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# Predicting adverse health outcomes in older community-dwelling adults: a prospective cohort study 

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## CITATION

Wallace, Emma (2016): Predicting adverse health outcomes in older community-dwelling adults: a prospective cohort study. Royal College of Surgeons in Ireland. Thesis. https://doi.org/10.25419/rcsi.10809050.v1

DOI
10.25419/rcsi.10809050.v1

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## Predicting adverse health outcomes in older

 community-dwelling adults: a prospective cohort study
## A thesis submitted to the Royal College of Surgeons in Ireland for the degree of Doctor of Philosophy in the Department of General Practice

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HRB PhD Scholar's Programme in Health Services Research

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February 2016

## Candidate Declaration

I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree of Doctor of Philosophy, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own.

I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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## List of abbreviations

A\&E
ACG
ACS
ADE
ADLs
ACEI
ATC
CDS
CHF
Cl
COPD
CPM
DDD
EARLI

ED
EQ-5D
EQ-5D VAS
GMS
GP
HADS
HIPE
HRB
HRQOL
HSE-PCRS

ICPC-2

IPET
IQR
IRR
MAI

Accident and Emergency
Adjusted Clinical Groupings
Ambulatory care sensitive
Adverse drug event
Activities of daily living
Angiotensin converting enzyme inhibitor
Anatomical Therapeutic Chemical
Chronic Disease Score
Congestive heart failure
Confidence interval
Chronic obstructive pulmonary disease
Combined Predictive model
Defined daily doses
Emergency admission risk likelihood index

Electoral division
EuroQuol-5Dimensions
EQ-5D Visual analogue scale
General Medical Services
General Practitioner
Hospital Anxiety and Depression Scale
Hospital In-Patient Enquiry
Health Research Board
Health-related quality of life
Health Services Executive-Primary Care Reimbursement Scheme

International Classification of Primary Care-Second edition Improving Prescribing in the Elderly Tool Inter-Quartile Range

Incidence rate ratio
Medication Appropriateness Index

## List of abbreviations

## MMSE

MMAS
MOS

MPR
NHS
NSAID
OR
PIP
PPI
Pra
QOF
RCT
RCSI
SAHRU
SD

## SE

SF-36
SPARRA

SSRI
STOPP

STROBE

TCA
TRIPOD

UK

## US

VES-13
WHO

Mini Mental State Examination
Morisky Medication Adherence Scale
Medical Outcomes Social Support Survey

Medication Possession Ratio
National Health Service
Non-steroidal anti-inflammatory drug
Odds ratio
Potentially Inappropriate Prescribing
Proton Pump Inhibitor
Probability of repeated admission
Quality Outcomes Framework
Randomised controlled trial
Royal College of Surgeons in Ireland
Small Area Research Unit
Standard deviation
Standard error
Short form health survey-36
Scottish People At Risk of Readmission and Admission
Serotonin Selective Reuptake Inhibitor
Screening Tool of Older Person's
Potentially Inappropriate Prescriptions
Strengthening the Reporting of Observational studies in Epidemiology
Tricyclic antidepressant
Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
United Kingdom
United States
Vulnerable Elders Survey
World Health Organisation

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#### Abstract

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## Summary

## Background

This thesis aimed to investigate if adverse health outcomes in older community-dwelling people can be predicted, through the application of measures of prescribing, multimorbidity and emergency admission risk models. There were five objectives: 1) to determine if there is a longitudinal association between potentially inappropriate prescribing (PIP) and future adverse drug events (ADEs), reduced health related quality of life (HRQOL) and increased use of Accident \& Emergency (A\&E) and emergency admissions; 2) to assess the performance of different measures of multimorbidity and vulnerability in predicting emergency hospital attendance and functional decline; 3) to conduct a systematic review of emergency admission risk prediction models developed for use in community-dwelling adults; 4) to systematically review and meta-analyse the validation studies of the Probability of repeated admissions (Pra) risk model; and, 5) to externally validate the Pra risk model in predicting emergency hospital admission over the following year.

## Methods

A prospective cohort study with two year follow-up was conducted linked to the national Health Services Executive Primary Care Reimbursement Services (HSE-PCRS) pharmacy claims database (2010-2012). At baseline a total of 904 older ( $\geq 70$ years) communitydwelling people were recruited from 15 general practices. The Screening Tool of Older Persons Prescriptions (STOPP) and Beers 2012 prescribing indicator sets were applied to the pharmacy data to elicit PIP. ADEs were recorded through patient interview with corresponding review of the GP medical record. HRQOL was determined through the Euro-Qul-5Dimensions (EQ-5D) administered through a patient questionnaire. Emergency attendance was ascertained through a detailed review of the GP medical record. Multilevel regression modelling was used to investigate if PIP was longitudinally associated with ADEs, HRQOL and emergency hospital attendance (Poisson (incidence rate ratio (IRR) (95\% CI) and linear regression models (regression co-efficient ( $95 \% \mathrm{CI}$ )). Different medication and diagnosis based measures of multimorbidity, the Vulnerable Elders Survey (VES-13) and the Pra model were investigated by examining their discrimination (the ability of the model to
distinguish correctly the patients with different outcomes, c-statistic ( $95 \% \mathrm{CI}$ )) and calibration (reflects how closely predicted outcomes agree with the actual outcomes, Hosmer-lemeshow statistic).

## Results

Of 791 participants eligible for follow-up, 673 ( $85 \%$ ) returned a questionnaire and 605 (77\%) also completed an ADE interview. Baseline STOPP PIP prevalence was 42\% and 445 (74\%) patients reported $\geq 1$ ADE at follow-up. In multivariable analysis, $\geq 2$ STOPP PIP was associated with ADEs (adjusted IRR: 1.29 ( $95 \% \mathrm{Cl} 1.03,1.85, \mathrm{p}=0.03$ ); poorer HRQoL (adjusted regression co-efficient: -0.11 (-0.16, -0.06; p<0.001)); and, $\geq 1$ A\&E visit (adjusted OR: 1.85 (1.06, 3.24; $p=0.03$ )). All multimorbidity measures demonstrated poor discrimination for the outcome of emergency admission (c-statistic range: $0.58,0.62$ ) but the VES-13 demonstrated reasonable model discrimination for the outcome of functional decline (c-statistic: 0.74 ( $95 \% \mathrm{Cl} 0.69,0.80$ ). The Pra model demonstrated poor discrimination for the outcome of emergency admission (c-statistic: 0.63 ( $95 \% \mathrm{Cl} 0.58,0.68$ ) but model specificity was high (95\%).

## Conclusions

Older community-dwelling people, prescribed $\geq 2$ PIP, as defined by the STOPP prescribing criteria, are more likely to report ADEs, poorer HRQOL and attend A\&E over two year followup. Both medication and diagnosis-based measures of multimorbidity demonstrated similar performance in predicting emergency admission. The VES-13 may be useful in identifying older people at risk of functional decline in the community. In certain circumstances, while acknowledging the limitations of risk stratification, the Pra tool may have a role in targeting older people at higher risk of emergency admission.

## Acknowledgements

First and foremost, thank you to the study participants and general practices who gave so generously of their time in taking part in this study. Several research assistants and undergraduates contributed to this study through data collection and data inputting. I gratefully acknowledge Annette Burns and Teresa Lawless who conducted telephone interviews, Niall Vaughan, Trish Doherty, Blaithin Guninan, Marie Boland and Catherine Casey for their hard work in helping administer questionnaires and input data, and Drs Ellen Stuart, Tim Hinchey, Muireann de Paor, Mark Murphy, Janine Cooper and Prof Susan Smith for their contribution to the systematic and academic reviews. Thank you to the Health Research Board of Ireland (HRB) who funded my PhD through a Research Training Fellowship for Healthcare Professionals (grant number HPF/2012/20), and the academic and administrative team of the HRB PhD Scholar's programme in Health Services Research for their support and for providing a structured environment for this research.

I have been very fortunate to receive excellent supervision and mentorship throughout my PhD. Huge thanks to Professor Susan Smith and Professor Tom Fahey for their direction, reassurance and support, and to Dr Kathleen Bennett for her methodological expertise and advice, and for applying the prescribing indicators to the pharmacy data at follow-up. I'm very grateful to Dr Ron McDowell, who gave so generously of his time and biostatistics expertise, and to Dr Caitriona Cahir who conducted the baseline study and, with Frank Moriarty, applied the prescribing indicators to the baseline pharmacy data. Thank you to my classmates on the HRB PhD Scholars programme and my colleagues at RCSI who are a great source of inspiration. Special thanks to Drs Rose Galvin and Barbara Clyne whose friendship and encouragement is much appreciated.

Finally, thank you to Heather and Alan for their support throughout, and to my incredible husband Mike, for his constant encouragement and loving support, who made this thesis possible.

## Dedication



My parents, Marie and Arnold, very much believe in the value and power of education, and gave me every opportunity. Thank you for making all of this possible.

## Peer reviewed publications and oral presentations

Parts of this thesis have been published as follows:

## Peer reviewed publications

1. Wallace E, Smith SM, Fahey T, Roland M. Reducing emergency admissions through community-based interventions. B MJ 2016;352:h6817.
2. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care: clinical review. BMJ 2015 Jan 20;350:h176.
3. Wallace E, Stuart E, Vaughan N, Bennett K, Fahey T, Smith SM. Risk prediction models to predict emergency hospital admission in community-dwelling adults: a systematic review. Med C are2014 Aug;52(8):751-65.
4. Wallace E, Hinchey T, Dimitrov BD, Bennett K, Fahey T, Smith SM. A systematic review of the Probability of repeated admission (Pra) score in community-dwelling adults. J Am Geriatr S 00013 Mar;61(3):357-64.

## Oral conference presentations

1. Wallace E, Stuart E, Vaughan N, Bennett K, Fahey T, Smith SM. 2015. Risk prediction models to predict emergency hospital admission in community-dwelling adults: a systematic review. HRB SPHeRE Conference, 9th January 2015, RCSI, Dublin.
2. Wallace E, Stuart E, Vaughan N, Bennett K, Fahey T, Smith SM. Risk prediction models to predict emergency hospital admission in community dwelling adults: a systematic review. NAPCRG 21-24th November 2014, New York, USA.
3. Wallace E, Stuart E, Vaughan N, Bennett K, Fahey T, Smith SM. Risk prediction models to predict emergency hospital admission in community dwelling adults: a systematic review. (Elevator Pitch) Annual meeting of the Society of Academic Primary Care, 9th-11th July 2014, Edinburgh, UK.
4. Wallace E, Stuart E, Vaughan N, Bennett K, Fahey T, Smith SM. Risk prediction models to predict emergency hospital admission in community dwelling adults: a systematic review Academic University Departments of Ireland annual scientific meeting, 6-7th March 2014, Cork, Ireland.

## Invited oral presentation

1. Wallace E, Bennett K, Fahey T, Smith SM. Predicting the risk of adverse health outcomes in older community-dwelling adults. Population Health Sciences Divisional Seminar, 30th April 2015, RCSI, Dublin.

Chapter 1 Introduction

### 1.1 Background

Global population demographics are changing. Internationally, the proportion of people aged greater than 60 years is expected to increase from $11.7 \%$ in 2013 to $21.1 \%$ in 2050.(1) In 2011, there were a total of 535,393 people aged 65 or older living in the Republic of Ireland representing $11.6 \%$ of the total population.(2) By 2041, it is estimated that this number will rise to 1.4 million people, accounting for $22 \%$ of the total population. $(2,3)$ The number of very old in this cohort (aged $\geq 85$ years) is expected to rise to 356,000 over this time period.(3) This represents a significant shift in population demographics and will result in substantial capability and financial pressure for health services.

Older people bear the greatest burden of illness and as a result account for the greatest proportion of prescribed medication. Predicting which older people are most likely to experience future adverse health outcomes is an essential part of the efficient allocation of health resources where they are most likely to be of benefit. Particularly pertinent for older people are the challenges of managing multiple chronic medical conditions and prescribed medications and an increased risk of emergency hospital admission, which may result in functional decline and adverse events such as falls.(4-6)

### 1.2 Medicines management in older people

Good quality prescribing has been defined as the appropriate choice of medication from both the patient and clinician's perspective, which aims to maximise therapeutic effectiveness while minimising risk and cost.(7) However, there are well established challenges in prescribing for older patients in primary care. First, older people have altered pharmacokinetic profiles which reduce their physical ability to metabolise and excrete medications.(5) Second, polypharmacy can result in difficulties as each medication has its own potential side-effects and there is an increased risk of drug-drug interactions, diseasedrug interactions and adverse drug events (ADEs).(8, 9) Third, many prescriptions issued in primary care are actually initiated in specialist care which can be problematic for the general practitioner (GP) who is responsible for the co-ordination and ongoing management of prescriptions from multiple care providers.(9)

Over the past two decades, both the volume and cost of prescribed medications have increased exponentially.(9-11) In older populations this rise may have been due to improved access to medical care, an increased use of proven treatments and the consistent application of evidence-based medicine.(12) However, prescribed medication can also be hazardous resulting from potentially inappropriate prescribing (PIP), drug interactions, drugdisease interactions and ADEs with resultant increased morbidity and mortality. $(13,14)$

### 1.2.1 Measures of prescribing

Indicators are commonly used to ascertain the quality of a service and if developed robustly and used correctly, can help to identify potential problems and encourage quality improvement and/ or improved patient safety.(9) Appropriateness +of prescribing can be assessed by process (i.e. what healthcare providers do) or outcome measures (e.g. patient outcomes) that are explicit (criterion-based) or implicit (judgement-based).(5) Explicit measures are preferred as they have the advantage of being based on both literature review and expert consensus and if developed appropriately should demonstrate both validity and reliability. Validity relates to the indicators measuring what they claim to measure and involves three key aspects.(15) First, face validity which requires the indicators to be both clinically relevant and sensible, second, content validity, which means that each item is evidence-based and developed through expert consensus and third, construct validity which relates to each indicator corresponding to a theoretical concept of quality.(15) Reliability relates to the indicators being consistent across test-retest with high inter-rater agreement.(16)

### 1.2.2 Prescribing related adverse health outcomes

Adverse health outcomes related to prescribing include ADEs, increased healthcare utilisation (e.g. ADE-related emergency admission) and reduced health related quality of life (HRQOL).(17-20) Older people are particularly at risk of experiencing an ADE due to altered pharmacokinetics and polypharmacy. $(8,21)$ A recent systematic review focusing on ambulatory care ADEs reported prevalence rates ranging from 2.8\%-34.7\%.(17) Up to one quarter of these ADEs were judged to be preventable.(17) A second systematic review
which focused on emergency hospital admissions as a result of ADEs reported that 9.9\% of all older people ( $\geq 65$ years) were admitted as a result of an ADE.(19)

### 1.3 Multimorbidity

Multimorbidity is commonly defined as the presence of two or more chronic medical conditions in an individual.(4) Recent estimates suggest that one in six patients in the United Kingdom (UK) have more than one of the Quality and Outcomes framework (QOF), the pay for performance scheme for UK GPs, defined long-term conditions and these patients account for approximately one-third of all GP consultations.(22) A recent large scale Scottish study reported that approximately $65 \%$ of those aged over 65 years and almost $82 \%$ of those $\geq 85$ years were living with multiple chronic conditions. (23) Prevalence increases substantially with age, and multimorbidity is strongly linked to socioeconomic deprivation. $(23)$ In Ireland, a recent primary care study $(n=3,309)$ reported prevalence of multimorbidity at $81.6 \%$ in those aged over 65 years.(24) Eleven percent of these patients had four or more chronic medical conditions.(24)

However, prevalence estimates depend largely on the measure used to define multimorbidity and the data used e.g. self-report versus clinical record data.(25) Research indicates that clinical record data is superior to patient self-report in accurately identifying chronic medical conditions. $(26,27)$ Many measures of multimorbidty have been developed and tested including simple disease counts, prescribed medication counts and weighted morbidity indices such as the Charlson index.(28) Research to date suggests that the best choice of measure may depend on the outcome of interest; medication based indices perform better in predicting healthcare utilisation while morbidity indices have superior predictive accuracy for health outcomes such as mortality.(29)

More recently the concept of 'complex' multimorbidity has emerged in an effort to capture patients with more intensive care needs. Evidence is limited to guide this area but options include considering complex multimorbidity as the presence of three or more chronic conditions affecting at least three body systems, polypharmacy at the level of >10 prescribed medications or using a subset of chronic conditions selected based on patient
health impact as well as prevalence. $(23,30,31)$ In the broader frailty literature, the concept of vulnerability has been defined as older people who are more likely to experience functional decline or death.(32) Measures of vulnerability tend to focus on the patient's age and current physical functioning primarily and use these factors to predict future functional decline. Conceptually there is some overlap between complex multimorbidity and vulnerability, as one would expect a patient identified as vulnerable to have higher morbidity burden. However, it may be that focusing on function rather than morbidity burden may have advantages in identifying older people who are more likely to need support in the future.

### 1.3.1 Measures of multimorbidity and vulnerability to predict emergency admission and functional decline

From a patient perspective managing multiple medical conditions is associated with increased psychological distress, decreased quality of life and an increased risk of functional decline.(33-38) Systematic reviews have quantified the healthcare utilisation of this vulnerable population. $(39,40)$ Increasing numbers of chronic medical conditions was found to be associated with increased care needs, a greater number of prescriptions, increased referral rates to secondary care, more emergency hospital admissions and longer inpatient stays. $(39,40)$ These high levels of healthcare utilisation result in increased healthcare expenditure; patients with multimorbidity account for $95 \%$ of all United States (US) Medicare spending and up to $80 \%$ of European healthcare expenditure. $(41,42)$ In Ireland, there is no current prospective research in patients recruited from primary care, however, a cross-sectional study has demonstrated higher rates of hospital admissions and increased cost associated with multimorbidity.(24) A recent systematic review of multimorbidity and functional decline, which included nine cohort studies, concluded that the majority reported an association between increasing counts of conditions and functional decline.(43) There have been several measures developed to identify frail older people at risk of nursing home admission and death.(44) These measures tend to include a variety of variables relating to function, mental health, cognition, medical conditions and previous healthcare use.

### 1.4 Predicting emergency hospital admission

Emergency hospital admission in older people is associated with an increased risk of adverse events including falls, functional decline and nosocomial infections. $(6,45)$ With advancing age patients also tend to be more vulnerable to medication related adverse events such as errors at transition points in care (e.g. at discharge).(46) Hospitalised patients are also at higher risk of developing specific adverse clinical outcomes such as venous thromboembolism.(6) Apart from these clinical implications, older people have longer average lengths of stay when admitted to hospital which has both cost and capability implications for the health service.(47)

Irish research indicates that people aged $>85$ years are eight times more likely to be hospital inpatients.(47) The reasons for this are twofold; first, this group are three to four times more likely to be admitted to hospital and second, following admission their average length of hospital stay is twice as long. Therefore, reducing potentially avoidable emergency admissions could have considerable clinical and cost saving potential.

### 1.4.1 Risk prediction models to identify risk of future emergency admission

A previous systematic review reported that risk prediction models designed to predict which hospital inpatients are most likely to be readmitted to hospital following discharge perform poorly overall.(48) The authors' concluded that considering variables best captured in the community setting such as functional status and GP visits may have a role to play in improving the predictive accuracy of risk prediction models in predicting future emergency hospital admissions.(48) This shift in focus to community-dwelling people at risk of future emergency admission would allow targeted community-based interventions for older people identified as high risk.(49) However, there is a need to quantify existing risk prediction models developed for this purpose both in terms of stage of development and predictive accuracy. Furthermore, if planning to utilise a risk model for identifying higher risk people then external validation in the new clinical setting is critical.(50) This is to allow ascertainment of model performance as risk models may perform differently when applied outside their development cohort.(51)

### 1.5 Research context: the Irish Healthcare system

Ireland has a mixed public and private healthcare system. There are two broad categories of entitlement to public health services determined through means testing. Public health services include prescribed medications, GP visits, secondary and tertiary care services such as outpatient visits and hospital admission, community services such as public health nurse and physiotherapy and social services. Category 1 individuals who meet specified income thresholds (and their dependents) are granted a medical card through the General Medical Services (GMS) scheme and are entitled to all public health services free of charge. The exception to this is a fee per prescription item ( 50 cent per item to a maximum of $€ 10$ monthly), which was introduced in 2010 and has subsequently been increased to $€ 2.50$ per item to a maximum of $€ 25$. Approximately $40 \%$ of the entire Irish population qualifies for a GMS medical card.(52) Until 2008, all people aged 70 years and over automatically qualified for a GMS medical card. Since January 2009 a new income threshold for eligibility for the scheme has been applied.(53) Despite this, the vast majority of older people still quality for free medical care with more than 348,000 people ( $96 \%$ ) of the population aged 70 and over eligible for the GMS scheme in 2013.(52)

In 2005, an additional scheme was introduced for individuals not meeting the income thresholds for a full GMS medical card, which provides certain services free of charge. This scheme is called a GP Visit Card, which grants the recipient (and their dependents) free access to GP services but fees must be paid for prescriptions and other primary care services. Approximately $2.7 \%$ of the population qualifies for this scheme.(52) The remainder of the population (Category 2) pay for all GP services and prescribed medications (capped at $€ 144$ per family monthly) with entitlement to free public health services such as public hospital services (subject to statutory co-payments) and maternity services. Many people, who do not meet the eligibility criteria for a GMS medical card or GP Visit card, and a proportion of those that do, purchase supplementary private health insurance, which typically offers cover for both private care in a public hospital and part-payment of GP fees. In 2013, 44.6\% of the population were covered by private health insurance, of which $13 \%$
were aged over 60 years.(54) An average of $45 \%$ of people aged over 60 years were covered by private health insurance in 2013.(54)

Prescribed medications are funded through the Health Services Executive-Primary Care Reimbursement Service (HSE-PCRS). This service funds the GMS scheme and the excess of the capped payment schemes for individuals not meeting income thresholds for free care, known as the Drugs Payment Scheme. Two other prescription schemes are in existence; namely, the Long-term illness scheme, which covers the costs for medications relating to 15 defined medical conditions and the High Tech Drugs scheme which relates to high-cost medications such as biologics and some chemotherapy agents. The HSE-PCRS is responsible for providing reimbursement services to primary care contractors such as GPs for the provision of health services under these schemes. GPs are self-employed and are contracted by the State through the HSE to provide services.

