing globally, primarily but not exclusively in older adults, and predominantly involving prescription drugs (but also over-the-counter drugs and herbal remedies), with the number of daily medications being generally proportional to the number of concurrent chronic medical conditions.

The number of patients experiencing polypharmacy is growing worldwide. In the UK, this number doubled between 1995 and 2010.²⁴ In the USA, Australia, and Europe, the prevalence of polypharmacy among care home residents is estimated to range from 38·1% to 91·2%.²⁵ In China, the prevalence of polypharmacy among community-dwelling adults ranges from 11·5% to 17·5%.²⁶ Older people are more vulnerable than younger people to polypharmacy-induced harm, as a consequence of age-related physiological changes that commonly alter the pharmacokinetic and pharmacodynamic response to medication.²⁷ The impact of these changes is compounded by a high burden of multimorbidity that often results in older patients attending consultations with multiple doctors in various health-care settings, resulting in the accumulation of drug prescriptions without due consideration of potential adverse drug–drug and drug–disease interactions.^{28,29}

Inappropriate prescribing³⁰ is highly prevalent in older people in various clinical settings (table). Inappropriate prescribing is important because it substantially increases the risk of adverse drug reactions, adverse drug events, drug–drug interactions, and adverse drug–disease

interactions. Polypharmacy, in turn, is the principal risk factor for inappropriate prescribing in older people.³¹ This occurrence is more evident in older women than in older men because women older than 70 years substantially outnumber men in the same age category in most countries.³²

Modern medical practice has, to a large extent, been organised according to a framework in which diseases are managed as individual, independent entities. Consequently, patients with multimorbidity often interact with several different specialists, who apply best practice guidelines optimised for the particular condition they are treating, rather than the patient's overall multimorbid clinical status. Treatment guidelines are usually derived from clinical trials focused on single diseases, and from which older, comorbid people are often excluded.³³ Adherence to evidence-based management guidelines for common conditions such as hypertension, chronic obstructive pulmonary disease (COPD), and coronary artery disease has been shown to improve clinical outcomes for individuals with such conditions.^{34–36} However, physicians often fail to recognise the impact of the complex, interlinked, pathophysiological changes that multimorbidity induces on older patients' overall health.³⁷ Application of multiple disease treatment guidelines to an older individual can result in complex, costly, and at times contradictory treatment regimens³⁸ that increase the risk of polypharmacy and of subsequent medication-related harm. Reporting on patient care in six countries, Schoen and colleagues³⁹ found that patients who were cared for by four or more doctors were substantially more likely to be affected by serious medication errors than those who attended consultations with fewer than four doctors.

Medication-related harm also has a substantial impact on prescribers.⁴⁰ Psychological distress, loss of self-perceived competence, and burnout are reported by prescribers when their patients undergo serious iatrogenic harm.⁴¹ In addition, despite the adverse events faced by patients, doctors might hide their mistakes from both their colleagues and their patients due to feelings of guilt and shame, or fear of criticism or litigation, which results in missed opportunities to strengthen the safety of health-care settings.⁴²

Economic consequences of polypharmacy

Polypharmacy places an economic burden on health-care systems by increasing drug expenditure and the costs of managing medication-related harm. WHO estimates that mismanaged or suboptimal prescribing accounts for approximately 4% of the world's total avoidable health-care costs.⁴³ Morgan and colleagues⁴⁴ examined the cost of potentially inappropriate medications prescribed to adults older than 65 years in Canada, and estimated that CA\$419 million were spent on potentially inappropriate medication across the country in 2013 alone. Research conducted by the Intercontinental Medical Statistics

Institute for Healthcare Informatics estimated that US\$ 42 billion are spent annually in the USA as a consequence of medication errors.³¹ The same report also estimated that optimising polypharmacy management could save approximately 0–3% of the current global total health expenditure. A 2022 British prospective observation study³² estimated that morbidity arising from adverse drug reactions accounts for approximately one-eighth of total expenditure on acute hospital admissions, costing the UK's National Health Service approximately £2.21 billion annually, with most of the excess hospitalisations occurring in older people with multimorbidity and polypharmacy.

The economic benefits of any programme designed to address polypharmacy and its adverse effects must be considered alongside patient engagement, patient health promotion, and staff wellbeing—the so-called quadruple aim strategy.³⁴ With these targets in mind, we propose the idea of polypharmacy stewardship as a multicomponent intervention to reach these aims in a coordinated manner.

Polypharmacy stewardship

Polypharmacy stewardship is a novel concept that aims to promote the appropriate use of medication and minimise medication-related harm. We define polypharmacy stewardship as a coordinated intervention designed to assess, monitor, improve, and measure the pharmacotherapeutic treatment of multimorbidity, taking into account potentially inappropriate medications, potential prescribing omissions, drug–drug and drug–disease interactions, and prescribing cascades, with the aim of aligning treatment regimens with the overall condition, prognosis, and preferences of the individual patient.

The concept of clinical stewardship first appeared in the medical literature in 1996 and it referred to antibiotic use in hospital,³⁵ for which it has been shown to improve clinical and economic outcomes.^{36,37} Since then, several other models of treatment-specific stewardship programmes have emerged and become established in routine clinical practice in many countries, such as corticosteroids for COPD³⁸ and opioid therapy for chronic pain syndromes.³⁹

However, the idea of medication stewardship in older people is a relatively new one. In a 2018 Australian study, Pellicano and colleagues⁴⁰ reported on a psychotropic stewardship intervention in older patients in a general internal medicine ward. The stewardship intervention was delivered by pharmacists and was designed to identify unnecessary or inappropriate psychotropic drugs during structured multidisciplinary medication rounds, with the goal of bringing these prescriptions to the attention of the attending medical team for careful review and possible deprescribing. This study showed that the stewardship intervention was both feasible and effective, with the recommendations of the stewardship team being adopted for 57% of potentially problematic psychotropic medications within 24 h of admission, and

for 53% of psychotropic medications at discharge. In a 2021 Dutch study,⁴¹ the effect of a broader-spectrum stewardship intervention on drug-related problems was examined in a subgroup of 53 individuals from a larger cohort of 127 older hospitalised patients. The intervention involved a pharmacist and a geriatrician. Although the prevalence of drug-related problems was not statistically significantly reduced in patients receiving the medication stewardship intervention, drug-related complaints (eg, pain, drowsiness, nausea, and constipation) were reduced by approximately 50%. However, the study was of a small scale, used a before-versus-after design, and involved older surgical patients only. A 2023 Australian study³² examined the effect of a medication stewardship intervention in hospitalised patients aged 75 years and older. Patients were identified by screening of their electronic medical records for drug burden index scores greater than 0, indicating potentially problematic exposure to anticholinergic and sedative medications. The medication steward—a skilled and experienced pharmacist—then undertook a structured medication review to identify possible opportunities for deprescribing of non-essential drugs contributing to the high drug burden index score. Drugs considered by the steward as potentially suitable for deprescribing were discussed with the senior physician of the attending medical team. In the 256 patients reviewed, the steward identified 170 potential opportunities for deprescribing in 117 patients (46%). 82.9% of deprescribing recommendations by the steward were agreed to by the senior physicians as appropriate, and were for the most part subsequently implemented in the patients' medication regimens. Although this open-label, non-randomised feasibility study was of narrow spectrum in terms of medication focus, it nevertheless clearly shows the potential benefit of medication stewardship in older patients with multimorbidity in the hospital setting.

As with antimicrobial stewardship, no single operational model for polypharmacy stewardship exists. Implementation of polypharmacy stewardship requires flexibility to adapt to a wide variety of health-care settings. For example, in the hospital setting, polypharmacy stewardship could operate as a specialist consultation service for older patients identified as being at high risk of medication-related morbidity, in conjunction with a dedicated outpatient service for patients similarly identified as high-risk in the community. The principles of polypharmacy stewardship and its core components are intended as a framework to guide implementation for a variety of models of polypharmacy stewardship. Core principles of polypharmacy stewardship include optimisation of the technical aspects of prescribing (eg, dose, formulation, and frequency), setting of realistic treatment goals, avoidance of adverse drug events, and provision of support and follow-up to patients with multimorbidity and, if necessary, their carers, who might have

responsibility for supervising medication. Polypharmacy stewardship also entails liaison with key stakeholders, including primary care physicians and community pharmacists. The process model for polypharmacy stewardship is illustrated in the figure.

Technical aspects of prescribing

Appropriate prescribing requires accurate diagnosis, careful selection of medications and doses, and focused monitoring of therapeutic response. Appropriate deprescribing encompasses similar principles and, within polypharmacy stewardship, prescribing and deprescribing will often happen simultaneously.⁴³ Deprescribing is a systematic process that includes medication reconciliation—ie, the process of creating an accurate and comprehensive list of all medications (prescription or not) that a patient is taking and identifying instances of non-adherence. Non-prescription (ie, over-the-counter) drugs present a particular challenge in older people during medication review. Patients might not consider over-the-counter drugs as actual medications, but rather as discretionary additions to address symptoms they find bothersome but not serious enough to require the attention of their doctors. However, over-the-counter drugs can have serious side-effects and induce adverse drug–drug and drug–disease interactions. An example of an adverse interaction between an over-the-counter drug and a prescription drug is that of a first-generation antihistamine (eg, diphenhydramine) interacting with prescription hypnotics such as zolpidem or triazolam, resulting in excessive sedation or confusion. The interaction of pseudoephedrine (a widely available nasal congestion remedy) and hypertension is an example of an adverse over-the-counter drug–disease interaction.

Deprescribing also requires consideration of the cumulative risk from multiple simultaneous drugs and diseases, and identification of potentially important

adverse drug–drug interactions and drug–disease interactions. Over the past 30 years, multiple criteria-based tools (eg, STOPP/START,⁴⁴ STOPP/Frail,⁴⁵ Beers Criteria,⁴⁶ and EURO-FORTA⁴⁷) have been developed and validated to support physicians in making prescribing decisions specifically for older patients. The criteria are explicit (ie, clearly defined statements that highlight inappropriate prescribing in particular clinical circumstances) and are based on systematic reviews, clinical trial evidence, expert opinion, and Delphi consensus validation. The STOPP/START criteria, which are endorsed by the UK National Institute for Health and Care Excellence, Royal College of General Practitioners, and British Geriatrics Society for use in routine medication review for older people,^{48,49} are more commonly used in Europe. The Beers Criteria, which are published by the American Geriatrics Society, feature more prominently in clinical practice in the USA and Canada.

Nuanced prescribing and deprescribing

Effective management of polypharmacy in older patients with multimorbidity requires a nuanced approach, and two main questions should be considered when assessing medication appropriateness. The first question is whether the goals of treatment align with what matters most to the patient. The goals of the physician and the patient are often easily aligned, such as in the prescribing of analgesics for control of pain. Disease control medications (eg, antihypertensive drugs) or disease preventive medications (eg, anticoagulants for patients with atrial fibrillation) do not usually make the patient feel better, and the prescriber should therefore translate technical targets (eg, blood pressure control) into goals that are meaningful to the patient (eg, stroke prevention); the patient is thus more likely to accept and comply with a long-term preventive drug to avoid a major adverse

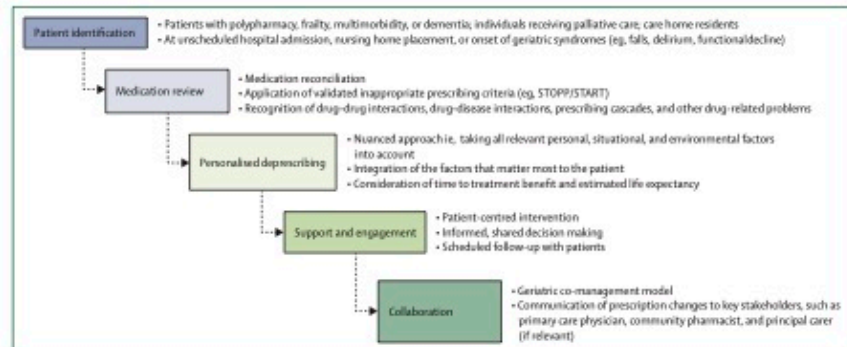


Figure: Schematic representation of the stages of the polypharmacy stewardship model
STOPP=Screening Tool of Older People's Prescriptions. START=Screening Tool to Alert to Right Treatment.

outcome. In the context of advanced physical frailty, or when a patient is approaching the end of life, achieving technical goals might be of little or no benefit to the patient, and placing greater emphasis on important patient-related goals (eg, control of pain) represents a higher-value intervention. Establishing what matters most to an individual patient will guide prioritisation of treatment goals and thereby specific drug selection.⁷⁹

The second question is whether the prescribed drug will achieve its intended benefit within the context of a patient's circumstances. In patients with advanced frailty or severe chronic disease, the benefits of preventive drugs might not be reaped within the remaining life expectancy of the patient. When reviewing medications, such as statins and bisphosphates for secondary disease prevention in frail older patients, deprescribing should be considered when there is a clear mismatch between time to treatment benefit and estimated life expectancy.⁴⁵ Although precisely predicting remaining life expectancy is not possible, the so-called surprise question (ie, "would I be surprised if this patient were to die within the next 12 months?"), can be useful to physicians as a method to identify individuals approaching end of life.⁷¹

Support and engagement

Deprescribing is a patient-centred intervention, associated with inherent uncertainty and requiring shared decision making.³ Patients might be reluctant to accept medication changes because they overestimate the adverse effects of discontinuing certain drugs, and underestimate the risks associated with continuing inappropriate drugs. Effective communication, sharing of drug information, and support with medication choice can help overcome this deprescribing challenge and could facilitate the patient's participation in informed, shared decision making about their medication.^{41,70} Follow-up clinical encounters allow prescribers to monitor treatment response and to assess for any changes in the patient's clinical status. Assessment of medication appropriateness is a dynamic process, and changes in patients' clinical and functional status should trigger discussions about treatment goals.

Involvement of key stakeholders

Fragmented health care is one of the key contributors to medication-related harm.^{28,75} Polypharmacy stewardship attempts to overcome such challenges through effective communication with key stakeholders in patient care. Information obtained and medication changes undertaken during polypharmacy stewardship should be documented and conveyed to key stakeholders, including primary care physicians, community pharmacists, community health care providers (eg, home support staff who supervise and dispense medications to frail patients with multimorbidity), and relevant hospital specialists involved in patients' care when multimorbidity is present. This collaborative, co-management model wherein all stakeholders commit to improving the treatment of older

patients with multimorbidity with specific emphasis on medication safety should, in theory, increase the likelihood of better clinical and economic outcomes.

Patients most likely to benefit from polypharmacy stewardship

WHO proposes seven groups of patients who are most likely to benefit from medication review (panel).³⁹ These patients have the highest incidence of adverse drug reactions and adverse drug events^{41,71,72} and therefore stand to gain the most from polypharmacy stewardship. Opportune timepoints for polypharmacy stewardship intervention include admission to hospital with acute illness, transition to home care or nursing home care, presentation at a specialist geriatric medicine clinic, and consultation with community geriatric medicine teams.

Seven core elements of clinical stewardship programmes

Seven core elements of antimicrobial stewardship have been described by the US Centers for Disease Control and Prevention.⁷⁴ Application of all seven elements is likely to be required for the successful implementation of polypharmacy stewardship.

Leadership support

Senior leadership support at the organisational level is vital to the initiation and sustainability of polypharmacy stewardship. Health-care managers must commit to polypharmacy stewardship by providing adequate resources (human, financial, and technical) and engaging regularly with the polypharmacy stewardship team through service review and audit.

Accountability

Polypharmacy stewardship programmes must have a designated leader or co-leader to be accountable for their programme's activities and outcomes. In antimicrobial stewardship programmes, the most commonly employed model is the co-leadership of a physician and a pharmacist. Apart from expertise in pharmacotherapy, required competencies include well developed skills in leadership, interpersonal relationships, and management.

Panel: Patient groups most likely to benefit from medication review

- Residents in a care home setting
- Patients taking high-risk medications (eg, anticoagulants, immunosuppressive agents)
- Patients with hyperpolypharmacy (≥ 10 daily medications)
- Patients with multimorbidity
- Patients with measurable frailty
- Patients with dementia
- Patients receiving palliative care

Pharmacy expertise

Specific geriatric pharmacotherapy expertise is essential to facilitate deprescribing and optimal drug selection in polypharmacy stewardship. Previous work shows that trained pharmacists can facilitate safe and effective deprescribing by identifying older patients who are most at risk of inappropriate prescribing and associated adverse drug reactions and adverse drug events.⁷³

Action

Three priority interventions are required for effective stewardship programmes: prospective audit feedback, preauthorisation of high-risk medications, and facility-specific treatment guidelines.

First, prospective audit feedback involves the review of prescribing and deprescribing by an external expert (ie, not directly involved in the patient's day-to-day care), with provision of recommendations on how to optimise polypharmacy in patients with multimorbidity. The effectiveness of prospective audit feedback can be maximised through face-to-face engagement between prescribers and a member of the polypharmacy stewardship team (ie, geriatric medical co-management).

Second, preauthorisation places a restriction on the use of certain high-risk medications without approval from the polypharmacy stewardship team. This element of polypharmacy stewardship aims to reduce the inappropriate use of medications known to carry a particularly high risk of harm for older patients with frailty, such as high-potency antipsychotics for behavioural or psychotic symptoms of dementia. Preauthorisation requires polypharmacy stewardship staff to clearly complete an authorisation review in a timely manner.

Third, facility-specific treatment guidelines assist the polypharmacy stewardship team in making consistent and evidence-based decisions about patient care by offering explicit recommendations. These guidelines can help to optimise the pharmacological management of commonly encountered conditions in older frailer adults with multimorbidity, such as delirium.

Other interventions and strategies to improve medication safety are also available, such as automatic referrals from electronic prescribing platforms when markers of problematic prescribing are identified (eg, new anti-psychotic prescriptions, drug-drug interactions), or when patients are admitted to hospital with a suspected or probable adverse drug reaction.

Tracking

Evaluation of the safety and efficacy of polypharmacy stewardship is essential to identify areas for improvement and to ensure that the goals of polypharmacy stewardship are being achieved. This evaluation can be done through assessment of the process and outcomes. Assessment of processes include measurement of medication overuse and underuse, inappropriate prescribing, clinically

significant drug-drug interactions, and drug-related hospital admissions. Improvement in patient outcomes could be assessed by means of a validated core outcome set of measurements, including quality-of-life measurement and symptom control evaluation in line with what matters most for the patient.⁷⁴

Reporting

The polypharmacy stewardship team should provide regular update reports on findings from evaluation of processes and outcomes to key stakeholders (ie, attending physicians and other prescribers, pharmacists, nurses, and hospital managers). Sharing performance reports between institutions and organisations can motivate individuals and teams to improve prescribing practices when required standards of care are clarified.

Education

Education on appropriate prescribing in older patients with multimorbidity and polypharmacy is essential to provide safe and effective treatment for the growing global population of older patients. Integrating multiple forms of education, from teaching and online learning to case-based learning, should improve patient outcomes. Linking education to interventions and outcomes has been shown to be particularly effective in antimicrobial stewardship programmes.⁷⁴

Conclusion

WHO's Medication Without Harm global patient safety challenge targets one of the most pressing public health issues of present times—iatrogenic harm. Advances in modern therapeutics have largely neglected the oldest and frailest patients with chronic multimorbidity, which is often complicated by fragmented health care. This rapidly growing subset of patients is particularly susceptible to adverse drug reactions and adverse drug events that arise from exposure to polypharmacy.⁷⁵ The current challenge for all prescribers is how to make polypharmacy safer and more effective for these patients. In this Personal View, we have proposed the novel concept of polypharmacy stewardship for older people, a multifaceted intervention targeting medication safety as a practical way of dealing with this public health challenge. The safety and efficacy of polypharmacy stewardship will—similarly to the comprehensive geriatric assessment that has been increasingly used in recent decades—need to be evaluated through well designed clinical trials, which are urgently needed to identify interventions to improve clinically important outcomes in older people with multimorbid chronic illness who are exposed to polypharmacy.

Contributors

RD, DC, and DO'M contributed equally to the writing and revising of this Personal View.