### 1.6 Summary

This thesis will concentrate on what measures can be used to identify older communitydwelling people at higher risk of adverse health outcomes. If prescribing criteria are to be disseminated in clinical practice designed to improve prescribing quality and safety, it is very important to determine their longitudinal association with adverse health outcomes namely ADEs, poorer HRQOL and increased emergency healthcare use. Similarly, while several different measures of multimorbidity and vulnerability exist very little research has been conducted in applying these measures in the same study population to determine comparative predictive accuracy for outcomes such as emergency admission and functional decline. Knowing which, if any, of these measures should be used preferentially is important both clinically and in informing future research studies. Finally the use of risk prediction models to stratify community-dwelling people at high risk of future admission is gaining momentum. However, relatively little research exists to support clinicians and researchers in terms of the comparative predictive accuracy of various models. Furthermore, before adopting one of these models for use in the Irish healthcare setting, it is critical that a validation study is conducted to investigate the performance in a new clinical setting.

### 1.7 Research question, aims and objectives

The research question underpinning this thesis is: ‘Can adverse health outcomes (ADEs, HRQoL, emergency hospital attendance) be predicted in older community-dwelling people, through assessment of prescribing indicators, multimorbidity and the application of risk prediction models?'. The overall aim of this thesis is to determine if adverse health outcomes in older community-dwelling people can be predicted through assessment of prescribing indicators, multimorbidity and risk prediction models.

There are five main objectives:
i. To determine if there is a longitudinal association between potentially inappropriate prescribing (PIP), as defined by two different sets of prescribing criteria, and future adverse health outcomes including ADEs, reduced HRQOL and increased emergency healthcare use in a cohort of older ( $\geq 70$ years) community-dwelling adults followed up for two years.
ii. To assess the performance of different measures of multimorbidity and vulnerability in older people ( $\geq 70$ years) in predicting emergency hospital attendance and functional decline at two year follow-up.
iii. To conduct a systematic review of risk prediction models developed for use in community-dwelling adults to predict emergency hospital admission.
iv. To conduct a systematic review and meta-analysis of the validation studies of the Probability of repeated admissions (Pra) risk model.
v. To externally validate the Pra risk model in a cohort of older ( $\geq 70$ years) communitydwelling adults in predicting emergency hospital admission over the following year.

### 1.8 Thesis outline

The first chapter of this thesis presents a literature review of current research relating to medicines management, multimorbidity and admission risk prediction in communitydwelling people (Chapter 2). The next chapter (Chapter 3) presents the methodology of the establishment and prospective follow-up of the cohort utilised as the basis of this thesis. Chapter 4 presents the context, specific methods and results of thesis objective 1, PIP and
health outcomes. Chapter 5 presents the background specific methods and results of the impact of different multimorbidity and vulnerability measures in predicting emergency hospital attendance. Chapter 6 focuses on emergency admission risk prediction and presents a systematic review of risk prediction models to predict emergency hospital admission, a systematic review and meta-analysis of one risk model, the Pra risk score, and the external validation of the Pra tool in a cohort of older Irish community-dwelling adults. This chapter also includes a critical analysis of recent UK policy changes which aim to reduce emergency admissions through community-initiated identification of high-risk people and case management. The final chapter (Chapter 7) summarises the findings and discusses clinical, research, policy and societal implications of this thesis.

Chapter 2 Literature review

### 2.1 Data sources used for literature review

The electronic sources searched for this literature review chapter included PubMed, the Cochrane library and Google scholar. Searches were conducted using a combination of search terms and MeSH terms, where available. These searches were supplemented by a review of the International Research Community on Multimorbidity archive (University of Sherbrooke, Canada), the UK King's fund, the US Agency for Healthcare Research and Quality and the John Hopkins Adjusted Clinical Groupings (ACG) publication list.

### 2.2 Introduction and conceptual framework for thesis

Predicting adverse health outcomes in older people requires consideration of several factors. First, is the context in which the patient lives; their age, gender, living arrangements and socioeconomic status. Second, are the relationships that develop and evolve over time relating to the patient's chronic medical conditions, psychosocial support and use of health services. Important factors to consider include the severity and impact of the patient's chronic conditions, the burden of engaging with treatments including medicines management and the impact of co-morbid mental health difficulties. Polypharmacy, which may be defined as the concurrent prescription of four or more medications for an individual, is a particular challenge for older people and the number and types of medications may evolve over time with the attendant risks of PIP.(9,55) Framing these biomedical issues is the psychosocial environment in which the patient lives. This includes their social network, structure and support, their belief system about illness, taking medication and growing older and their lifestyle factors, such as smoking, that may impact upon health. Other important factors include how the patient functions in terms of managing their day to day activities and their mobility, and their perception of how healthy they are compared to others. Parallel to these issues, is the patient's access to and use of health services, and the quality of care received.

All these relationships interact and change over time and may impact upon the patient's experience of adverse health outcomes such as ADEs, poorer HRQOL, emergency hospital attendance (emergency admissions, Accident and Emergency (A\&E) visits) and mortality. A
conceptual framework developed for the Scottish Multiple And Long-Term (MALT) prospective cohort study captures this theory of how relationships between chronic conditions, and broader contextual issues such as personal resources, treatment burden and access to and quality of clinical care, influence patient outcomes.(56) From a social science perspective, Busfield argues that increasing medication use is influenced by four key factors.(57) First, is the patient's desire to regain wellness and their beliefs regarding the value of and risks associated with medication use. Second, are prescriber factors which include increased medication availability, a desire to translate knowledge into action, perceived pressure to prescribe and clinical uncertainty. Third, is the broader healthcare system, which will determine patients' access to medical care and personal costs of care. Finally, the pharmaceutical industry plays an important role in developing new medications but has a clear interest in actively encouraging medication use. For the purposes of this thesis, a conceptual framework was developed which combines the theory of relationships evolving over time framed by contextual issues, as described by the MALT framework, but also includes factors influencing prescribing and medication use, considering how all of these issues may influence adverse health outcomes in older people (Figure 2-1).


Figure 2-1: Conceptual framework for the prediction of adverse health outcomes in older community-dwelling people

In attempting to predict these types of health outcomes consideration of the often complex and intertwining ills of growing older is essential. In this chapter, three key areas relevant to determining the risk of adverse health outcomes in older community-dwelling people are considered. First, the role of prescribing indicators in identifying potentially inappropriate prescribing is discussed and the existing evidence for such criteria increasing the risk of adverse outcomes for patients. Second, the concept of multimorbidity is introduced and a summary of the challenges it presents both for patients and the broader healthcare system. Finally, the potential for predicting future emergency hospital admissions is examined and current research in this area summarised.

### 2.3 Medicines management in older people

Over the past number of decades, both the volume and cost of prescribed medications have increased exponentially.(9-11) In older populations this rise may be due to improved access to medical care, an increased use of proven treatments and the consistent application of evidence-based medicine.(58) However, prescribed medication can also be hazardous resulting in drug interactions, drug-disease interactions and ADEs, with consequent increased morbidity and mortality. $(13,14)$

### 2.3.1 Challenges in prescribing for older people

Good quality prescribing has been defined as the appropriate choice of medication from both the patient and clinician's perspective, which aims to maximize therapeutic effectiveness while minimising risk and cost.(7) However, there are well-established challenges in prescribing for older patients in primary care due to variability in each individual's general health, cognition and functional ability. This results in difficulties in generalizing prescribing guidance for older people and the selection of appropriate pharmacotherapy may be a significant challenge.(5)

First, older people have altered pharmacokinetic profiles, which reduce their physical ability to metabolise and excrete drugs. $(59,60)$ Second, polypharmacy can result in difficulties as each medication has its own potential side-effects and there is an increased risk of drug-
drug interactions and ADEs. $(8,10,61-63)$ Third, many prescriptions issued in primary care are actually initiated in secondary care which can be problematic for their GP who is responsible for the co-ordination and ongoing management of prescriptions of multiple care providers.(9)

### 2.3.2 Measures of appropriate prescribing

Appropriateness of prescribing can be assessed by process (i.e. what providers do) or outcome measures (i.e. patient outcomes) that are explicit (criterion-based) or implicit (judgment-based).(5) Explicit measures are preferred as they have the advantage of being based on both literature review and expert consensus and if developed appropriately should demonstrate both validity and reliability as outlined in Section 1.2.1. However, explicit measures often do not capture other important factors such as multimorbidity and patient preference. In addition, these sets of criteria are often applied to large prescribing datasets in the absence of clinical information regarding diagnoses or engagement with patients or prescribers regarding rationale for medication decision making.

In implicit approaches, a clinician uses information from the patient and published literature to decide about medication appropriateness. This type of approach is potentially more sensitive and can account for patients' preferences, but is very time-consuming, dependant on the reviewer's knowledge and attitudes, and can have low reliability.(5) Overall, there is no ideal approach, but an awareness of the strengths and limitations of criteria designed to measure prescribing appropriateness allows for acknowledgment of limitations in any conclusions drawn.

### 2.3.3 Explicit measures of prescribing appropriateness

A recent systematic review identified 46 tools developed to assess inappropriate prescribing.(64) Of these, 28 (61\%) were explicit, 8 (17\%) were implicit and $10(22 \%)$ used a mixed approach. A total of $36(78 \%)$ tools targeted older people.(64) Some of the most commonly used criteria are summarised below.

### 2.3.3.1 Beers criteria

The Beers criteria, originally developed in the United States (US), are the most commonly applied set of criteria for measuring potentially inappropriate prescribing. $(65,66)$ These criteria were originally developed in 1991 using a modified Delphi process for use in older nursing home patients and were then updated to include all older people in the general population (aged $\geq 65$ years) in $1997 .(67,68)$ To reflect changes in medications and the accrual of more evidence, further updates were published in 2003 and 2012. $(69,70)$ The most recent Beers criteria (2012) consist of 53 criteria grouped across three domains; medications to be avoided independent of medical diagnoses, medications to be avoided in the presence of certain medical diagnoses and medications to be used with caution in older people.(70)

Numerous limitations in applying the earlier versions of the Beers criteria in Europe have been identified. $(71,72)$ Several of the medications included were not contra-indicated in older people as per the British National Formulary (e.g. amiodarone in recurrent ventricular tachycardia, doxazosin in resistant hypertension), many of the drugs were off the market or rarely used in Europe (e.g. guanedrel) and some important contra-indications were omitted (e.g. use of tricyclic antidepressants in patients with history of glaucoma). The 2012 Beers update has addressed some of these criticisms by following a more robust evidence-based approach in selecting criteria, removing obsolete medications and providing more clinical context for certain criteria.(73)

##  and Screening Tool to Alert doctors to the Right Treatment (START)

The STOPP and START criteria were developed by a process of Delphi consensus involving 18 experts from multidisciplinary backgrounds including pharmacy, geriatrics and clinical pharmacology in Ireland and the UK. $(74,75)$ STOPP is a physiological based system and is comprised of 65 criteria covering domains including; drug-drug interactions, drug-disease interactions, optimal dose and duration of treatment, prescribing with appropriate clinical indication, the co-prescription of prophylactic treatment (e.g. proton pump inhibitor with
the prescription of non-steroidal anti-inflammatory medication in an older person) and the duplication of certain drug treatments. START is concerned with prescribing omissions and is made up of 22 prescribing indicators. The STOPP/START criteria have been validated in several European studies and settings of care and have demonstrated good inter-rater reliability with reported kappa co-efficient of 0.93 (IQR $0.90,0.96) .(75,76)$

### 2.3.3.3 High risk prescribing indicators

Prescribing indicators developed to identify potentially inappropriate prescribing require clinical and healthcare context specific information to determine if their use is truly inappropriate or justified by clinical need. More recently there has been increasing interest in the concept of 'high risk' prescribing.(77) A relatively small number of prescribed medications are associated with most harm, highlighted by a recent systematic review which reported that just seven medications namely, methotrexate, warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), digoxin, opioids, acetylsalicylic acid, and $\beta$-blockers are responsible for $47 \%$ of all serious medication errors.(78) There is significant overlap with these drugs and the drugs most associated with ADEs resulting in emergency admission, namely, aspirin, diuretics, NSAIDs, warfarin, opioids, $\beta$-blockers, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers.(79) ADE related deaths are most often associated with aspirin and NSAIDs.(80)

Considering a relatively small number of medications are responsible for significant harm it seems logical and pragmatic to focus efforts on the identification of these prescriptions to maximize risk-reduction. Guthrie et al have recently developed a set of 'high risk' prescribing indicators for this purpose.(77) Developed through a modified RAND process, these criteria were selected on the basis that the prescribing being measured was clearly stated to be contraindicated or to be avoided in routine practice, either in the British National Formulary or through national UK clinical guidelines, prescribing advice, or safety alerts. Indicators were additionally required to be measureable using routine electronic clinical data in primary care, which precluded those based on laboratory monitoring that is inconsistently recorded in GP records which resulted in the exclusion of indicators related to warfarin and hypoglycaemic drug monitoring.(77) The outcome of interest was receipt of a
drug defined as high risk for a patient because of their age, a pre-existing medical condition, or the potential for drug-drug interactions. Spencer at al recently updated a previously developed set of prescribing safety indicators for the Royal College of General Practitioners in the UK, through a modified RAND process, and identified 56 indicators of which 19 were considered high risk.(81) These indicators are concerned with hazardous prescribing across a range of indications, drug-drug interactions, and inadequate laboratory test monitoring of certain medications, and are concerned primarily with safety rather than appropriateness of prescribing.

### 2.3.3.4 Other explicit prescribing measures

Several other measures have been developed to capture PIP including the Improved Prescribing in the Elderly Tool (IPET) and the Assessing Care Of Vulnerable Elders (ACOVE) criteria. $(82,83)$ The IPET was developed in 2000 in Canada and comprises of 14 indicators focused on cardiovascular drugs, antipsychotics and NSAIDs.(82) However, several of these criteria are obsolete and need updating to reflect current clinical and prescribing guidelines.(84) The ACOVE indicators were developed in 2004 in the US for use in older people and consist of 12 indicators.(83) These indicators have been validated outside the US but it's argued that these indicators are not as comprehensive as other available criteria and further research regarding their inter-rater reliability is required. $(85,86)$ In addition, few studies have used these criteria for the purposes of identifying PIP specifically and have instead utilised them for the assessment of the quality of care for a specific condition. Finally, country-specific PIP criteria have been developed for several countries including the French Laroche list, German PRISCUS list and Canadian Rancourt criteria, but these criteria tend to be developed by expert groups to suit local healthcare systems and concerns exist regarding their external validity.(87-89)

### 2.3.4 Implicit criteria of prescribing

Implicit measures of prescribing are based on clinical judgement and based on using clinical information in the context of current evidence to judge if a drug is appropriate. As implicit criteria rely on clinical judgment for application, they are used much less often than explicit
criteria as are believed to be less reliable and are limited by the time required applying these in practice. The Medication Appropriateness Index (MAI) is one of the most commonly used implicit based measures. The MAI was designed to assess prescribing appropriateness across 10 domains including indication, dose, directions for use, drug-drug and drug-disease interactions, duplication and cost.(90) Each element is scored and a summary score generated per drug. While application of the MAI has been found to be more comprehensive than use of the Beers criteria and the IPET, it is limited by the time needed to apply it and lower reliability when validated in different settings.(91, 92)

### 2.3.5 Summary of PIP explicit and implicit measures of prescribing

Overall, the use of explicit measures of PIP is preferable for several reasons. First, these criteria are subject to robust development using evidence-based guidance and expert consensus. Second, they demonstrate high reliability and have been validated in different settings. Third, their application is transparent and reproducible. Of the explicit criteria outlined the STOPP criteria have several advantages. These criteria underwent robust methodological development in Ireland and the UK and so are relevant to local clinical practice. The STOPP criteria have been validated in several settings and have demonstrated high inter-rater reliability and reproducibility. In cross sectional studies, these criteria have demonstrated an association with ADEs, reduced HRQOL and increased healthcare utilisation. There has not been any prospective evaluation of STOPP in primary care to investigate if these prescribing indicators are associated with future adverse health outcomes including ADEs and reduced HRQOL.

### 2.3.6 Prevalence of PIP

The US developed Beers criteria are the most commonly utilised tool to identify PIP in both hospital and community settings. $(91,93)$ Prevalence rates determined by earlier versions of the Beers have raised concerns that these criteria may underestimate PIP in European countries. Significant variation in PIP as determined by the Beers criteria exists. In North American, community-based studies PIP prevalence ranged from 14\%-37\%, while a large scale European study that included eight countries reported a mean prevalence rate of $15.8 \%$ using three different sets of prescribing criteria including Beers. This varied between
countries from $5.8 \%$ in Denmark to $41.1 \%$ in the Czech Republic.(94) When applied in other countries, PIP prevalence ranged from $18 \%$ in Norway, $32 \%$ in the UK to $49 \%$ in Australia.(95-97) This international variation reflects the issue of applying subsets or modified versions of the original Beers criteria.

When compared to the Irish developed STOPP criteria, the Beers criteria generally identify fewer instances of PIP. A recent systematic review identified 13 studies that identified PIP and/or prescribing omissions using the STOPP/START criteria, the majority of which have been carried out in Europe.(98) The prevalence of patients with at least one PIP identified by the STOPP criteria ranged from 21.4\%-79\%; however, there was significant heterogeneity between study populations and how the criteria were applied. For instance, only five studies applied all criteria, with the majority choosing a subset to apply and the settings of care varied including long-term care and primary care. In a large European study involving six countries, the mean prevalence rate of PIP was $51 \%$ and ranged from $35 \%-77 \%$.(99) The START criteria also identified a high rate of prescribing omissions in the same cohort with mean prevalence rate of 59\% ranging from 51\%-73\%.(99)

In Ireland, population-based studies have been conducted examining the prevalence of PIP. Cahir et al reported PIP prevalence of $36 \%$ using the STOPP criteria in a population-based study of older people ( $n=338,801$ ) aged over 70 years in 2007.(100) This study was conducted using a national pharmacy claims database where only 30 of the 65 STOPP criteria could be applied as there was no medical diagnoses information available. Therefore, this figure may be seen as a conservative estimate of the level of PIP among older people in the Republic of Ireland. In a similar Northern Irish study ( $\mathrm{n}=166,108$ ) of older community-dwelling people using 28 of the same 30 STOPP criteria, the prevalence of PIP was $34 \%$.(101) A second study was conducted on a population based sample of Irish adults aged $\geq 65$ years ( $\mathrm{n}=2,051$ ) using data from The Irish LongituDinal Study on Ageing (TILDA) and reported prevalence of at least one PIP as per a subset of the STOPP criteria of $52.7 \%$.(63) A total of 26 STOPP criteria were applied in this study. A second study using the TILDA cohort that examined repeated cross-sectional Irish prescribing patterns over a 15year period (1997-2012), reported that the prevalence of polypharmacy (defined as $\geq 5$
medications concurrently) increased from $17.8 \%$ in 1997 to $60.4 \%$ in 2012 in people aged $\geq 65$ years.(102) However, once age, gender and numbers of medications were adjusted for in regression analysis, the odds of being in receipt of any PIP reduced over time; odds ratio (OR) 0.39 ( $95 \% \mathrm{Cl} 0.39,0.4$ ).(102)

Three studies identified as part of this literature review have been conducted in Irish community settings; the first, a six-month prospective primary care study ( $n=500$ ) of older people recruited from one Cork town, reported PIP rate of $13 \%$ using the Beers criteria.(103) The second was a cross-sectional primary care study ( $n=1,329$ ) of older people recruited from three general practices and reported PIP prevalence rate of $21 \%$ according to STOPP.(104) Prevalence rates were significantly higher in the third study based in one longterm care setting with over $59 \%$ of patients having at least one PIP as per the STOPP criteria.(105) These studies were able to include a full list of both Beers and STOPP criteria. The differences in prevalence rates according to choice of prescribing criteria applied reflect international variation in clinical practice and medication availability as outlined in Section 2.2.3.1.

A subset of 15 high risk prescribing indicators developed by Guthrie et al (see Section 2.2.3.3) and largely focusing on NSAID, methotrexate and antipsychotic prescriptions, were validated in a large Scottish primary care cohort of 1.76 million people of whom 13.9\% had been in receipt of at least one high-risk prescription in the last year.(8) This was the first large-scale application of these criteria which focus on a smaller subset of higher risk medications and, as such, lower prevalence rates would be expected. It could be argued that this smaller subset offers the greatest opportunity for risk-reduction if patient safety is the primary driver for applying prescribing indicators. However, if cost and overall quality of prescribing are the main concerns, then existing PIP criteria, such as STOPP and Beers, have an important role to play.

### 2.3.7 PIP criteria and increased risk of adverse health outcomes

To date research regarding the association between the PIP criteria and future adverse health outcomes such as ADEs, reduced HRQOL and increased emergency hospital use is very limited and largely based on cross-sectional studies.

### 2.3.7.1 PIP and adverse drug events

An ADE may be defined as an event that results in unintended harm to the patient and is related to the treatment provided rather than the patient's underlying medical condition.(106) One US study ( $\mathrm{n}=5,077$ ) estimated the frequency and rates of hospitalisation after ED visits for ADEs in older adults, including those identified as high-risk or potentially inappropriate by national quality measures.(107) It reported that four medications (warfarin, insulin, oral antiplatelet and hypoglycaemic agents) were responsible for twothirds of ADE-related ED visits and that the Beers 2003 criteria only identified $3.2 \%$ of those who experienced an ADE.(107) Another small cross-sectional US study ( $\mathrm{n}=211$ ), which included community-dwelling older people, reported no association between Beers or IPET and subsequent ADEs.(10) One retrospective US study found a significant association between a subset of 'high risk' Beers criteria and subsequent fall or fracture (hazard ratio (HR), 1.22; $95 \% \mathrm{Cl}, 1.10-1.35$ ), but not of delirium or hallucinations compared to controls (HR, 1.03; 95\% CI, 0.91-1.16).(108) Studies outside the US, in both Europe and Japan have found no association between the Beers criteria and ADEs. $(109,110)$

Only three studies (two hospital-based and one in primary care) have examined the longitudinal association of PIP as defined by the STOPP criteria with ADEs. In a prospective study ( $\mathrm{n}=715$ consecutive emergency admissions of older patients), PIP identified by the STOPP criteria accounted for approximately $11 \%$ of ADEs while the Beers criteria identified only $6 \%$ of ADEs.(76) In a second study of older patients attending the ED ( $n=600$ ), the likelihood of a serious avoidable ADE increased significantly when STOPP PIPs were prescribed (odds ratio (OR), 1.85; 95\% CI, 1.51, 2.26; $\mathrm{p}<0.001$ ). $(76,111)$ Cahir et al examined the cross-sectional association of STOPP identified PIPs and ADEs in older communitydwelling adults.(112) This study reported that primary care patients with $\geq 2$ PIP indicators
were twice as likely to have an ADE (adjusted OR $2.21 ; 95 \% \mathrm{Cl} 1.02,4.83, \mathrm{p}<0.05$ ) as well as significantly lower mean HRQOL utility score (EQ-ED: adjusted coefficient -0.09, SE 0.02, p < 0.001 ) and an almost two-fold increased risk in the expected rate of A\&E visits (adjusted incidence rate ratio (IRR) 1.85 ; $95 \% \mathrm{Cl} 1.32,2.58, \mathrm{p}<0.001$ ).(112) This thesis is the prospective follow-up of the cohort Cahir et al utilised for their analysis and will allow prospective investigation of the longitudinal association of PIP, identified by the STOPP and Beers 2012 criteria, in identifying PIP with ADEs.