Declaration of interests

We declare no competing interests.

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Ruth Daunt, Denis Curtin & Denis O'Mahony

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REVIEW



Optimizing drug therapy for older adults: shifting away from problematic polypharmacy

Ruth Daunt^{a,b}, Denis Curtin^{a,b} and Denis O'Mahony^{a,b}

^aDepartment of Medicine (Geriatrics), School of Medicine, University College Cork, Cork, Ireland; ^bDepartment of Geriatric Medicine, Cork University Hospital, Cork, Ireland

ABSTRACT

Introduction: The accelerated discovery and production of pharmaceutical products has resulted in many positive outcomes. However, this progress has also contributed to problematic polypharmacy, one of the rapidly growing threats to public health in this century. Problematic polypharmacy results in adverse patient outcomes and imposes increased strain and financial burden on healthcare systems.

Areas covered: A review was conducted on the current body of evidence concerning factors contributing to and consequences of problematic polypharmacy. Recent trials investigating interventions that target polypharmacy and emerging solutions, including incorporation of artificial intelligence, are also examined in this article.

Expert opinion: To shift away from problematic polypharmacy, a multifaceted interdisciplinary approach is necessary. Any potentially successful strategy must be adapted to suit various healthcare settings and must utilize all available resources, including artificial intelligence.

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1. Introduction

Physicians have never had more access to pharmaceutical therapeutic agents than they do today. The British National Formulary (BNF), a pharmaceutical reference book containing prescribing information about drugs available in the United Kingdom's National Health Service (NHS), included approximately 650 medicinal products in the mid-1970s [1]. By 1981, 4500 individual products were included, a figure that has increased manifold in the latest edition of the BNF [2]. This proliferation of pharmaceutical products, referred to as 'the pharmaceutical revolution,' has influenced the approach to treating and managing diseases and illness symptoms, reshaping not only the medical framework but also society's expectations around therapeutics [3]. One significant consequence of this pharmaceutical revolution is problematic polypharmacy, which increases the risk of medication-related harm, especially among vulnerable older adults [4,5]. Although there have been global efforts to reduce problematic polypharmacy, no single reproducible strategy has effectively addressed this challenge. In addition to the marked expansion of pharmaceutical agents over the last 50 years, there has also been an exponential advancement within the medical software sector. Specifically, in recent years, the proliferation of artificial intelligence (AI) driven applications has revolutionized several industries and traditional processes [6]. Artificial intelligence will become increasingly important in healthcare in the coming years, particularly in diagnostic and decision-support applications [7]. In this review article, we will discuss one of the most important

consequences of the pharmaceutical revolution – problematic polypharmacy – and suggest how new models of care, supported by innovative AI-based technologies, can help physicians counteract this problem.

2. Multimorbidity and polypharmacy

The expansion of pharmaceutical products has been broadly positive, providing prescribers and patients with an ever broader range of treatment options. Curative treatments are available for many previously lethal illnesses (e.g. antibiotics for many infectious diseases [8], chemotherapy for certain cancers [9]) and disease modifying treatments are available for many chronic, debilitating conditions such as multiple sclerosis [10], rheumatoid arthritis [11] and, most recently, dementia [12]. Many individuals have benefited greatly from increased availability of treatments such as these and are living longer, healthier lives. With life expectancy increasing in most countries since the early 20th century, there has been a major demographic shift in the world's population towards old age, an unprecedented modern sociological phenomenon. The World Health Organization estimates that, globally, the number of people over 80 years will treble between 2020 and 2050 reaching an estimated 426 million people [13]. As people age, they are more likely to develop chronic medical conditions, and, when two or more co-morbidities coexist this is referred to as multimorbidity [14,15]. Multimorbidity is associated with worse clinical outcomes, reduced quality of life,

CONTACT Ruth Daunt  ruthdaunt@gmail.com  Department of Medicine (Geriatrics), School of Medicine, University College Cork, Wilton, Cork T12 DC4A, Ireland

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Article highlights

- Over the last 50 years, there has been an unprecedented proliferation of medications available. This has influenced the approach to treating and managing diseases and illnesses and is one of the drivers of polypharmacy in modern medicine.
- Problematic polypharmacy encompasses a range of phenomena, including inappropriately prescribed medications, avoidable drug–drug interactions or drug–disease interactions, and inappropriate prescribing cascades.
- Problematic polypharmacy is associated with a range of adverse patient outcomes, including ADRs, increased hospitalization, reduced health-related quality of life, and ultimately, increased mortality.
- Despite significant investment, no trial has yielded an intervention that is reproducible and effective in improving outcomes for older adults with problematic polypharmacy. This underscores the complexity of deprescribing in a heterogeneous, complex, and multimorbid population.
- Further clinical trials are required to examine novel interventions that optimize drug therapy. Successful interventions will likely be multifaceted, interdisciplinary, patient centered and will utilize new technological resources such as AI.

and increased healthcare utilization [15–18]. Living with multimorbidity in this era of medication proliferation is associated with increasing levels of polypharmacy. Polypharmacy is commonly defined as the concurrent use five or more different medications [19]. Polypharmacy and multimorbidity are inextricably linked, the relationship being cause-and-effect i.e. an increasing number of diagnosed conditions leads to a proportionate increase in the number of daily medications [20]. Midao et al. analyzed the SHARE (Survey of Health, Ageing and Retirement in Europe) database, which includes detailed information on over 32,000 participants over 65 years in 17 European countries. They found that almost one-third (32.1%) of older adults in Europe take five or more daily medications [21]. Similarly, in the US, Charlesworth et al. examined medication use in adults over 65 years between 1988 and 2010. Over this twenty-two-year period, the prevalence of polypharmacy increased 3-fold, rising to 39% [22]. Trends are similar in Asian countries, where a recent study reported a prevalence of 38.8% and 46.6% in older adults in Taiwan and South Korea, respectively [23]. Other studies have reported varying levels of polypharmacy, ranging from 2.6% to 86.6% [24]. This variation reflects heterogeneity in the definitions of polypharmacy used and the settings in which the studies were conducted. For example, some studies include over-the-counter medications and non-regular medications when assessing whether a patient has polypharmacy.

Polypharmacy is not exclusive to older individuals. Many younger individuals with multimorbidity also experience polypharmacy. However, reduced physiological reserve and age-related changes in pharmacokinetics (i.e. absorption, distribution, metabolism, and excretion) and pharmacodynamics (the predictability of the effect of the drug on the individual patient) predispose older people to medication-related harm [25].

3. Problematic polypharmacy

Polypharmacy is not inherently problematic. Many individuals with multimorbidity are appropriately prescribed five or more

medications to manage their chronic health conditions, i.e. appropriate polypharmacy [19]. However, as the quantity of consumed medication increases, there is a proportional increase in risk of patients experiencing medication-related harm in the form of adverse drug reactions (ADRs), adverse drug events (ADEs), drug–drug interactions (DDIs), drug–disease interactions, and drug–geriatric syndrome interactions [4,5]. Problematic polypharmacy encompasses a wide range of phenomena, including inappropriately prescribed medications, inappropriately missed medications, ADRs, avoidable DDIs or drug–disease interactions, inappropriate prescribing cascades, and a failure to align the goals of treatment with the goals of an individual [26–29]. Multiple tools have been developed to help prescribers identify problematic prescribing. Among a large number of explicit screening tools designed to detect problematic polypharmacy are STOPP/START criteria [30], STOPP/Frail criteria [31], Beers criteria [32], and EURO-FORTA criteria [33]. Through the use of explicit criteria – clearly defined statements that highlight instances of potentially inappropriate prescribing in particular clinical circumstances – the prescriber is alerted to inappropriate medication use. These tools have been deployed to investigate the prevalence of problematic polypharmacy in multiple settings worldwide, including, acute hospital and community settings and in long-term residential care settings. One study investigating the prevalence of potentially inappropriate medications (PIMs) using STOPP/START version 2 criteria and Beers 2015 criteria identified the presence of one or more PIMs in 66.8% and 54% in community dwelling adults, respectively [34]. Implicit approaches have also been identified as means for assessing medication appropriateness. These include the Medication Appropriateness Index [35], SMART tool [36], and the 10-Step Discontinuation Guide [37]. These tools rely on clinical judgment, expertise, and patient preferences when evaluating medication appropriateness. Due to the complex nature of these interventions, there is limited research investigating these tools in large-scale settings.

4. Factors contributing to problematic polypharmacy

Advancing age and multimorbidity are recognized inter-related factors associated with problematic polypharmacy [20,21]. However, the organization of healthcare delivery is also important. The organization of modern medicine into an individual disease framework giving rise to fragmented healthcare undoubtedly contributes to problematic polypharmacy [38]. Careful consideration of these factors, along with ageing, multimorbidity, and increasingly complex pharmaceutical options, is crucial for a comprehensive understanding of the necessary interventions to address this public health crisis. Individuals living with multimorbidity commonly attend multiple healthcare providers (HCPs) in various different healthcare settings for their medical conditions [38]. This stems from the development of modern medicine around a single disease management framework. Within this framework, HCPs are encouraged to treat each chronic disease in isolation according to evidence-based best practice guidelines. These guidelines are based on evidence from clinical trials, which

commonly exclude older multimorbid people [39]. The concern, therefore, is that many treatment guidelines that are applicable to the treatment of individuals with a single chronic disease have the potential to be problematic in multimorbid patients commonly encountered in clinical practice. Application of multiple single-disease treatment guidelines to individual multimorbid patient results in multiple prescriptions, some of which can be ineffective, contradictory, and harmful [40]. This trend toward medication accumulation is further compounded by poorly established communication and coordination structures within fragmented healthcare systems [38].

Evidence-based pharmacotherapy, defined as a decision-making approach guided by appraisal of the best available scientific evidence, aims to ensure that prescribers base their decisions on credible scientific evidence rather than relying on less reliable and potentially biased information such as anecdotal evidence, case reports, or small case series reports [41]. However, the application of all evidence-based guidelines on pharmaceutical products in multimorbid patients can result in evidence-biased pharmacotherapy, i.e. the overuse of evidence-based pharmacotherapy in an undiscerning manner that ultimately amounts to problematic polypharmacy. Factors contributing to evidence-biased pharmacotherapy include faulty methodology [42,43], exclusion of older multimorbid ('real-world') patients [39], ambiguity in trial design aspects [43,44], publication bias [44], translation challenges from population-based results to individual patients, and bridging the gap between statistical significance and clinical relevance [45]. Clinical trials often employ specific inclusion and exclusion criteria, leading to recruitment of participants who may not represent the general population [46]. Additionally, clinical trials are frequently designed by pharmaceutical companies with a vested interest in positive results. Sometimes, negative clinical trial results may not be subsequently put forward for publication, a problem that is compounded by publication bias, wherein trials with favorable outcomes are more likely to be published [44]. Although considerable efforts have been made in recent years to ensure research integrity and to increase the reporting of 'negative' trials results with balanced interpretation of trial data, considerable work is still required in this domain [45,47].

The International Union of Basic and Clinical Pharmacology (IUPHAR) geriatric committee has recognized the significant gap in the inclusion of older adults in research literature and has published strategies to improve medication safety and efficacy for this cohort [48]. The committee recommends improvements in clinical trial design, emphasizing the inclusion of adults with frailty and the measurement of geriatric syndromes, such as falls, frailty, and cognition, both at baseline and as outcomes. This approach is particularly important when older adults are the intended recipients of the medication. The committee advocates for a pragmatic approach to trial design to facilitate the inclusion of frail older adults, suggesting provisions such as home visits and video calls with caregivers. By adopting an improved, collaborative, inclusive, and pragmatic trial design, older people can be better represented in research. This will ultimately

lead to enhanced medication safety and appropriateness for older adults.

5. Consequences of problematic polypharmacy

Problematic polypharmacy is associated with a range of adverse consequences for individual patients, including increased risk of ADRs, increased hospitalization, reduced health-related quality of life, and ultimately, increased mortality [26–28,49–51]. A UK prospective, observational study reviewed all patients admitted via the medical assessment unit over a one-month period [50]. The authors reported that ADRs were the main reason for or a contributing factor in 18.4% of hospital admissions and that those admitted with an ADR were older, had more co-morbidities, and were more likely to have polypharmacy than patients admitted for reasons other than ADRs [50].

Several studies have demonstrated a significant association between polypharmacy and mortality. A systematic review and meta-analysis by Leelakanok et al. identified a dose-response relationship, with increasing numbers of medications being significantly associated with increased mortality ($p < 0.05$) [51]. Older women are intrinsically more vulnerable to experiencing these negative consequences, due to intrinsic differences in drug pharmacodynamics and pharmacokinetics compared to older men [52,53]. In addition, beyond the age of 75 years, women outnumber men by approximately 2:1 in most developed countries, a survival difference that becomes more accentuated the older the age cohort [54].

Polypharmacy and resultant medication-related harm place a considerable economic burden on healthcare systems through increased drug expenditure and expenses related to treating medication-induced harm. Research conducted by the Intercontinental Medical Statistics (IMS) Institute for Healthcare Informatics, entitled 'Advancing the Responsible Use of Medicines: Applying Levers for Change' reported that approximately 4% of the world's total avoidable healthcare cost can be attributed to mismanaged or suboptimal prescribing [55]. A Canadian study by Morgan et al. reported that the use of PIMs can increase the annual per-patient costs by approximately \$2000, resulting in an estimated total annual cost of \$419 million to the country [56]. Similarly, a Japanese study by Akazawa et al. reported a significant financial impact from PIM prescribing, with older adults prescribed PIMs incurring 33% average higher medical cost than those not exposed to PIMs [57]. In the UK, it is estimated that the NHS spends approximately £2.21 billion annually as a result of ADR-related hospital admissions, most of which occur in multimorbid older people on long-term polypharmacy [50].

6. WHO challenge

The growing body of evidence highlighting iatrogenic harm caused by problematic polypharmacy prompted the launch of the third World Health Organisation (WHO) patient safety challenge 'Medication without Harm' in 2017 [58]. Through this initiative, the WHO strove to raise awareness about the importance of medication safety and to seek new and specific commitments from global leaders in healthcare to make policy

changes to support safer medication practices. The specified target was to reduce severe and avoidable harm from medication by 50% within five years. The WHO challenge aimed to improve medication safety at each stage of the medication process, from prescribing, to dispensing, to administering, to monitoring, and utilization of drug therapy. It specifically targeted three contexts where patients face a particularly high risk of experiencing medication-related harm. These contexts were to be the basis for change implementation and included high-risk situations, polypharmacy, and transitions of care. High-risk situations encompass scenarios which pose a significant risk of medication-related harm to patients, such as the use of higher-risk medications like insulin and warfarin and interruptions during critical processes such as prescribing and administration of medication. Transitions of care from community to hospital and later from hospital to home are commonly associated with unintentional medication discrepancies that can be potentially harmful. Older individuals with multimorbidity frequently encounter all three contexts (high-risk situations, polypharmacy, and transitions of care) simultaneously, compounding the risk of adverse drug events in this cohort. The challenges of optimizing medications in the heterogeneous group of multimorbid older adults are evidenced by the fact that over five years since this ambitious goal was set, there is no published evidence to indicate that the initiative has significantly reduced medication-related harm, as expressly intended by the WHO. To emphasize the persistent necessity of achieving this goal, the WHO Safety Action Plan 2021–2030 prioritizes the Medication without Harm Challenge in one of its key strategies (strategy 3.2) [59]. This strategy outlines key actions for governments, healthcare, stakeholders, and the WHO secretariat, including establishing expert groups and leadership teams, appointing medication officers/teams in healthcare, promoting patient involvement and medication literacy, recognizing and reporting of ADRs, and monitoring of progress. A strategic and coordinated approach is recommended to work toward this goal.

7. Evidence-based interventions to reduce harm associated with problematic polypharmacy

Since the WHO launched this challenge, several large-scale multicentre trials have investigated novel interventions designed to reduce problematic polypharmacy. A cluster randomized clinical trial in Canada, the MedSafer Study, utilized an electronic deprescribing support tool which created personalized deprescribing reports in older adults with polypharmacy [60]. MedSafer enrolled 5698 hospitalized participants who were randomized to standard care or personalized deprescribing reports. This study's aim was to evaluate the effect of this support tool on adverse drug events after hospital discharge. For the primary outcome in MedSafer, ADEs, there was no significant difference between the treatment groups. However, use of the deprescribing support tool successfully identified opportunities for deprescribing, although uptake of these recommendations by attending clinicians was variable. In the case of certain medications with high side effect profiles

in older patients, substantial levels of deprescribing took place in the intervention cohort i.e. benzodiazepines and sedative hypnotics, gabapentinoids, and trazadone were deprescribed in 40%, 35%, and 30% of users, respectively.

Low implementation of prescribing advice points was also a feature of the SENATOR trial, a large multicentre, randomized control trial, which enrolled 1537 hospitalized patients [61]. Patients were randomized to usual pharmaceutical care or to the intervention arm, which involved provision of individualized software generated reports with prescribing advice points to attending doctors. The prescribing advice was largely based on STOPP/START version 2 criteria. There was no significant difference in the incidence of ADRs as the primary endpoint between the groups, not surprising, given that only 15% of the advice points were implemented in the intervention patient cohort. An accompanying qualitative study [62] investigating factors that influenced prescribing advice implementation identified a number of key factors that mitigate against prescribing advice implementation, including low clinical relevance of some recommendations in the acute setting, time constraints in a busy hospital setting, prescribers level of experience, and patient-specific issues. Failure of the MedSafer and SENATOR trials to show significant reductions in the incidence of ADRs in the intervention groups was fundamentally linked with suboptimal implementation of prescribing advice.

Challenges with reducing PIMs were also a feature in the SPPIRE trial [63]. This was a community-based cluster randomized controlled trial that enrolled 404 participants. The intervention was delivered by general practitioners (GPs) who underwent pre-trial training on polypharmacy management in older people. PIMs were identified by GPs based on learning through training videos. Medication changes were implemented by GPs using clinical judgment. There was no change in the number of PIMs prescribed or other outcome measures in the intervention patient cohort compared to the control cohort.

These trials underscore the complexity of deprescribing PIMs both in the acute hospital setting and in the community. Furthermore, they highlight the challenges of implementing medication changes when recommendations are generated by an external source or by primary care physicians who know their multimorbid older patients in greater detail.

A cumulative update, i.e. a review of systematic reviews evaluating interventions designed to improve polypharmacy management was recently published by Keller et al. in which fourteen systematic reviews, accounting for 179 unique published studies were evaluated [64]. Their results highlighted the ongoing lack of sufficient high-quality evidence to endorse the widespread implementation of interventions targeting polypharmacy. The authors noted that detailed comprehensive medication reviews (involving prescription review, medication adherence review, and a face-to-face review of medications and conditions with the patient) were the most effective interventions and the only intervention associated with a reduction in unplanned hospital admissions.

As highlighted, the absence of high-quality evidence around interventions to address problematic polypharmacy

does not stem from a lack of substantial investment in this area. Furthermore, the inherent heterogeneity of multimorbid older adults with complex medical conditions and associated problematic polypharmacy complicates the response patterns of prescribers to interventions. The results from large, multi-center, trials such as Senator and MedSafer, have shown that simply applying explicit PIM criteria such as STOPP/START criteria or Beers criteria to medication lists may not result in a meaningful improvement in clinically important patient outcomes. Some smaller, single-center studies have reported benefits in patient outcomes. O'Connor et al. demonstrated that the application of STOPP/START criteria to medication lists of hospitalized older adults resulted in significantly fewer ADRs compared with usual pharmaceutical care [65]. Garcia et al. highlighted that patients who received a deprescribing intervention were less likely to experience falls, delirium, and hospital admissions [66]. Similarly, Frankenthal et al. reported a reduction in falls in patients who received a deprescribing intervention [67]. The variability of results likely relates to factors beyond simply applying explicit criteria. For example, in smaller studies implementation rates tend to be higher, for example, O'Connor et al. reported a implementation rate of 83.4% [65]. In the study by Garcia et al., the patient's own physicians were trained to identify PIMs using explicit criteria. These physicians, who had established relationships with patients, likely adopted a nuanced approach to deprescribing informed by their own understanding of the individual patient histories. Moreover, their authority to deprescribe eliminated challenges with implementation [66]. This emphasizes the necessity for a multifaceted, personalized approach to successfully improve problematic polypharmacy in this high-risk cohort of patients. The Geriatrics 5 Ms framework has been proposed as

a method of approaching medication optimization in older adults [68]. The 5 Ms brings focus to broader aspects of older person care, including Mobility, Mind, Multicomplexity, What Matters Most, in addition to Medications. The goal is to provide an Age-Friendly Health System where these elements of high-quality care are reliably provided across healthcare settings. While elegant and holistic, it is a framework for high-quality care rather than a specific tool or procedure for addressing complex polypharmacy.