### 2.3.7.2 PIP and healthcare utilisation and mortality

A systematic review published in 2007 ( $\mathrm{n}=12$ studies), found no evidence to support PIP identified by the Beers criteria (1997 and 2003 iterations) being associated with increased mortality or healthcare utilisation with the exception of emergency admissions.(113) Since the publication of this systematic review, several further studies have examined PIP identified by the Beers criteria and future increased healthcare utilisation. Pozzi et al reported a slightly increased risk of hospitalisation (HR 1.03, 95\% CI 1.0-1.06) in a cohort of 1,022 Italian community-dwelling older people.(114) In a US administrative claims database study ( $n=7,459$ ) of retirees, Beers identified PIPs increased the risk of hospitalisation significantly.(115) A recent large scale Swiss study ( $n=49,668$ ) of older community-dwelling adults reported that Beers 2012 identified PIPs were associated with an increased risk of hospitalisation (adjusted HR 1.13 ( $95 \% \mathrm{Cl} 1.07-1.19$ ) for 1 PIP, 1.27 ( $95 \% \mathrm{Cl} 1.19-1.35$ ) for 2 PIPs, 1.35 ( $95 \%$ Cl 1.22-1.50) for 3 PIPs, and 1.63 ( $95 \%$ CI 1.40-1.90) for >3 PIP compared to no PIP use).(116)

A retrospective cohort study ( $\mathrm{n}=904$ ) of older Irish community-dwelling people reported that patients with $\geq 2$ STOPP indicators had an increased risk in their rate of hospital visits (adjusted IRR=1.32; 95\% CI = 1.14, 1.54; p < 0.01).(117) The Beers 2012 criteria were not associated with increased hospital visits. A systematic review published in 2013, focusing on the clinical and humanistic impact of the application of the STOPP criteria, did not identify any study that attempted to determine the association between STOPP identified PIPs and future healthcare utilisation.(98)

### 2.3.7.3 PIP and health related quality of life

Research to date has been largely based in the US and focused on PIP identified by the Beers criteria (1997 and 2003 iterations).(113) In three US studies of community dwelling adults with sample sizes ranging from 506-3,234 participants, Beers identified PIP was not found to be associated with reduced HRQOL.(118-120) These studies included validated measures of HRQOL such as the EuroQuol-5 Dimensions (EQ-5D), as well as functional measures such as the instrumental activities of daily living and activities of daily living. In a systematic review of the impact of the STOPP criteria, no study focusing on HRQOL was identified.(98)

### 2.3.8 Summary prevalence and predictive ability of different measures of PIP for adverse health outcomes

Overall, the STOPP criteria are more relevant to European healthcare settings than the US Beers criteria, due to variation in prescribing practices and differences in available drugs. To date, research regarding the longitudinal association of PIP identified by prescribing criteria with future adverse health outcomes is very limited. Existing cross-sectional research has largely focused on health outcomes associated with the Beers criteria and has been limited by a paucity of prospective research. If these criteria are to be disseminated in clinical practice to improve prescribing, it is essential to establish if a longitudinal association with adverse health outcomes, namely ADEs, reduced HRQOL and increased emergency healthcare use, exists.

### 2.4 Multimorbidity

### 2.4.1 Definition and measurement of multimorbidity

With an ageing population, the management of chronic medical conditions is at the forefront of healthcare planning and policy. Traditionally chronic disease management has had a single disease focus treating each condition as an independent entity without much consideration of overlap and coherence in management approach. It is increasingly recognised that patients living with multimorbidity require a different approach both in conceptualising and in delivering care. While multimorbidity affects all age groups it is a
particular issue for older people who are more likely to accumulate chronic conditions over time.

As described in Section 1.3, prevalence estimates of multimorbidity vary depending on the measurement method, the setting of care and the data source utilised to record chronic conditions. A recent systematic review indicates that simple disease counts, the Charlson comorbidity index, and the Adjusted Clinical Groups system, are the most commonly utilised measures of multimorbidity in primary care but that relatively little research has been conducted comparing different measures in this setting.(28) It seems reasonable to assume that using simple disease counts to define multimorbidity may underestimate the complexity certain combinations of conditions present. Existing morbidity indices, such as the Charlson index and the Adjusted Clinical Groupings, which weight diagnoses, seem to offer more scope for considering impact.(28) However, much seems to depend on the outcome of interest. Simple disease counts and medication counts appear to be accurate in predicting healthcare utilisation and are simpler to apply. $(121,122)$ Diagnosis-based measures such as the weighted Charlson comorbidity index perform best in predicting mortality.(29) However, if the outcome of interest relates to quality of life or functional decline then measures that account for disease burden or impact may well have greater predictive accuracy.(28)

The importance of considering both prevalence and disease burden in any measure of multimorbidity was also advocated by a systematic review which suggested concentrating on a subset of prevalent chronic diseases with high impact or burden in a given population.(123) A large-scale Scottish study by Barnett et al in 2012 has adopted this approach and developed a list of 40 conditions for use in an adult population based on condition prevalence and impact on health outcomes.(23) However, these criteria have not been tested in terms of their predictive accuracy for patient outcomes in primary care. To date, there is little consensus regarding which chronic medical conditions to include in diagnosis-based measures of multimorbidity. A systematic review examining multimorbidity prevalence rates reported that the majority of studies did not specify criteria for inclusion or exclusion of chronic conditions.(124) Of those studies that did include specific conditions
three factors were considered important; 1) the prevalence of the condition (either at population level or in the study cohort); 2) chronic conditions associated with an increased mortality rate and 3) the impact of the condition on function or need for intensified management.

More recently the concept of 'complex multimorbidity' has emerged. A large prospective Australian primary care study has defined complex multimorbidity as $\geq 3$ chronic conditions affecting $\geq 3$ body systems.(30) This definition results in lower multimorbidity prevalence estimates and better differentiation amongst older patients, which may be more useful for the purposes of identifying more complex patients in general practice. Other factors which affect prevalence estimates include the study setting (e.g. primary care versus population based) and the type of data used (e.g. patient self-report versus clinical record review vs. insurance claims administrative databases).(26)

### 2.4.2 Prevalence and patterns of multimorbidity

Given these issues it is unsurprising that existing multimorbidity prevalence rates vary widely as summarised in Section 1.3. Reported prevalence rates of multimorbidity across different countries range from $3.5 \%$ to $98.5 \%$, depending on the approach used in measurement and the setting of care studied. $(26,125)$

In the US, a large primary care cross-sectional study of 226 practices and 43 states ( $\mathrm{n}=$ 667,379 ) reported prevalence of multimorbidity (defined as two or more chronic medical conditions) of 45.2\%.(54) As outlined in Section 1.3, recent UK research suggests that patients with multimorbidity account for approximately one-third of all GP consultations.(22) The 2012 Scottish study reported that approximately 65\% of those over 65 years and almost $82 \%$ of those $\geq 85$ years were living with multiple chronic conditions.(23) This study also highlighted that while prevalence increases substantially with age, in absolute terms, multimorbidity is more prevalent in those $\leq 65$ years and its presence is strongly linked to socioeconomic deprivation, with people living in more deprived areas developing multimorbidity up to 10 years earlier than those living in more affluent areas.(23) In Ireland, cross-sectional primary care based study ( $\mathrm{n}=3,309$ ) published in 2011
reported prevalence of multimorbidity at $81.6 \%$ with $11 \%$ of these patients living with four or more chronic conditions.(24)

Three systematic reviews have focused on common patterns of multimorbidity. Common combinations of conditions include; i) osteoarthritis and cardiovascular disease with or without metabolic conditions and ii) co-morbid depression with hypertension and/or diabetes mellitus. $(108,125,126)$ In Ireland research using the Irish Longitudinal study on Ageing (TILDA), which includes over 8,000 people aged $\geq 50$ years, reported a total of nine associative multimorbidity clusters presented in Table 2-1. To examine the concept of disease clustering in a meaningful way, very large study sample sizes are required and prevalent clusters may vary according to age. $(125,127)$

Table 2-1: Multimorbidity clusters of conditions in the Irish Longitudinal Study on Ageing (TILDA)(128)

| Cluster name | Conditions |
| :--- | :--- |
| Coronary Heart Disease | Angina and heart attack |
| Cardiovascular risk factors | High blood pressure and high cholesterol <br> Cerebrovascular <br> Sensory <br> Cardio irregularities |
| Stroke, TIA, heart failure and alcohol abuse <br> Visual and hearing impairments |  |
| Musculoskeletal and incontinence | Heart murmur and abnormal heart rhythm <br> Diabetes, other arthritis, cancer, stomach and varicose <br> ulcers |
| Musculoskeletal and respiratory | Rheumatoid arthritis, fractures, incontinence and falls |

### 2.4.3 Health outcomes associated with multimorbidity

Multimorbidity is associated with increased mortality rates, decreased health related quality of life, functional decline and psychological distress.(33-36,39) Medicines management is often complex resulting in polypharmacy with its attendant risks.(8, 9, 129) In addition, patients with multimorbidity have higher use of healthcare services including emergency admissions and account for a significant proportion of total healthcare expenditure.(39, 41)

### 2.4.3.1 Mortality risk

Internationally, multimorbidity has been shown to be associated with an increased risk of mortality. In Europe, a community-based study ( $\mathrm{n}=2,285$ ) which included older men in three countries reported significantly increased ten year mortality risk in those with two or more chronic conditions.(130) A Dutch study ( $n=2,141$ ) of community-dwelling people aged 65 to 85 years reported an increased three year mortality in the multimorbidity group.(131) In the US a large-scale study which examined over 28 million hospital discharges reported significantly higher mortality rates for patients with multimorbidity.(132) Mortality risk is dependent on the individual's combination of chronic conditions and the severity of those conditions.

### 2.4.3.2 Health related quality of life

Several studies have demonstrated the association between multimorbidity and poorer HRQOL. $(39,133$ ) In a population-based survey of Canadian adults ( $n=4,946$ ) all chronic conditions were associated with a clinically meaningful reduced HRQOL but the highest burden was seen with anxiety or depression (reduction in EQ-5D index coefficient score: $-0.19,95 \% \mathrm{Cl}-0.21,-0.16$ ) and chronic pain (reduction in EQ-5D index coefficient score: $-0.19,95 \% \mathrm{Cl}-0.21,-0.17$ ).(134) A German study ( $\mathrm{n}=4,565$ ) which focused on six chronic conditions in a population of older ( $\geq 65$ years) adults reported a synergistic effect of certain combinations of chronic conditions (stroke and coronary artery disease) in impacting most upon EQ-5D HRQOL scores.(135) Another study of 3,189 older people ( $\geq 65$ years) which included a broader range of chronic conditions $(n=45)$ reported that the overall HRQOL of multimorbid patients decreased with increasing numbers of conditions and the severity of
these conditions.(136) Parkinson's disease, depression and obesity had the strongest impact on overall reduction in HRQOL.(136) A recent cross border population based Irish crosssectional study of over 6,000 people aged $\geq 50$ years with four named chronic conditions reported that multimorbid patients reported worse quality of life but did not find correlations with any groups of conditions and outcomes.(137)

### 2.4.3.3 Functional decline

Prospective cohort studies have examined the impact of multimorbidity on predicting reduced physical functioning and reported that increasing numbers of chronic conditions incrementally increases the risk of functional decline.(36, 52, 138-140) One primary care study of adults ( $n=1,184$ ) followed up for six years reported a significant association with poorer physical functioning in patients with multimorbidity, with a steep decline noted between years three and six of follow-up.(52) In a Dutch study focusing on very old patients ( $\geq 85$ years), an accelerated rate of progression of activities of daily living disability was reported incrementally with increasing numbers of chronic conditions at five year followup.(139) In Ireland, cross-sectional population-based research has demonstrated an association between multimorbidity and physical disability but this study was limited by the inclusion of only four conditions and its cross-sectional design.(137) As outlined in section 1.3.1 a recently published systematic review of multimorbidity and functional decline ( $\mathrm{n}=9$ cohort studies), concluded that the majority reported an association between increasing numbers of chronic conditions and functional decline.(43)

### 2.4.3.4 Psychological distress

Considering all the difficulties faced by patients with multimorbidity, it is unsurprising that psychological distress is commonly experienced.(33) A recent Australian survey of 7,620 primary care patients demonstrated a clear relationship between increasing numbers of chronic medical conditions and co-morbid depression.(141) Patients with one chronic condition reported depression prevalence rates of $23 \%$ compared to $40 \%$ for those with $\geq 5$ conditions.(141) Older patients with co-morbid depression have a higher rate of healthcare utilisation and increased costs of care.(142)

Qualitative research indicates that multimorbid patients attribute their depressive symptoms to loss of 'normal' roles and reduced functional ability.(54) In areas of socioeconomic deprivation psychological distress is more common and patients are more likely to have psychosocial issues to discuss during their GP consultations, resulting in an increased burden of managing conditions for patients and in care delivery for healthcare professionals.(143) Overall, caring for patients with both mental health and physical comorbidities adds to clinical complexity and this group of patients' have worse health outcomes. $(128,144)$

### 2.4.3.5 Treatment burden and experiences of care

In addition to the increased risks of functional decline, poorer health related quality of life and psychological distress associated with multimorbidity this vulnerable group are also tasked with learning about their various conditions, engaging with healthcare professionals across different clinical sites and adhering to medication regimes and lifestyle changes, which are often challenging.(145) This results in a substantial burden of treatment and increases the work of being a patient, as highlighted by qualitative research, which captures the "endless struggle" patients" experience in trying to manage their conditions well.(146148)

A large-scale UK survey of over 900,000 adults registered with general practice reported that patients with multimorbidity were less likely to report positive experiences of primary care than those with one or no chronic conditions.(53) This was particularly true for patients with chronic pain who reported poorer HRQOL. Two issues were highlighted: 1) greater difficulty in accessing care; and 2) poorer communication across providers (doctor, nurse and receptionist). However, these patients were more likely to see their preferred doctor indicating good continuity of care provision.(53) In more deprived areas, access to care generally takes longer, and patient satisfaction with access is significantly lower.(143)

### 2.4.4 Medicines management in multimorbidity

A recent UK study of 180,815 adults in primary care reported that approximately $20 \%$ of patients with multimorbidity (defined as $\geq 2$ chronic conditions) were receiving between four
and nine medications and $1 \%$ were receiving $\geq 10$ medications.(11) For patients with at least six conditions, these values rose to $47.7 \%$ and $41.7 \%$, respectively. In Scotland, between 1995 and 2010, the proportion of patients receiving $\geq 5$ medications rose from $9.7 \%$ to $16.3 \%$ and $19.6 \%$ of patients aged $\geq 70$ were prescribed $\geq 10$ medications.(10) In Ireland, between 1997 and 2012, there was a substantial overall increase in prescribing rates with a four-fold increase in polypharmacy and a ten-fold increase in those prescribed $\geq 10$ medications, independent of age and gender.(63) For older people (aged $\geq 65$ years), this increase was even more marked, with the proportion of patients prescribed $\geq 5$ medications rising from $17.8 \%$ in 1995 to $60.4 \%$ in 2012 and those prescribed $\geq 10$ medications increasing from $1.5 \%$ to $21.9 \%$ over the same time period.(63)

Polypharmacy is associated with medication-related morbidity such as ADEs, PIP and reduced medication adherence. $(9,63)$ Older people in particular are at higher risk of experiencing an adverse outcome related to their prescribed medication.(8) However, there is an important differentiation between appropriate and inappropriate polypharmacy and, therefore, identifying patients at particular risk of adverse health outcomes is crucial.(9) Explicit prescribing criteria to identify PIP, can be useful in identifying problematic medications and will be addressed in more detail later in this chapter.(75) In addition to polypharmacy related sequelae, multimorbidity has been found to be independently associated with ADEs and repeated emergency hospital admission for ADEs in the primary care setting.(128, 149, 150)

A major difficulty for GPs is that many prescriptions are specialist initiated, but repeat prescribing occurs in primary care.(9) Without clear communication it can be very difficult to judge the rationale of drug treatment. Optimising drug regimens is certainly an important component of care and regular medication reviews are required for patients with multimorbidity to achieve this.(9) The concept of 'deprescribing', which encompasses stopping medications that are not indicated, have inadequate prognostic benefit or are causing side-effects are increasingly recognised as an important part of this process.(151) Medication reviews in the community may be GP or pharmacist-led. To date, evidence is mixed regarding the additional benefit of pharmacist-led medication reviews for complex
polypharmacy in this setting of care.(152-154) Close collaboration between pharmacists and GPs/specialists seems to be the most sensible approach for this patient group.

### 2.4.5 Healthcare utilisation and costs of care

Increasing numbers of chronic medical conditions have been found to be associated with increased care needs, a greater number of prescriptions, increased referral rates to secondary care, more emergency hospital admissions and longer inpatient stays. $(39,40)$ In the UK, a large study examining emergency admission rates reported that both all-cause emergency and potentially preventable emergency admissions were independently associated with increasing physical multimorbidity (for $\geq 4$ vs. 0 conditions, odds ratio [OR] 5.87 [ $95 \%$ confidence interval (CI) 5.45-6.32] for emergency admissions, OR 14.38 [ $95 \% \mathrm{Cl}$ 11.87-17.43] for potentially preventable emergency admissions) and with co-existing mental health conditions (for $\geq 1$ vs. 0 conditions, OR 2.01 [ $95 \% \mathrm{Cl} 1.92-2.09$ ] for emergency admissions, OR 1.80 [ $95 \%$ CI 1.64-1.97] for potentially preventable emergency admissions).(155)

A German primary care study that included over 120,000 older ( $\geq 65$ years) adults, reported that patients with multimorbidity (defined as $\geq 2$ chronic medical conditions) visited an average of five doctors annually and had between 35-50 healthcare contacts per year. Higher utilisation rates depended largely on condition counts and patterns of multimorbidity and were not related to age or gender.(156) These high levels of healthcare utilisation result in increased healthcare expenditure; patients with multimorbidity account for $95 \%$ of all US Medicare spending and up to $80 \%$ of European healthcare expenditure.(41, 42) In Ireland, to date, no prospective research in primary care has been conducted but a cross-sectional study demonstrates higher rates of hospital admissions and increased cost.(24)

### 2.4.6 Challenges for GPs in delivering care for patients with multimorbidity

GPs have identified areas where they experience difficulties in caring for patients with multimorbidity namely: 1) disorganisation and fragmentation of care; 2) barriers to shared decision making; and 3) challenges in chronic disease management due lack of an evidence
base to guide decision making.(157) Other difficulties include short consultation times and uncertainties around the role of self-management for these patients. $(158,159)$ These issues are summarised in more detail in Sections 2.4.6.1 to 2.4.6.5 and outline some of the issues faced in attempting to identify older patients who are most at risk of future adverse health outcomes in primary care.

### 2.4.6.1 Disorganisation and fragmentation of care

Patients with complex multimorbidity usually see many different healthcare providers working across multiple sites. Communication between providers is often suboptimal which can impact negatively on patient outcomes.(160) Changes in the delivery of general practice service have reduced the provision of continuity of care. $(161,162)$ Patients do value continuity with over $80 \%$ of older patients in a recent UK survey reporting a preference for seeing a particular doctor in their GP practice.(163) Continuity of care is also associated with improved outcomes, such as, preventative care delivery and reduced preventable admissions. $(164,165)$ In a recent US study, higher levels of continuity was associated with lower rates of hospital and emergency department visits, lower complication rates, and less healthcare expenditure.(166) GPs are uniquely positioned to provide the necessary relational, informational and managerial continuity of care and the importance of this function should not be underestimated. $(167,168)$ Another great strength of primary care is the access it affords patients and regular planned reviews may be helpful in 'ordering the chaos' for this group.(169)

### 2.4.6.2 C hallenges in achieving shared decision making for patients with multimorbidity

Shared decision making has been defined as 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'.(170) Research shows that shared decision making improves patients knowledge about their condition and treatment options, increases patient satisfaction with care and improves patient self-confidence and self-care skills.(171) In the context of multimorbidity, where multiple competing demands exist, it can be particularly challenging to engage in shared
decision making. Fundamental to the consultation is to first elicit what matters most to the patient. Asking this at the outset of the consultation allows the rest of the consultation be utilised most effectively.(172)

To support shared decision making a recent model has been proposed for use in clinical practice.(173) There are three key steps: 1) Choice talk, which refers to the step of making sure that patients know that reasonable options are available; 2) Option talk, which refers to providing more detailed information about options; and 3) Decision talk, which relates to supporting the work of considering preferences and deciding what is best. At the centre of this model is eliciting what matters most to the patient, providing appropriate information and basing management decisions on this. Useful online materials are available to support this process, such as OptionGrid which offers information regarding different management options for specific conditions.(174) However, these tools are not specific to multimorbidty and there is an evidence gap in terms of how best to approach and achieve shared decision making for patients with multiple chronic conditions.

### 2.4.6.3 Challenges in chronic disease management: lack of evidence to guide clinical decision making

Managing several chronic conditions with the current single disease focus of clinical guidelines and research is a challenge GPs face in their daily practice. A recent systematic review of 28 guidelines for chronic conditions found that eight did not mention multimorbidity at all. Of those that did, all explored shared biological/risk factor development rather than providing guidance on how best to manage added clinical complexity and workload.(175)

The paucity of available evidence to inform clinical decision making partly stems from the underrepresentation of patients with multiple chronic conditions in clinical trials, and the focus of such trials on single diseases. $(176,177)$ Consider the application of five clinical guidelines for a hypothetical 79 year old woman with five chronic conditions; diabetes mellitus, osteoporosis, hypertension, osteoarthritis and chronic obstructive pulmonary disease.(178) She would be prescribed 12 medications and be at risk of potential harm
through drug interactions. She would also be expected to follow 14 non-pharmacological recommendations such as increased exercise and smoking cessation, some of which are conflicting, in addition to attending multiple specialists and other service providers. An example of conflicting advice is that if the patient has peripheral neuropathy, the osteoporosis guideline recommends that she perform weight-bearing exercise, while the diabetes guideline cautions that certain patients with advanced peripheral neuropathy should avoid weight-bearing exercise.(178)

One potential solution is for future guideline developers to consider the production of guidelines that address the commoner clusters of chronic conditions. While this would be an important step, guidelines to cover all combinations of conditions are unlikely, and so the value of clinical judgement should be recognised.(167) At times clinical judgement may mean an acceptance of suboptimal disease specific targets while focusing instead on optimising a patient's physical functioning. Alternatively, it may mean prioritising the treatment of depression which has been shown to impact the ability of patients to manage their other chronic conditions.(179) Policymakers who base performance related payment on disease specific targets need to be aware that such trade-offs based on clinical judgement may be necessary and lead to more patient-centred care and should consider other performance measures which truly capture quality of care for this patient group.