8. Polypharmacy stewardship

A new concept referred to as 'polypharmacy stewardship' addresses many of the shortcomings of previously described interventions and has been proposed as a model of care to reduce the risks associated with problematic polypharmacy in older people [69]. Polypharmacy stewardship is defined as a coordinated intervention designed to assess, monitor, improve, and measure the pharmacotherapeutic treatment of multimorbidity, taking into account potentially inappropriate medications, potential prescribing omissions, potentially or actually detrimental drug – drug and drug – disease interactions, and prescribing cascades, with the aim of aligning treatment regimens with the overall condition, prognosis, and preferences of the individual patient. The concept of this stewardship model is adapted from the principles of antimicrobial stewardship, which has been shown to improve both patient and economic outcomes [70–73]. A polypharmacy stewardship program includes the following core components: optimization of the technical components of prescribing, personalized prescribing, and deprescribing in view of realistic treatments goals, avoidance of medication-related harm,

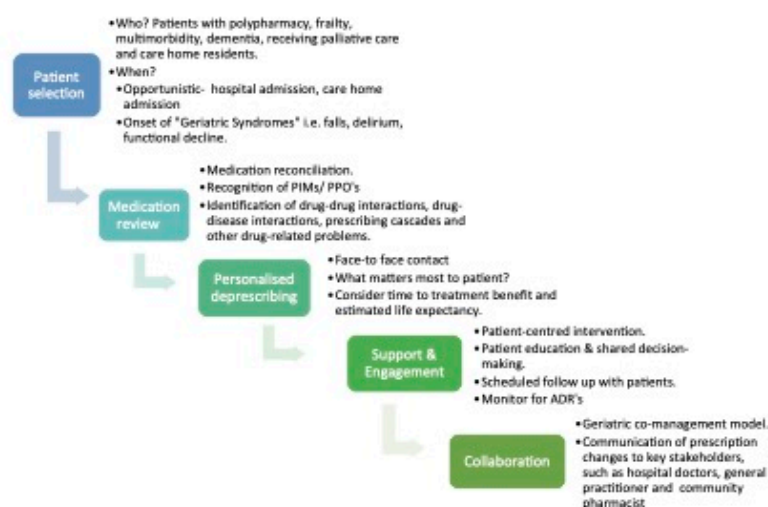


Figure 1. Process model for polypharmacy stewardship. PIMs =Potentially inappropriate medications, PPOs= potential prescribing omissions, ADRs= adverse drug reactions – adapted from [69] under creative commons CC-BY-NC-ND license.

patient-centered care with provision of supports and follow-up as necessary and collaboration with key stakeholders including community-based health care providers (Figure 1). Several of these core components align closely with the ten recommendations published by the International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP), such as recommendation four, 'employ mixed implicit and explicit approaches to polypharmacy,' and recommendation ten, 'decisions in older complex patients should routinely consider expected survival and quality of life, giving the highest priority to patient/family preferences' [74]. There is no single evidence-based preferred operational model for a polypharmacy stewardship program. Nevertheless, as healthcare providers strive to implement the key actions outlined in the WHO Safety Action Plan 2021–2030 [59], a polypharmacy stewardship program serves as an effective strategy to meet these targets. Initial steps to integrate a stewardship program into practice include securing leadership support, establishing accountability and reporting structures, appointing physicians and pharmacists with appropriate expertise, and monitoring outcomes. Successful implementation of polypharmacy stewardship across a diverse range of healthcare settings is theoretically feasible and requires adaptation of the core components while considering the resources available and the financial viability of the program.

9. Artificial intelligence (AI)

One rapidly evolving resource that is anticipated to play an increasing role in polypharmacy management is AI [7]. To date, AI-based advances in healthcare have been most prominent in radiology and surgery [75–78], where the application of AI-based techniques has shown improved patient outcomes compared to conventional clinical practice. The Radiology Health AI register provides an overview of AI software available in Europe for clinical radiology practice. Over 200 products are currently listed that can enhance diagnostic precision and identification of abnormalities on imaging [79]. AI in surgery is currently transforming traditional surgical treatment approaches. Robotic surgical systems are being increasingly utilized in specialties such as urology and gynecology where they offer increased precision of surgical intervention, safer procedures and improved patient outcomes compared to traditional surgical treatment [76–78,80].

The role of AI in supporting physicians to manage polypharmacy has been evaluated more recently. In a 2023 single-center study, Akyon et al. described the development of a rule-based auxiliary tool and AI supported web application to aid physicians' management of polypharmacy [81]. This tool was created to incorporate patients' age, medications, and comorbidities and applies prescribing criteria and guidelines. Drugs were screened according to six PIM criteria and classified as 'usable,' 'risky' and 'no warning found.' Medications were also screened for and classified according to drug–drug interaction and drug–disease interactions. Medications were evaluated in 296 older adults. The comparison between physicians and the

AI tool revealed a substantial difference in the time taken to detect PIMs, PPOs, and DDIs, with physicians averaging 38 min while the AI tool took only 34 s.

Dil Nahlili et al. validated an Artificial Pharmacology Intelligence (API) system [82]. The API system integrated data from patients' health records and other sources, incorporating medications, medical history, and personal parameters. This enabled the API system to generate prioritized personalized assessments of drug-related risk in accordance with up-to-date medical literature and guidelines. API system significantly outperformed clinical pharmacist reviews ($p=0.0001$) in identifying medication-related problems. Both these studies underscore the potential of AI as an aid to healthcare professionals, particularly in synthesizing extensive amounts of data efficiently.

TIME (Turkish inappropriate medication use in the elderly) criteria were developed by a group of pharmaceutical experts in Turkey and include recommendations for both prescribing and deprescribing medications in older people [83]. Recognizing the challenge of integrating comprehensive criteria into busy clinical settings, the group designed and developed a smartphone application of TIME enabling clinicians to efficiently deploy the tool in clinical practice.

Other studies have utilized AI technology to improve dosing in patients using warfarin, as well as predicting DDIs in patients through a framework which integrated phenotypic, chemical, therapeutic, and genomic properties [84,85].

These initial research findings indicate that AI can support prescribers by synthesizing large volumes of drug safety and interaction data on a practical and accessible platform. However, it is crucial to also consider the challenges associated with AI. Key challenges include understanding the complexity of AI algorithms, overcoming technical issues, mitigating bias, ensuring data security, and avoiding overdependence on technology. Notwithstanding these challenges, given the scale of the task of improving medication safety, leveraging advanced technologies to tackle complex polypharmacy seems unavoidable. With appropriate safeguards and governance, AI has the potential to enhance decision-making and efficiencies in the care of patients with complex polypharmacy.

10. Conclusion

Problematic polypharmacy is a growing concern with increasing prevalence internationally despite a global effort to reduce this problem for over five years. Failure to successfully reduce problematic polypharmacy in multimorbid older adults stems largely from the challenges of tackling a multi-factorial problem in a rapidly growing heterogeneous population. Successful interventions will need to be multi-faceted, involve face-to-face contact with multimorbid older patients, and will likely benefit from incorporating AI technologies. We contend that such an intervention can be developed and deployed successfully, which will improve outcomes for millions of older adults living with problematic polypharmacy worldwide.

11. Expert opinion

Problematic polypharmacy is a major healthcare and patient safety concern worldwide, stemming from multiple factors including ageing populations, multimorbidity, fragmented healthcare systems, over-emphasis on evidence-based pharmacotherapy, and the organization of healthcare around an individual disease treatment framework. The multi-layered, multifactorial nature of polypharmacy in late life underscores its complexity, making it challenging to manage. Nonetheless, it is imperative that progress is made in reducing problematic polypharmacy due to its wide-ranging negative consequences for patients, healthcare systems and macro-economics. Therefore, any intervention targeting problematic polypharmacy should aim to improve outcomes across these domains. Despite numerous randomized controlled trials seeking to address problematic polypharmacy, successes have been limited in terms of impact on clinically relevant endpoints. That is, while many of these clinical trials, such as SENATOR [61] and MEDSAFER [60] have demonstrated methods that identify PIMs and PPOs to prescribers, implementation of advice points has been poor, and they have generally failed to demonstrate clear improvements in patient outcomes such as hospital readmission, medication-induced impairment of quality of life and mortality. A significant issue lies in the complexity of the polypharmacy-attenuating interventions in question and the financial resources needed to support them. Unlike many other areas of pharmacotherapy where pharmaceutical companies promote and fund pharmacotherapy research, interventions focusing on deprescribing will struggle to attract such support. While this helps maintain research integrity, it poses a challenge to researchers to successfully undertake polypharmacy-improving research through federal and state government and philanthropic funding sources.

Another obstacle with determining successful interventions to target problematic polypharmacy is the complexity of patients living with multimorbidity-induced polypharmacy and the complex multitude of factors that contribute to problematic polypharmacy. To address this challenge, we propose polypharmacy stewardship as a novel collaborative, multifaceted, intervention approach. The framework for polypharmacy stewardship is modeled on the anti-microbial stewardship program which has been applied successfully in many countries to improve patient and economic outcomes related to antimicrobial pharmacotherapy. A key component of polypharmacy stewardship involves optimizing the technical aspects of prescribing, encompassing optimal dosing, formulation, dispensing, as well as identification of PIMs and PPOs, DDIs, and prescribing cascades. It is within this domain that artificial intelligence (AI) will likely demonstrate its practical value, particularly in reducing the time taken to identify prescribing errors, potentially inappropriate prescribing (IP), and potential medications for deprescribing. AI technologies can be applied to operationalize and automate IP criteria such as STOPP/START criteria [30] and Beers criteria [32] enabling prescribers to streamline the identification of PIMs and PPOs. Integration and utilization of such technologies would then afford physicians more time to focus on more nuanced aspects of polypharmacy, such as establishing patient

preferences, involving patients in the decision-making process to a greater extent, and providing follow-up. While initial research has been undertaken, further research is required to fully explore the potential benefits of AI within a polypharmacy stewardship program. Without leveraging the clinical potential of AI, the feasibility of funding interventions that require significant manpower will remain a challenge to researchers and healthcare systems alike. We expect that the integration of AI into polypharmacy stewardship programs will help to optimize resource allocation and improve patient and economic outcomes.

Looking ahead to the next 10–20 years, polypharmacy is expected to become more prevalent in tandem with ageing demographic changes which will inevitably generate higher levels of multimorbidity and its by-product, polypharmacy. A more focused, better structured and funded approach to polypharmacy research is needed to elucidate the theoretical value of multifaceted interventions like polypharmacy stewardship, augmented by innovative AI-based technologies. If such approaches are proven to be successful, the patient safety and economic dividends could be very substantial indeed.

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ORCID

Ruth Daunt  <http://orcid.org/0000-0003-0464-3057>

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Detection of Potential Prescribing Cascades in Multimorbid Older Patients Hospitalised with Acute Illness—An Observational Prospective Prevalence Study

Ruth Daunt^{1,2} · Siobhán McGettigan^{1,2} · Lorna Kelly² · Denis Curtin² · Denis O'Mahony^{1,2}

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Abstract

Background Prescribing cascades occur when a new drug is prescribed to treat an adverse drug event caused by an existing medication, resulting in unnecessary, or potentially hazardous additional drugs. To date, there are no published studies assessing the prevalence of prescribing cascades in older hospitalised adults.

Objective To investigate the prevalence of prescribing cascades in hospitalised older adults.

Methods We conducted a prospective observational study of adults aged ≥ 65 years with multimorbidity and polypharmacy presenting to hospital with acute unselected medical or surgical illness. Prescribing cascades were identified using two pre-defined validated explicit cascade lists, i.e. ThinkCascades, and a list derived from a recently published systematic review of prescribing cascades in community-dwelling adults, referred to here as the 'Doherty list'. Potential prescribing cascades were classified as 'definite', 'probable', 'possible', 'uncertain' or 'indeterminate' according to pre-specified criteria.

Results The study included 385 consecutive patients (55.1% female, mean age 80.2 years, standard deviation 7.3 years). A total of 281 potential prescribing cascades (drug A $\rightarrow$ drug B) were identified in 152 patients (39.4%). Probable or possible prescribing cascades were identified in 48 patients (12.4%) using the Doherty list and in 44 patients (11.4%) using ThinkCascades. Patients exposed to potential prescribing cascades experienced greater levels of polypharmacy than patients not exposed to prescribing cascades (median interquartile range [IQR] of 12 [9–14] daily drugs versus 9 [IQR 7–11], $p < 0.001$).

Conclusions Potential prescribing cascades were highly prevalent in older hospitalised adults. Practical tools are needed to assist prescribers in prevention, recognition and management of inappropriate prescribing cascades.

1 Introduction

A prescribing cascade occurs when a new drug is prescribed to treat a side effect or an adverse drug event (ADE) caused by an existing medication and can be classified as either appropriate or inappropriate [1, 2]. Appropriate prescribing cascades occur when a new medication is intentionally prescribed to manage a well-recognized drug side effect, with the benefits of initiation outweighing the risk, such as laxatives to counteract the common and predictable problem of constipation arising from opioid

Key Points

Prescribing cascades are clinically significant as they can result in prolonged burden of symptoms and accumulation of unnecessary medications which increases the risk of medication-related harm.

This study demonstrates that potential prescribing cascades are substantially prevalent in older adults with multimorbidity and polypharmacy.

Potential prescribing cascades are more common in patients with hyperpolypharmacy (prescribed ≥ 10 daily medications) and higher mean Charlson Comorbidity Index scores.

✉ Ruth Daunt
Ruth.Daunt@ucc.ie

¹ Department of Medicine, University College Cork, College Road, Cork, Ireland

² Department of Geriatric and Stroke Medicine, Cork University Hospital, Wilton T12DC4A, Cork, Ireland

treatment [3]. In contrast, inappropriate prescribing cascades occur when drug side effects are misdiagnosed as new conditions, leading to the inappropriate prescription of an unnecessary or potentially dangerous secondary medication to treat the misdiagnosed new condition or symptom, thereby increasing the risk of medication-related harm [3]. One well-known example of an inappropriate prescribing cascade is the prescription of diuretics to treat lower limb oedema arising as a side effect from prior treatment with dihydropyridine calcium channel blockers, the oedema being misdiagnosed as a sign of heart failure rather than as a side effect of the calcium channel blocker. Inappropriate prescribing of cascades may result in prolonged and excessive burden of symptoms arising from adverse drug events, avoidable additional medication burden and further inappropriate use of medications [4–6].

Numerous examples of prescribing cascades have been reported in literature through case reports, case series, case-control studies, cross-sectional studies and original research [7, 8]. The likelihood that a concurrent drug pair represents a prescribing cascade may be investigated through so-called prescription sequence symmetry analysis (PSSA) methodology [7, 9, 10]. PSSA compares the number of patients prescribed the index drug (drug A) before introduction of the marker drug (drug B) to those who were prescribed the marker drug before the index drug (so-called crude sequence ratio). PSSA may be affected by prescribing trends such that many studies also report a null-effect sequence ratio or adjusted sequence ratio, which is the crude sequence ratio divided by the null-effect sequence ratio, to account for prescribing trends. Although PSSA is an effective and validated method of establishing whether a drug pair constitutes a potential prescribing cascade, it cannot determine the actual clinical relevance of a suspected inappropriate prescribing cascade, nor cannot it establish causality [9].

A recent systematic review by Doherty et al., designed to identify published prescribing cascades in community-dwelling adults, examined 101 published studies. From their systematic analysis of literature, the authors highlighted the 25 most commonly identified prescribing cascades in community-dwelling adults, the majority of which were identified by studies that utilised PSSA methodology [7]. Separately, the iKASKADE consortium recently published a consensus list (called “ThinkCascades”) of nine clinically relevant prescribing cascades validated by the Delphi consensus method [11]. Not surprisingly, the list of the 25 most common prescribing cascades identified by Doherty et al. and the ThinkCascades list overlap to some extent. Nevertheless, they represent an advance in prescribing cascades research in that they embody explicit validated lists of cascades not previously described in literature.

Although it is nearly 30 years since the original concept of prescribing cascades was described by Rochon and Gurwitz, there are no studies describing the real-world prevalence of prescribing cascades in older multimorbid people exposed to polypharmacy, i.e. the population at highest risk of inappropriate prescribing cascades [12]. This deficiency in the prescribing cascades literature relates largely to the lack of validated explicit prescribing cascades lists prior to 2022. In addition, the need to carefully evaluate the probability of true cascades being observed has not been addressed through prospective prevalence studies in real-world multimorbid older patients experiencing polypharmacy. Older people undergoing hospitalization because of acute illness represent one of the most multimorbid patient cohorts who experience long-term polypharmacy [13]. Accordingly, the principal aim of this study was to investigate the prevalence of prescribing cascades in hospitalised older adults with multimorbidity and polypharmacy using the explicit prescribing cascades lists of Doherty et al. and ThinkCascades in combination.

2 Methods

This study was a single-centre observational prospective prevalence study conducted in a major tertiary referral medical centre in Cork, Ireland. The local Clinical Research Ethics Committee approved this research study. Participants were recruited between October 2022 and July 2024.

Eligible participants were adults aged ≥ 65 years admitted through the emergency department with acute surgical or medical illness, with preadmission multimorbidity (i.e. ≥ 3 chronic co-morbidities diagnosed prior to admission) and associated polypharmacy (i.e. ≥ 5 prescribed daily medications). Exclusion criteria were: acute psychiatric illness (not including delirium) and patients at end of life or admitted directly to the intensive care unit (ICU). Patients were also excluded if they or their legally authorised representative (if they lacked capacity) were unable or unwilling to give consent to study participation. Apart from their high prevalence of multimorbidity and polypharmacy, hospitalised older patients were selected as the focus of this study because hospital admission provides a unique opportunity to perform a comprehensive medication review, facilitating the identification of prescribing cascades [14].

To achieve a statistically valid detection of prescribing cascades, a sample size of 384 was determined. This was calculated on the basis of a margin of error of 5% at 95% confidence. This sample size was calculated using an assumed prevalence of 50%, an estimate that requires the largest sample size ensuring adequate power regardless of the true prevalence within the population. Furthermore, the

sample size was calculated under the assumption of a large at-risk population (more than 5000) [15, 16].

Patients' data were collected at two timepoints, i.e. at recruitment within 72 h of admission and at discharge. At recruitment, three trained research physicians (R.D., S.M., and L.K.) conducted patient and/or carer interviews, contacted patients' community pharmacists and reviewed medical records to obtain the following patient information: age, sex, admitting speciality, long-term regular medications, admitting diagnosis, specific diagnoses and cumulative comorbidity as quantified by the Charlson Co-morbidity Index score (CCI), number of reported falls in the preceding 12 months, number of admissions in the preceding 12 months, delirium status on admission based on the 4AT screening test and Clinical Frailty Scale (CFS) score. At discharge, the research physicians obtained the following information: length of hospital stay (days), discharge destination (home or long-term care facility) and updated list of regular medications.

Potential prescribing cascades were identified at the point of recruitment using the ThinkCascades list (Table 1) and the list compiled by Doherty et al. (hereafter referred to as the 'Doherty list') (Table 2). Patients' long-term daily medications were screened for potential prescribing cascades using the two explicit cascades lists separately and in combination. When potential cascades were identified, the temporal relationship between drug A and drug B was determined, where ascertainable, through discussions with the community pharmacist and review of patients' medical records. Establishing the temporal relationship involved firstly determining whether drug A was initiated before drug B and, where possible, assessing the timeframe between initiation of both drugs. If drug B was initiated after drug A, further investigation was conducted to determine whether an ADE was implicated as the potential indication for drug B. Patients were interviewed and their medical records carefully scrutinized, including correspondence letters and inpatient progress notes, to determine whether drug B was initiated to treat a known ADE caused by or relating to drug A. In this assessment, only ADEs documented on the ThinkCascades list and the Doherty list were considered as indicating potential cascades. Potential ADE's were only included if the ADE was documented in the patients' medical records. The likelihood of a prescribing cascade being present was categorized as 'definite', 'probable', 'possible', 'uncertain', or 'indeterminate' according to pre-defined criteria (Table 3). This classification system was developed in alignment with the World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) system for standardised case causality assessment [17]. Similar to the WHO-UMC's ADR causality assessment, this system cannot provide an accurate quantitative measurement of the drug A/drug B cascade relationship likelihood, but it helps reduce assessor

disagreement and improve the overall evaluation of potential prescribing cascades. The standardized process to ascertain prescribing cascade likelihood is illustrated in Fig. 1.

Prevalence, the primary outcome of interest, was determined as the proportion of patients identified with a potential prescribing cascade, categorised as definite, probable, possible or uncertain. Patients were then classified into two groups—those with a potential prescribing cascade and those without—to evaluate statistical difference in demographic and clinical characteristics. The selected covariates were chosen on the basis of review of the relevant literature of related studies on inappropriate prescribing in older multimorbid adults [18–20].

At discharge, patients' medications were reviewed to determine whether any potential prescribing cascades identified at recruitment were still included in their regular prescriptions.

2.1 Statistical Analysis

Statistical analysis was conducted using SPSS® version 28.0 software. Descriptive statistics included the mean and standard deviation (SD) for normally distributed variables and the median and inter-quartile range (IQR) for non-parametric variables. Deceased patients were excluded from the analysis of medication prescriptions at discharge. Differences in the distribution of categorical variables were compared using Pearson's chi-squared test and continuous variables using the independent *t*-test. The Mann-Whitney *U* test was used to determine independence of two nonparametric variables. A probability value of < 0.05 was considered statistically significant. The probability values were selected to show the differences between the two groups – those with potential prescribing cascades and those without potential prescribing cascades – allowing for testing of the null hypothesis, which assumes no difference between the groups. To ensure strong reliability in the classification of potential prescribing cascades and ADE's among the three researchers, inter-rater reliability was calculated using the intra-class correlation coefficient, a two-way mixed model, assessing for absolute agreement.

3 Results

In total, 385 patients were enrolled in this study, of whom 212 patients (55.1%) were female with a mean (SD) age of 80.2 (7.3) years. Baseline patient characteristics are presented in Table 4. The median (IQR) number of comorbid chronic conditions in patients with a potential prescribing cascade was 8 (6–10) versus 7 (5–9) in patients without a potential prescribing cascade ($p = 0.003$). The most

Table 1 Prescribing cascades according to the ThinkCascades list

No.	Drug A	Suspected ADE	Drug B	Total (probable/ possible/uncertain)	Prob- able cascade	Possible cascade	Uncer- tain cascade	Remains prescribed at discharge	Indeter- minate cascade	Prescribed in the Sequence drug B→ drug A
1	Calcium channel blocker	Peripheral oedema	Diuretic	39	0	17	22	25	3	13
2	Diuretic	Urinary incontinence	Overactive bladder medication	30	4	17	9	19	2	16
3	Antipsychotic	extrapyramidal symp- toms	Antiparkinsonian agent	3	1	2	0	3	0	2
4	Benzodiazepine	Cognitive impairment	Cholinesterase inhibitor or memantine	1	0	1	0	0	0	1
5	Benzodiazepine	Paradoxical agitation or agitation secondary to withdrawal	Antipsychotic	11	0	2	9	7	1	2
6	SSRI/SNRI	Insomnia	Sleep agent (e.g. benzo- diazepine, benzodiaze- pine receptor agonist, sedating anti-depres- sant, melatonin)	16	1	7	8	10	8	31
7	NSAID	Hypertension	Antihypertensive	2	0	2	0	1	0	1
8	Urinary Anticholinergics	Cognitive impairment	Cholinesterase inhibitor or memantine	2	0	2	0	1	0	0
9	Alpha-1 Receptor Blocker	Orthostatic hypotension, dizziness	Vasibular sedative (e.g. benzidine, antihis- tamines, benzodiaze- epines)	0	0	0	0	0	0	0
Total				104	6	50	48	66	14	66

NSAID nonsteroidal anti-inflammatory drug, SSRI selective serotonin reuptake inhibitor, SNRI serotonin-norepinephrine reuptake inhibitor

Table 2 Prescribing cascades according to the list published by Doherty et al.

No.	Drug A	Suspected ADE	Drug B	Total (probable/ possible/uncer- tain)	Probable cascade	Possible cascade	Uncertain cascade	Remains prescribed at discharge	Inter- mediate cascade	Prescribed in the Sequence drug B→ drug A
1	DH-CCB	Oedema	Loop diuretic	29	0	10	19	20	1	6
2	Amiodarone	Hypothyroidism	Thyroxine	2	1	1	0	2	0	1
3	Inhaled CS	Oral candidiasis	Topical antifungals	2	0	2	0	2	0	0
4	Neuroleptics/antipsy- chotics	Parkinsonian symp- toms/extrapyramidal symptoms	Anti-Parkinson's meds/ PD diagnosis	3	1	2	0	3	0	2
5	Acetylcholinesterase inhibitors	Urinary incontinence	Drugs for urinary frequency and incontinence/drugs for treating LUTS symptoms	3	0	2	1	2	0	4
6	Mexoclopramide	Parkinsonian symptoms	Levodopa	0	0	0	0	0	0	0
7	ACEi	Cough	Antitussive	0	0	0	0	0	0	0
8	NSAID	GI symptoms	Anti-ulcer med	0	0	0	0	0	0	3
9	Ranitidine	Heart failure	Furosemide	0	0	0	0	0	0	0
10	Rosiglitazone	'Failure'	Furosemide	0	0	0	0	0	0	0
11	SGLT2	Genital infections	Antifungal	0	0	0	0	0	0	0
12	DOAC	Depression	Antidepressant	21	0	2	19	16	1	28
13	High ceiling diuretics (Loop diuretics)	Hypokalaemia	Potassium	0	0	0	0	0	0	0
14	Statins	LUTS	Drugs for urinary frequency and incon- tinence	59	0	17	42	40	9	11
15	Statins	Skin soft tissue infection	Antibiotics—dicloxacil- lin/flucloxacillin	2	0	1	1	2	0	0
16	Statins	Depression	Antidepressant	70	0	10	60	60	5	21
17	Statins	Muscle cramps	Quinine	1	0	0	1	1	0	2
18	Brinzolamide	Heart failure	Furosemide	0	0	0	0	0	1	0
19	Latanoprost	Heart failure	Furosemide	3	0	1	2	2	0	1
20	Carbamazepine	Hypothyroidism	Levothyroxine	1	0	1	0	1	0	1
21	Valproate	Hypothyroidism	Levothyroxine	1	0	1	0	1	0	0
22	Lithium	Drug induced tremor/ parkinsonism	Anti-Parkinson drug	0	0	0	0	0	0	0
23	Lithium	Hypothyroidism	Thyroxine	0	0	0	0	0	0	0
24	Benzodiazepine	Dementia	Anti-dementia drug	1	0	1	0	0	0	1

Table 2 (continued)

No.	Drug A	Suspected ADE	Drug B	Total (probable/ possible/uncertain/ indeterminate)	Probable cascade	Possible cascade	Uncertain cascade	Remains prescribed at discharge	Indeter- minate cascade	Prescribed in the Sequence drug B → drug A
25	SSRI	Urinary incontinence	Drugs for urinary frequency and incontinence (or incontinence products)	12	0	10	2	7	0	4
Total				210	2	61	147	159	17	85

ACEi angiotensin-converting enzyme inhibitors; CS corticosteroid; DH-CCB, dihydropyridine calcium channel blocker; DOAC direct oral anticoagulant; GI gastro-intestinal; LUTS lower urinary tract infections; NSAID nonsteroidal anti-inflammatory drug; PD Parkinson's disease; SSRI selective serotonin reuptake inhibitor; SGLT2 sodium-glucose cotransporter-2

common diagnoses were hypertension (72.7%), dyslipidaemia (50.6%) and atrial fibrillation (34.2%). A total of 3950 daily medications were prescribed to the 385 patients, i.e. an average of 10.3 daily drugs per patient. Statistically significant p values are highlighted in bold in Table 4.

Using both the ThinkCascades list and the Doherty list in combination, a total of 281 individual potential prescribing cascades were identified in 152 patients, i.e. 39.4% prevalence, with 63 patients (16.3%) classified as having possible cascades and 7 patients (1.8%) classified as having probable cascades (Table 5). Owing to overlap between the Doherty list and the ThinkCascades list, the total number of unique patients and prescribing cascades in the combined analysis is lower than the sum of the individual lists. Each patient and prescribing cascade was counted only once. Cascades categorized as 'indeterminate' were excluded from overall prevalence calculations. The overall prevalence of potential prescribing cascades, including those classified as probable, possible and uncertain, is highlighted in bold in Table 5.

The ratio of drug pairs prescribed drug A followed by drug B to those prescribed drug B followed by drug A was 1.57 (104/66) using the ThinkCascades list and 2.47 (210/85) using the Doherty list.

The four most common probable or possible prescribing cascades according to the Doherty list were:

- statin → drugs for urinary frequency and incontinence ($n = 17$)
- dihydropyridine calcium channel blocker → loop diuretic ($n = 10$)
- statin → antidepressant ($n = 10$)
- selective serotonin reuptake inhibitor → drugs for urinary frequency and incontinence (or incontinence products) ($n = 10$).

By comparison, the four most common probable or possible prescribing cascades according to the ThinkCascades list were:

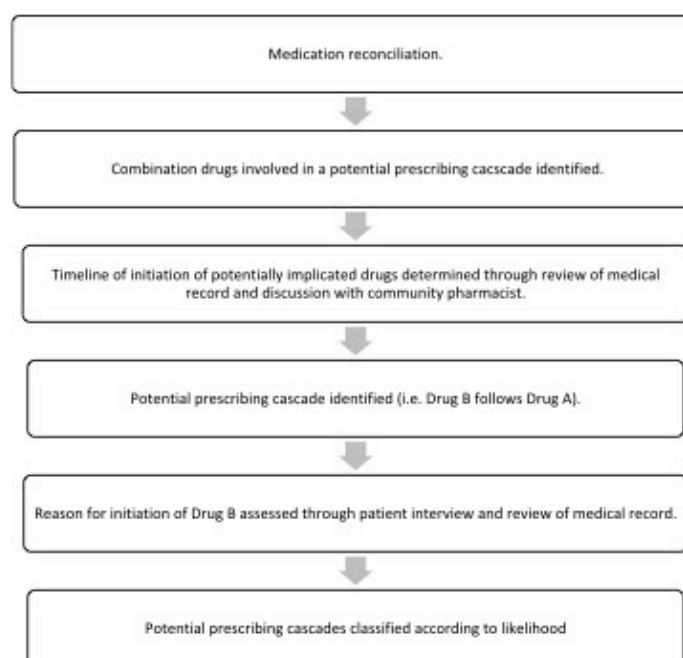
- diuretic → overactive bladder medication ($n = 21$)
- calcium channel blocker → diuretic ($n = 17$)
- selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor → sleep agent (e.g. benzodiazepine, benzodiazepine receptor agonist, sedating anti-depressant and melatonin) ($n = 8$)
- antipsychotic → antiparkinsonian agent ($n = 3$).

Potential prescribing cascades were more common in patients with hyperpolypharmacy (i.e. taking ≥ 10 daily long-term medications) compared with patients taking ≤ 9 daily medications (70.3% versus 37.3%, $p < 0.001$). In addition, patients exposed to potential cascades had higher mean

Table 3 Prescribing cascade likelihood criteria

	Cascade likelihood	Assessment criteria
1	Definite	Drug B follows Drug A Drug B initiated to treat ADE caused by drug A Initiation of drug B cannot be explained by other disease/indication Withdrawal challenge of drug A results in improvement/cessation of the side-effect
2	Probable	Drug B follows drug A Drug B initiated to treat ADE caused by drug A Initiation of drug B unlikely explained by another disease or symptom
3	Possible	Drug B follows drug A Drug B possibly initiated to treat ADE caused by drug A (documentation of ADE in medical records after drug A prescribed and before drug B prescribed) Initiation of drug B could be explained by other disease/indication
4	Uncertain	Drug B follows drug A Unclear if drug B initiated to treat ADE caused by drug A (no documentation of ADE in medical chart) Initiation of drug B could be explained by other disease/indication
5	Indeterminate	Drug A and drug B co-prescribed Cannot determine temporal relationship between drug A and drug B Data cannot be supplemented or verified

ADE adverse drug event

Fig. 1 Standardized process to ascertain prescribing cascade likelihood

Charlson Comorbidity Index (CCI) scores compared with patients not exposed to potential cascades (mean 6.13 [SD 2.06] versus 5.57 [SD 1.68]), $p = 0.006$). When comparing

patients with a prescribing cascade categorised as 'probable' or 'possible' in combination to 'uncertain' no significant differences were observed except for length of hospital stay

Table 4 Baseline characteristics and univariate analysis of association

Variables	No cascade group (n = 233 (60.6%))	Cascade group (n = 152 (39.4%))	P-value
Female (%)	131 (55.9)	80 (52.6)	0.438
Age, median (years, IQR)	80.5 (74.75–86)	80 (75–85)	0.95
Living arrangements pre-admission			
Home, number of patients (%)	218 (93.6)	139 (91.4)	0.435
Long-term care facility, number of patients (%)	15 (6.4)	13 (8.6)	
Charlson Comorbidity Index, mean (SD)	5.57 (1.68)	6.13 (2.06)	0.006
Number of daily medications, median (IQR)	9 (7–11)	12 (9–14)	< 0.001
Hyperpolypharmacy, number of patients (%)	87 (37.3)	107 (70.3)	< 0.001
Clinical frailty Scale score, median (IQR)	5 (4–6)	5 (4–6)	0.476
Comorbidities, median (IQR)	7 (5–9)	8 (6–10)	0.003
Fall in last 12 months, number of patients (%)	123 (52.7)	79 (52.0)	0.875
Admitted in last 12 months, number of patients (%)	128 (55.0)	88 (57.9)	0.567
4AT score, median (IQR)	1 (0–2)	0 (0–2)	0.886
Admitted under geriatric medicine, number of patients (%)	42 (18)	18 (11.8)	0.102
Admitted under			
Medical speciality, number of patients (%)	218 (93.6)	141 (92.8)	0.760
Surgical speciality, number of patients (%)	15 (6.4)	11 (7.2)	
Primary diagnosis (ICD code)			
Fall (W19) (%)	50 (21.5)	29 (19.1)	0.572
Acute lower respiratory infection (J22) (%)	22 (9.4)	25 (16.4)	0.040
Urinary tract infection (N59.0) (%)	17 (7.3)	8 (5.3)	0.429
Syncope (R55) (%)	14 (6)	4 (2.6)	0.125
Decompensated congestive heart failure (I50.0) (%)	13 (5.6)	5 (3.3)	0.298
Length of hospital stay, days (IQR)	9 (4–17)	11 (5–21)	0.276
Survival outcome (death), number of patients (%)	21 (9)	10 (7)	0.391
Discharge destination			
Home, number of patients (%)	183 (78.5)	113 (74.3)	0.93
Long-term care facility, number of patients (%)	50 (21.5)	39 (25.7)	

4AT Arousal, Attention, Abbreviated Mental Test—4 and Acute change

(median: 7 days [IQR 3–13] versus 6 days [IQR 6.25–22], $p = 0.018$) (Appendix 1).

Hospital discharge prescriptions were reviewed to determine whether potential prescribing cascades identified at recruitment remained in patients' regular prescriptions, i.e. whether both drug A and drug B were still prescribed. Using both cascades lists in combination, 76.5% ($n = 215$) of the identified potential prescribing cascades remained at discharge. In isolation, 75.7% ($n = 159$) of the Doherty list cascades and 63.4% ($n = 66$) of the ThinkCascades cascades remained at discharge.

Inter-rater reliability for prescribing cascade detection and ADE classification was also evaluated to ensure acceptable reliability among the three researchers. In total, 39 cases (10%) were selected at random for evaluation by the researchers. The intra-class correlation coefficient (ICC), a two-way mixed model, assessing for absolute agreement was calculated. For prescribing cascade classification, the

ICC for the consistency of ratings was 0.935 (95% CI [0.884, 0.964]) and for consistency of ratings of ADE classification, ICC was 0.896 (95% CI [0.813, 0.943]), which indicates excellent inter-rater reliability for detection and classification of potential cascades and ADE's.

4 Discussion

This is the first prospective prevalence study of potential prescribing cascade prevalence in hospitalised multimorbid older adults exposed to polypharmacy. It demonstrates that prescribing cascades are substantially prevalent in this population to a clinically significant degree, particularly among those who experience hyperpolypharmacy. The analysis of drug pairs where drug A was prescribed followed by drug B compared with the reverse order suggests that the suspected prescribing cascades identified in this study are likely to

Table 5 Prevalence of potential prescribing cascades

		Potential prescribing cascades (includes probable, possible and uncertain)	Probable prescribing cascades	Possible prescribing cascades	Uncertain prescribing cascades	Remains prescribed at discharge	Indeterminate (sequence drug A → drug B unknown)	Prescribed in the sequence drug B → drug A
Combined lists	Individual patients no. (%)	152 (39.4%)	7 (1.8)	63 (16.3)	101 (26.2)	110 (28.6%)	25 (6.5)	80 (20.7)
	No. individual prescribing cascades	281	7	98	176	215	30	142
Doherty list	Individual patients no. (%)	135 (35.1%)	2 (0.5)	46 (11.9)	95 (24.7)	107 (27.8)	15 (3.9)	64 (16.6)
	No. individual prescribing cascades	210	2	61	147	159	17	85
Think cas- cades list	Individual patients no. (%)	75 (19.4%)	6 (1.5)	39 (10.1)	39 (10.1)	46 (11.9)	11 (2.9)	46 (11.9)
	No. individual prescribing cascades	104	6	50	48	66	14	66

be clinically valid. Although the more frequent prescribing in the sequence drug A → drug B does not definitively confirm their status as prescribing cascades, it supports the hypothesis that the potential prescribing cascades identified in this study are true prescribing cascades. This is important, as true prescribing cascades can have serious adverse consequences for patient safety and healthcare outcomes [5].

As ageing demographic trends intensify as a global phenomenon, the prevalence of multimorbidity is increasing in tandem, resulting in ever increasing levels of polypharmacy and hyperpolypharmacy [21–23]. As older people are prescribed more medications, their risk of experiencing inappropriate prescribing (IP) in general also rises [13, 24]. The present study aligns with this observed association, confirming that potential prescribing cascades as another manifestation of IP are associated with a higher number of prescribed medications [25].

While the management of patients with complex multimorbidity and associated polypharmacy has traditionally been the responsibility of general practitioners and geriatricians, the responsibility for medication management will increasingly extend to all physicians dealing with multimorbid older people in their own areas of clinical practice. In the present study, 84% ($n = 326$) of patients were under the care of physicians who were not geriatricians, i.e. specialists without specific training in age-related multimorbidity and associated complex polypharmacy. Without the necessary

training and experience in geriatric medicine, these physicians may struggle to recognise prescribing cascades, as was evident in the present study where very little curtailment of potential cascades was evident between admission and discharge, possibly related to lack of recognition of potential cascades. This challenge is compounded by the fact that ADEs in older adults with multimorbidity are more challenging to recognise and can often present with non-specific symptoms, such as new-onset confusion, gastrointestinal upset and dizziness [4, 26, 27].