The Cochrane systematic review of community based interventions to improve outcomes for patients with multimorbidity identified only ten randomised controlled trials (RCTs).(159) Of these, six involved changes to the organisation of care delivery, usually through case management, and the remaining four interventions were predominantly patient orientated, including support for self-management. Though results were mixed, interventions directed towards particular risk factors shared across co-morbid conditions or generic functional difficulties experienced by patients seem promising. One RCT delivered by occupational therapists and physiotherapists' targeted functional difficulties of older patients with multimorbidity and demonstrated a significant impact on health outcomes including mortality. This highlights the potential importance of a multidisciplinary approach
in management and a focus on generic outcomes relevant across conditions.(180) The update of this Cochrane review is currently underway and should be published in 2016.

There is clearly a need for further research in this area and recently commissioned research by the National Institute for Health Research in the UK to examine a complex intervention for multimorbidity patients in general practice is a welcome development.(181) The intervention is a co-ordinated review of multimorbidity in a three-dimensional (3-D) manner. This approach includes the assessment of dimensions of health including quality of life, patients' priorities and disease measures, the identification and treatment of depression and measures relating to simplification of drug regimens and adherence. It also includes components relating to increased continuity of care. In Canada, the PatientCentred Innovations for Persons with Multimorbidity (PACE) team have recently received funding to develop and test interventions of integrated chronic disease prevention and management for patients with multimorbidity in primary care.(182) Such research is essential in determining how best to meet the current and future needs of this patient group. In addition the National Institute for health and Care Excellence (NICE) have set up a multimorbidity guidelines group led by Professor Bruce Guthrie. This guideline is due to be published in late 2016.(183)

### 2.4.6.4 Time constraints as a baier to care provision

Internationally, GPs have highlighted lack of time as a barrier to providing care for patients with multimorbidity. $(158,184)$ There is some evidence that longer consultations result in more preventative health advice, less prescribing and increased patient satisfaction rates.(185) In deprived areas, increased consultation times have been shown to increase patient enablement and reduce GP stress.(186)

Managing patients' expectations of what can be achieved in the GP consultation is also important. One study found that in the most deprived areas, almost one-third of patients wanted to discuss a psychosocial problem in their GP consultation and almost two-thirds of these patients expected to discuss more than one problem.(187) It is difficult to see how all this can be achieved to the mutual satisfaction of both the patient and doctor in the
standard GP consultation timeframe of 10-15 minutes. Practically speaking, with demand for GP services increasing, it is difficult to schedule extra consultation time for patients with multimorbidity. To maximise what can be achieved within consultations therefore, good information systems are essential to facilitate informational continuity. Involving the wider multidisciplinary team is also very important, where available, and referrals will depend on patients evolving care needs over time.(188)

### 2.4.6.5 Evidence to support the promotion of selfanagement in patients with multimorbidity

There is some evidence to support lay-led self-management education programmes for single chronic diseases in improving certain outcomes, such as self-efficacy and self-rated health. $(189,190)$ However, the evidence for such an approach with multimorbidity is mixed.(159) The evaluation of the UK Expert Patient Programme demonstrated improved self-efficacy and energy levels at six month follow-up, but no reduction in healthcare utilisation.(191) A recent RCT in the UK trained GP practice staff about available resources including an assessment tool regarding the support needs of patients, guidebooks on selfmanagement and a web-based directory of local resources. At 12 month follow-up there were no reported improvements in shared decision-making, self-efficacy, or generic health related quality of life.(192) The authors' concluded that the active components required for effective self-management support need to be better understood.

### 2.4.7 Multimorbidity summary

In summary, it is clear that multimorbidity is highly prevalent, and is a significant challenge for GPs as summarised in section 2.3.6. Considering the clinical relevance of this research area, there is relatively little prospective observational research conducted in primary care examining health outcomes for older patients living with multimorbidity.(40) Existing research has focused on quantifying the prevalence, measurement and impact of multimorbidity largely using cross-sectional study designs or utilising large population research databases, rather than primary care. $(39,40)$ Focusing research efforts on
identifying which older people are most likely to experience poorer health outcomes is both important and topical.

### 2.5 Predicting the risk of emergency admission in older community-dwelling people

### 2.5.1 Challenge of rising emergency admissions

There is increasing interest internationally in reducing emergency admissions both as a measure of care quality and to contain spiralling healthcare expenditure. In the UK emergency admissions have risen by $47 \%$ from 3.6 million to 5.3 million over the past 15 years, with only a $10 \%$ increase in population over this period.(193) These episodes of care account for a significant proportion of healthcare expenditure; in 2012 alone emergency admissions cost the National Health Service (NHS) $£ 12.5$ billion and it is estimated that $50 \%$ of all inpatient bed days in the UK are attributable to just $5 \%$ of the population. $(193,194)$ In the US, almost one-third of all healthcare spending is for inpatient services and average hospital costs increased 2\% per year from 2003-2013.(195) In Ireland, inpatient discharges, of which approximately $75 \%$ related to emergency admissions, increased by $3 \%$ between 2008 and 2012, with a higher mean increase of $4.8 \%$ between 2011 and 2012. Older people (aged $\geq 65$ years) accounted for over one-third of all inpatient discharges over this time period.(196) As outlined in Section 1.4, hospital admissions in older people are often associated with adverse health outcomes such as falls and functional decline $(197,198)$ Reducing potentially avoidable emergency admissions could have benefits for patients and in reducing healthcare expenditure.

### 2.5.2 Emergency admission as a performance measure of quality of care

 Identifying community-dwelling people at high risk of a future emergency admission and targeting this group for a community-based intervention to reduce this risk seems like a logical endeavour and has been widely adopted by policymakers internationally. Recent US legislative changes enacted by the Patient Protection and Affordable Care Act 2010 recommended the development of Accountable Care organisations.(199) This initiative provides incentives for healthcare providers to work collaboratively to achieve high qualitycare while reducing costs. Quality is measured by pre-specified performance measures, including emergency admissions for three chronic medical conditions where patients are judged to be at high risk of admission; chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF) and asthma.(200)

In the UK, policymakers have taken a step further. In 2014, the QOF pay for performance scheme for UK GPs, was expanded to include risk stratification for emergency admissions.(201) In order to receive remuneration, GPs are required to identify, as a minimum, $2 \%$ of their practice population considered to be at highest risk of a future emergency admission. Identified patients are then targeted for community-based case management, which involves creating an action plan and setting individual targets based on the patient's medical history and psychosocial context.(82) This policy represents a significant shift for UK GPs, who must now consider how best to identify those at highest risk and then implement the required individualised case management plan. Deciding how best to predict and then prevent emergency admissions is therefore a topical area of research internationally.

### 2.5.3 Identifying community-dwelling people at high risk of future emergency admission

There are three main approaches in trying to predict which community-dwelling patients will experience future emergency admissions. The first is through use of clinical knowledge alone which is the default position of most health services but is very limited in terms of research evidence to support its effectiveness.(86) The second is through threshold modelling where a set of criteria, such as a history of repeated emergency admissions, may be applied to determine risk stratification. However, this approach is limited by the concept of 'regression to the mean' which means that patients who have experienced repeated emergency admissions over a period of time will tend to have fewer admissions in the next year, even without intervention.(202) Alternatively, a risk stratification approach may be employed designed to identify people at high risk of future emergency admission. There are two main types of risk stratification approaches available. The first involves the administering of a patient questionnaire using a set of questions designed to identify higher risk individuals. These questionnaires have the advantage of being able to include clinical
and non-clinical variables (e.g. caregiver availability, social support, functional difficulties), but are more prone to response bias in terms of reporting clinical information such as previous healthcare use and chronic medical conditions. An example is the Probability of repeated admissions (Pra) tool, an eight item questionnaire, which includes questions about age, gender, prior doctor visits and hospital admissions, presence of diabetes mellitus and ischaemic heart disease, self-rated health and the availability of a caregiver (

Table 2-2). This tool was developed in a US elderly cohort ( $n=5,876$ ) in the 1980s and has been validated in other settings since its development.(203) However, many of these studies took place in the 1980s and 1990s so recent validation is lacking.

## Table 2-2: Probability of repeated admission (Pra) score

## Questions used to calculate the Pra score:

1. In general, would you say your health is: Excellent, Very good, Good, FAio,or
2. In the previous 12 months, have you stayed overnight as a patient in a hospital? Not at all, One time, Two or three times, More than three times
3. In the previous 12 months, how many times did you visit a physician or clinic? Not at all, One time, Two or three times, Four to six times, More than six times
4. In the previous 12 months, did you have diabetes? Yes/No
5. Have you ever had coronary heart disease, angina pectoris, a myocardial infarction or any other heart attack? Yes/No
6. Is there a friend, relative or neighbor who would take care of you for a few days, if necessary? Yes/No
7. Are you? Male/ Female
8. What is your date of birth? Month, day, year

The score is derived using a logistic regression equation resulting in a score betweg̣n 0 and ǎ Ǒz NJŜ indicative of high risk of repeated hospital admission in the next year.

An alternate risk stratification approach uses predictive risk modeling. This involves identifying and testing a large number of variables with predictive ability and then developing a statistical model, which can then be applied via healthcare administrative
databases or general practice software systems to identify those at highest risk of emergency admission in a particular population. These models are usually developed using very large, linked (i.e. healthcare utilisation data from inpatient, outpatient and GP settings linked to pharmacy claims databases) and the final models usually include a large number of variables. An example is the Scottish Patients at Risk of Readmission and Admission (SPARRA) model (Version 3), which was developed in a Scottish cohort of over 3.5 million individuals to predict emergency admission over the next year.(204) Researchers used linked hospital utilisation and pharmacy claims databases to develop the final model which includes more than 40 variables. These types of statistical models have the advantage of being able to test and include a larger number of variables using more reliable data sources but are limited by the lack of non-clinical factors that can be included e.g. social support and functional status and the use of administrative databases which are not designed for the purposes of conducting research. Risk stratification using both risk questionnaires and statistical models is increasingly being advocated as a way of quantifying the risk of future emergency admission for older community-dwelling people. $(205,206)$ However, there is a current literature gap regarding how many risk prediction tools developed for use in the community to predict future emergency admission exist, the predictive accuracy of existing tools and if these are suitable for use outside their development setting.

### 2.5.4 Risk stratification process

The rationale for risk stratification is that if high risk patients can be identified early then a community-based intervention may be implemented to prevent future emergency admissions. With this approach there are four potential outcomes when a risk prediction model is applied:
i. True positive (the patient is correctly identified as high risk and has a future emergency admission)
ii. True negative (the patient is correctly identified as low risk and does not experience a future emergency admission)
iii. False positive (the person is incorrectly identified as high risk and does not experience an emergency admission)
iv. False negative (the patient is incorrectly identified as low risk but does experience an emergency admission)

Sensitivity (true positive) refers to the proportion of patients identified as high risk that are correctly classified and therefore experience a future emergency admission. Specificity (true negative) is the proportion of patients not admitted correctly classified as low risk. Arguably the most important attribute for an ideal risk prediction model for emergency admission would be high sensitivity and therefore one could be confident that patients categorised at low risk would not experience a future admission. Risk stratification tools often present risk strata according to deciles ranging from 0-9 to 90-99 where 0-9 is the lowest risk decile and 90-99 represents highest risk decile possible. The impact of any risk stratification tool depends on the risk threshold point chosen to define a patient as high risk and requiring intervention. Usually there will be a trade-off between sensitivity and specificity with this approach. For instance, if a lower risk threshold cut-off is chosen (e.g. 60+) then the number of false negatives would be reduced but the number of false positives would increase. Conversely if a higher risk threshold is chosen (e.g. 80+) the number of false positives will be reduced but the number of false negatives will increase. There are harms associated with false positive results with the potential for iatrogenic harm (e.g. new medications added to a patient's medication list to intensify management which then leads to an ADE) and increased treatment burden for the patient. In addition, choosing a higher risk threshold with the attendant increase in false positive cases may not be the best use of healthcare expenditure.

### 2.5.5 Which emergency admissions can be prevented?

The premise of risk stratification depends on emergency admissions being amenable to prevention. In reality however many emergency admissions, such as acute appendicitis, are unavoidable. There is, therefore, increasing interest in a subset of emergency admissions thought to be preventable with intensified primary care management, referred to as ambulatory care sensitive (ACS) admissions. In the UK these account for approximately $20 \%$ of all emergency admissions and over half occur in older people aged $\geq 65$ years. $(207,208)$ An analysis of Irish ACS admissions (2005-2008) reported a $9.5 \%$ increase over this time
period, increasing from 63,619 in 2005 to 69,664 in 2008. A complication of diabetes mellitus was the commonest reason for admission accounting for $29.8 \%$ of all ACS admissions. Associated estimated costs increased from €267.8 million in 2005 to €352.2 million in 2008.(190) Definitions of what constitutes an ACS condition vary internationally but the Australian Victoria State Health Department condition list is a good example and is commonly used in the UK NHS.(209) (See Table 2-3) It may be argued that for communitybased interventions, focusing efforts on ACS conditions may be more effective than interventions targeting all-cause emergency admissions in reducing overall emergency admissions.

Table 2-3: Ambulatory care sensitive conditions as defined by the Australian Victoria State Health Department

| Acute conditions | Chronic conditions | Other and vaccine- <br> preventable conditions |
| :--- | :--- | :--- |
| Cellulitis | Angina | Influenza |
| Dehydration | Asthma | Pneumonia |
| Dental conditions | COPD | Other vaccine-preventable |
| Ear, nose and throat infections | Congestive heart failure |  |
| Gangrene | Convulsions and epilepsy |  |
| Gastroenteritis | Diabetes complications |  |
| Nutritional deficiencies | Hypertension |  |
| Pelvic inflammatory disease | Iron deficiency anaemia |  |
| Perforated/bleeding ulcer |  |  |
| Pyelonephritis |  |  |

### 2.5.6 Community-based interventions to reduce emergency admissions

Once those at higher risk of emergency admission are identified, the next step is delivering a community-based intervention to prevent future emergency admissions. The evidence for existing community-initiated admission avoidance schemes is limited. Case management has been employed as an intervention of choice in several countries to reduce admissions. Case management may be defined as a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an
individual's and family's comprehensive health needs through communication and available resources to promote quality, cost-effective outcomes.(210) It typically includes a case finding mechanism, assessment, individualised care plans for those stratified as high risk, care co-ordination and multidisciplinary team involvement.(211) While existing evidence supports the role of case management in increasing patient satisfaction with care received, promoting high levels of professional satisfaction and reducing caregiver strain (49, 212215), but systematic reviews of community-based case management RCTs have not demonstrated an impact on reducing future emergency admissions.(90, 216-218).

An example of risk stratification and case management in action is the US Guided Care model. This intervention aims to provide primary care that includes comprehensive geriatric assessment, case management, self-management support and caregiver support provided by a team that includes a specially trained nurse who acts as care coordinator. Patients are targeted using age and multimorbidity as risk stratification criteria. In a 32 centre RCT, this intervention was found to improve participants' chronic care, reduce caregiver strain and resulted in high levels of healthcare professional satisfaction.(214) However, apart from one sub-group, compared to usual care, participants' utilised similar levels of healthcare at 20 month follow-up, with the exception of home health care which was significantly reduced.(49) There is some evidence to support other approaches such as integrated disease management for certain conditions such as COPD, inpatient interventions to reduce readmission rates and optimising community-based end of life care.(219-221) These interventions are explored in more detail in Chapter 6.

### 2.5.7 Summary of emergency admissions risk prediction

Internationally, emergency admissions are rising and represent a healthcare policy priority due to the significant cost and capability concerns this issue presents for health services. In the community setting risk stratification using risk prediction models are increasingly advocated and utilised to identify high-risk older people who are most likely to experience a future emergency admission. This patient group may then be targeted for a communitybased intervention. However, it is not known how many of these models have been developed and how existing models perform comparatively. These are important questions
to answer in considering use of risk prediction models to identify older community-dwelling people at higher risk of future emergency admission.

### 2.6 Overall chapter summary

With an ageing population, determining which older people are most likely to experience future adverse health outcomes is important for patients, clinicians and healthcare policymakers. Conducting a prospective cohort study in primary care to determine which existing prescribing indicators, multimorbidity measures and emergency admission prediction approaches can best identify older people at risk of adverse health outcomes is an important step in addressing this research gap.

Chapter 3 Methodology

### 3.1 Cohort study establishment and follow-up

This cohort study was established in 2010 to examine the association between PIP as defined by the STOPP and Beers 2012 criteria, and patient reported outcomes including ADEs, health related quality of life and healthcare utilisation in community-dwelling older people (aged $\geq 70$ years). The Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidelines were utilised in reporting this methods section and a summary is presented in Appendix 1. $(222,223)$

### 3.2 Study design

This is a prospective cohort study with two-year follow-up. Baseline data collection was conducted in 2010 by Dr Caitriona Cahir as part of her PhD.(224) Follow-up of this cohort, which was conducted by the PhD candidate, commenced in May 2012 and forms the basis of this PhD thesis. Ethical approval was originally granted for this study in 2009 from the Royal College of Surgeons in Ireland (RCSI) research ethics committee. An extension of ethical approval, to allow adequate time for follow-up data collection to occur, was granted in 2011 (Reference number: REC462bbb, see Appendix 2). Patients consented at baseline to their GP medical record being reviewed, use of their GMS number to link to the national PCRS database and to the completion of an ADE interview and a self-report questionnaire. Patients also consented to these outcome measures being repeated at follow-up.

### 3.2.1 Setting

This study was set in primary care in Leinster, Ireland. General practices affiliated to either RCSI or Trinity College, Dublin through undergraduate teaching were invited to take part in the study. In 2010, a total of 15 practices out of 19 practices approached agreed to take part (response rate 81\%).(224) The practices were distributed as follows: four in Dublin city centre, five in south county Dublin, five in north county Dublin and one in the greater Leinster area. Participating GPs were awarded continuing professional development points for their participation. The follow-up GP letter is presented in Appendix 3.

### 3.2.2 Participants

### 3.2.2.1 E ligibility criteria

To be considered eligible for this study, potential participants' were required to meet the following criteria; aged $\geq 70$ years with a HSE-PCRS general medical services card on the $1^{\text {st }}$ January 2010. A total of 931 patients consented to take part in this study in 2010.(224) Of these 931 participants, 27 patients (3\%) could not be linked to the HSE-PCRS pharmacy claims database and so were excluded, resulting in 904 patients included in baseline data analysis. These 904 patients were considered eligible for follow-up (see Figure 3-1).(224)

Patients were excluded from follow-up if they met any one of the following exclusion criteria as determined by their GP:
i. Diagnosis of dementia, as this would impact upon their ability to complete the outcome measures. Dementia was defined as current mini mental state examination (MMSE) <20. Patients with a recorded MMSE of 20-24 were deemed eligible/ineligible by their GP.
ii. Suffering with end-stage disease or receiving palliative care.
iii. Severe visual, hearing or speech impairment, which would impact upon their ability to understand and/or complete the outcome measures.
iv. Diagnosis of a psychotic illness and currently experiencing symptoms.
v. Hospitalised long-term, in a nursing home, homeless or in sheltered accommodation.
vi. Recent (<one month) bereavement.
vii. Patients who had left the practice.
viii. Incomplete or missing contact details.


Figure 3-1 - Number of patients at each stage of baseline cohort study $(112,224)$

### 3.2.2.2 Sample size

Sample size was calculated at baseline for the study aim of determining an association between PIP and the primary outcome of patient self-report ADEs. In 2007, a study using the Irish HSE-PCRS database reported that approximately $36 \%$ of those aged $>70$ years received at least one PIP as per the STOPP criteria.(100) Based on published literature, an ADE rate of $10 \%$ was assumed for those not prescribed any PIP and $20 \%$ for those prescribed any PIP. $(119,225,226)$ Applying a two-sided significance level of $5 \%$ and power of $90 \%$ a sample size of 800 participants was required. ( $N=160-$ exposed to PIP group, $n=640-$ unexposed to PIP group, total $n=800$ ). For a power of $80 \%$, a smaller sample size of 656 participants was required ( $\mathrm{n}=131$ exposed group and $\mathrm{n}=525$ unexposed group).(224)

### 3.2.2.3 Recruitment process: baseline and follewp

Baseline participant recruitment took place from June-October 2010.(224) A random sample of patients from each practice was invited to take part in the study. The sample number was calculated using proportionate stratified random sampling based on the overall required study sample size and the total number of eligible patients per practice, assuming a $50 \%$ response rate. Each potential participant was assigned a unique identifier number and a random sample of patients was generated for each practice using the method of sampling without replacement. Two days after posting the study information to eligible patients they were contacted by telephone by a researcher to determine whether they wished to participate. If during this contact the participant was found to be ineligible, they were excluded. A sample patient letter of invitation for follow-up is presented in Appendix 4. Timelines for patient recruitment and data collection are presented in Figure 3-2.


Figure 3-2: Timeline for participant recruitment and baseline data collection(224)

### 3.2.2.4 Two-year follow-up of study participants

All fifteen participating GP practices were contacted between May 2012 and June 2012 by letter to announce that study follow-up was to commence. Each GP was then provided with a list of study participants from their practice with a copy of the exclusion criteria and asked to indicate if their patients' were still eligible to take part and if not to provide a reason from the list of exclusion criteria provided. Between July 2012 and October 2012, patients determined to be eligible for follow-up by their GP were posted a cover letter and questionnaire. (See Appendices 3 and 4) This postal questionnaire was very similar to the questionnaire participants' had completed at baseline, but contained some additional questions regarding healthcare utilisation, caregiver availability and costs of care. Two weeks after questionnaires were posted reminder telephone calls were conducted, if necessary. If a participant was no longer eligible to take part in the study, a reason for exclusion was documented according to exclusion criteria. If a study participant had mislaid
or not received a questionnaire, a second questionnaire and cover letter was posted. Corresponding GP medical record reviews of study participants' commenced in July 2012 and continued until June 2013.

Study participants' who returned a completed postal questionnaire and were currently taking any prescribed medication were considered eligible for a telephone interview regarding ADEs. Eligible patients were telephoned and asked to complete this interview of approximately 20 minutes duration. Reasons for non-participation were recorded where possible. An overall timeline of contact with participating GP practices and follow-up of study participants is presented in Figure 3-3.