A recent systematic review by Adrien et al. assessed recommendations for addressing prescribing cascades [10]. Fewer than half of the studies included in the review provided specific guidance on reversing inappropriate prescribing cascades. Among those that did, recommendations for dose reductions were often made without confirmation of a dose-dependent association, with most studies recommending the discontinuation of the index drug but not specifying an alternative medication. The persistence of potentially problematic drug combinations at hospital discharge identified in this study highlights the challenge physicians face in recognising and addressing prescribing cascades. It also points to the need for expert medication review at admission and particularly at discharge of older patients with multimorbidity and associated polypharmacy.

The identification and management of prescribing cascades are further complicated by the limitations of existing

assessment tools. The ThinkCascades list, developed through three rounds of a modified Delphi validation process and involving international experts in geriatric pharmacotherapy, produced a list of only nine common and clinically important prescribing cascades [11]. This list very likely underrepresents the true number and prevalence of clinically relevant prescribing cascades. Although the Doherty list includes the 25 most commonly published appropriate and inappropriate prescribing cascades [7], some of the prescribing cascades listed raise questions about some of the cascades' frequency and clinical relevance. Examples include lower urinary tract symptoms arising from statins leading to drugs for urinary frequency/incontinence and depression arising from direct oral anticoagulants (DOACs) leading to antidepressant drug prescription. These examples highlight the limitations of relying heavily on statistical methods such as PSSA to define cascades without clinical data, expert endorsement and clinical plausibility to validate proposed prescribing cascades. Nevertheless, a recent follow-up study evaluating the strength of the evidence supporting the prescribing cascades identified by Doherty et al. found that 84% of these prescribing cascades were supported by moderate evidence, i.e. single high-quality study or strong evidence, i.e. multiple high-quality studies [28].

Most prescribing cascades in the present study were categorized as 'possible' or 'uncertain'. Accurate identification of the prevalence of probable or definite prescribing cascades using the criteria applied in this study is likely to be challenging during medication review. Categorization of any clinical event as 'probable' or 'certain' in relation to multimorbid older patients requires rigorous assessment and therefore, as we have demonstrated, reliance on patient recall and physician or pharmacist documentation in patients' medical records may not be sufficient. A prospective study design involving contemporaneous assessment of patients' symptoms, as well as prescriber interviews, at the onset of possible prescribing cascades would be required for greater clarity. The feasibility of conducting such a labour-intensive study, likely with major recruitment challenges and resource implications, was beyond the scope of the present study.

A more comprehensive validated explicit list of clinically relevant prescribing cascades is likely required to enhance identification during routine medication review. In a recent commentary, O'Mahony and Rochon pointed out that the number of inappropriate prescribing cascades is potentially enormous but that more clinically relevant and common cascades can be identified more readily using a systems-based structured explicit cascades list approach that can be applied readily in a manner that is more suitable for routine medication review [29]. Such a structured, systems-based list of prescribing cascades could also be valuable as an educational tool in this important area of geriatric

pharmacotherapy. Heightened awareness of potential cascades is likely to facilitate their prevention.

4.1 Study Limitations

This study has some limitations. First, the absence of a national electronic healthcare system in most public hospitals in Ireland, coupled with frequent transitions of care and missing medication initiation dates, made reconstruction of the chronology of potential prescribing challenging and at times wholly uncertain. This limited our ability to establish clear timelines between drug A and drug B initiation in some cases. However, there is no consensus in literature on the appropriate timeframe for defining prescribing cascades, which can range from a short number of weeks to several years. The timeframe can also vary according to the onset of ADE symptoms, which may vary between medications, as well as the recognition of ADEs which may depend on the timing of patients' presentation to healthcare settings. For example, it may take many months to some years before antipsychotic medication leads to drug-induced parkinsonism leading to antiparkinsonian medication. In contrast, gastrointestinal upsets induced by acetylcholinesterase inhibitor therapy may lead to inappropriate proton pump inhibitor or antidiarrheal prescription within days. Second, as mentioned, patients' medical records in the Irish public hospital system are still predominantly paper-based, with no widespread integrated electronic platform between community healthcare settings and hospital settings. This resulted in incomplete access to clinical data, particularly that relating to general practitioner assessments. Third, this study was conducted in a single hospital, which may limit the generalizability of the finding to other hospitals or healthcare settings. Finally, as this was an observational rather than an interventional study, we were unable to apply the definitive test for prescribing cascades, i.e. observation for resolution of ADE symptoms by discontinuing drug A.

5 Conclusions

This study, the first of its kind to report the prevalence of prescribing cascades in multimorbid older people exposed to polypharmacy in the acute hospitalization setting, indicates that inappropriate prescribing cascades are both prevalent and poorly recognised in hospitalised older adults in southern Ireland. Explicit prescribing cascades lists can facilitate prescribers and medication reviewers with identification and intervention towards curtailment of this under-reported element of inappropriate prescribing in multimorbid older people. Further research is needed to help the development of practical tools to support prescribers in the prevention, identification and management of inappropriate prescribing cascades.

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Declarations

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Conflicts of Interest Denis O'Mahony is an Editorial Board member for *Drugs & Aging*. Denis O'Mahony was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The authors; Ruth Daunt, Siobhán McGettigan, Lorna Kelly and Denis Curtin have no competing interests to declare that are relevant to the content of this article.

Availability of Data and Material The datasets generated and/or analysed in this study are available from the corresponding author on reasonable request.

Ethical Approval This study was approved by the local Clinical Research Ethics Committee, Cork, Ireland.

Consent to Participate Written informed consent was obtained prior to enrolment from all participants or their legally authorised representative in circumstances where they were deemed to lack sufficient decision-making capacity to provide valid informed consent.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions All authors contributed to the study conception and design. Data collection was performed by Ruth Daunt, Siobhán McGettigan and Lorna Kelly. Material preparation and analysis were performed by Ruth Daunt. The first draft of the manuscript was written by Ruth Daunt and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Factors Influencing Hospital Physicians' Recognition of Prescribing Cascades: A Qualitative Interview Study

Ruth Daunt^{1,2} · Kieran Dalton³ · Denis Curtin² · Denis O'Mahony^{1,2}

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Abstract

Introduction A prescribing cascade occurs when a medication is prescribed to manage a side effect of another medication. Prescribing cascades represent a key component of problematic prescribing and can result in harm to patients, especially older adults with multimorbidity and polypharmacy.

Objective The objective of this study was to explore factors influencing hospital physicians' recognition of prescribing cascades using the Theoretical Domains Framework (TDF), a validated theory-based qualitative methodology.

Methods Semi-structured interviews were conducted in May–July 2024 with hospital physicians of all grades. Interviews were audio-recorded and transcribed verbatim. Transcripts underwent conventional and directed content analysis to identify themes and TDF domains.

Results From 14 interviews, four predominant TDF domains were identified: (i) environmental context and resources: busy work conditions, lack of up-to-date medication lists and limited information technology (IT) infrastructure hinder prescribing cascade recognition; (ii) knowledge: physicians demonstrated limited knowledge of the term 'prescribing cascade' and highlighted education and training deficiencies at undergraduate and postgraduate level; (iii) skills: recognition skills are often developed through experiential learning while working (especially with geriatric medicine consultants) and (iv) social/professional role and identity: physicians perceived themselves as primarily responsible for recognising prescribing cascades, while pharmacists enable their recognition through medication reconciliation, medication review and ward round participation.

Conclusions This study highlights significant gaps in the knowledge and understanding of prescribing cascades among hospital physicians, as well as potential targets for future intervention. Focused education, integrated IT solutions, and a collaborative physician–pharmacist approach would likely improve prescribing cascade recognition in at-risk older people with multimorbidity and polypharmacy.

1 Introduction

A prescribing cascade occurs when a new drug is prescribed to manage an adverse effect of another drug [1]. Prescribing cascades can be either appropriate or inappropriate [2]. The latter typically occur if an adverse drug event (ADE) is misdiagnosed as a new medical condition

and a second drug is inadvertently prescribed to manage it. Inappropriate prescribing cascades are clinically important as they represent an avoidable component of inappropriate prescribing and are associated with increased risk of hospitalisation, drug-related harm and, ultimately, increased morbidity and mortality [3, 4]. A prescribing cascade can be considered inappropriate when the risks associated with the combined use of the initial drug and the subsequent drug outweigh the potential benefits [5].

Older adults are particularly vulnerable to inappropriate prescribing cascades due to multimorbidity and associated polypharmacy, both of which increase the risk of inappropriate prescribing generally [6, 7]. Furthermore, this risk is increased due to age-related reduction in physiological systems reserve as well as pharmacokinetic (e.g. decreased renal and liver function) and pharmacodynamic (e.g. altered sensitivity to medications) changes that predispose patients to ADEs. The cumulative effect of multiple medications also

✉ Ruth Daunt
Ruth.Daunt@ucc.ie

¹ Department of Medicine, School of Medicine, University College Cork, Cork, Ireland

² Department of Geriatric and Stroke Medicine, Cork University Hospital, Room G18, Clinical Sciences Building, Wilton, Cork T12DC4A, Ireland

³ Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, College Road, Cork, Ireland

Key Points

In this study, hospital physicians across all grades demonstrated limited knowledge and understanding of prescribing cascades.

Heavy workloads and understaffing limit physicians' available time to comprehensively review medications and recognise prescribing cascades.

Other important barriers to prescribing cascade recognition include lack of access to up-to-date medication lists, limited software infrastructure and prescribing education deficiencies.

increases the risk of ADEs which can result in the prescription of additional medications to manage these ADEs, thus initiating a prescribing cascade [8, 9]. Recognition of prescribing cascades in this cohort is particularly challenging as ADEs often present with non-specific symptoms such as confusion, dizziness or malaise [3, 10, 11]. These symptoms can easily be misattributed to known concurrent comorbidities or misdiagnosed as new conditions, potentially perpetuating ADEs and resulting in further inappropriate medication. Therefore, interventions to reduce inappropriate prescribing cascades should be a priority for all healthcare providers, especially those caring for older people experiencing multimorbidity and associated polypharmacy.

To date, research has focused predominantly on identifying and validating drug combinations that may represent prescribing cascades, with limited research exploring why and how prescribing cascades occur [12–14]. A recent study investigating the prevalence of potential prescribing cascades in acutely hospitalised older adults found that 39.4% of patients were prescribed potential prescribing cascades [15]. This finding suggests that the problem of prescribing cascades is under-recognised by clinicians and that opportunities to appropriately manage prescribing cascades are missed, highlighting the need for interventions to improve recognition in hospitalised patients.

For these reasons, a knowledge gap exists for research to explore the factors (facilitators and barriers) influencing recognition of prescribing cascades amongst hospital physicians. Using the Theoretical Domains Framework (TDF), a validated theory-informed framework often used in qualitative research, allows an effective method for exploring these factors [16]. The TDF has been widely used to guide data collection on factors influencing prescribing behaviours in various healthcare settings, including qualitative research on prescribing cascades [17]. It provides a valuable framework for systematically identifying these factors, which can then be targeted in behaviour-change interventions to improve practice.

Previous studies have examined perspectives and awareness of prescribing cascades amongst primary care physicians and patients [18, 19], as well as problematic polypharmacy and prescribing cascades with multiple stakeholders [20]. These studies indicate that both physicians and patients often struggle to recognise and manage prescribing cascades. This challenge arises due to difficulties in identifying new symptoms as potential drug adverse effects, limited awareness of specific prescribing cascades and the time required to address potential prescribing cascades even when recognised. No study to date has focused specifically on hospital physicians. We identified this as a key knowledge gap, as hospitalisation presents a unique and underutilised opportunity for medication reviews and recognition of inappropriate prescribing cascades. Therefore, the aim of this study was to utilise the TDF to identify the key behavioural factors influencing hospital physicians' recognition of prescribing cascades, including an evaluation of their knowledge and understanding of this aspect of inappropriate prescribing.

2 Methods

2.1 Study Approval and Reporting

Ethical approval for this study was granted by the Social Research Ethics Committee, University College Cork (reference: 2024-048). Study reporting was guided by the COREQ checklist for reporting qualitative research findings (Online Resource 1).

2.2 Study Design, Setting and Recruitment

Semi-structured interviews were undertaken as the preferred method of data collection because they are well suited to generating detailed, nuanced descriptions of participants' experiences and perspectives, especially with an under-researched phenomenon [21].

One-to-one semi-structured interviews were conducted with hospital physicians working in a large university teaching hospital in Ireland. At the time of the interviews, all physicians had clinical responsibility for patients admitted either electively or non-electively through the hospital emergency department.

The hospital medical records were primarily paper-based, including patients' prescribed medication lists which were recorded both in ward-based Kardex® prescription sheets and in discharge reports.

To obtain a range of physicians' perspectives, a sampling matrix was used to ensure that the interviews were conducted with at least three participants from each grade of physician (intern [house officer], senior house officer [SHO or junior resident], registrar/specialist registrar [SpR or senior resident]

and consultant or senior attending physician) and that at least one male and at least one female was represented within each grade. This reflects the highly organised social context and well-established hierarchical structure of clinical medicine within the Irish public hospital system [22]. In addition, previous research suggests that prescribing practices differ between grades of physician and that junior doctors often defer complex prescribing decisions to senior colleagues [23, 24]. While prescribing patterns do not differ significantly according to physician sex, it can influence patient interactions and outcomes and was therefore included in the sampling matrix [20, 25].

The inclusion criteria required that participants were registered with the Irish Medical Council and working in a recognised medical specialty in the university teaching hospital at the time of the interview. Doctors working at any grade in a surgical specialty, psychiatry, paediatrics or obstetrics/gynaecology were not included in the study, as comprehensive medication review involving larger medication lists is less of a routine task in their usual care delivery. Physicians were also excluded from the study if they worked in geriatric medicine at consultant or SpR grade or if they held an additional degree in pharmacy. Participants were recruited via convenience and snowball sampling. Potential participants were identified through the professional network of the research team, and were invited to participate via email, which included an information sheet and consent form.

2.3 Application of the TDF

The TDF provides an accessible and structured means of identifying factors that impact practice across a comprehensive range of potential behavioural determinants [17]. Compared with conducting qualitative research without theory-based approaches, using the TDF allows the generation of broader range of responses, partially due to its ability to mitigate against cognitive bias [26, 27].

In the context of the present study, the recognition of prescribing cascades was conceptualised as a behaviour. To acquire a thorough understanding of the facilitators and barriers influencing this behaviour, the development of the topic guide was informed by the 14 TDF domains and their constructs, and these domains were used as pre-determined codes during directed content analysis.

2.4 Data Collection

Immediately prior to their interviews, participants completed a short questionnaire collecting demographic information (gender, grade, years of post-qualification experience, specialty, university in which medical degree was obtained and whether they received any prior education on prescribing cascades, either formally or informally) and whether they recalled having ever identified a prescribing cascade or witnessed a colleague

recognise a prescribing cascade. A topic guide was developed on the basis of reviewing relevant literature [18, 19, 28], the Theoretical Domains Framework (TDF) version 2 [29] and the authors' knowledge of prescribing cascades. At least one question was included for each of the 14 TDF domains. The topic guide (Online Resource 2) aimed to elicit factors affecting recognition of prescribing cascades based on interviewees' knowledge and experience, as well as barriers to and recommendations for improving the recognition of prescribing cascades. The topic guide was pilot tested with one physician not affiliated with the research team; this interview was not included in the data analysis (as planned a priori).

All interviews were conducted by a research physician with 8 years of postgraduate clinical experience (R.D.). All interviews were conducted in person in a private room within the hospital between May and July 2024. All participants provided written consent prior to interview and verbal consent immediately prior to the interview. Field notes were recorded by the interviewer after each interview. All interviews were audio-recorded and transcribed verbatim, with transcripts subsequently deidentified.

It was decided a priori that interviews would continue until there were at least two additional interviews where no new major themes appeared, as this would help ensure that the topic has been adequately explored [30].

2.5 Data Analysis

NVivo® software version 14 was used to facilitate analysis. Data were analysed in four phases. In the first phase, transcripts were read and re-read to ensure familiarity. In the second phase, the research physician conducted conventional content analysis, which involved open coding to create non-hierarchical codes that were then grouped into initial themes [31]. The third phase involved directed content analysis, using constructs and domains from the TDF as predetermined codes [31]. To enhance the reliability of coding, a second researcher (K.D., pharmacist) independently identified themes and TDF domains across all transcripts. Factors considered when identifying predominant TDF domains included the frequency of beliefs, presence of conflicting beliefs, and the strength of beliefs expressed [32]. Finally, in the fourth phase, themes identified through conventional coding were categorised under the TDF domains that best reflected the themes and its associated codes [16].

2.6 Reflexivity

2.6.1 Research Team Background and Professional Experience

The research team included a research physician with specialist training in geriatric medicine (R.D.), a senior academic pharmacist with experience in qualitative methods

(K.D.) and two consultant geriatricians (D.O.M. and D.C.). A total of three of the interviewees had previously worked clinically with R.D. All participants were aware that D.O.M. and D.C. were consultant colleagues working in the same hospital. K.D. had no contact with study participants. Acknowledging the influence of the researcher team's background on the study design and methods, the following steps were taken to leverage the advantages of the team's background and mitigate biases [33].

2.6.2 Topic Guide Development

The topic guide was developed using the research team's experience in prescribing cascades, along with the TDF and review of relevant literature. This approach had the advantage of creating a well-rounded guide based on current evidence and suited to the clinical context of the study.

2.6.3 Insider Positionality

As a physician with higher specialist training in geriatric medicine, R.D. recognised her 'insider position' and was aware of the need to set aside her own perspectives and try to remain neutral when interviewing physician colleagues as a researcher [34, 35]. Potential study participants were aware that R.D. had specialist training in geriatric medicine; this knowledge was beneficial in accessing potential participants within the hospital. Creating a pre-planned sampling matrix ensured diversity in participant characteristics, thus minimising the risk of selecting participants with potentially similar perspectives. During the interviews, the insider position meant that RD had the advantage of a shared clinical language and contextual understanding, facilitating rapport and easing the flow of interviews. One potential challenge of a shared language is the 'deadening effect', where shared understanding is assumed and participants do not elaborate on their views [36]. To overcome this, R.D. encouraged participants to elaborate and clarify their answers where needed.

2.6.4 Data Interpretation

It is almost inevitable that the researchers' own professional background will influence data interpretation, with views most congruent with the team's own most easily received [37]. Consequently, R.D. debriefed the team regularly throughout the analytical process to maintain openness and critical reflection among the participants. Prior to finalising the TDF codes, R.D. and K.D. met to discuss the data findings and the code development.

3 Results

A total of 15 potential hospital physician participants were contacted, of whom 14 were interviewed. These physicians had varying levels of training and experience aligned to the sampling matrix (Table 1). One physician agreed to participate but was unable to schedule an interview within the study timeframe due to other commitments. A total of seven participants were male and seven were female, with a mean of 6 years of postgraduate experience (range 10 months to 23 years). The mean interview duration was 18 minutes (range 14–35 min). At the time of the interviews, participants were practising in the following specialities: respiratory medicine ($n = 4$), rheumatology ($n = 3$), acute internal medicine ($n = 2$) and one each in cardiology, geriatric medicine, endocrinology, stroke medicine and infectious diseases.

All 14 TDF domains were identified in the transcripts, with corresponding quotations shown in Table 2, noting that some quotations are aligned to more than one TDF domain. All TDF domains are presented below, whereby the first four were identified as predominant in influencing hospital physicians' recognition of prescribing cascades: environmental context and resources, knowledge, skills and social/professional role and identity.

3.1 Environmental Context and Resources

3.1.1 Lack of Access to Up-to-Date Medications

Interviewees highlighted difficulties accessing details of up-to-date lists of patients' medications, as well as information relating to indications for medications, initiation

Table 1 Sampling matrix details of physician participants.

Physician Characteristic	Number of interviewees	Minimum number required as part of sampling strategy
Gender		
Male	7	4
Female	7	4
Grade		
Intern/house officer ^a	4	3
Senior house officer ^b	3	3
Registrar/specialist registrar ^c	4	3
Consultant	3	3

^a < 1 year post-qualification experience

^b ≥ 1 year post-qualification experience (typically 2 years in duration after internship).

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

Table 2 Illustrative quotations.

Descriptor	Quotations
Environment	
Lack of access to up-to-date medications	'...if everybody just starts writing what this medication is indicated for and we kept it in the patient's medical records, that would be really helpful.' [SHO 1] '...you don't know what medications they're on...significant problem with then trying to manage their medication when they come in, because maybe you have a prescribing cascade that happens because they're on something you just don't realise they are on...' [Consultant 3] '...often, we don't know what drugs patients are on...if they come into the emergency department, you don't know what they're on, so you might start instituting some treatment, for example...you might start a diuretic but unbeknownst to you they're actually on a calcium channel blocker that was started by the GP a couple of weeks ago.' [Consultant 2] 'If [patients] write down their medications and the dates of things were changed...can be helpful because we don't have a unified prescribing log between GPs and pharmacies and hospitals...' [SHO 2] '...they [patients] come in and they're not sure what medications they are on and they don't have a list...you're looking at their list...hoping this is right.' [Registrar 4] '...in general, when patients are in hospital, (they) don't tend to know what they're on...' [Intern 1] 'Like the hospital's undersaffed simple as. I think if we have more staff, more time to think about things, we are more likely to identify [prescribing cascades].' [Intern 1] '...there's lack of staff members in the hospital because if we have more staff, we will reduce clinical workload and then hospital doctors can spend the time looking through the Kardex® and making decisions...' [SHO 1] '...with a busy inpatient list, you're running around the ward, you're often dealing with one or two key aspects of the patient care...we do try and look at the Kardex® each time...you have to try and keep it all in your head, where you remember the background medical history of the patient, what drugs they're on...sometimes, I think due to time constraints, you don't realise that maybe the side effect of the drug is contributing to the symptom that you're now looking at...' [Consultant 2] '...we just couldn't find a time to dedicate ourselves to work on that [identifying prescribing cascades] on top of our already massive clinical workload.' [SHO 3] '...a busy inpatient service...ideally it would be great to have a proper sit down with every patient's Kardex® to go through the medications. But the reality is, if you have 30 odd patients on an inpatient list, and you have to see all of them every day, you might overlook some of the Kardex's...' [Registrar 2] 'The number one barrier that jumps out to me would be time pressure...the speed at which ward rounds happen...' [SHO 3] 'In an ideal world, if we were doing electronic prescribing, you could probably have something say, "is this medication warranted?" or "what is your reason for starting it?"' [Registrar 1] 'We're living in a very archaic system that doesn't help with flagging when prescribing cascade might be happening...a simple intervention would be having an electronic health record prescribing system, but it's a very complex intervention to put in place unfortunately.' [Consultant 3] 'I would just type in the name of the medication and look at the SPC and then look at the information of what side effects are common. On the computers in the hospital, they have medicines, i.e., I can get information on it as well.' [Intern 3] 'I know that there's new ways to access it [the BNF], but it's always, in the last few years, been tricky.' [Consultant 1] '...if you had an app-based system where you have common prescribing cascades, for example, you click in opiates and then common co-prescribers, and then you could have a list of inappropriate common prescribing cascades.' [Consultant 2] 'I think it'd be brilliant if everyone [patients] had...an app or something that would have their medications on it, so that...if they had swelling in their legs, you'd know they were on amlodipine or...' [Registrar 4]
Staffing	
Excessive workload	
Information technology	
Knowledge	
Recognising the term 'prescribing cascades' and its conceptual understanding	'I didn't know what they [prescribing cascades] were before coming here today. And I certainly don't think a lot of the doctors in training would be familiar with the concept.' [Consultant 2] 'I think people would recognise what happened...the laxative for constipation in the opioid patient...but they wouldn't group it together as "oh look at this interesting prescribing cascade"...' [Consultant 1] 'People are paralysed by lack of knowledge in regard to deprescribing, so they do nothing...' [Consultant 3]

Table 2 (continued)

Descriptor	Quotations
Knowing examples of prescribing cascades	'... sometimes opioids can have side effects ... nausea and then people need an anti-emetic to manage that ... it's not something I've thought about much...' [Intern 3] '... ACE inhibitor → cough, opioid → constipation → laxative. Antihypertensive and then hypotension and then, I don't know, adding in something to raise the heart rate or something... ah, inotrope, or vasopressor... other barriers, just not being aware of them... I only know the ones I mentioned and that's not very many.' [Intern 4] '... if somebody is on a PPI like lansoprazole, and they get put on clopidogrel, or they are on omeprazole and get put onto clopidogrel and then you have to change the omeprazole to something else.' [Registrar 1] 'So I'm trying to come up with examples, but I keep thinking of contraindications as opposed to prescribing cascades ...' [Registrar 2] 'I don't really remember being taught anything about it in college or ... BST teaching [formal post-graduation teaching for SHO] or anything ...' [SHO 2] 'I think it's very important to have like the foundation level of education as an undergraduate, but also have constant reminders post-grad ...' [Registrar 2] '... general education about "the most common inappropriate prescribing cascades that happened", "can you screen for them" [Consultant 1] '... a medication alert system ... just to highlight that these were the inappropriate prescribing errors that have occurred... builds your awareness of it... always comes back to education, education, re-education and reminders ...' [Consultant 2]
Education and training deficiencies	
Skills	
Experiential learning	'... at an intern level, just a lack of experience and the lack of seeing these patterns from before and ... anticipating these treatments.' [Consultant 3] 'I think as time goes on, maybe when you become a reg ... you try and take more of that in perspective and look at people's Kardex® before they go home and see do they need to be on everything.' [Registrar 4] 'In medical school, it's a bit theoretical at that point... if we had a prescribing safety course in... your first year as an intern... where you could refresh things and... talk about common drugs and common errors, that might be a bit more practical at that point ... and as an SHO as well.' [Registrar 4] 'You can start by training the young doctors so when they become consultants to keep that in mind.' [SHO 1]
Improvement with training	
Social and Professional Role and Identity	
Physicians' responsibility in prescribing cascade recognition	'It's probably everyone's responsibility to recognise prescribing cascades to the best of their ability ... senior staff would probably be much more used to it and probably better at it in general.' [SHO 3] '... the medical team ... the back stops with them ... you're the one prescribing, you're the one reviewing prescriptions on a regular basis ...' [Consultant 1] '... the more junior, the less likely that they would be to pick it up and [more likely] to kind of give something a little bit more "blindly" ...' [Registrar 1] 'Being an intern, I'm not the one deciding to start the new medication, it'd be someone more senior on my team saying, "start this medication for this patient" ...' [Intern 3] '... if we really want to solve this problem ... having a specific team that review medication would be good, without interfering with the normal ward jobs ...' [SHO 1] 'People tend to "pass the buck" to someone else when it comes to deprescribing, especially if unsure why someone is on a medication, don't know who started it, don't know when it was started, don't know why it was started - in all that uncertainty some people just pass the buck.' [Consultant 3] 'In my own experience, the pharmacist has been my primary source of flagging "this medication is inappropriate", "this adverse effect might be due to a medication" ...' [SHO 1] '... if there was if a prescribing cascade or unwanted side effects from medications, more often than not the pharmacists ... flag them to us.' [Registrar 2] '... if there was (a) joint ward round with the pharmacist ... (and) consultants ... where you sit down and go through the medications and things like that, that might be more of a structured way ...' [SHO 2] 'In my previous rotation, my consultant was really good at reviewing patients' Kardex® but partly because he was the consultant geriatrician ...' [SHO 1] 'I previously worked in geriatrics ... [the consultant] was really big on stopping the extra medication.' [SHO 2] '... what we see a lot is people come into hospital with respiratory exacerbations, they're put on antibiotics, they're put on steroids... you can often end up with people who develop peripheral oedema. So they end up developing volume overload... then you're into your prescribing cascade of giving them furosemide. Now they're hypotensive so you're giving them potassium ... that's a prescribing cascade that we'd see frequently and recognise very, very quickly ...' [Consultant 3]
Pharmacists' role	
Speciality role	

Table 2 (continued)

Descriptor	Quotations
Social influences	
Hierarchy and modelling within medical teams	'... our consultants change every 2 weeks, if I don't know a consultant, I'm less likely to speak up. Whereas there are some consultants... I know them more... so I'd be more comfortable speaking up.' [Intern 4] '... it depends on the team structure and how comfortable they feel in asking for help or asking for advice or, you know, I suppose even having things explained to them...' [Consultant 3] '... you wouldn't want to challenge... someone more senior that has like prescribed... the team I'm working with at the moment, I would be very happy... to bring it up with someone. But I can't say that for every team that I've been on... it's difficult to challenge someone more senior... if you did feel that you were really challenging them... then you might not be as inclined.' [Intern 2] '... we all admire the SHO and intern who do speak up... I think we want people to be challenging us. And we want the status quo to be challenged all the time... Empower the nurses, empower the pharmacists, empower every level of doctor to do the same thing [speak up about medication concerns]' [Consultant 1] 'I think everyone has their preferences for the drugs they prescribe... if you're with a consultant who tends to prescribe a certain thing... you kind of copy that.' [SHO 2]
Support from patients	The patients themselves can also say "I'm not feeling well since this has started. These are my symptoms" ... [Intern 3] 'Patients need to take responsibility for... their own healthcare management. I think it is their responsibility to have an up-to-date medication list that they bring to each clinical appointment and... to the hospital. They also probably need to take a role in the prompt recognition of change to their prescription and the prompt delivery of that prescription to their GP practice or their pharmacy...' [Consultant 2] '... it's unfair to ask them [patients] to read up on medications... that's not their job, that's not what they're trained for...' [Registrar 2] 'We should be empowering them to challenge us on all of these things... by giving them prompts, between printed prompts and things like that saying, "it would be in your best interest to prompt the doctors with these questions every time you see them" ...' [Consultant 1] '... any senior clinician... any pharmacists... and any senior nursing staff should have a role in that [recognising prescribing cascades] it's the whole MDT.' [Consultant 3]
Support from other healthcare professionals	'... nurses... they're exquisitely positioned to do it [recognise medication side effects/prescribing cascades] because they're giving the medicine to the patient... they have a huge amount of experience... it's more opportunistic... Although I understand that they might have less formal training in it, but they might have excellent experience... and we shouldn't discount their experience...' [Consultant 1] 'I think as well people are probably quite speciality focused. And while I would be comfortable changing someone's diabetes medication and things like that, and I mightn't necessarily be comfortable... you'd write to the rheumatologist and say, "does this person need to be on steroids"? ... but I wouldn't necessarily stop if it's been prescribed by another specialist.' [Registrar 4]
Goals	
Focus tends to be on treating the acute issue and often a 'quick fix'	'... as a hospital doctor reviewing inpatients... we often just focus on the primary issue and try to get the patient out of hospital as soon as possible. We don't often go and review the medication, although I believe a lot of patients probably have polypharmacy issues that are caused by prescribing cascades.' [SHO 1] 'We're always quick to start someone on a medication and less quick to look at a medication we start and go "is that maybe causing that"? ... we need to be looking more at deprescribing as opposed to increasing the number of drugs...' [Intern 1] '... it sounds really bad that we don't care. We, people would rather have a quick fix "oh their overcooked give them diuretics" than going back and reviewing the medications if there's any reason for them having this rather than just fixing it easily...' [Registrar 3]
Memory, attention and decision processes	
A 'fresh set of eyes' can help identify potential errors	'... on call [doctors] would review them [patients] and question things and a fresh set of eyes is good... sometimes reviewing the Kardex® yourself as the registrar on the ward every second day that someone has not been prescribed something completely off the charts...' [Registrar 3] 'I don't even think it would cross my mind [prescribing cascades] ...' [Intern 4]
Less attention given to medication reviews	'... if people have been put on medications, they [doctors] don't always wonder if they still need to be on them. Sometimes they just add rather than actually review... people are thinking more of the acute issue at hand rather than the long-term things...' [Registrar 4]

Table 2 (continued)

Descriptor	Quotations
Beliefs about consequences	
Prescribing cascades leading to patient harm	'...the risk of harm to the patient... that'd be readily avoidable if we had recognised it... longer length of stay, patient harm... more investigations, more anxiety for the patient...' [Consultant 2] 'I think both short term and long term quite significant effects to it [prescribing cascades], maybe less so short term if it's something where it's just the symptom that you're trying to get under control... but you're not thinking about the long-term outcomes.' [Intern 1] '...polyparmacy, more interactions, longer patient stay... confusion... probably leading to frustration amongst families and the patients and most GPs if things aren't made clear.' [Registrar 1] 'I'd probably wonder if I need to tell the patient [about a prescribing cascade] if I'm not 100% certain myself. I would do my best to prevent or stop this happening in future... I wouldn't be a 100% certain if I would... inform the patient exactly that this happened.' [SHO 3] 'Open disclosure is very important. It's key to making sure that patients feel safe... patients prefer open disclosure rather than finding out down the line... it's sometimes just as easy to be honest with the patient...' 'I made this mistake, now we've fixed it, and it's something that we can, you know, continue to improve upon...' [Registrar 3]
Personal impact on physicians and patient disclosure	'I'd actually say that it has become maybe a bit more prominent, just as I have become more experienced. Maybe in my entire intern year, I would have been happy knowing what the drug was and knowing what a drug did... I probably wouldn't have known much else about a particular drug other than the more obvious side effects, but in terms of recognising a drug that might cause a certain side effect and then recognising the negative cascade, I would not have been able to do that in the intern year and maybe only slightly picking it up at this stage.' [SHO 3] 'I don't know if I would be very confident about, for some obviously, the obvious ones that you hear about, but maybe other stuff I wouldn't really know. And then, I suppose, recognising... I'm not sure...' [Intern 2] 'It's something intuitively that we see all the time, well recognised.' [Consultant 3] 'I think people would recognise what happened [a prescribing cascade]... but they wouldn't group it together as "oh look at this interesting prescribing cascade"...' [Consultant 1]
Intentions	
Motivations are centred on symptom management	'[Prescribing cascades are] probably not recognised enough... a lot of time on ward rounds, there's a reflex just to treat rather than to think...' [Consultant 3] '...that's [prescribing cascades] not something I would have consciously been thinking of, we look at their medication list and pharmacy would do their medication [reconciliation]... but prescribing cascades isn't something I've actively been looking for...' [Intern 3] 'On call I don't even think it [prescribing cascade] would cross my mind. I'd never change a medication on call. I'd maybe write it in the notes and say for team to review. But I'd never change it myself.' [Intern 4]
Emotion	
Fear of asking questions	'... it's probably a knowledge and experience piece... but scared perhaps to ask questions.' [Registrar 4] 'I know other staff members would have fear of bringing up a question that they'd have and they would just choose not to bring it up... for fear of looking silly or inappropriate or unintelligent and fear of that being known...' [SHO 3] 'If I was the one that made the mistake, I would feel terrible.' [SHO 1]
Emotions after a mistake	'I'd feel reasonably okay if it was the first experience of it, making sure I actually made an effort to learn from it and not make the same mistake again.' [SHO 3]
Behavioural regulation	
Desire to learn from errors	'...if I didn't recognise it, then I won't recognise the next time if it hasn't been pointed out, you know that sort of way. So that's just like, uh, not learning from it then...' [Intern 2] '...in previous institutions where I've worked there used to be a medication alert system that went around maybe once a month, just to highlight that these were the inappropriate prescribing errors that have occurred... builds your awareness of it...' [Consultant 2]

Table 2 (continued)

Descriptor	Quotations
Optimism	
Potentially 'benign' consequences of prescribing cascades	'Usually they would be benign [consequences of prescribing cascades] ...' [Registrar 1]
Pessimism about recognition	'... we probably miss opportunities in clinic to do a reconciliation or something of someone's drugs.' [Registrar 4] 'I'm not sure if they've [prescribing cascades] recognised...' [Intern 1] '... in my limited experience, I have probably seen... less than five... think there's a lot more of them [prescribing cascades] that go on, that are missed...' [SHO 3]
Reinforcement	
Report with patients influences response	'It depends on... prior interactions with the patient... they're just some patients that seem to find an issue with everything, so when they say stuff, it's like the boy who cried wolf, you're less likely to take it on board... other patients it's just the way they say things... it's the rapport you have with [them]...' [Intern 4]
Learning opportunity is an incentive to report	'... people are less likely to own up to errors that are made because... lo!l! ... what would happen if they did own up. So, they need to be reassured that you're not going to give out to them. No one's going to lose their job over it, but it's very important that we have discussed it, so we all learn from it.' [Consultant 2]
Kardex [®] (medication prescription and administration record); BST (hospital-based training programme completed by senior house officers); ACE inhibitor/angiotensin converting enzyme inhibitor; app smartphone applications; BST basic specialist training; GP, general practitioner (primary care physician); MDT multidisciplinary team; PPI proton-pump inhibitor; SHO senior house officer; SPC Summary of Product Characteristics	

dates and intended duration as significant barriers to recognising prescribing cascades. This challenge was particularly evident in the emergency department outside routine working hours, when it is often impossible to access patients' full medical records or communicate with community healthcare providers.

3.1.2 Staffing

Perceived chronic staff shortages, among both medical and pharmacy teams, contributes negatively to the recognition of prescribing cascades because they reduce the time available for comprehensive medication reviews.

3.1.3 Excessive Workload

Many participants identified excessive workload, specifically the responsibility for reviewing large numbers of patients within a limited timeframe as a key factor limiting their ability to devote time for recognising prescribing cascades. Time constraints leading to 'fast-paced' ward rounds limit the opportunity for thorough medication reviews.

3.1.4 Information Technology

Participants highlighted deficiencies in healthcare information technology (IT), including inadequate infrastructure and limited online resources. Ireland's predominantly paper-based medical records system was seen as a significant hindrance, with participants expressing a desire for electronic records systems capable of providing alerts for potential prescribing cascades.

Online resources, such as the Summary of Product Characteristics, were commonly cited as resources used to check drug side effects. Access to other resources, such as the online British National Formulary (BNF), was inconsistent and challenging for some participants. Several interviewees proposed ideas for enhancing IT resources, including the development of smartphone applications for healthcare professionals to check for common prescribing cascades and for patients as a method for maintaining up-to-date medication records.

3.2 Knowledge

3.2.1 Recognising the Term 'Prescribing Cascade' and its Conceptual Understanding

Familiarity with the term 'prescribing cascade' varied across professional grade. Consultant physicians generally seemed unfamiliar with the term; however, they identified with the concept once provided with the definition. In contrast, all interns were able to define the term 'prescribing cascades' but admitted limited knowledge about specific prescribing cascades. During the interviews some participants had difficulties explaining precisely what a prescribing cascade entailed and mistakenly described them as drug–drug interactions and non-specific prescribing errors.

3.2.2 Knowing Examples of Prescribing Cascades

When asked, most participants had difficulty providing examples of specific prescribing cascades. When examples were provided, they were mostly 'appropriate' prescribing cascades (e.g. anti-emetic for nausea while on an antibiotic) with very few examples of inappropriate prescribing cascades provided (e.g. angiotensin-converting enzyme [ACE] inhibitor and anti-tussive).

3.2.3 Education and Training Deficiencies

All participants reported limited education on prescribing cascades. Few recalled undergraduate tuition on the topic, and none had received formal postgraduate teaching on cascades. Interviewees emphasised the need for targeted education, particularly for the most junior physicians (e.g. interns and SHOs), to improve recognition of prescribing cascades in clinical settings.

3.3 Skills

3.3.1 Experiential Learning

Several participants noted that most of their knowledge about prescribing and deprescribing—including prescribing cascades—developed informally during postgraduate training, often through experiential learning while working with geriatric medicine consultants.

3.3.2 Improvement with Training

Participants reported that their ability to recognise prescribing cascades improved with experience. Intern physicians in

particular reported challenges with recognising cascades due to limited exposure. Participants suggested that case-based learning and early career training (during intern/SHO years) could enhance skills.

3.4 Social/Professional Role and Identity

3.4.1 Physicians' Responsibility in Prescribing Cascade Recognition

All interviewees stated that recognising prescribing cascades is primarily the responsibility of the prescriber, with ultimate accountability resting with the most senior attending physicians, i.e. consultants. Some junior physicians felt less responsible, as they reported prescribing most medications under the direction of more senior colleagues. This perspective contrasted with that of senior physicians, who noted that junior physicians can sometimes prescribe without complete understanding of the clinical context, increasing the risk of prescribing cascades. This leads to senior physicians feeling responsible for monitoring and overseeing the prescribing practices of junior colleagues.