Follow-up eligibility determined

May-June 2012

Eligibility of study participants for self-
report outcome measures (postal
questionnaire and $A D E$ interview)


Follow-up data collection

July 2012-June 2013


Patient self-report measures:
GP medical record review

1) Postal questionnaires administered

July 2012-June 2013
reminder telephone calls, questionnaires
returned

July 2012-November 2012
2) $A D E$ telephone interviews

November 2012-June 2013

Data input to Microsoft Access

Figure 3-3-Timeline for follow-up of cohort study participants

### 3.2.3 Outcomes and outcome measures

### 3.2.3.1 Adverse drug events (ADEs)

As detailed in section 2.2.7.1, an ADE was defined as: "an event which results in unintended harm to the patient, and is related to the care and/or services provided to the patient, rather than to the patient's underlying medical conditions".(106) This definition meets the requirements of an ADE published in existing literature regarding the terminology of drug related harm and is consistent with previous studies examining ADEs in the community settling.(20, 227-230) Patient reported outcomes (PROMs) are increasingly recognised as an essential component of research outcome measurement and patient-reported ADEs have been showed to correctly identify ADEs in previous research studies.(52, 226, 231, 232)

Patient self-reported ADEs were determined using the following process. Each patient's medical record and medication list (repeat and acute) was retrieved from his or her GP record. Details regarding chronic medical conditions, GP and practice nurse attendances, attendances at secondary care (out-patient department, $A \& E$, emergency and elective hospital admissions) and use of other services (public health nurse, physiotherapy, occupational therapy, counselling etc.) was recorded. GP medical records were also reviewed for any documented allergies to medications or ADEs (see Appendix 5 for the data collection form utilised). Healthcare utilisation information was recorded retrospectively at baseline in 2010, for the six months prior to ADE interview and was recorded two years prospectively for the follow-up study.

GP medical record review data was then used as the basis of a patient interview regarding ADEs to prescribed medication in the previous six months. At baseline, the interview was piloted on 20 patients and amended according to feedback and then interviews were conducted between July 2010-December 2010.(224) Follow-up ADE interviews using an identical interview template took place between October 2012 and June 2013. This interview could be completed either by telephone or in person. The interview comprised of an initial general question regarding ADEs followed by detailed questions relating to specific symptoms. The initial question was as follows: 'In the last six months have you noticed any
side effects, unwanted reactions or other problems with the medications you were taking'. The use of this question was based on previously published research in which it correctly identified $94 \%$ of ADEs. $(225,226,232)$ Questions were asked regarding 74 symptoms categorised according to physiological system. This interview developed for the baseline study was based on previous research and included a generic self-report symptom measure, self-report measures of ADEs and the Undersogelser (UKU) side effect rating scale for psychotropic drug side effects. $(129,226,232-234)$ If the patient reported a specific symptom during the interview then this triggered further questions. These included whether the patient attributed the symptom to their medication, and if so the name of the medication, the date (approximately) the symptom began, the duration of the symptom, the degree to which it bothered the patient and whether or not they had discussed the symptom with their GP. If they had discussed the symptom with their GP, then they were asked what the GP had done (if anything) and whether or not they had attended the outpatient department or were hospitalised as a result. If a patient had a documented ADE in their GP record, they were asked about it at the end of the interview, if not previously referred to during the interview. If the patient was unaware of the documented $A D E$, then this was added to their interview as a symptom and that the patient did not believe it to be caused by any medication. The final interview questions related to any over the counter medication use and smoking status and/or history (see Appendix 6 for the full interview).

Once interviews were completed patients' self-reported ADEs were reviewed independently by two academic GPs who were blinded to the STOPP and Beers 2012 prescribing criteria. The process utilised is based on similar research using a self-report scale to categorise ADEs.(129) The academic GP reviewers were also given a copy of the patient's medical record (including prescribed medications), their attendances at secondary care and a drug formulary: the Irish Medicines formulary (Edition 14).(140) Reviewers were asked to rate the likelihood of the reported ADEs based on the information available. A six point scale was provided as follows: 1) little or no confidence; 2) slight to moderate confidence; 3) < $50 \%$ confidence; 4) $>50 \%$ confidence but a close call; 5) strong confidence; and 6) virtually certain.(129) Only symptoms with a confidence level $\geq 4$ from both reviewers were considered ADEs.

A percentage of agreement and kappa (к) statistic was calculated for the two reviewers. This was undertaken to examine the reliability of the classification system used. The percentage of agreement was calculated as the number of agreed cases/ total cases. The kappa statistic is calculated using this formula; $\left(\mathrm{P}_{0}-\mathrm{P}_{\mathrm{c}}\right) /\left(1-\mathrm{P}_{\mathrm{c}}\right)$ where $\mathrm{P}_{0}=$ proportion of observed agreement and $\mathrm{P}_{\mathrm{C}}=$ proportion of agreement expected by chance (ranges from -1 (complete disagreement) to +1 (perfect agreement)). A kappa score of 0.4-0.6 is moderate agreement, $0.6-0.8$ considered substantial agreement, $0.8-1.0$ is almost perfect agreement.(235)

In addition, once ADEs were established at two-year follow-up (and verified); each ADE was then further classified according to severity. A different academic GP and an academic pharmacist independently reviewed reported ADEs and decided upon severity. Three categories were applied: i) mild (e.g. diarrhoea); ii) moderate (e.g. falls due to postural hypotension); and iii) severe or life threatening (e.g. emergency admission due to hyperkalaemia). This classification system has been utilised in previous studies and is helpful clinically in considering the impact of these events for patients. $(52,236)$ Guidance notes on this classification system were provided to the two reviewers. Where consensus was not reached in rating ADE severity, a third GP (the PhD candidate) made the final decision.

### 3.2.3.2 Health related quality of life (HRQOL)

Traditional disease end-points, such as mortality and disease specific end-points do not adequately capture the intricacies of living with chronic medical conditions. The biomedical conceptualisation of what it is to age well focuses on physiological aspects of ageing such as presence of disease.(237) However, these measures are not holistic and do not account for other aspects of ageing such as psychosocial issues.(238) While agreeing a definition of HRQOL has been a source of debate, consensus exists that any measure of HRQOL should include two key elements of multidimensionality and subjectivity.(239)

Erickson and Patrick defined the concept of HRQOL as follows: "The value assigned to the duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy."(240) Additionally, particular care must be taken in applying measures of HRQOL developed for use in younger,
healthier populations to older populations.(239) Adopting a holistic approach to the determinants of HRQOL, therefore, merits assessment of biomedical, psychological, social and environmental factors. For the purposes of this study, these elements were captured through assessment of physical functioning; psychological well-being, social support, functioning and structure, emotional well-being and general health status measured by a postal questionnaire using validated measures (see Appendix 5).

### 3.2.3.3 Physical functioning

Outcome measurethe Vulnerable Elders-13 survey

The Vulnerable Elders-13 survey (VES-13) comprises 13 questions regarding the respondent's subjective appraisal of function (activities of daily living, instrumental activities of daily living and physical function), self-rated health and age.(32) This tool was developed in a cohort of older ( $\geq 65$ years) community-dwelling people in the US using longitudinal data.(32) It successfully predicted which older people were most at risk of functional decline and death over two years of follow-up. This tool was validated in the US to predict functional decline and death over five years of follow-up.(241) It has also been validated in Ireland where a similar proportion of older people were classified as vulnerable as the derivation cohort (approximately 32\%) and it successfully predicted functional decline and subsequent healthcare utilisation. $(241,242)$ A cut-off score of $\geq 3$ is used to identify vulnerability.(117)

### 3.2.3.4 Psychological wellbeing

## Outcome measurethe Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was originally developed in the 1980s to detect anxiety and depression in the medical outpatient setting.(243) It has subsequently been validated across multiple settings in different countries and is both a valid and reliable instrument for case- finding of depression and anxiety in primary care. $(244,245)$ Based on a systematic review which examined the diagnostic predictive ability of the HADS in detecting
a major depressive disorder, a cut-off score of $\geq 11$ offers a pooled specificity of approximately $92 \%$.(246)

### 3.2.3.5 General health status

Outcome measurehe Euro-Qol 5-Dimensions (EQ-5D) and EQ-5D visual analogue scale The EQ-5D is a standardised measure of health status that comprises assessment of five domains, namely: 1) Mobility; 2) Self-care; 3) Usual activities; 4) Pain or discomfort; and 5) Anxiety or depression. Each domain is rated according to one of the following; no problems, moderate problems or extreme problems (3-Level). $(247,248)$ A set of utility values have been developed for predicted EQ-5D health states based on the UK population using the time trade off valuation statistical technique.(249) This method calculates a single value on a continuum from 0 to 1 , where 1 is the best health state and 0 corresponds to dead, with some health states regarded as worse than death (<0).(249) In addition, the EQ visual analogue scale (EQ-VAS) allows patients' record their self-rated health on a visual analogue ranging from 0 (worst health state imaginable) to 100 (best health state imaginable).(247, 248) The EQ-5D has been validated in community settings across Europe with test-retest reliability reported between 0.69 and 0.94 .(250)

### 3.2.3.6 Social functioning, support and structure

Three specific tools were used for social functioning, support and structure, including the social functioning scale from the short form health survey (SF-36), the Medical Outcomes Social Support (MOS) survey and the Lubben's social network scale.

Social functioning was measured using the subjective social functioning scale from SF36.(251) This scale measures the degree to which the patient's health interferes with their day-to-day social functioning. It consists of two items both scored from 0 to 100, where 100 equals optimal social functioning. Those scoring $\geq 50$ on this scale were classified as having high social functioning.(251) Social support was measured using the MOS survey that includes subjective measures of affectionate support, emotional support and tangible support. $(251,252)$ This is rated on a five point Likert scale and then classified into low (0-2),
medium (3) or high (4-5) levels of support.(252) Social network structure was measured using the Lubben's social network scale that is an objective composite measure of family and friends networks.(253) This scale provides an objective assessment of social structure by asking patients the number of people they have contact with and how often contact occurs.

### 3.2.3.7 E motional wellbeing

Three measures of emotional wellbeing, the Life satisfaction scale, the single item selfesteem scale and the brief illness self-perception questionnaire were administered.

The Life Satisfaction Index aims to assess general life satisfaction and well-being and consists of 18 questions.(254) Positive well-being is indicated by taking pleasure in daily activities, reporting a feeling of success in achieving major goals, having a positive self-image and optimism for the future. All items are scored and summed with a final score ranging from 1-18.(254) Self-esteem was measured using a single question; the Single Item SelfEsteem scale, which asks patients to rate their self-esteem on a five Point Likert scale where 5, represents highest self-esteem.(255) It was derived from a longer scale, the Rosenberg self-esteem scale, and though shortened has demonstrated similar reliability and validity.(254) Self-efficacy was assessed using the single item Brief Illness Perception Questionnaire (Brief IPQ) that measures the respondent's perceived extent of personal control over illness on a 10-point Likert scale ( $0=$ absolutely no control, 10=extreme amount of control).(256) Perceived control has been shown to correlate with self-efficacy in previous research studies. $(256,257)$

### 3.2.3.8 Healthcare utilisation

Participants' healthcare use was measured in two ways. First, as part of the postal questionnaire patients were asked to report their use of health services over the previous 6 months. (See Appendix 5) Health service use questions related to GP visits, A\&E visits, hospital admissions, outpatient visits, use of allied health professional services including therapies (occupational therapy, physiotherapy, speech and language therapy), use of other
services such as dietetic services, optician, audiology and use of public health nurse, home help and respite care. The measure used for reporting health service use has previously been used in a prospective cohort study of health and social services for older people.(2)

Second, each participant's GP medical record was accessed and reviewed. For the baseline study in 2010, six months of GP record data was retrospectively reviewed. For the follow-up, two years of healthcare utilisation data was recorded from the date of the baseline GP record review for each patient. Data was collected on the number of GP and practice nurse visits, number of prescription only visits, hospital outpatient visits, A\&E visits and both emergency and elective hospital admissions. The number of episodes and dates of A\&E visits was recorded as well as detailed information regarding emergency hospital admissions (date of admission, length of stay, reason for admission). An emergency hospital admission was defined as 'an admission or readmission with an overnight stay that was not previously planned, scheduled or elective' and the number of these episodes, date of admission, length of hospital stay and reason for admission was recorded.(217) Referral to allied health professionals e.g. physiotherapy, public health nurse and use of respite care were recorded where this information was available. Hospital outpatient visits were classified using the Irish Hospital inpatient inquiry system.(3)

### 3.2.4 Variables

### 3.2.4.1 Measures of potentially inappropriate prescribing

PIP was measured using two different sets of explicit prescribing criteria; the STOPP and Beers 2012 criteria. $(74,96)$ These prescribing criteria have been described in detail in Chapter 2 (Section 2.2.2.1). The GMS card number was used for each patient as a unique identifier to extract information from the HSE-PCRS pharmacy claims database. At baseline, the 6 months prior to the patient's ADE interview was used as the point for which the STOPP and Beers 2012 criteria were applied. If the patient did not complete the ADE interview but had consented to take part in the study then the date of consent for study participation was used to apply both sets of prescribing criteria.(224) At follow-up the same process was adhered to with the date of the follow-up ADE interview used as the date from which the
prescribing criteria were applied retrospectively for six months. If the patient did not complete the ADE interview then their date of follow-up postal questionnaire completion was used as the reference date.

### 3.2.4.2 STOPP déria

A total of 51 of 65 (78\%) STOPP prescribing indicators could be applied to the patients' pharmacy claims data for the baseline study (See Table 3-1). The same 51 STOPP criteria were applied to patients' dispensed medications for the follow-up period using the same reference period of six months prior to ADE interview. Fourteen criteria could not be applied due to a lack of clinical information necessary for their application (e.g. loop diuretic for dependent oedema only, aspirin to treat dizziness not attributed to cerebrovascular disease, use of long term powerful opiates as first line treatment in patients with mildmoderate pain). Duplicate classes of medications (on the same pharmacy claim) were assessed for five medication classes namely; non-steroidal anti-inflammatories (NSAIDs), opiates, loop diuretics, angiotensin converting enzyme inhibitors (ACEIs) and selective serotonin reuptake inhibitors (SSRIs).

## Table 3-1: STOPP criteria applied at baseline and follow-up ( $n=51$ )(74)

## A. Cardiovascular System

1. Digoxin at a long-term dose $>125 \mu \mathrm{~g} /$ day with impaired renal function (increased risk toxicity).
2. Loop diuretic as first-line monotherapy for hypertension (safer, more effective alternatives available).
3. Thiazide diuretic with a history of gout (may exacerbate gout).
4. Beta-blocker with COPD (risk of increased bronchospasm).
5. Beta-blocker in combination with verapamil (risk of symptomatic heart block).
6. Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).
7. Calcium channel blockers with chronic constipation (may exacerbate constipation).
8. Use of aspirin and warfarin in combination without histamine H 2 receptor antagonist (except cimetidine because of interaction with warfarin) or PPI (high risk of gastrointestinal bleeding).
9. Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for efficacy).
10. Aspirin with a past history of peptic ulcer disease without histamine H 2 receptor antagonist or PPI (risk of bleeding).
11. Aspirin at dose $>150 \mathrm{mg}$ day (increased bleeding risk, no evidence for increased efficacy).
12. Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event (not indicated).
13. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration (no proven added benefit).
14. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit).
15. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (high risk of bleeding).

## B. Central Nervous System and Psychotropic Drugs.

1. Tricyclic antidepressants (TCA's) with dementia (risk of worsening cognitive impairment).
2. TCA's with glaucoma (likely to exacerbate glaucoma).
3. TCA's with cardiac conductive abnormalities (pro-arrhythmic effects).
4. TCA's with constipation (likely to worsen constipation).
5. TCA's with an opiate or calcium channel blocker (risk of severe constipation).
6. TCA's with prostatism or prior history of urinary retention (risk of urinary retention).
7. Long-term (i.e. > 1 month), long-acting benzodiazepines e.g. chlordiazepoxide, fluazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam (risk of prolonged sedation, confusion, impaired balance, falls).
8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics (risk of confusion, extra-pyramidal side effects, falls).
9. Long-term neuroleptics (> 1 month) in those with Parkinsonism (likely to worsen extra-pyramidal symptoms)
10. Phenothiazines in patients with epilepsy (may lower seizure threshold).
11. Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications (risk of anticholinergic
toxicity).
12. Prolonged use (> 1 week) of first generation antihistamines (e.g. chlorpheniramine, cyclizine) (risk of sedation and anti-cholinergic side effects).

## C. Gastrointestinal System

1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis).
2. Prochlorperazine (Stemetil) or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonism).
3. PPI for peptic ulcer disease at full therapeutic dosage for $>8$ weeks (dose reduction or earlier discontinuation indicated).
4. Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation).

## D. Respiratory System.

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

## E. Musculoskeletal System

1. NSAID with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 receptor antagonist, PPI or misoprostol (risk of peptic ulcer relapse).
2. NSAID with heart failure (risk of exacerbation of heart failure).
3. Long-term use of NSAID (>3 months) for relief of mild joint pain in osteoarthritis (simple analgesics preferable and usually as effective for pain relief)
4. Warfarin and NSAID together (risk of gastrointestinal bleeding).
5. NSAID with chronic renal failure (risk of deterioration in renal function) "Estimated GFR 20-50ml/min.
6. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects).

## F. Urogenital System

1. Bladder antimuscarinic drugs with dementia (risk of increased confusion, agitation).
2. Antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma).
3. Antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation).
4. Antimuscarinic drugs with chronic prostatism (risk of urinary retention).

## G. Endocrine System

1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia).
2. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
3. Oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer).
H. Drugs that adversely affect those prone to falls (1 fall in past three months)
4. Benzodiazepines (sedative, may cause reduced sensorium, impair balance).
5. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism).
6. First generation antihistamines (sedative, may impair sensorium).

## I. Analgesic Drugs

Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation).

## J. Duplicate Drug Classes

Any duplicate drug class prescription e.g. two concurrent opiates, NSAID's, SSRI's, loop diuretics, ACE inhibitors (optimisation of monotherapy within a single drug class should be observed before considering a new class of drugs)

### 3.2.4.3 Beers criteria 2012

A total of 35 of the 53 ( $66 \%$ ) Beers 2012 criteria were applied ( $n=22$ drugs to avoid and $n=13$ drugs to avoid in the presence of certain medical conditions) (See Table 3-2 and Table 3-3). Of the original 53 Beers indicators, there was inadequate information to apply seven (e.g. insulin sliding scale (unable to determine from pharmacy claims data), anti-arrhythmic drugs to be avoided as first line treatment for atrial fibrillation (unable to determine from pharmacy claims and medical conditions data) and drugs to avoid in delirium (this diagnosis was not extracted from the GP medical record). A further 11 drugs listed as drugs to avoid by the US Beers 2012 criteria are not licensed for use in Ireland (e.g. mineral oil, pentazocine, chloral hydrate and meprobamate). The same 35 Beers 2012 criteria were applied to participants' dispensed medications at follow-up using the same reference period of six months prior to ADE interview.

### 3.2.4.4 Overlap between STOPP and Beers 2021 prescribing indicators

There is some overlap between medications included in both the STOPP and Beers 2012 prescribing indicators. Both sets include the following drug classes in older people to be avoided under specific circumstances: 1) NSAIDs; 2) Benzodiazepines; 3) Digoxin; 4) Calcium channel blockers; 5) Dipyridamole; 6) Long-term neuroleptics; 7) Prochlorperazine/metoclopramide; 8) Anticholinergic antispasmodics; 9) TCAs; 10) First generation antihistamines; 11) Glibenclamide; and 12) Oestrogens.

Of 51 STOPP prescribing indicators applied in the current study, a total of 16 (31\%) appear in both the STOPP and Beers 2012 prescribing indicator sets (SeeTable 3-4), and a further 9 (18\%) had partial overlap. The remaining 26 STOPP indicators varied both in terms of medication classes included and type of PIP indicator.

Table 3-2: 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (n=22) (96)


Organ System or Therapeutic Category or Drug
6. Alpha agonists, central e.g. Clonidine
7. Digoxin $>0.125 \mathrm{mg} / \mathrm{dl}$
8. Nifedipine, immediate release**
9. Spironolactone $>25 \mathrm{mg} / \mathrm{dl}$

## Anti-infective

10. Nitrofurantoin

## Central nervous system

11. Tertiary TCAs, alone or in combination e.g. Amitriptyline
12. Antipsychotics, first (conventional) and second (atypical) generation

## Rationale

High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension

In heart failure, higher dosages associated with no additional benefit and may increase risk of toxicity; slow renal clearance may lead to risk of toxic effects

Potential for hypotension; risk of precipitating myocardial ischemia

In heart failure risk of hyperkalaemia is higher in older people especially if taking $>25 \mathrm{mg} / \mathrm{d}$ or taking concomitant NSAID, ACE inhibitor or potassium supplement.

Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with $\mathrm{CrCl}<60 \mathrm{ml} / \mathrm{min}$

Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin ( $\geq 6 \mathrm{mg} / \mathrm{d}$ ) is comparable with that of placebo

Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia

## Recommendation

Avoid clonidine as a first-line antihypertensive.

Avoid

Avoid

Avoid in patients with heart failure or CrCl <30ml/min

Avoid for long term suppression; avoid in patients with $\mathrm{CrCl}<60 \mathrm{ml} / \mathrm{min}$

## Avoid

Avoid use for behavioural problems of dementia unless nonpharmacological options have failed and patient is threat to self or others

## Organ System or Therapeutic Category

 or Drug14. Benzodiazepines

Short and intermediate acting: e.g.
Alprazolam Lorazepam

Long acting: e.g. Diazepam Flurazepam
15. Nonbenzodiazepine hypnotics e.g. Zolpidem

## Endocrine

## Rationale

Older adults have increased sensitivity to benzodiazepines and slower metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents in older adults

May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anaesthesia, end-of-life care

Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); minimal improvement in sleep latency and duration

Potential for cardiac problems and contraindicated in men with prostate cancer

Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women

Evidence that vaginal oestrogens for treatment of vaginal dryness is safe and effective in women with breast cancer, especially at dosages of oestradiol < 25 $\mu \mathrm{g}$ twice weekly

## Recommendation

Avoid benzodiazepines (any type) for treatment of insomnia, agitation, or delirium

Avoid chronic use (> 90 days)

Avoid unless indicated for moderate to severe hypogonadism

Avoid oral and topical patch.

Acceptable to use low-dose intravaginal oestrogen for the management of dyspareunia, lower urinary tract infections, and other vaginal symptoms

## Organ System or Therapeutic Category or Drug <br> 18. Sulfonylureas, long duration e.g. <br> Chlorpropamide, Glyburide

## Gastrointestinal

19. Metoclopramide

Pain
20. Meripidine
21. Non-COX-selective NSAIDs, oral
22. Indomethacin and Ketorolac includes parenteral

## Rationale

Chlorpropamide: prolonged half-life in older adults; can cause prolonged
hypoglycaemia; causes syndrome of inappropriate antidiuretic hormone secretion. Glyburide: greater risk of severe prolonged hypoglycaemia in older adults

Can cause extrapyramidal effects including tardive dyskinesia; risk may be even greater in frail older adults

May cause neurotoxicity; safer alternatives available

Increases risk of GI bleeding and peptic ulcer disease in high-risk groups, including those aged > 75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelets. Use of PPI or misoprostol reduces but does not eliminate risk. Upper Gl ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately $1 \%$ of patients treated for $3-6$ months and $2-4 \%$ treated for 1 year. These trends continue with longer duration of use.

Increases risk of GI bleeding and peptic ulcer disease in high-risk groups. Of al the NSAIDs, indomethacin has most adverse effects

## Recommendation

## Avoid

Avoid, unless for gastroparesis

Avoid

Avoid chronic use unless other alternatives are not effective and patient can take gastroprotective agent (PPI or misoprostol)

Avoid

CNS = central nervous system; COX = cyclooxygenase; $\mathrm{CrCl}=$ creatinine clearance

Table 3-3: 2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome ( $\mathrm{n}=13$ )(96)

| Disease or Syndrome | Drug | Rationale | Recommendation |
| :---: | :---: | :---: | :---: |
| C ardiovascular |  |  |  |
| 1. Heart failure | NSAIDs and COX-2 inhibitors, Nondihydropyridine CCBs (avoid only for systolic heart failure), Diltiazem, Verapamil, Pioglitazone, Rosiglitazone | Potential to promote fluid retention and exacerbate heart failure | Avoid |
| 2. Syncope | ACEIs, Peripheral alpha blockers, Doxazosin, Prazosin, Terazosin, Tertiary TCAs, Chlorpromazine, Olanzapine | Increases risk of orthostatic hypotension or bradycardia | Avoid |
| Central nervous system |  |  |  |
| 3. Chronic seizures or epilepsy | Bupropion, Chlorpromazine, Clozapine, Olanzapine, Tramadol, Anticholinergics, Benzodiazepines, Chlorpromazine, Corticosteroids, $\mathrm{H}_{2}$-receptor antagonist, Meperidine, Sedative hypnotics | Lowers seizure threshold; maybe acceptable when wellcontrolled seizures and alternative agents not effective | Avoid |
| 4. Dementia and cognitive impairment | Anticholinergics | Avoid because of adverse CNS effects. | Avoid |
|  | Benzodiazepines | Avoid antipsychotics unless nonpharmacological options have failed, and patient is a threat to themselves or others. |  |

## Rationale

## Recommendation

$\mathrm{H}_{2}$-receptor antagonists, Zolpidem, Antipsychotics, chronic and as-needed use
5. History of falls or fractures
6. Insomnia
7. Parkinson's disease

Anticonvulsants, Antipsychotics, Benzodiazepines, Nonbenzodiazepine hypnotics, Eszopiclone, Zaleplon, Zolpidem, TCAs, SSRIs

Oral decongestants, Pseudoephedrine, Phenylephrine, Stimulants, Amphetamine, Methylphenidate, Theophylline

All antipsychotics, Antiemetics, Metoclopramide, Prochlorperazine, Promethazine

Antipsychotics are associated with an increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia

Ability to produce ataxia, impaired psychomotor function, syncope, and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones

CNS stimulant effects

Dopamine receptor antagonists with potential to worsen parkinsonian symptoms. Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson's disease

Avoid unless safer alternatives not available; avoid anticonvulsants except for seizure disorders

Avoid

Avoid

## G astrointestinal

Oral antimuscarinics, Fesoterodine, Oxybutynin, Solifenacin Tolterodine, Trospium,
Nondihydropyridine CCB, Diltiazem, Verapamil, First-generation antihistamines, Chlorpheniramine, Hydroxyzine, Promethazine, Anticholinergics antispasmodics Antipsychotics, Scopolamine, Tertiary TCAs

Can worsen constipation; agents for urinary incontinence: antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops

Avoid unless no other alternatives
. History of gastric
or duodenal ulcers

Aspirin ( $>325 \mathrm{mg} / \mathrm{d}$ ) Non-COX-2 selective NSAIDs

## Rationale

May exacerbate existing ulcers or cause new or additional ulcers

## Recommendation

Avoid unless other
alternatives are not effective and patient can take gastroprotective agent (PPI or misoprostol)

## Kidney and urinary tract

10. Chronic kidney disease Stages IV or V

NSAIDs, Triamterene (alone or in combination)

Oestrogen oral and transdermal (excludes anticholinergic drugs, except antimuscarinics for
11. Urinary incontinence (all types) in women
12. Lower urinary tract symptoms, benign prostatic hyperplasia
intravaginal oestrogen)

Inhaled anticholinergic agents Strongly urinary incontinence

May increase risk of kidney injury
Avoid

Aggravation of incontinence

May decrease urinary flow and cause urinary retention

Alpha blockers Doxazosin Prazosin Terazosin
Aggravation of incontinence

Avoid in women

Avoid in men

Avoid in women

Table 3-4: Prescribing indicators that appear in both the STOPP and Beers 2012
Prescribing indicator description as per STOPP
Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence for
efficacy).
TCA's with dementia (risk of worsening cognitive impairment).
TCA's with glaucoma (likely to exacerbate glaucoma).
TCA's with cardiac conductive abnormalities (pro-arrhythmic effects).
Long-term neuroleptics (> 1 month) in those with Parkinsonism (likely to worsen extra-
pyramidal symptoms)
Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonism).
Phenothiazines in patients with epilepsy (may lower seizure threshold).
NSAID
Long-term use of NSAID (>3 month with history of peptic ulcer disease or gastrointestinal bleeding, unless with
analgesics preferable and usually as effective for pain relief).
concurrent histamine H2 receptor antagonist, PPI or misoprostol (risk of peptic ulcer
relapse).
Thisk of severe constipation).
Trisk of exacerbation of heart failure).
Thild joint pain in osteoarthritis (simple
Ther

Prescribing indicator description as per Beers 2012

Drug to avoid: dipryidamole

Drug to avoid: TCAs

Drugs to avoid in patients with Parkinson's disease: Antipsychotics Drugs to avoid in patients with Parkinson's disease: chlorpromazine

Drugs to avoid in patients with epilepsy: chlorpromazine

Avoid with history of gastrointestinal ulcers: non-COX selective NSAIDs

Drugs to avoid in heart failure: NSAIDs
Avoid chronic use of non-COX selective NSAIDs for pain

| Prescribing indicator description as per STOPP | Prescribing indicator description as per Beers 2012 |
| :--- | :--- |
| NSAID with chronic renal failure (risk of deterioration in renal function) | Avoid in chronic kidney disease: NSAIDs |
| Benzodiazepines (sedative, may cause reduced sensorium, impair balance) in patients with <br> falls/history of fracture. | Drugs to avoid: Benzodiazepines |
| Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism) in patients with falls/history of <br> fracture. | Drugs to avoid in patients with a history of falls/fracture: antipsychotics <br> Antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation). |
| anticholinergics patients with history of chronic constipation: |  |

Certain prescribing criteria require duration of treatment information (e.g. NSAIDs prescribed for >3 months consecutively) and these were assessed using consecutive months of pharmacy claims for the six-month period prior to the ADE interview. Other criteria required additional dosage information e.g. proton pump inhibitors (PPIs) at maximum therapeutic dosage for $>8$ weeks. These medications were examined using the defined daily dose (DDD), medication strength, quantity of tablets dispensed, mode of administration, unit of measurement of the prescribed medication and number of medications per pack. The total number of prescriptions filled for different medication classes (using the first three characters of the World Health Organisation-Anatomical Therapeutic Chemical (WHO-ATC) code) were calculated on a patient basis for the same time period.

The WHO-ATC classification system divides medications into different groups according to the organ or system on which they act and according to their pharmacological and therapeutic properties.(258) Medications are classified in groups at five different levels. Level one has 14 main groups followed by two therapeutic/pharmacological subgroups (levels two and three). Level four is a therapeutic/pharmacological/chemical subgroup and level five is the chemical substance. The diabetic medication glibenclamide is detailed below to illustrate how the ATC classification works.(258)

A: Alimentary tract and metabolism (first level, main anatomical group)
A10: Drugs used in diabetes (second level, main therapeutic group)

A10B: Oral blood-glucose-lowering drugs (third level, therapeutic/pharmacological subgroup)

A10B B: Sulphonamides, urea derivatives (fourth level, chemical/therapeutic/pharmacological subgroup)

A10B B01: Glibenclamide (fifth level, subgroup for chemical substance)

Each patient was required to have received at least three prescriptions for each different medication class to be included as a repeat medication. The STOPP and Beers

2012 criteria were then included as a composite indicator into separate models as follows: no PIP indicators, one PIP indicator and $\geq 2$ PIP indicators.

### 3.2.4.5 Socioeconomic status

The baseline postal questionnaire contained a number of questions to establish socioeconomic status. Questions included level of education and previous occupation. Patients were classified into one of seven potential social class groups based on their previous occupation. The classification system used was the Irish Central Statistics Office population classification system (www.cso.ie). The groups are as follows: professional workers; managerial and technical; non-manual; skilled manual; semiskilled; unskilled; all others gainfully occupied; and unknown. Those reporting working full-time in the home were assigned to the same class as their partner or spouse, if married.(259)

Information regarding gender and date of birth was extracted from the patient's GP medical record and patient addresses were geocoded according to electoral division. Patient deprivation was estimated from the deprivation score of the patient's address. Electoral division deprivation level was based on the Small Area Health Research Unit (SAHRU), which shares similarities with the Townsend and Carstairs deprivation indices widely used in the UK.(260) Socio-economic status was calculated using this deprivation sore as well as education level or social class. This combination was based on previous research, which reported that the elements of social class or education level combined with deprivation score were most accurate in calculating socio-economic status in older people.(261) To facilitate this process, education was reclassified as either basic education (no formal education, primary education or lower secondary education only) or upper and post-secondary (all other higher levels of education). Two social class groups were created as follows: unskilled (unskilled, gainfully occupied, unknown); and skilled (all other categories).

### 3.2.4.6 Multimorbidity

The International Classification of Primary Care (ICPC-2) disease coding system definition of a chronic disease was used for the purposes of this study.(262) This definition states a chronic disease should fulfil four criteria: 1) be of at least six months duration; 2) have a pattern of recurrence or deterioration; 3) have prognostic implications; and 4) produce consequences or sequelae that may impact on the individual's quality of life. Multimorbidity was defined as the presence of two or more chronic medical conditions in an individual.(4)

Multimorbidity represents the norm in clinical practice and is strongly linked to both ageing and deprivation. $(4,23)$ A recent systematic review indicates that simple disease counts and the Charlson comorbidity index are two of the most commonly utilised measures of multimorbidity in the primary care and community setting.(28) Recent Irish research utilising national cross-sectional data also supports use of disease counts as the most accurate measurement of multimorbidity in the community setting.(137) There is, however, increasing interest in examining certain chronic conditions proven to be associated with higher impact or burden for patients.(123) The majority of existing studies examining multimorbidity do not specify criteria for inclusion of chronic conditions.(25) According to a recent systematic review those that do include conditions based on the following criteria: 1) the prevalence of the condition (either at population level or in the study cohort); 2) conditions associated with an increased mortality rate; and 3) the impact of disease on function and health or need for intensified management.(25)

For the baseline study, multimorbidity was measured in two ways utilising the Charlson comorbidity index and the RxRisk-V (veterans) tool. The Charlson comorbidity index includes 17 diseases that have been selected and weighted in relation to their association with mortality risk. $(263,264)$ Since its development in the 1980s, the index has been updated to allow use with the International Classification of Diseases-version 10 (ICD-10).(265) In two systematic reviews comparing available comorbidity measures, the Charlson index demonstrated good predictive accuracy for outcomes of mortality, healthcare utilisation and quality of life in community settings. $(28,29)$ For the purposes
of baseline data analysis, the Charlson index weights were re-categorised into two groups; no Charlson conditions=0 and $\geq 1$ Charlson conditions.

The RxRisk-V was developed from the Chronic Disease Score (CDS), a risk prediction tool developed using outpatient pharmacy dispensing data, for the older age population.(266) The RxRisk-V classifies patients' chronic disease conditions based on the WHO-ATC medication classification system of their dispensed prescribed medications.(267) The RxRisk-V was developed for use in older people and has demonstrated good reliability and criterion validity when compared to medical diagnoses and also in predicting healthcare utilisation and mortality.(28, 60-62, 268) Measuring comorbidity using these two different data sources offers a mechanism for capturing gaps in both GP medical record coding of chronic medical diagnoses and instances where prescriptions are not adhered to by patients.(269)

To examine the impact of accounting for disease severity and burden in multimorbidity measurement for the follow-up study and current PhD two additional multimorbidity measures were included. Simple disease counts were calculated for each patient based on any chronic medical conditions recorded in their GP medical record. Disease counts were also calculated for a pre-specified list of 40 conditions described by Barnett and colleagues due to their prevalence and impact on patient health outcomes.(23)

### 3.2.4.7 Number of repeat medication classes

The number of repeat medication classes was established by examining the HSE-PCRS pharmacy claims database of dispensed medications. This database provides details of all dispensed medications on a monthly basis for each patient. Prescriptions are coded using the WHO-ATC classification system.(267) Medication information available includes: defined daily doses; strength; quantity of medication; mode of administration; and unit of administration. There is a proven link between increasing numbers of prescribed medications and adverse health outcomes including ADEs, PIP, functional decline, healthcare utilisation and emergency admission.(9, 31, 100, 270) Each patient was required to have received at least three prescriptions of a drug class for a prescription to be considered a repeat drug class.

### 3.2.4.8 Medication adherence

Medication adherence is commonly defined as the extent to which patients take their medications as prescribed.(7) Medication adherence was measured in ways: 1) the Medication Possession Ratio (MPR); and 2) the Morisky Medication Adherence scale. (MMAS) (58, 271-273)

The MPR is a measure of prescription refill and was calculated using the HSE-PCRS pharmacy claims database for the six months prior to the patient's ADE interview. This measure is calculated as the sum of days supplied for all medications (i.e. the medication quantity supplied) divided by the time period (i.e. six months).(58) The average MPR rate for medication classes, categorised according to the WHO-ATC classification system, was determined for each patient. This calculation required at least two prescription refill dates and was analysed for each medication (ATC code) and therapeutic class (first three letters of the ATC code) as a proxy measure for adherence to medication classes prescribed for different medical conditions.(274) The MPR rate ranged from 0 to 1 , where $1=$ fully adherent and $0=$ non-adherent.(271) In addition, the MPR was categorised as follows: $<50 \%, 50-79 \%$ and $\geq 80 \%$.(274) Of note the MPR is only calculated for medications of tablet or capsule administration, and therefore excludes inhalers, topical agents and injectable agents.

The MMAS was included in the postal questionnaire completed by patients (see Appendix 5). This self-report questionnaire measures intentional and non-intentional non-adherence to prescribed medications.(272) Non-intentional non-adherence may arise as a result of cognitive impairment or difficulties with literacy. $(275,276)$ Intentional non-adherence occurs when a patient decides not to take prescribed medications, and may be influenced by a number of factors including illness beliefs, perceived risks (e.g. dependence, ADEs) and benefits, the patient-prescriber relationship, physical and mental illnesses, financial difficulties and issues relating to polypharmacy and medication complexity.(277) The MMAS is scored from 1 to 13 , with those scoring $\geq 11$ considered to be adherent to their medications.(272) The scale has been validated in different countries for conditions such as hypertension and diabetes mellitus. $(278,279)$ For hypertension, it demonstrates good internal consistency and
predictive accuracy for adherence and blood pressure control.(273) Recording both the MPR and MMAS gives both an objective measure of prescription refills (MPR) and a subjective measure of patient adherence to medication (MMAS).

### 3.2.4.9 GP practice

GP practice deprivation index was estimated based on the electoral division approach (location of the practice) as previously described in Section 3.1.5.2.

### 3.2.5 Process of data collection

Baseline GP record review data collection was carried out by eight RCSI medical students who completed a three-day training course before commencing data collection and used standardised data collection forms.(224) (See Appendix 7). All follow-up GP record review data collection was conducted by Dr Emma Wallace, the PhD candidate, who is a GP.

For baseline ADE data collection (July 2010-January 2011), three research nurses who completed a one-day training course and used a standardised interview template, conducted interviews.(224) This template included sample text for interview questions and interviewers were asked to record patient responses verbatim (see Appendix 7). Identical training and interview templates were provided for the follow-up ADE interviews, which were conducted by a research nurse and a health psychologist. The interviewers were blinded to the study hypothesis and the STOPP and Beers 2012 criteria. Follow-up ADE interviews were conducted between November 2012 and June 2013.

### 3.2.6 Management of data

All follow-up data was entered into Microsoft Access using the same template as utilised for baseline data input. Data was thoroughly checked and cleaned using a number of queries developed within Microsoft Access designed to detect erroneous, duplicate or missing data. Any data errors were double-checked against the original hard copies and corrected, where necessary. A random sample of $10 \%$ of all patient data was double-checked against the original hard copy postal questionnaires, GP
medical record data collection forms and ADE interview records.(224) Medical conditions recorded from the GP medical record review were coded according to ICPC2.(280) Patients with missing data across any of the three outcomes of interest, the confounder variables or the exposure of interest were excluded from data analysis.

### 3.2.7 Statistical analysis

The approach used for statistical analysis depended on the specific research question, so detailed statistical methods for each study are presented in the methods section of Chapter 4, Chapter 5 and Chapter 6. In Chapter 4, descriptive statistics are presented for all studies and Poisson, linear and logistic regression models were used to investigate the longitudinal association of PIP and adverse health outcomes (ADEs, HRQOL and emergency hospital attendance). In Chapters 5, diagnostic test accuracy (discrimination) analysis was conducted to examine the predictive accuracy of different count measures of multimorbidity and vulnerability for the outcomes of emergency admission and functional decline. A similar statistical approach (discrimination and calibration) was used to externally validate the Pra score in predicting future emergency admission in Chapter 6.

### 3.2.8 Risk of bias

The Cochrane methodological checklist for non-randomised studies was utilised to assess the methodological quality of the prospective cohort.(281) This consists of eight criteria including: selection of exposed and non-exposed study participants; exposure assessment; assessment and matching of prognostic variables; outcome assessment; and losses to follow-up. In addition, the Bradford-Hill criteria were applied to explore the various issues around establishing causality in observational research, for example, temporal relationship, strength of the observed association, plausibility, and consideration of alternate hypotheses.(282)

Chapter 4 Investigating the longitudinal association of PIP, as defined by STOPP and Beers 2012, with adverse health outcomes in older community-dwelling people

### 4.1 Introduction

According to a recent systematic review, it is estimated that approximately one in five of all prescriptions issued in primary care are potentially inappropriate.(283) This is despite increased interest in and recognition of the potential harms associated with prescribed medications. However, the extent to which existing explicit prescribing measures, such as the STOPP criteria and updated Beers 2012 criteria are associated with adverse health outcomes for older people remains unclear due largely to a limited and conflicting evidence base, particularly in relation to longitudinal data.

### 4.1.1 PIP and ADEs

As described in section 2.2.7, ADEs are an important cause of morbidity and healthcare utilisation in older people. An 11-year US analysis reported that there were over 4.3 million ADE-related OPD visits annually and more than 107,000 emergency admissions.(18) Increasing age, female gender and increasing number of medications were found to be associated with ADEs.(18) In a large-scale Australian retrospective cohort study of older people ( $n=28,548$, aged $\geq 65$ years) between 1980-2000, a total of $17.7 \%$ had a repeat emergency admission for an ADE.(149) Interestingly, this study found age not to be a predictor of ADE with this outcome largely driven by increasing comorbidity.

A systematic review has reported an ADE-admission rate of $10.7 \%$ in older people, with higher rates of ADEs reported in studies using both patient interview and medical record review rather than medical record review alone.(19) Another systematic review of studies set in acute care reported that the median prevalence of ADEs leading to hospital admission was $10.0 \%$ ( $95 \%$ confidence interval (CI) $7.2 \%, 12.8 \%$ ) with variation in the overall ADE prevalence, from $5.8 \%$ to $46.3 \%$.(284) Female sex, increased comorbidity, and increased number of medications were significantly associated with an increased risk of an ADE. Overall, studies with a retrospective design reported lower ADE prevalence rates. Critically, many of these events are believed to be avoidable. Four studies, conducted across different countries in Europe and North America, assessed the perceived 'preventability' of studied ADEs and reported that between 27\%
and $54 \%$ were considered preventable by an expert panel. $(20,87,230,285)$ In addition, many ADEs were judged to be at the more serious end of the severity scale, with between $35 \%$ and $46 \%$ categorised as serious, life-threatening or fatal. $(20,87,285)$

The role of PIP in predicting future ADEs is unclear due to limited research in this area, which is made more challenging by the many different explicit measures of PIP available. Table 4-1 and Table 4-2 summarise studies conducted to date investigating PIP and ADEs in the community and hospital settings.