3.4.2 Pharmacists' Roles

Pharmacists were identified as crucial for recognising prescribing cascades through routinely performing an accurate medication reconciliation and review, identifying side effects and highlighting potentially inappropriate medications to the attending physicians. Several participants also suggested that a combined pharmacist–physician ward round would be an effective method to monitor and review patients' medications for potential prescribing cascades.

3.4.3 Specialty Role

Geriatricians were frequently mentioned for their expertise in deprescribing inappropriate medications and greater capacity to recognise prescribing cascades. Several participants indicated that they were more confident recognising prescribing cascades within their own specialty.

3.5 Social Influences

3.5.1 Hierarchy and Modelling within Medical Teams

Junior physicians, particularly interns/SHOs, described hesitancy with discussing medications with senior colleagues, influenced by relationships and team culture. They also reported that they tended to imitate the prescribing and deprescribing practices of their senior colleagues and would hesitate to question the prescribing decisions of senior

colleagues. In contrast, consultants indicated that they welcomed junior physician input on patients' medications (e.g. if they were to highlight potential adverse effects and/or potential prescribing cascades).

3.5.2 Support from Patients

Participants expressed mixed views on patients' roles in supporting physicians to recognise prescribing cascades. Several expected patients to maintain an accurate medication list and to report any suspected adverse symptoms to their doctor, while others perceived that it was 'unfair' to expect patients to do this, particularly older adults and those with limited knowledge about their medications.

3.5.3 Support from Other Healthcare Professionals

Many interviewees emphasised the possibly beneficial supportive role of other healthcare professionals in recognising prescribing cascades, including nurses, occupational therapists and physiotherapists. Nursing staff in particular were noted to be well positioned to identify adverse effects following medication changes. One participant commented that all healthcare professionals should be 'empowered' to speak up regarding any medication-related concerns which could help prescribing cascade recognition.

3.5.4 Reluctance to Change Medications Prescribed by Others

Participants reported reluctance with discontinuing medications initiated by other physicians, particularly when the physician had expertise in the relevant area, even when they suspected a prescribing cascade had occurred.

3.6 Goals

Interviewees reported that the focus during hospital admissions tends to be primarily on acute issues rather than reviewing longstanding medications which may be contributing to prescribing cascades. Even when a patient presents with a new symptom or change of clinical status, the goal is usually to address the acute problem by prescribing a symptom-relieving drug rather than a more thorough medication review to identify a potential side effect.

3.7 Memory, Attention and Decision Processes

Interviewees noted challenges with distinguishing between side effects and new medical conditions, highlighting that a 'fresh set of eyes' can help in identifying side effects and potential prescribing cascades.

Participants noted that the focus in the acute hospitalization context is primarily on the acute problem that led to admission. Therefore, less attention is given to reviewing medications (especially long-term medications), limiting the opportunity to recognise pre-existing prescribing cascades.

3.8 Beliefs about Consequences

3.8.1 Prescribing Cascades Leading to Patient Harm

Participants commented on the potential for harm associated with unrecognised prescribing cascades (polypharmacy, pill burden and increased hospitalisation). However, several participants appeared to downplay the consequences, viewing certain prescribing cascades as 'benign', and had an acceptance that side effects and associated prescribing mistakes happen frequently.

3.8.2 Personal Impact on Physicians and Patient Disclosure

Interviewees perceived low personal consequences for failing to recognise prescribing cascades. Several indicated they would only inform the patient if severe consequences occurred.

3.9 Beliefs about Capabilities

Junior physicians, particularly interns/SHOs, expressed low confidence in recognising prescribing cascades, despite familiarity with the term. By contrast, other participants, particularly consultants, expressed confidence in recognising prescribing cascades even if they were not familiar with the term prior to the interview.

3.10 Intentions

When new symptoms appear, hospital physicians' primary motivations are centred on symptom management and not actively inclined to identify potential prescribing cascades.

3.11 Emotion

Several participants highlighted that they would avoid asking questions of senior colleagues regarding potential prescribing cascades for fear of appearing 'silly' or 'unintelligent'.

In the theoretical setting of recognising that they had caused an inappropriate prescribing cascade, some participants described that they would feel 'horrible', whereas others described that they would feel 'okay' about this.

3.12 Behavioural Regulation

Participants expressed a desire for external mechanisms, either through feedback from colleagues or from alert systems, to learn from prescribing errors and recognise prescribing cascades more easily in the future.

3.13 Optimism

Several participants seemed less concerned about the consequences of prescribing cascades, describing them as 'benign' consequences.

Additionally, participants were generally pessimistic regarding the frequency of inappropriate prescribing cascade recognition, stating that 'most are not recognised' and opportunities to recognize prescribing cascades are frequently missed.

3.14 Reinforcement

One interviewee noted that the rapport they developed with patients reinforced their response to patients reporting side effects (e.g. less likely to recognise if lower rapport or high level of complaints in general).

Several participants suggested that junior doctors could be incentivised to report errors related to suspected prescribing cascades by framing it as a learning opportunity and reassuring them that reporting would not result in punitive consequences.

4 Discussion

This research has uniquely identified key factors that impact hospital physicians' recognition of prescribing cascades using the TDF, which served as the theoretical model to gain comprehensive insights into the clinical behaviour of recognising of prescribing cascades [16].

In essence, our findings indicate that knowledge about prescribing cascades is very limited among hospital physicians. While more junior physicians recalled being taught about prescribing cascades during their medical education, senior physicians were generally unfamiliar with the term. This suggests that the topic of prescribing cascades has only relatively recently been incorporated into medical education and that, as a therapeutics concept, it has yet to integrate into routine clinical practice. This is emphasised by the fact that no participant recalled hearing the term 'prescribing cascade' mentioned in the clinical setting. Although in the three decades since prescribing cascades were first described, considerable research has been conducted in the topic, further efforts are needed to ensure that all physicians are familiar with prescribing cascades

as a clinical term and concept to increase awareness and recognition in practice [38]. Participants in this study were generally unable to name more than a few examples of specific prescribing cascades, most of which are classified as appropriate (e.g. opioid → constipation → laxative) rather than inappropriate (e.g. ACE-inhibitor → cough → anti-tussive). A recently published explicit cascades list, called 'ThinkCascades', includes only nine inappropriate prescribing cascades in older adults, significantly under-representing their number [39]. A more comprehensive, validated list could serve as a resource for physicians, improving awareness, which has been identified in previous research as a key priority to improve recognition of prescribing cascades [18, 20].

In addition to limited knowledge of prescribing cascades, participants also demonstrated uncertainty distinguishing between polypharmacy, prescribing errors, prescribing cascades and drug-drug interactions during the interviews. For example, physicians sometimes provided examples of drug-drug interactions when asked for prescribing cascade examples. While previous research on deprescribing interventions has largely focused on reducing inappropriate or unnecessary medications, recognising prescribing cascades requires an additional layer of complexity, i.e. identifying when a drug has been prescribed to treat the side effect of another drug [40]. The conceptual overlap and confusion around the terminology is likely to further hinder efforts to recognise prescribing cascades.

Participants indicated that the primary responsibility for recognising prescribing cascades lies with them as prescribers. However, despite this acknowledgement, recognising cascades was seemingly not a priority. One possible explanation is that participants often perceived the consequences of failing to recognise prescribing cascades in hospital as 'benign' or inconsequential to the patient's acute hospitalisation episode. Previous research has highlighted that the absence of clear evidence of patient harm can result in 'deprescribing inertia' [20]. Similarly, the present study displays 'recognition failure'. Additionally, participants did not perceive any personal negative consequences for failing to recognise and correct inappropriate prescribing cascades, with several suggesting that side effects and prescribing errors are an inherent and to some extent unavoidable part of clinical practice [20].

This attitude may reflect a broader view that failing to recognise prescribing cascades is an acceptable deficiency driven by systemic challenges and the day-to-day realities of busy clinical practice. The lack of a well-established clinical focus on prescribing cascades, combined with the consensus from interviews that 'most are not recognised' emphasises the low priority placed on their detection and management. Furthermore, errors related to unrecognised prescribing cascades are rarely the sole responsibility of one physician [18].

More often, they result from a combination of systemic and environmental challenges within the healthcare environment that influence the decision-making process. These challenges, frequently highlighted by interviewees, contribute to a culture wherein the relative lack of concern may stem from an acceptance of working in a flawed healthcare system.

Several prominent environmental challenges repeatedly highlighted by participants included lack of accurate information regarding patients' medications, insufficient staffing and time constraints. A key issue identified was the lack of basic information during medication reviews, such as accurate medication lists, the original prescribing indications and medications' intended duration. The Irish public hospital system remains predominantly paper-based, with no widespread integrated electronic platform between community healthcare settings and hospital settings. This fragmentation often results in incomplete access to documentation, including medication changes made in other clinical settings.

A recent study by Jennings et al. reported that communication failures and a lack of prescribing stewardship during healthcare transitions added to the degree of risk when making prescribing decisions in such settings [20]. In line with this finding, interviewees in the present study emphasised that this issue was particularly problematic in the emergency department, where they described medication decision-making as 'hoping it is right'. In addition, physicians often make prescribing decisions in the context of limited, or at times inaccurate, information due to what one interviewee described as an 'archaic' health record system. This lack of comprehensive transfer of accurate information is a significant barrier to recognising prescribing cascades and increases the risk of medication-related harm to patients. It is unsurprising, therefore, that medication safety in transitions of care has been identified as a priority in the World Health Organisation's 'Medication Without Harm' challenge [41].

Physicians in this study also stressed the need for improved documentation, noting that medications are very often prescribed without clearly documented indication, a similar finding to previous research which noted that patients' health records often contain insufficient information to support decisions on prescribing and deprescribing [5, 24]. Research on deprescribing has similarly reported that clearer documentation of drug indications and long-term plans of each medication, as well as records of previously prescribed medications, in tandem with the reasons for their discontinuation, could facilitate easier recognition of prescribing cascades [42].

To improve recognition of inappropriate prescribing cascades, participants in this study suggested implementation of integrated IT solutions, aligning with previous research on prescribing cascades [28]. Such systems could support screening for prescribing cascades by improving documentation around prescribing and ensuring that all healthcare

providers have access to all current medication information. Several participants suggested software-based systems such as electronic alerts. For electronic alerts to be effective, they must capture users' attention whilst minimising 'alert fatigue', a challenge highlighted in the present study and previous studies [28, 43]. Other considerations for electronic alert systems include grading the priority of alerts, choosing appropriate timing, avoiding excessive number of alerts and cognitive overload and ensuring that they do not undermine clinical autonomy [43, 44]. A critical factor highlighted in a previous study is the importance of accurate information in generating alerts, without which the alerts may be misleading [45]. In well-organized and fully resourced hospital systems, physicians could decide to refer patients with suspected potentially inappropriate prescribing cascades to polypharmacy clinics for assessment, if such clinics are available. However, in most hospitals, physicians will need to assess and decide on deprescribing when they receive electronic alerts to potential cascades, or to refer to specialists for advice. Furthermore, as suggested by participants, IT solutions could incorporate the development of smart phone applications both for patients and healthcare professionals. For patients, an application could help them maintain a personal record of their medication regimen and identify potential side effects, empowering them to have an active role in medication management and prescribing cascade recognition [18, 46]. For physicians, an application with a searchable database of common prescribing cascades capability could be clinically valuable.

During inpatient admissions and ward rounds, staffing shortages, time constraints and acute issue prioritisation were frequently cited as obstacles to comprehensive medication reviews, with the cumulative effect of these factors limiting opportunities for identifying prescribing cascades [19]. Routine tasks, such as rewriting medication charts, are often delegated to the most junior members on the team due to time pressures, possibly representing a missed opportunity for prescribing cascade recognition [24].

Interviewees highlighted several challenges related to recognising prescribing cascades in older adults particularly. Hospitalised patients are increasingly older, frailer people who live with polypharmacy and multimorbidity, in line in global demographic trends [47]. Identifying and classifying a prescribing cascade as appropriate or inappropriate in this cohort of patients, often with complex polypharmacy, has previously been described as 'unfeasible' [20]. One strategy proposed by the present study's participants to address these challenges was the implementation of routine expert medication reviews through a collaborative, interdisciplinary model including pharmacists and physicians. Such a model aligns with existing pharmacotherapy optimisation recommendations and could be integrated within a polypharmacy stewardship programme. Effective management of prescribing cascades involves several key steps: identifying

the cascade, determining the indication for the original medication, assessing whether this indication remains and de-prescribing the original and/or subsequent medications where appropriate [48]. This model is likely to be more effective than simply increasing staff without ensuring the additional staff have the required training and skills to effectively recognise and manage prescribing cascades.

In the present study, participants also commented that many older adults had difficulty managing their medications, identifying side effects and communicating concerns regarding side effects to their physician, making the detection of prescribing cascades more challenging. These challenges are exacerbated by the organisation of modern medicine around a single-disease framework, in which each condition is treated in isolation [49]. This framework is evident in hospital settings, where patients' assessments focus primarily on immediate presenting problems. Interviewees generally agreed with this, commenting that hospitalisation is usually focused on the acute presenting problem. Many participants also discussed the reluctance among doctors to modify or discontinue long-standing medications, especially those prescribed by other specialists expressing concerns about overstepping professional boundaries, even when they suspected that an inappropriate prescribing cascade had occurred.

This present study highlighted that the hierarchical structure in hospital medical teams influences both the initiation and discontinuation of inappropriate prescribing cascades. More senior physicians commonly direct prescribing adjustments, with more junior physicians unlikely to question instructions from their senior colleagues [23]. This reduces the opportunity to scrutinise whether a prescription might create an inappropriate prescribing cascade [38]. More junior physicians also reported lower self-confidence in identification of prescribing cascades, often perceiving their prescribing patterns as lower risk. These findings highlight the need for targeted education to enhance junior physicians' knowledge and confidence in recognising medication side effects and prescribing cascades. While formal educational programmes are essential, informal learning remains invaluable [23]. Many physicians in this study reported that they gained much of their knowledge on prescribing and de-prescribing through working with consultants, especially geriatricians, because of their expertise with routine management of multimorbid patients who experience polypharmacy. They also suggested that leveraging teachable moments when prescribing cascades are identified and using these cases as direct learning opportunities may be valuable.

4.1 Potential Behaviour-Change Interventions

The findings from this study highlight multiple opportunities for behaviour change interventions aimed at improving the recognition of prescribing cascades. One key value of

using the TDF is its ability to provide a validated, structured, theory-based approach to understanding current practice-related challenges and supporting intervention design [16]. Previous research has indicated that theory-based behaviour change interventions are more effective than those without a theoretical foundation [50]. The TDF is often applied with the behaviour change wheel (BCW) to systematically design targeted, theory-based interventions [51]. A key strength of identifying all 14 TDF domains is that it allows for a multifaceted intervention to be designed. While the results of this study were not specifically analysed according to the BCW, the BCW may be applied in a number of ways. For example, in this study, 'knowledge' was identified as a key domain influencing physicians' recognition of prescribing cascades. According to the BCW model, knowledge maps onto 'capability', which can be addressed through intervention functions such as modelling, education and enablement [51]. A potential intervention could involve interactive, case-based learning sessions for junior doctors, where prescribing cascade scenarios are discussed. Additionally, while 'beliefs about consequences' was identified as a less influential domain, it could still be integrated into the intervention as 'motivation' and 'education' components. Incorporating discussions on the potential harm to patients and the clinical responsibility to recognise and de-prescribe prescribing cascades could enhance the effectiveness of the intervention.

Ultimately, the integration of IT resources, a collaborative approach with specialists in pharmacotherapy (both physicians and pharmacists) and medication educational initiatives for both healthcare providers and patients would likely empower all parties to recognise and address prescribing cascades effectively, improving medication safety across healthcare settings.

4.2 Strengths and Limitations

All interviews in this study were conducted by the same interviewer, ensuring consistency in data collection and data analysis. Reflexivity was considered throughout, enhancing the study's rigour by accounting for potential biases in data interpretation. The TDF was utilised both in topic guide development and content analysis. This framework is beneficial as it provides a structured approach to exploring behaviours, and it has been shown to reveal additional themes that may not be generated through other approaches [26, 27]. Furthermore, TDF domains can be mapped to the BCW, which can be utilised to identify and design suitable interventions to address the barriers identified [51]. However, while an example of how the BCW can be utilised is provided in the discussion, a limitation of this study is that the results were not specifically analysed according to the BCW.

The main limitation of the present study is the potentially low degree of transferability of the results, as this

study was conducted in a single hospital in Ireland. This hospital operates within a particular social and environmental context, where health records are predominantly primarily paper-based. Consequently, the findings may be less generalisable to other healthcare settings, particularly those with different systems, resources and cultures.

5 Conclusions

This study highlights the barriers that hospital physicians encounter in recognising inappropriate prescribing cascades, including gaps in knowledge, systemic and environmental challenges and cultural attitudes. Limited awareness of prescribing cascades, combined with fragmented healthcare information systems and often inadequate documentation of medication indication and duration, contribute to unrecognised prescribing cascades increasing the risk of harm to patients, particularly multimorbid older adults with polypharmacy. Addressing these challenges requires targeted behaviour-change interventions informed from these findings. These interventions could include integrated IT solutions, improved documentation of diagnoses and medications prescribed, interdisciplinary expert medication reviews and enhanced education and training opportunities. Such interventions could empower physicians to recognise inappropriate prescribing cascades more effectively, thus facilitating their minimisation—ultimately reducing medication-related harm and improving patient safety.

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Declarations

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Conflict of interest Denis O'Mahony is an Editorial Board member *Drugs and Aging*. Denis O'Mahony was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. The authors Ruth Daunt, Kieran Dalton and Denis Curtin have no competing interests to declare that are relevant to the content of this article.

Availability of data and material The datasets generated in this study are available from the corresponding author on reasonable request.

Ethical approval Ethical approval for this study was granted by the Social Research Ethics Committee, University College Cork (reference: 2024-048).

Consent to participate Written informed consent was obtained prior to enrolment from all participants.

Consent for publication Not applicable

Code availability Not applicable

Author contributions All authors contributed to the study conception and design. Material preparation was performed by Ruth Daunt. Analysis was performed by Ruth Daunt and Kieran Dalton. The first draft of the manuscript was written by Ruth Daunt and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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APPENDIX 2

STROBBE, COREQ AND GRIPP2 Checklists

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Checklist for study described in Chapter 2.

	Item No.	Recommendations	Page number
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	56
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Provided in published article
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	57-58
Objectives	3	State specific objectives, including any prespecified hypotheses	59
Methods			
Study design	4	Present key elements of study design early in the paper	59
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	59-61
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	59
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	60-62
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	61
Bias	9	Describe any efforts to address potential sources of bias	65
Study size	10	Explain how the study size was arrived at	60
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	65
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	65
		(b) Describe any methods used to examine subgroups and interactions	65
		(c) Explain how missing data were addressed	
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	66
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	68

		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15	Report numbers of outcome events or summary measures	69
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	77
Discussion			
Key results	18	Summarise key results with reference to study objectives	78
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	81
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	78 & 82
Generalisability	21	Discuss the generalisability (external validity) of the study results	82
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A (no funding)

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist
for Chapter Three.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	88
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	89
Occupation	3	What was their occupation at the time of the study?	89
Gender	4	Was the researcher male or female?	Not relevant to the subject matter.
Experience and training	5	What experience or training did the researcher have?	88 & 89
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	89 & 90
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	89 & 90
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	89 & 90
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	89 & 90
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	85 & 86
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	85 & 86
Sample size	12	How many participants were in the study?	91
Non-participation	13	How many people refused to participate or dropped out? Reasons?	91
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	85
Presence of nonparticipants	15	Was anyone else present besides the participants and researchers?	No

Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	91
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	See Appendix 3
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	No
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	88
Field notes	20	Were field notes made during and/or after the inter view or focus group?	88
Duration	21	What was the duration of the inter views or focus group?	91
Data saturation	22	Was data saturation discussed?	N/A –data saturation techniques not recommended.
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	No
Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	88
Description of the coding tree	25	Did authors provide a description of the coding tree?	88
Derivation of themes	26	Were themes identified in advance or derived from the data?	88
Software	27	What software, if applicable, was used to manage the data?	88
Participant checking	28	Did participants provide feedback on the findings?	No
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	100
Data and findings consistent	30	Was there consistency between the data presented and the findings?	115
Clarity of major themes	31	Were major themes clearly presented in the findings?	92 - 95
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	95-99

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist
for Chapter Four.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	131
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	131, 139
Occupation	3	What was their occupation at the time of the study?	138
Gender	4	Was the researcher male or female?	Not relevant to the subject matter.
Experience and training	5	What experience or training did the researcher have?	138 , 139
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	138
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	139
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	138-139
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	131
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	130
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	130
Sample size	12	How many participants were in the study?	144, 149
Non-participation	13	How many people refused to participate or dropped out? Reasons?	144
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	130
Presence of nonparticipants	15	Was anyone else present besides the participants and researchers?	No

Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	144, 149
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Appendix 3
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	No
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	131
Field notes	20	Were field notes made during and/or after the inter view or focus group?	131
Duration	21	What was the duration of the inter views or focus group?	144, 149
Data saturation	22	Was data saturation discussed?	N/A –data saturation techniques not recommended.
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	No
Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	131
Description of the coding tree	25	Did authors provide a description of the coding tree?	131
Derivation of themes	26	Were themes identified in advance or derived from the data?	131
Software	27	What software, if applicable, was used to manage the data?	131
Participant checking	28	Did participants provide feedback on the findings?	No
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	146- 151
Data and findings consistent	30	Was there consistency between the data presented and the findings?	See Results and Discussion Sections
Clarity of major themes	31	Were major themes clearly presented in the findings?	145, 149
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	145, 149

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Guidance for Reporting Involvement of Patients and the Public 2 (GRIPP2)

Checklist for Chapter Four.

Section	Description of section	Reported on page No.
1. Aim	Report the aim of PPI in the study	136
2. Methods	Provide a clear description of the methods used for PPIE in the study	137
3. Study results	Outcomes – Report the results of PPI in the study, including both positive and negative outcomes	165
4. Discussion and conclusions	Outcomes – Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	170
5. Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that didn't, so others can learn from this experience	170

Abbreviation: PPI, Patient and Public Involvement.

APPENDIX 3

Topic Guides

Topic Guide for semi-structured interviews with hospital physicians (Chapter 3).

Section 1: Current knowledge base

1. Before being invited to participate in this interview, what was your understanding of the term ‘prescribing cascade’?
2. Could you provide me with example(s) of (a) prescribing cascade(s) you are aware of?
3. You indicated that you learned about prescribing cascades in (undergraduate/postgraduate training): tell me more about that.

Prior moving to section two: ‘Prescribing cascades can be described as appropriate or inappropriate; for example, an appropriate prescribing cascade would be using laxatives for a patient who has constipation secondary to opioid use required for cancer-related pain. An inappropriate prescribing cascade would be a calcium channel blocker causing ankle oedema resulting in the prescription of a diuretic. For the purpose of this study, we will focus primarily on inappropriate prescribing cascades for the rest of the interview’.

Section 2: Clinical practice

4. How often do you think prescribing cascades are recognised amongst general medical inpatients in this hospital?
5. What do you see as the barriers to recognising prescribing cascades? (memory/attention)
 - a. Environment
 - b. Social influences (team dynamic)
 - c. Resources (phone, apps etc)

If participant indicated they personally have recognised a prescribing cascade or if they have witnessed a colleague recognising a prescribing cascade, ask Question 8

6. You indicated that you have/ your colleague has recognised a prescribing cascade: can you tell me more about it?
 - a. Can you describe to me how you/your colleague determined it was a true prescribing cascade?

7. What resources do you find help you recognise adverse drug reactions /drug side effects/ prescribing cascades? (*e.g. other HCPs/ apps etc*)
8. What are the risks associated with not recognising a prescribing cascade?

Section 3: Priorities and social behaviours

9. Where are prescribing cascades on your list of priorities/considerations when reviewing a patient?
10. How would you feel about informing a patient that you (unintentionally) initiated a prescribing cascade? i.e., that you did not recognise symptoms as a drug side effect and prescribed a second drug - instead of stopping the first drug.
11. Whose responsibility is it to recognise prescribing cascades?
 - a. **Why do you feel it is your/their role?**
 - b. **If they do not say it is their role: ask what is their role in recognising prescribing cascades.**
12. What do you see as the role that patients play in aiding the recognition of prescribing cascades?
13. If a patient attributed a symptom they were experiencing as a medication side effect, how might this change your review or management of them?

Section 4: Improvement strategies

14. What would help you or other doctors recognise prescribing cascades?
 - a. Environment
 - b. Social/ belief about capabilities
 - c. Strategies to enhance knowledge/ understanding and recognition

That brings us to the end of the interview. Based on the topic or what we have discussed, do you have any other comments that you would like to add or anything that you would like to expand on?

Topic Guide for semi-structured interviews with older adults attending the geriatric medicine out-patient department (Chapter 4).

Opening question

1. Having just completed the MRB-QoL tool, do you have any initial feedback?
 - a. Can you expand on this?

Accessibility

2. How did you find the wording of the statements?
 - a. Are there any statements that were particularly confusing / difficult to understand?
 - b. Are there any statements that were particularly clear and easy to understand?
3. What do you think about the general length of statements?
 - a. For example, statement 2 and statement 9?
4. Could you comment on the readability?
 - a. Font size / statement / answer layout

Relevance

5. Do you think the statements are relevant to the topic of medication related burden (how medication impacts your health and well-being)?
6. Are there any statements you think are unnecessary / irrelevant?
7. Are there any statements you think are repetitive?

Completeness

8. Do your medications impact your health and well-being in ways that weren't asked in the MRB-QoL tool?

Length

9. How did you find the length of the tool?
 - a. If answers that it is too long, ask: how long would you recommend it to be?

Recommendations

10. What changes do you think we could make that would help you and your peers complete the MRB-QoL tool?

That brings us to the end of the interview. Based on the topic or what we have discussed, do you have any other comments that you would like to add or anything that you would like to expand on?

Topic Guide for the focus group with experts in geriatric medicine (Chapter 4).

Introduction

Welcome. The purpose of this focus group is to gather insights and suggestions as to how best to modify the MRB-QoL tool to improve its usefulness with older adults.

Overview

1. What are your initial thoughts on using the MRB-QoL tool as it is for older adults?
2. In your opinion, how would your patients find this tool?

Relevance

3. Do you think the statements are relevant to the topic?
4. Can you rank the statements in each section according to relevance?

Completeness

5. Are there any important topics missing from the MRB-QoL Tool?

Recommendations

6. What changes do you think we could make that would help your patients complete the MRB-QoL tool?

That brings us to the end of the focus group. Based on the topic or what we have discussed, do any of you have any other comments that you would like to add or anything that you would like to expand on?

APPENDIX 4

Scoring Method for MRB-QoL

Conversion formula for MRB-QoL score

Total MRB-QoL score =

Total actual raw score of each item – number of items in the subscale X 100

Maximum possible raw score or all items – number of items in the subscale

The score ranges from 0 to 100, where,

0 = no medication-related burden and thus, the best possible medication-related quality of life

100 = highest level of medication-related burden and thus, the worst possible medication-related quality of life

APPENDIX 5

Document for modified Nominal Group Technique

Document for modified Nominal Group Technique

Subscale/ Section A: The following statements are about the **burden associated with the medicine regimen and routines of taking medicines.**

General themes from interview with doctors:

- Subscale one cover 3 main concepts – scheduling, organising your medications and physical administration.
- Very relevant section but could be streamlined, a lot of duplication
- Older adults often need external assistance with their medications

General themes from interviews with patients: Some statements could be incorporated together

Original statement		Quantitative data CFA loadings	Qualitative Doctors		Expert Opinion	Proposal	Your Feedback	
			Ranking	Comments				
1	I find it difficult organising my medicines	.59	1	1,2,3,7 all similar	No Change	Retain as is, 'I find it difficult organising and maintaining an up-to-date list of my medicines'	☐ Yes ☐ No	
2	I find it hard keeping my medicines record	.52	7	1,2,3,7 all similar	Change wording	Incorporated into item 1	☐ Yes ☐ No	
3	It is difficult for me to manage my routines associated with my medicine taking	.53	6	1,2,3,7 all similar	Overlap in items 3-6,10	Reframe as new item to increase relevance to older adults with multimorbidity and polypharmacy 'I need help organising my medications (carer assistance / blister pack)'	☐ Yes ☐ No	
4	Fitting medicine routines into my other life schedules is a difficult task for me	.79	9	4, 5, 6 and 10 similar/ duplication	Overlap in items 3-6,10 Wording	Reword as, 'My medicine schedule restricts me in my daily routine'.	☐ Yes ☐ No	
5	Taking medicine/s interferes with my physical activities	.81	8	Scheduling not a massive issue for older people			☐ Yes ☐ No	

6	It is difficult to balance my daily life schedules with taking medicine	.83	10				☐ Yes ☐ No	
7	My current medication regimen is not simple for me to manage (e.g. injections, tablets, eye drops)	.46	2	Very relevant	Overlap with 9 and improve wording	Reword as, 'Taking my medicines is challenging (e.g. injections, swallowing tablets, eye drops, inhalers, opening medicine containers)'	☐ Yes ☐ No	
8	Understanding the instruction on my medicine/s is challenging at times	.53 Cross-loadings with subscale B	3	Important	Improve wording	Reword as, 'Understanding the exact instruction on my medicine's label is challenging at times (e.g. timings in relation to other medications/ food etc)	☐ Yes ☐ No	
9	My current medicine/s are not in a convenient form for me to take (e.g. difficult to swallow, unpleasant taste/ smell)	.38	4	3, 7, 9 and 11 similar – practical considerations	Overlap and wording	Incorporated into item 7 (Poor individual loading)	☐ Yes ☐ No	
10	Sometimes I have to cancel my daily schedules because of my medicines	.72	11	Less relevant	Overlap in items 3-6,10	Incorporated into item 4- less relevant and overlap	☐ Yes ☐ No	
11	Opening the package of my medicines is sometimes a difficult task for me (e.g. child proof caps)	.35	5	Important statement to include	Improve wording	Incorporated into item 7. (Low CFA loading)	☐ Yes ☐ No	

Subscale/ Section B: The following statements are about the impact of medicines associated burden on psychological wellbeing.

General themes from interview with doctors:

- Less duplication compared to section
- Relevant section to older adults

Original statement	Quantitative data CFA loadings	Qualitative Doctors		Expert Opinion	Proposal	Your Feedback
		Ranking	Comments			

12	It bothers me that I have to take medications for the long term	.70	2	Relevant	Incorporate into item 13	Incorporate into item 13	☐ Yes ☐ No	
13	I am concerned about the number of medicines I am on	.74	1	Relevant	Overlap with 12	Reword as: 'I am concerned about the number of long-term medications I am on'.	☐ Yes ☐ No	
14	I worry about the long-term effects of medicines on my health	.75	4		Improve wording	Reword as, 'I worry about the long-term side-effects of medicines on my health'	☐ Yes ☐ No	
15	Taking medicines on a regular basis reminds me of my health problems	.51	5	Not a theme encountered in clinical practise	No change	Low factor loading, not deemed relevant. Remove	☐ Yes ☐ No	
16	I am concerned that my medicines may interact with each other	.73 Cross-loadings with item 24	3		No change	Retain as and reword, 'I am anxious that my medicines may interact with each other'	☐ Yes ☐ No	
17	My medicines signify me as not being healthy	.65 Cross-loadings with subscale C	6	Less relevant to older people	Possible to remove, overlap	Remove, less relevant and cross-loading	☐ Yes ☐ No	

Subscale/ Section C: The following statements are about the impact of medicines associated burden on physical wellbeing.

General themes from interviews with patients:

- Patients: important to ask about sex 'it would be necessary to some people'
- More clarity on questions relating to side effects- difficult to know if symptom caused by ageing of meds

Original statement	Quantitative data CFA loadings	Qualitative Doctors		Expert Opinion	Proposal	Your Feedback	
		Ranking	Comments				
18	I am sometimes sexually frustrated because of my medicine/s	Selected as N/A 83.9%	6	18 & 19 similar-important to include	Improve wording to be more relevant	Reword as, 'Some of my medications negatively affect my sex life'	☐ Yes ☐ No

19	I am unable to relax and enjoy sex because of my medicine/s	Selected as N/A 89.7%	4		Incorporate into item 18		☐ Yes ☐ No	
20	Some of my medicines slow down my physical health	.80	5	Vague, non-specific	Overlap, remove	Retain and improve clarity 'Some of my medicines slow me down'.	☐ Yes ☐ No	
21	I often have a bad night's sleep because of my medicine/s	.52	2	21 & 22 similar-	Reword	Reword as, 'I often sleep poorly because of my medicine's'.	☐ Yes ☐ No	
22	Because of my medicine/s I feel too tired to perform physical activities	.75	3	Hard for a patient to quantify	Improve wording	Because of my medications I have less energy for daily activities	☐ Yes ☐ No	
23	I work less than usual because of the effect of my medicine/s	Selected as N/A 73%	7	Less relevant	Remove-less relevant	Remove	☐ Yes ☐ No	
24	Some of my medicine make me feel uncomfortable due to side effects	.57 Cross-loadings with subscale B	1	High relevance	Improve wording	Reword to improve clarity (and cross-loadings) 'Some of my medications cause unpleasant side-effects'	☐ Yes ☐ No	

Subscale/ Section D: The following statements are about medication burden **related to health services**.

General themes from interview with doctors:

- Important section
- Another point raised is the challenge of medication management in healthcare- reliance on patient to bring meds to appointments/ED. No integrated system

Significant floor effect in this section

Original statement	Quantitative data CFA loadings	Qualitative Doctors		Expert Opinion	Proposal	Your Feedback	
		Ranking	Comments				
25	I am not treated with respect and dignity as a patient	.53	3	Too broad- doesn't clearly state healthcare professionals	No change	Reword as 'I am not treated with respect and dignity by healthcare professionals'	☐ Yes ☐ No

26	My doctor doesn't take into account the health of my body, mind and spirit	.64	2	Older people less familiar with this terminology	Improve wording	Reword as, 'My doctor doesn't consider my opinions and preferences regarding my medication'	☐ Yes ☐ No	
27	My doctor/s talk about my medicine/s as if I'm not there	.78	1		Overlap with item 26	Incorporate into item 26	☐ Yes ☐ No	
	Additional Item			'Poor communication about my medications between healthcare services places a burden on me'. This item was added based on focus group feedback highlighting that healthcare services are poorly coordinated regarding medications, potentially placing a significant burden on patients.			☐ Yes ☐ No	

Subscale/ Section E: The following statements are about the impact of medicines associated burden on social wellbeing.

General themes from interview with doctors:

- This section seems less relevant
- Could be summarised into one statement
- Other aspect- complex medication regimes can interfere with people sense of independence as family/ carers may need to get involved

General themes from interviews with patients:

- Embarrassment not a significant factor for most older adults 'everyone is on tablets'

Significant floor effect in this section

	Original statement	Quantitative data CFA loadings	Qualitative Doctors		Expert Opinion	Proposal	Your Feedback	
			Ranking	Comments				
28	I would rather not tell others I'm taking medicines regularly	.58	3		Low relevance in older adults	Incorporate into item 30	☐ Yes ☐ No	
29	I get embarrassed using my medicines in public	Selected as N/A 20%	1			Remove	☐ Yes ☐ No	

30	I feel stigmatized because of what people say about the medicine's I take	.85	2	Side effects can be more limiting than stigma		Reword as, 'I would feel embarrassed if people knew about the number and/or types of medicines I take regularly'.	☐ Yes ☐ No	
31	If people found out I was on medicines, they would see me as weak	.74	4	Not necessary to include this	Remove-low relevance	Remove, not relevant	☐ Yes ☐ No	
	Additional Item					'It bothers me that someone else has to organise my medicines'. This item was added based on focus group feedback that needing assistance with medications may impact social wellbeing	☐ Yes ☐ No	

APPENDIX 6

Ethical approval for research described in this thesis

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: 4 (i) 09/08/2022
& ECM 5 (6) 31/08/2022 & ECM 3 (m) 01/11/2022

Date: 29th September 2022

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

Study Title: Medication Review of Multimorbid Older Patients Admitted with Unselected Illness Including Detection of Inappropriate Medications, Falls Risk Increasing Drugs and Drug-Drug Interactions.

Dear Professor O'Mahony

The following documents have been approved:

Application Form	Signed 16 th September 2022
Participant Information Leaflet (PIL)	Version 2 dated 16 th September 2022
Revised Study Protocol	Version 2 dated 16 th September 2022
Revised Consent Form	Version 2 dated 16 th September 2022
CV for Chief Investigator.	

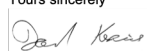
Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018/2021.

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). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
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
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely



Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Note. Ethical approval for the data collected in Chapter 2 is covered under this broader study.

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901

Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: 4 (i) 09/08/2022
& ECM 5 (6) 31/08/2022 & ECM 3 (ff) 14/02/2023

Date: 19th January 2023

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

Study Title: Medication Review of Multimorbid Older Patients Admitted with Unselected Illness Including Detection of Inappropriate Medications, Falls Risk Increasing Drugs and Drug-Drug Interactions.

Dear Professor O'Mahony

The following amendment has been approved:

- Amendment Application Form signed 10th January 2023
- Study Protocol Version 3 dated 10th January 2023
- Patient Information Leaflet Version 3 dated 10th January 2023.

Yours sincerely



Professor David Kerins
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.



Ruth Lydia Daunt <111322631@umail.ucc.ie>

Ethics Application

Ethics Committee, Social Research <srec@ucc.ie>
To: Ruth Lydia Daunt <111322631@umail.ucc.ie>

Tue, Apr 2, 2024 at 8:46 AM

Dear Ruth,

The Social Research and Ethics Committee has now approved your application Log **2024-048** entitled "An Investigation into Factors Influencing Recognition of Prescribing Cascades Amongst Medical Hospital Doctors".

The Committee wishes you every success with your research.

Kind regards,
Maria

Maria FitzGerald Houlihan | Research Ethics Support | SRECI University College Cork | srec@ucc.ie
Website: <https://www.ucc.ie/en/research/support/ethics/socialresearch/>

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (o) 14/05/2024

Date: 15th May 2024

Professor Denis O'Mahony
Consultant Geriatrician
Department of Geriatric Medicine
Cork University Hospital
Wilton
Cork

Study Title: Development of a short form of the tool, Medication - Related Burden Quality of Life (MRB-QoL), for older adults on long-term medications.

Dear Professor O'Mahony

Approval is granted to carry out the above study at:

Geriatric Medicine Outpatient Department and Assessment and Treatment Centre, HSE Assessment Hub, Ballincollig, Cork

The following documents have been approved:

Document	Approved	Version	Date
Application Form	Yes		Signed: 26 th April 2024
Proof of Insurance (CIS)	Yes		
CV for Chief Investigator	Yes		
Study Protocol	Yes	1	16 th April 2024
Participant Information Form (Phase 1)	Yes	1	16 th April 2024
Consent Form (Phase 1)	Yes	1	16 th April 2024
Participant Information Form (Phase 2.1)	Yes	1	16 th April 2024: Correct "this this research" prior to use.
Consent Form Phase (2.1)	Yes	1	16 th April 2024
Participant Information Form (Phase 2.2)	Yes	1	16 th April 2024
Consent Form (Phase 2.2)	Yes	1	16 th April 2024
Data Collection Document (Phase 1 and Phase 2.1)	Yes		
Medication Related Burden Quality of Life Tool	Yes		
Data Collection Document (Phase 2.2)	Yes		
Semi-structured Interview Topic Guide	Yes	1	26 th March 2024
Focus Group Topic Guide	Yes	1	26 th March 2024.

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

Name	Appointment Details
Dr Denis Curtin	Consultant Physician CUH, Dept of Geriatric Medicine
Dr Ruth Daunt	Research NCHD CUH Geriatric Medicine SpR.

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. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018/2021.

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). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**