Table 4-1: Studies conducted in the community setting of PIP and outcome of ADE
$\left.\begin{array}{lllllll}\hline \begin{array}{l}\text { Author, } \\ \text { Year }\end{array} & \begin{array}{l}\text { Country, setting, study } \\ \text { type }\end{array} & \begin{array}{l}\text { Study } \\ \text { participants } \\ \text { (N, age) }\end{array} & & \text { Prevalence PIP } & \text { Prevalence ADE } & \text { Adjusted Odds ratio (OR) } \\ \text { (95\% CI) }\end{array}\right]$

Table 4-2: Studies conducted in the emergency department or inpatient setting of PIP and outcome ADE

| Author, Year | Country, setting, study type | Study participants | Prevalence PIP | Prevalence ADE | $\geq 1$ PIP adjusted OR (95\% CI) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Tostato, 2014(290) | Italy, inpatient, seven hospitals | $\mathrm{N}=871,$ <br> $\geq 65$ years | 50.4\% STOPP criteria; 58.4\% applying Beers criteria | $\mathrm{N}=37$ (4.2\%) | $\begin{aligned} & \geq 2 \text { STOPP: } 2.36(1.10,5.06) \\ & \geq 2 \text { Beers: } 2.15(0.90,5.14) \end{aligned}$ |
| $\begin{aligned} & \text { Dormann } \\ & \text { 2013(194) } \end{aligned}$ | Germany, one A\&E, prospective cohort | $\mathrm{N}=351,$ <br> $\geq 65$ years | $16.6 \% \geq 1$ PIP, PRISCUS | 21.2\%, medical record review | 1.99 (1.23, 3.52) |
| Hamilton, 2011(111) | Ireland, one A\&E, prospective cohort (four-month follow-up) | $\mathrm{N}=600,$ <br> $\geq 65$ years | 56.2\% $\geq 1$ PIP, STOPP criteria; 28.8\% $\geq 1$ PIP, 2003 Beers | 26.3\%, medical record review | STOPP; 1.85 (1.51, 2.26) <br> Beers; 1.28 (0.95, 1.72) |
| $\begin{aligned} & \text { Corsonello } \\ & \text { 2009(120) } \end{aligned}$ | Italy, inpatients in 11 acute hospital wards and three long term care and rehabilitation units, prospective cohort (oneyear follow-up) | $\mathrm{N}=506,$ <br> $\geq 65$ years | 20.6\% $\geq 1$ PIP, 2003 Beers | 16.3\% | Not significantly associated, ORs not presented |
| Laroche 2007(291) | France, inpatients in one hospital | $\mathrm{N}=2,018$ <br> $\geq 70$ years | 66\% $\geq 1$ PIP, 1997 Beers | 19.1\%, medical record review | 1.0 (0.8, 1.13) |
| Onder 2005(109) | Italy, inpatients in 81 hospitals, Retrospective cohort | $\mathrm{N}=5,152$ <br> $\geq 65$ years | 28.6\%, 2003 Beers | 4.6\%, medical record review | 1.2 (0.89, 1.61) |
| $\begin{aligned} & \text { Passarelli } \\ & \text { 2005(292) } \end{aligned}$ | Brazil, inpatients in one hospital, prospective during inpatient hospital stay | $\mathrm{N}=186,$ <br> $\geq 60$ years | $24 \%$ of those with ADE prescribed $\geq 1$ PIP, overall prevalence PIP in study sample not recorded | 62\%, medical record review | 2.32 (1.17, 4.59) |

### 4.1.2 PIP and other health outcomes (mortality, healthcare utilisation and healthrelated quality of life)

### 4.1.2.1 PIP and mortality

Several studies have examined the association between PIP and healthcare utilisation and/or mortality. A large-scale population based cross-sectional analysis of 1.8 million older US adults, which defined PIP using the Healthcare Effectiveness Data and Information Set (HEDIS) tool, reported an annual prevalence of acquiring at least one new PIP of 5.2\%.(293) In multivariate analysis PIP was associated with an increased risk of mortality (one PIP: adjusted odds ratio (OR)=1.62 (95\% CI 1.56, 1.68); $\geq 1$ PIP: adjusted OR=1.80, (95\% CI 1.45, 2.23)) and an increased risk of hospital admission (1 PIP: adjusted OR 2.31, 95\% CI 2.22, 2.40; $\geq 1$ PIP: adjusted OR $3.4495 \%$ CI $3.06,3.87$ ).(293) A Scottish study based in primary care $(n=70,299)$ reported a Beers 2003 PIP rate of $31 \%$ and, after adjustment for age, gender and polypharmacy, no increase in mortality was noted for those in receipt of at least one PIP (adjusted OR 0.98, 0.92, 1.05).(294) Similarly, an Italian study of older inpatients ( $n=5,152$ ) reported no increased risk of mortality in patients with PIP as defined by the Beers 2003 criteria (OR $1.05,95 \% \mathrm{Cl} 0.75,1.48$ ).(220)

### 4.1.2.2 PIP and healthcare utilisation

A US study ( $n=5,077$ cases) examined the association between specific prescribed medications (e.g. warfarin, insulin, anti-platelets) and medications defined as PIP by the HEDIS and Beers 2003 criteria and ADE-related admissions.(107) Four medications/ medication classes were responsible for the majority (67\%) of admissions, namely; warfarin (33.3\%), insulin (13.9\%), oral anti-platelets (13.3\%), and oral hypoglycemic agents (10.7\%). In contrast, PIP medications were implicated in only $1.2 \%(95 \% \mathrm{CI}, 0.7,1.7)$ of admissions.(107) Another US retrospective cohort study of older community-dwelling people ( $n=17,971$ ) used an administrative database to identify Beers 2003 PIP.(295) This
study found that one or more PIP resulted in increased hospital admissions (OR 1.99, 95\% CI $1.76,2.26$ ); increased outpatient visits (OR $1.53,95 \% \mathrm{Cl} 1.43,1.63$ ); increased primary care visits (OR $1.89,95 \% \mathrm{Cl}$ : $1.55,2.30$ ); and increased emergency room visits (OR $1.98,95 \% \mathrm{Cl}$ 1.77, 2.20) compared to no PIP.(295) A Taiwanese study of older ( $\geq 65$ years) patients recruited from one tertiary hospital and prospectively followed up for six months, reported an increased risk of hospital admission in patients receiving at least one PIP defined by the Beers 2003 criteria (Any PIP use; OR 1.62, 95\% CI 1.04, 2.53).(296)

### 4.1.2.3 PIP and other health outcomes

Overall, the evidence base for other health outcomes such as HRQOL is very limited. A systematic review of health outcomes associated with the Beers criteria published in 2007 ( $\mathrm{n}=18$ studies) concluded that, in community settings, evidence regarding quality of life and costs was inconclusive.(113) A US study of older people ( $n=3,234$ ) found no significant association between the Beers drugs to avoid and functional decline and two smaller Italian studies ( $\mathrm{n}=506$ and $\mathrm{n}=364$ respectively) also found no association with impaired physical performance.(16, 50, 120)

### 4.1.3 Clinician characteristics that may contribute to PIP

Clinician characteristics associated with a greater likelihood of PIP include male sex, older age and practicing as a single-handed GP.(297) Other factors that may contribute include the number of prescribers involved in patient care, with the risk of PIP increasing with multiple prescribers.(298) Other factors which may have a role to play include how information is communicated across the primary/secondary care interface regarding changes to prescriptions, the clinician's own knowledge of prescribing and challenges in shared decision making.(258)

### 4.1.4 Summary and study aim

Overall, the evidence in terms of an association between PIP and adverse outcomes is varied. The literature suggests that PIP may be associated with ADEs and increased
healthcare utilisation. However, research in this area has largely focused on the US Beers criteria and community-based studies have had some methodological limitations (e.g. small sample sizes, retrospective cohort study design, variation in adjustment for important confounding variables in statistical models, and use of self-reported medication use).

The aim of this study is to investigate the longitudinal association of two explicit measures of PIP (STOPP criteria and Beers 2012) with ADEs, HRQOL and emergency hospital attendance in a prospective cohort of older ( $\geq 70$ years) community-dwelling people followed up for two years.

### 4.2 Methods

The methods for this prospective cohort study are outlined in Chapter 3. Specific methodological issues for this study and statistical methods are outlined below.

### 4.2.1 Data collection, entry and quality checks

ADE interview and postal questionnaire data were entered into Microsoft Access by two research assistants using a template developed for the purposes of this research project. Dr Emma Wallace inputted all GP medical record review data into Microsoft Access. A total of $10 \%$ of all data was independently double-checked by a second reviewer for errors as part of data quality control checks (Blathin Guinan).

### 4.2.1.1 Exposure: Potentially Inappropriate Prescribing

As outlined in Chapter 3, the STOPP and updated Beers 2012 criteria for PIP were calculated using pharmacy claims data. This followed linkage of each study participant's GMS medical card number to the national HSE-PCRS pharmacy claims database, which contains details of all dispensed medication for those patients with a GMS card. STOPP and Beers 2012 were determined retrospectively using pharmacy claims data for the time period six months prior to the ADE interview date. An identical process was used for the follow-up with PIP criteria calculated six months prior to the ADE interview. For participants who did not complete an

ADE interview but had completed a postal questionnaire, the date of the questionnaire completion was used instead. If linkage to the HSE-PCRS was not possible (e.g. no GMS medical card) then this process was completed manually using the patient's GP medical record to retrieve medication data.

The continuation of PIP over the two-year follow-up was examined using both the STOPP and Beers 2012 criteria. Both measures saw relatively consistent levels of PIP over time and as the research question related to the longitudinal association of PIP with adverse health outcomes, rather than the cross-sectional association, the baseline exposure to PIP was used as the main exposure of interest.

### 4.2.1.2 Primary outcome: ADE

As detailed in Chapter 3, patient interviews were conducted by two trained research assistants (one research nurse and one health psychologist) in order to identify patientreported ADEs that had occurred over the previous six months. In addition, study participants' GP medical records were reviewed to identify any additional ADEs. All patientreported ADEs were then independently reviewed by two academic GPs, blinded to the STOPP and Beers 2012 criteria, who were provided with a list of the patient's medications and medical history. Both GPs independently rated the likelihood of each patient reported ADE being a true ADE on a Likert scale (0-6). Only ADEs where both reviewers rated the ADE as a true ADE ( $\geq 4$ on the Likert scale) were included. In instances where consensus was not reached, a third reviewer (the PhD candidate who is a GP) made the final decision.

Next, all true ADEs were independently reviewed by a different academic GP and academic pharmacist who rated each ADE in terms of severity (mild, moderate or severe/lifethreatening). Both reviewers were provided with guidance notes to help make decisions regarding ADE severity based on the literature in this area (See Appendix 8). Inter-rater reliability was determined for both the initial ADE review and the ADE severity review using
the kappa statistic. In instances where consensus was not reached, a third reviewer (the PhD candidate who is a GP) made the final decision.

### 4.2.1.3 Secondary outcomes: Health related quality of life and emergency hospital attendance

HRQOL was measured using the EQ-5D administered via postal questionnaire as described in Chapter 3. These questionnaires were reviewed before the ADE interview and any missing data was identified and clarified with the patient during the ADE interview thus minimising missing data for this outcome. Emergency hospital attendance was measured from review of the GP medical record where details regarding emergency admissions (number of admissions, date(s), length of stay, reason for admission) were recorded in addition to A\&E visits (number of visits and date(s) of the visit). The date of baseline medical record was recorded and used on a patient basis as the point from which to start the two years prospective data collection.

### 4.2.1.4 C onfounder variables

Potential confounders were determined from the literature prior to statistical analysis and were recorded from the GP medical record (age, gender, comorbidity), by linkage to the HSE-PCRS pharmacy claims database (number of drugs, medication possession ratio) and the postal questionnaire (social class, education, deprivation, adherence as per the Morisky scale, vulnerability as per the Vulnerable Elder's Scale, depression as per the Hospital Anxiety and Depression Scale and social support as per the Lubben's social network scale). All confounders included in statistical analysis were measured at baseline.

### 4.2.1.5 Missing data

For the primary outcome of $A D E$, patients with missing data across the exposure, confounders or outcome were excluded. For the secondary outcome of HRQOL, patients with incomplete or missing EQ-5D information were excluded. For the secondary outcome
of emergency hospital attendance, all patients with any prospective data available were included initially and then a subgroup analysis was conducted on those with two full years of data collection available.

### 4.2.2 Statistical methods

### 4.2.2.1 Primaryoutcome ADE

Descriptive statistics were calculated for the number of participants experiencing an ADE in the six-month outcome period, the types of ADEs recorded according to physiological system (e.g. cardiovascular, urogenital), the name of the medication responsible and the ATC code of the medication's drug class. In addition, the severity of reported ADEs were summarised according to severity (mild, moderate or severe/life-threatening). As the majority of study participants had also completed a baseline ADE interview (which followed an identical process to the follow-up interview), the persistence in ADE from baseline to follow-up was investigated and descriptive statistics presented in terms of the number of patients who never reported an ADE, those whose number of ADEs remained similar or unchanged over time and those who had gained or lost an ADE at follow-up compared to baseline. In addition, GP records were reviewed to identify any ADE related emergency admissions or A\&E visits for the study cohort over the same six month outcome measurement period.

Spearman's rank correlation coefficient and chi-squared statistics were used to examine the association between exposure to PIP at baseline (three levels no PIP, one PIP, $\geq 2$ PIP) and each of the confounding variables. The number and percentage of participants with at least one ADE at follow-up in relation to level of PIP and each predictor variable was presented. Random intercept models, which treat practices as a random variable rather than as a fixed effect, were used for all analyses to allow for clustering of patients within different practices. Multivariable two-level (patient and GP levels) regression models were used to examine how the presence of at least one ADE (binary outcome: 0 ADE vs. $\geq 1$ ADE) at
follow-up varied by exposure to PIP at baseline (three levels of PIP: no PIP, one PIP, $\geq 2$ PIP) with adjustment for potential confounders.

A confounder was defined as "an unobserved exposure associated with the exposure of interest and also a potential cause of the outcome of interest".(299) Confounder variables needed to meet three specific requirements; (See Figure 4-1)

- be a risk factor for the outcome (ADE)
- be associated with the exposure (PIP)
- not be an intermediate step in the causal pathway between PIP and ADE


Figure 4-1: Confounding variable

For the primary outcome of $A D E$, on reviewing the literature, the following variables met the criteria for confounding and were adjusted for in the final analysis: age, gender, deprivation, social class, education, number of drugs, comorbidity and medication adherence. $(18,68,129,149,300)$ Categorical variables were gender (male/female), social class (unskilled/skilled), education (basic/upper and post-secondary), adherence (MPR $<50 \%$, MPR $\geq 50 \%,<80 \%$, MPR $\geq 80 \%$ ) and comorbidity (Charlson index score=0, Charlson index score $\geq 1$ ). Age, deprivation and number of medication classes were continuous variables. Based on the literature in this area, patient-reported baseline ADE was considered to be an intermediate step on the causal pathway between PIP at baseline and

ADE at follow-up, and therefore was not included as a confounder in the data analysis.(18, 129)

A multilevel logistic regression model was used to simultaneously adjust for all confounders. Unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cl}$ ) and p-values were reported. The continuous variables age and deprivation were centred around their means in all models to reduce collinearity and aid interpretation.(301) In addition, a multilevel Poisson model was used to investigate the association between the number of ADEs at follow-up (count of ADEs per patient) and exposure to PIP at baseline. To account for over dispersion in the count data (where the variance is greater than that implied by the mean) three level random intercept models were used, with an additional random intercept included at the patient level for over dispersion. The number of ADEs was capped at eight due to very low numbers of patients reporting more than eight ADEs. Multilevel unadjusted and adjusted incidence rate ratios (IRRs) $(95 \% \mathrm{Cl}, \mathrm{p}$-value) were calculated accounting for confounding variables. For all adjusted models the potential for collinearity was assessed by examining the correlations of the estimated coefficients between the predictor variables.

### 4.2.2.2 Secondary outcome: HRQOL

Descriptive statistics (medians, range, numbers and proportion) were presented for the EQ5D utility score and the EQ-5D VAS. Spearman's rank correlation coefficient and chi-squared statistics were used to examine the association between exposure to PIP at baseline and the confounding variables. For this outcome of interest on reviewing the literature the following variables met the criteria for confounding: age, gender, deprivation, education, social class, number of drugs, comorbidity, medication adherence, vulnerability, social support and depression/anxiety. $(34,39,137)$ Baseline EQ-5D was not included as a confounder as it was considered to be on the causal pathway between PIP and future HRQOL.

Multilevel linear regression was used to examine how the EQ-5D utility score at follow-up varied by exposure to three levels of PIP at baseline (no PIP, one PIP, $\geq 2$ PIP) adjusting for confounding variables. Multilevel linear regression with unadjusted and adjusted coefficients is reported. In addition, multilevel linear regression was used to examine the effect of PIP on follow-up EQ-5D VAS scores using the same approach and accounting for the same confounding variables. EQ-5D and EQ-5D VAS were centred on the mean to reduce the potential for collinearity. Although the EQ-5D and EQ-5D VAS were not normally distributed, the residuals in the final model were normally distributed and so the fit of the model was deemed adequate. Individual level residuals in the final adjusted model were examined to ensure they were normally distributed.

### 4.2.2.3 Secondary outcome: emergency hospital attendance

Emergency hospital attendance was examined in relation to at least one A\&E visit in the two year follow-up period and in relation to at least one emergency admission and the number of emergency admissions in the same time period. Spearman's rank correlation coefficient and the chi-squared statistic were used to examine the association between exposure to PIP at baseline ( $0,1, \geq 2$ PIP) and each of the confounding variables. For this outcome the following variables met the criteria for confounding; age, gender, deprivation, social class, education, adherence, vulnerability, social support, depression/anxiety and previous emergency attendance (either A\&E visit or emergency admission). Emergency attendance was included as a confounder in this analysis as the literature in this area clearly shows that prior healthcare utilisation is a primary driver for future use of health services including A\&E visits and emergency admission. $(48,303)$

For the outcome of at least one A\&E visit (binary outcome: 0 vs. $\geq 1$ A\&E visit), a multilevel logistic regression model was used to report unadjusted and adjusted odds ratios (95\% CI, p value) for this outcome by exposure to baseline PIP (categorised as no PIP, one PIP and $\geq P I P)$ accounting for confounding variables. The number of $A \& E$ visits was not modeled due to the small number of patients experiencing multiple A\&E visits over the follow-up period.

A multilevel logistic model adjusting for the same confounding variables was used to investigate the effect of PIP on having at least one emergency admission over the follow-up period. In addition, a three-level Poisson model (accounting for over dispersion in the count data) was used to examine the association between the number of emergency admissions (count of emergency admissions) during follow-up and the different levels of PIP at baseline. The number of emergency admissions was capped at three for this analysis due to the very small number of patients who were admitted more than three times over the follow-up period. Multilevel unadjusted and adjusted IRR ( $95 \% \mathrm{CI}, \mathrm{p}$ value) are presented, adjusting for confounding variables. The differing lengths of follow-up time were accounted for in these analyses by setting the log of the follow-up time in proportion of years as the offset/intercept term in the models.

### 4.2.2.4 Statistical model assumptions

All statistical models accounted for clustering. The null hypothesis (no between-practice variation) was tested using an empty model (no predictors or clustering accounted for) versus a model which accounted for clustering and the resulting likelihood ratio statistic suggested significant between-practice variation. All models were also checked for multicollinearity by examining the correlations between the estimated coefficients in the final adjusted model. Interactions between PIP and confounding variables were not identified in the literature search a priori so these were not included in the analyses. For the Poisson regression models over dispersion (variance greater than the mean) was examined using the alpha statistic. The alpha statistic is the Stata test statistic for testing for over dispersion in the data. If this statistic was significantly different from zero in the adjusted model then over dispersion was accounted for using an additional random intercept.

### 4.2.2.5 Statistical software package

All descriptive statistics and multilevel modeling presented was completed using Stata (Version 13).(StataCorp, Texas, US) The 'xtmelogit' command was used for logistic regression models, the 'xtmixed' command for linear regression models and the 'xtmepoisson' command for Poisson regression models. The STOPP and Beers 2012 PIP criteria were applied to the HSE-PCRS database using SAS Version 9.1/9.2 by Dr. Caitriona Cahir and Frank Moriarty at baseline and by Dr. Kathleen Bennett at follow-up.

### 4.3 Results

### 4.3.1 Study participants

### 4.3.1.1 Postal questionnaire and ADE telephone interview

A total of 904 patients completed a baseline postal questionnaire and had a corresponding GP medical record review carried out by the research team in 2010. These patients were assessed regarding eligibility for follow-up. Participants were first considered regarding eligibility for the postal patient questionnaire and ADE interview section of the study. A flow diagram is presented below outlining study participants at each stage (See Figure 4-2). Of 904 eligible participants, a total of 113 patients were excluded by their GP as they met one or more of the exclusion criteria detailed in the cohort methods section in Chapter 3.

Of 904 patients:

- 50 had died
- 16 had moved GP practice
- 12 were cognitively impaired
- 14 had moved to a nursing home
- 9 were receiving palliative care
- 7 were too unwell to participate
- 2 had experienced a recent (<1 month) bereavement
- 1 was a long term inpatient in hospital
- 1 was now blind
- 1 was experiencing a current psychotic episode

This resulted in a total of 791 participants eligible for the postal questionnaire and ADE interviews. A total of 791 questionnaires were posted using the headed paper of the patient's GP practice and co-signed by the participant's GP and Dr Emma Wallace to maximise response rate. As a reminder each patient was contacted by telephone two weeks later, if the postal questionnaire was not returned within this timeframe. A total of 673 questionnaires were returned representing a response rate of $85 \%$.

Within one month of the postal questionnaire being returned, each participant was contacted regarding the telephone ADE interview component of the study. Of 673 participants contacted by telephone, a total of 605 completed the ADE telephone interview. Of the 68 patients that did not complete the ADE interview the reasons were as follows:

- 46 participants refused
- 15 were not taking any medications
- 3 were too unwell
- 3 were not contactable by telephone
- 1 was recently bereaved

The overall response rate for completion of both the postal questionnaire and ADE interview was 76.5\%.


Figure 4-2: Flow of patients: prospective cohort study (2010-2012)

### 4.3.1.2 G P medical record review

The second part of data collection related to a corresponding review of the GP medical record for each study participant. As all 904 participants had consented at baseline to have their medical record reviewed at follow-up, all were considered eligible for follow-up for this part of the study. Of these 904 patients, there was incomplete two-year data available for 97 participants as a result of the following;

- 53 had died
- 19 had moved GP practice
- 14 had moved into a nursing home
- 9 GP medical record reviews were missing
- 3 were long-term hospital inpatients

Full two-year follow-up GP medical record reviews were therefore completed for 859 study participants (including those who had died in the follow-up period) representing a loss to follow-up rate of 5\%. For statistical analysis purposes, study participants were included if there was a date recorded in their GP medical record indicating when their study follow-up ended, which could be used as a censor date. A total of 16 patients were excluded on this basis; seven had no censor date recorded (five had moved GP practice and two had moved to a nursing home) and nine had missing GP medical record reviews. Therefore, 888 participants could be included in the statistical analysis.

### 4.3.2 GP practices

Fifteen GP practices took part in this study from one province in the Republic of Ireland. A named GP was identified from each practice and nominated as study lead. Study leads were largely male ( $\mathrm{n}=12,80 \%$ ) and the deprivation level in the participating practices was above average (median deprivation 2.95, range 1.04, 4.86).

### 4.3.3 Study participants' socio-demographic characteristics

Of the 605 study participants, 286 (47\%) were male. The mean age was 77 years, median age was 79 (Inter Quartile Range (IQR) 76, 83) and the majority were classified as skilled in terms of social class ( $n=473,78 \%$ ). Patients were largely of White Irish background (97.4\%), with $2.6 \%$ ( $n=16$ ) from another Caucasian background. Table 4-3 presents the sociodemographic and clinical characteristics of the study population.

Table 4-3: Descriptive statistics for baseline ( $n=904$ ) and follow-up ( $n=605$ ) study participants' for primary outcome ADE

|  | Baseline ( $\mathrm{n}=904$ ) | Follow-up ( $\mathrm{n}=605$ ) |
| :---: | :---: | :---: |
|  | Median (IQR) | Median (IQR) |
| Age | $77(74,81)$ | $79(76,83)$ |
| Deprivation | 1.49 (-0.6, 3.1) | 1.36 (-0.64, 2.88) |
| Gender | Number (\%) | Number (\%) |
| Male | 415 (46) | 286 (47) |
| Female | 489 (54) | 319 (53) |
| Marital status~ |  |  |
| Married | 403 (45) | 275 (45) |
| Separated/Divorced | 45 (5) | 29 (5) |
| Widowed | 293 (32) | 199 (33) |
| Never married/single | 162 (18) | 102 (17) |
| Living arrangements ${ }^{\text {I }}$ |  |  |
| Husband/Wife/Partner | 393 (44) | 249 (42) |
| Family/Relatives | 116 (13) | 73 (12) |
| Live alone | 343 (38) | 240 (40) |
| Other | 40 (5) | 33 (6) |
| Education* |  |  |
| Basic education | 555 (61) | 355 (59) |
| Upper and post-secondary | 343 (38) | 247 (41) |
| Social class |  |  |
| Unskilled | 342 (38) | 132 (22) |
| Skilled | 562 (62) | 473 (78) |
| Private Health Insurance (PHI) cover^ |  |  |
| Yes | 509 (56) | 292 (49) |
| No | 395 (44) | 305 (51) |
| Charlson comorbidity weights ${ }^{\text {s }}$ |  |  |
| 0 | 358 (40) | 252 (41) |
| $\geq 1$ | 544 (60) | 353 (59) |

[^0]
### 4.3.4 Exposure to PIP as defined by the STOPP criteria

### 4.3.4.1 Prevalence of PIP as defined by the STOPP criteria

A total of 51 (78\%) of the 65 STOPP criteria were applied. There was inadequate clinical information to apply 14 criteria as detailed in Section 3.1.5.2. At baseline, the prevalence of at least one PIP following application of these STOPP criteria for the full cohort ( $n=904$ ) was $42 \%$. At follow-up, the prevalence of at least one PIP, having applied the same 50 STOPP criteria, was $47 \%$ ( $\mathrm{n}=282$ ). A total of 323 participants ( $53 \%$ ) were not prescribed any PIP, 157 (26\%) were prescribed one PIP and 109 (18\%) were prescribed two or more PIP. Appendix 9 presents the prevalence of each of the 51 STOPP criteria at baseline and at follow-up. The 10 most frequently prescribed STOPP PIP at baseline and follow-up are presented in Table 4-4.

## Table 4-4: The 10 most frequently prescribed PIP indicators as per the STOPP criteria at baseline and follow-up ( $\mathrm{n}=605$ )

## Criteria description Baseline ( $\mathbf{n}=605$ )

PPI for peptic ulcer disease (PUD)* at maximum therapeutic dosage for $>8$ weeks (dose reduction or discontinuation indicated)

Calcium channel blockers with chronic constipation**

Long term use of NSAID (>3 months) for pain relief (simple analgesics preferable)
Aspirin with a past history of PUD* without histamine H2-receptor antagonist or PPI (risk of gastrointestinal (GI) bleeding)

Regular opiates for >2 weeks in those with chronic constipation** without concurrent use of laxatives (risk of severe constipation)

All duplicates: two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors (optimise monotherapy within a single drug class)
$\beta$-adrenoceptor blocker with COPD* (risk of increased bronchospasm)
NSAID with history of PUD* or GI bleeding*, unless concurrent histamine H2-receptor antagonist/PPI/misoprostol (risk of PUD relapse)

Aspirin and warfarin without histamine H 2 -receptor antagonist (except cimetidine) or PPI (high risk of GI bleeding)

Long term (>1 month) long-acting benzodiazepines (risk of prolonged sedation, confusion, impaired balance, falls)

## N (\%) Criteria description Follow-up ( $\mathrm{n}=605$ )

PPI for PUD* at maximum therapeutic dosage for $>8$ weeks (dose
*Medical diagnoses extracted from GP medical record**Patient self-report in ADE interview

### 4.3.4.2 Change in PIP as defined by STOPP between baseline and follow

In addition to comparing individual PIP criteria between baseline and follow-up, the overall prevalence of PIP for study participants included in follow-up ( $n=605$ ) was compared between the two waves. This was to establish if the number of study participants with three levels of PIP (no PIP, one PIP or $\geq 2$ PIP) had changed significantly in the two-year follow-up period. The number of study participants $(n=605)$ with these three levels of PIP at baseline and follow-up is presented in Table 4-5. Overall, the two clinical domains that demonstrate the most change in PIP level were cardiovascular and musculoskeletal. Figure 4-3 presents the change in overall PIP level by STOPP domain. Prevalence of PIP and levels of PIP remained relatively constant between baseline and follow-up. For this reason baseline measurement of PIP and confounding variables were included in the regression models as predictor variables investigating the longitudinal association of PIP with ADEs at follow-up rather than using PIP at follow-up.

Table 4-5: Overall number of PIP as defined by the STOPP criteria at baseline and followup ( $n=605$ )

| Number of PIP | Study participants (n=605) <br> $\mathbf{N}(\%)$ Baseline | Study participants(n=605) <br> $\mathbf{N}(\%)$ Follow-up |
| :--- | :--- | :--- |
| $\mathbf{0}$ | $362(60)$ | $323(53)$ |
| $\mathbf{1}$ | $142(24)$ | $157(26)$ |
| $\mathbf{2}$ | $56(9)$ | $75(13)$ |
| $\mathbf{3}$ | $31(5)$ | $23(4)$ |
| $\mathbf{4}$ | $9(1.3)$ | $11(1.7)$ |
| $\mathbf{5}$ | $1(0.1)$ | $12(1.7)$ |
| $\mathbf{6}$ | $4(0.6)$ | $2(0.3)$ |
| $\mathbf{7}$ | 0 | $2(0.3)$ |



Figure 4-3: Change in PIP level between wave 1 and wave 2 ( $\mathrm{n}=605$ ) by STOPP domain

### 4.3.5 Exposure to potentially inappropriate prescribing as defined by the updated Beers 2012

### 4.3.5.1 Prevalence of PIP as per updated Beers 2012 criteria

A total of 35 (66\%) of the 53 Beers 2012 criteria could be applied to the pharmacy data as detailed in Section 3.1.5.2.(43) At baseline, the prevalence of at least one PIP following application of the Beers 2012 criteria was $29 \%$ ( $n=263$ ) At follow-up, the prevalence of at least one PIP having applied the same Beers criteria to the cohort of 605 , was $26 \%$ ( $n=155$ ). A total of 466 participants (77\%) were not prescribed any PIP, 115 (19\%) were prescribed one PIP and 24 (4\%) were prescribed $\geq 2$ PIP. Table $4-6$ presents the overall prevalence of the Beers 2012 (no PIP, one PIP, $\geq 2$ PIP) criteria at baseline and at follow-up ( $\mathrm{n}=605$ ).

Table 4-6: Change in PIP as defined by the updated 2012 Beers criteria between baseline and follow-up ( $\mathrm{n}=605$ )

| Number of PIP | Study participants baseline | Study participants follow-up |
| :--- | :--- | :--- |
|  | N (\%) | $\mathbf{N}(\%)$ |
| 0 | $450(74)$ | $466(77)$ |
| 1 | $96(16)$ | $115(19)$ |
| $\geq 2$ | $62(10)$ | $24(4)$ |

Appendix 10 presents the prevalence of each of the individual Beers 2012 criteria at baseline and at follow-up ( $\mathrm{n}=34$ ). The 10 most frequently prescribed Beers 2012 PIP at baseline and follow-up are presented in Table 4-7.

Table 4-7: The 10 most frequently prescribed PIP indicators as per the Beers 2012 criteria at baseline and follow-up ( $\mathrm{n}=605$ )

| Criteria description, baseline ( $\mathrm{n}=605$ ) | N (\%) | Criteria description follow-up ( $\mathrm{n}=605$ ) | N (\%) |
| :---: | :---: | :---: | :---: |
| Benzodiazepines | 41 (6.8) | Benzodiazepines | 36 (6.0) |
| Antipsychotics, first and second generation | 31 (5.9) | Non-COX-selective NSAIDs, oral | 31 (5.9) |
| Non-COX-selective NSAIDs, oral | 30 (5.0) | Antipsychotics, first and second generation | 29 (4.8) |
| Tertiary TCAs, alone or in combination | 17 (2.8) | Tertiary TCAs, alone or in combination | 25 (4.1) |
| Digoxin>125mcg | 13 (2.1) | Nifedipine (immediate release) | 10 (1.7) |
| Non-benzodiazepine hypnotics | 8 (1.3) | Non-benzodiazepine hypnotics | 8 (1.3) |
| History of falls or fractures* prescribed listed drug to avoid (see Table 3-2) | 32 (5.3) | History of falls or fractures* prescribed listed drug to avoid (see Table 3-2) | 25 (4.1) |
| Lower urinary tract symptoms, benign prostatic hyperplasia (BPH)* prescribed listed anticholinergic drugs (see Table 3-2) | 13 (2.2) | Chronic constipation** prescribed $\geq 1$ drugs to avoid (see Table 3-2) | 13 (2.2) |
| Chronic kidney disease (CKD)* stages IV and V prescribed NSAIDs or Triamterene | 12 (2.0) | Lower urinary tract symptoms, BPH* prescribed listed anticholinergic drugs (See Table 3-2) | 13 (2.2) |
| Chronic constipation** prescribed $\geq 1$ drugs to avoid (see Table 3-2) | 5 (0.8) | CKD* stages IV and V prescribed NSAIDs or Triamterene | 12 (2.0) |

### 4.3.6 Confounder variables

### 4.3.6.1 Exposure to STOPP PIP: Sakimographics (n=605)

The number and proportion of study participants for each of the confounding variables considered is presented across three levels of STOPP PIP (0 PIP, one PIP, $\geq 2$ PIP) in Table 4-8.

Table 4-8: Study participants by age, gender, socioeconomic status, Charlson morbidity weight, number of prescribed drugs, adherence and ADE reported at baseline by 0,1 and $\geq 2$ STOPP potentially inappropriate prescription indicators at baseline ( $\mathrm{n}=605$ )

|  | PIP at baseline* |  |  |
| :---: | :---: | :---: | :---: |
|  | 0 | 1 | $\geq 2$ |
|  | Median (IQR) | Median (IQR) | Median (IQR) |
| Age at baseline^ | $75(73,79)$ | $76(73,80)$ | $77(74,79)$ |
| Deprivation^ | 1.13 (-1.05, 2.88) | 1.13 (-0.64, 2.88) | 1.75 (-0.09, 2.93) |
| Drug classes at baseline | $4(2,6)$ | $6(5,7)$ | $8(6,10)$ |
| Gender | N (\%) | N(\%) | N(\%) |
| Male | 175 (48) | 73 (51) | 38 (38) |
| Female | 187 (52) | 69 (49) | 63 (62) |
| Social class |  |  |  |
| Unskilled | 77 (21) | 35 (25) | 20 (20) |
| Skilled | 285 (79) | 107 (75) | 81 (80) |
| Education |  |  |  |
| Basic | 209 (58) | 73 (51) | 73 (72) |
| Upper/post-secondary | 151 (42) | 68 (48) | 28 (28) |
| Comorbidity: Charlson weights |  |  |  |
| 0 | 171 (47) | 48 (34) | 33 (33) |
| $\geq 1$ | 191 (53) | 94 (66) | 68 (67) |
| Medication adherence |  |  |  |
| MPR < 50\% | 40 (11) | 8 (6) | 1 (1) |
| MPR $\geq 50 \%$ but <80\% | 76 (21) | 35 (25) | 25 (25) |
| MPR $\geq 80 \%$ | 219 (60) | 97 (68) | 75 (74) |

*PIP was categorised into 3 groups: no PIP, one PIP and $\geq 2$ PIP indicators. This calculation was based on the cumulative frequency distribution of the number of PIP indicators. ${ }^{k}$ Education data was missing for $n=3$. MPR data was missing for $n=37$. ^Age and deprivation were centred.

### 4.3.6.2 Exposure to Beers 2012 PIP: Sedėonographics ( $\mathrm{n}=605$ )

Table 4-9 presents the number and proportion of each of the study participants' confounder variables across three levels of Beers 2012 PIP (no PIP, one PIP, $\geq 2$ PIP).

Table 4-9: Study participants by age, gender, socioeconomic status, Charlson morbidity weight, number of prescribed drugs, adherence with 0,1 and $\geq 2$ Beers 2012 potentially inappropriate prescription indicators ( $\mathrm{n}=605$ )

|  | PIP at baseline* |  |  |
| :---: | :---: | :---: | :---: |
|  | 0 | 1 | $\geq 2$ |
|  | Median (IQR) | Median (IQR) | Median (IQR) |
| Age at baseline^ | $76(73,79)$ | $77(75,80)$ | $77(73,80)$ |
| Deprivation^ | 1.27 (-0.64, 2.88) | 1.58 (-0.80, 2.88) | 1.96 (-0.20, 3.39) |
| Drug classes at baseline | $5(3,7)$ | $7(5,9)$ | $7(5,10)$ |
| Gender | N (\%) | N(\%) | N(\%) |
| Male | 225 (50) | 39 (41) | 22 (47) |
| Female | 225 (50) | 57 (59) | 37 (63) |
| Social class |  |  |  |
| Unskilled | 92 (20) | 23 (24) | 17 (29) |
| Skilled | 358 (80) | 73 (76) | 42 (71) |
| Education |  |  |  |
| Basic | 258 (57) | 52 (54) | 45 (76) |
| Upper and post-secondary | 190 (42) | 43 (45) | 14 (24) |
| Comorbidity: Charlson weights |  |  |  |
| 0 | 194 (43) | 39 (41) | 19 (32) |
| $\geq 1$ | 256 (57) | 57 (59) | 40 (68) |
| Medication adherence |  |  |  |
| MPR < 50\% | 39 (9) | 6 (6) | 4 (7) |
| MPR $\geq 50 \%$ but $<80 \%$ | 94 (21) | 25 (26) | 17 (29) |
| MPR $\geq 80 \%$ | 291 (65) | 63 (66) | 37 (63) |

\$MPR data was missing for 29 study participants

### 4.3.6.3 Comorbidity and number of medications ( $n=605$ )

Table 4-10 presents the number of study participants classified according to two different measures of comorbidity; the RxRisk-V and Charlson comorbidity weights. In addition, the number of medication classes is presented. Charlson comorbidity weights were highly
correlated with the RxRisk-V (spearman's correlation (rs) 0.35, p<0.0001). As a result only one of these measures, the Charlson comorbidity weight, was included in multilevel model analysis as this was most consistent with previous studies. The Charlson comorbidity weight was calculated using data from the participant's GP medical record. In addition, the number of medications was included as a confounder variable in multilevel modelling. This was calculated by linking the participant's GMS medical card number to the national HSE-PCRS pharmacy claims database as described in Chapter 3.

Table 4-10: Number and percentage of participants according to three measures of comorbidity; RxRisk-V, number of medications and Charlson comorbidity weights ( $\mathrm{n}=605$ )

| RxRisk-V number of medical conditions | N (\%) | Number of drug classes | N (\%) | Charlson comorbidity weights | N (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 0 | 8 (1) | 0 | 21 (4) | 0 | 252 (42) |
| 1 | 41 (7) | 1 | 34 (6) | 1 | 152 (25) |
| 2 | 72 (12) | 2 | 61 (10) | 2 | 110 (18) |
| 3 | 101 (17) | 3 | 57 (9) | 3 | 52 (9) |
| 4 | 93 (15) | 4 | 76 (13) | 4 | 20 (3) |
| 5 | 83 (14) | 5 | 66 (11) | 5 | 12 (2) |
| 6 | 71 (12) | 6 | 75 (12) | 6 | 7 (1) |
| 7 | 51 (8) | 7 | 67 (11) |  |  |
| 8 | 39 (6) | 8 | 44 (7) |  |  |
| 9 | 23 (4) | 9 | 40 (7) |  |  |
| $\geq 10$ | 23 (4) | $\geq 10$ | 64 (10) |  |  |

### 4.3.6.4 Medication adherence

Adherence was measured in two ways using; i) the MPR calculated from pharmacy claims data and ii) self-report Morisky scale calculated from the postal questionnaire.

### 4.3.6.4.1 Medication Possession Ratio (MPR) ( $n=567$ )

MPR results were available for 567 study participants ( $n=38$ (6\%) missing) at follow-up. The MPR was calculated from the number of tablets dispensed, and therefore inhalers, topical agents and injectable agents were excluded. For the baseline cohort, overall median MPR was 0.83 (IQR 0.69, 0.91).(224) At follow-up, median adherence was 0.87 (IQR 0.77, 0.94). Adherence across different medication classes varied considerably. Overall, the highest adherence rates were recorded for thyroid agents and anti-Parkinson's agents ( $88 \%$ and 86\% adherent respectively) and the lowest for bone disease agents and antihistamines for systemic use (13\% and 14\% respectively). Table 4-11 presents the number and proportion of patients who were $>80 \%$ adherent, and the mean MPR by ATC drug class at follow-up.

Table 4-11: MPR per ATC drug class and mean MPR for medications as per ATC class at follow-up (n=567)

| ATC | Description | Study <br> participants $\mathbf{N}$ | MPR>80\% <br> $\mathbf{N ( \% )}$ | MPR <br> mean |
| :--- | :--- | :--- | :--- | :--- |
| A02 | Acid related disorders agents | 235 | $163(69)$ | 0.80 |
| A07 | Anti-diarrhoeals, intestinal anti-inflammatory/anti-infective agents | 4 | $3(75)$ | 0.92 |
| A10 | Diabetes agents | 64 | $53(83)$ | 0.89 |
| B01 | Antithrombotic agents | 326 | $258(79)$ | 0.86 |
| B03 | Anti-anaemic agents | 31 | $14(45)$ | 0.66 |
| C01 | Cardiac agents | 80 | $49(61)$ | 0.77 |
| C02 | Anti-hypertensives | 26 | $20(77)$ | 0.84 |
| C03 | Diuretics | 125 | $85(68)$ | 0.77 |
| C04 | Peripheral vasodilators | 4 | $1(25)$ | 0.72 |
| C07 | Beta-blockers | 221 | $179(81)$ | 0.86 |
| C08 | Calcium channel blockers | 190 | $148(78)$ | 0.84 |
| C09 | Renin-angiotensin system agents | 271 | $220(81)$ | 0.86 |
| C10 | Serum lipid reducing agents | 336 | $267(79)$ | 0.86 |
| G03 | Sex hormones and modulators of the genital system | 7 | $7(100)$ | 0.92 |
| G04 | Urological agents | 77 | $49(64)$ | 0.75 |
| H03 | Thyroid agents | 81 | $70(86)$ | 0.90 |
| L02 | Endocrine agents | 5 | $3(60)$ | 0.84 |


| ATC | Description | Study <br> participants $\mathbf{N}$ | MPR $>80 \%$ <br> $\mathbf{N ( \% )}$ | MPR <br> mean |
| :--- | :--- | :--- | :--- | :--- |
| L04 | Immunosuppressive agents | 5 | $3(60)$ | 0.68 |
| M04 | Anti-gout agents | 24 | $17(71)$ | 0.83 |
| M05 | Bone disease agents | 79 | $10(13)$ | 0.19 |
| N02 | Analgesics | 150 | $64(69)$ | 0.67 |
| N03 | Anti-epileptic agents | 35 | $24(69)$ | 0.80 |
| N04 | Anti-Parkinson agents | 8 | $7(88)$ | 0.90 |
| N06 | Psychoanaleptic agents | 74 | $44(59)$ | 0.75 |
| N07 | Other CNS agents | 12 | $6(50)$ | 0.77 |
| R06 | Antihistamines for systemic use | 21 | $3(14)$ | 0.42 |

### 4.3.6.4.2 Morisky scale ( $n=588$ )

Adherence to medications was also assessed by patient self-report using the Morisky scale detailed in Chapter 3. At baseline, the Morisky scale was completed by 603 patients of whom 528 ( $88 \%$ ) reported full adherence to medications, $10 \%$ ( $n=59$ ) medium adherence and $2 \%(n=16)$ low adherence. At follow-up, a total of 588 study participants completed this scale of whom 516 (88\%) reported being fully adherent to their medications, 60 (10\%) reported medium adherence and only 12 (2\%) reported low adherence. The median MPR for patients who reported low adherence was 0.83 (IQR $0.73,0.98$ ), compared to 0.86 (IQR $0.75,0.95$ ) for patients reporting medium adherence and 0.88 (IQR $0.78,0.94$ ) for those reporting full adherence to their medications.

### 4.3.7 Primary outcome ADE

### 4.3.7.1 Descriptive statistics

ADE was measured at baseline by the same outcome measurement as follow-up i.e. telephone interview and GP medical record review for ADEs over a six-month period. Of the 859 baseline study participants who completed an ADE interview, a total of 674 (78\%) participants reported at least one ADE during the outcome period which was classified as an

ADE by independent academic GP review.(224) Overall, 172 (20\%) reported one ADE, 152 (18\%) reported two ADEs, 118 (14\%) reported three ADEs and 232 (27\%) reported $\geq 4$ ADEs. The most commonly reported ADEs were as follows; easy bruising ( $\mathrm{n}=249$ ) and indigestion/heartburn ( $\mathrm{n}=92$ ) due to antithrombotic agents, nocturia ( $\mathrm{n}=147$ ) and urinary frequency ( $n=66$ ) due to diuretics, ankle swelling ( $n=66$ ) due to calcium channel blockers and cough ( $n=62$ ) due to agents acting on the renin-angiotensin system.(224)

At two year follow-up a total of 428 (71\%) of 605 participants reported at least one ADE during the six-month outcome measurement period. An additional 17 participants (2.8\%) had an ADE recorded in their GP medical record during that time period, that was not reported by the participant during interview. Of the 445 (74\%) participants with at least one ADE, 96 (16\%) had one ADE, 94 (16\%) had two, 64 (11\%) had three, 52 (9\%) had four, 38 (6\%) had five, 27 (5\%) had six and 74 (12\%) had seven or more ADEs. The median number of ADEs was 2 (IQR 0, 4).Thirty percent of patient-reported symptoms were established as an ADE when reviewed independently by two academic GPs. The inter-rater agreement was 94\% and the kappa statistic was 0.87 ( $95 \% \mathrm{Cl} 0.85,0.90$ ). The vast majority ( $\mathrm{n}=424,95.2 \%$ ) of ADEs were rated as mild in terms of severity, according to independent blinded review by an academic GP and an academic pharmacist. Inter-rater agreement between these two reviewers was lower at $84 \%$. The remainder of ADEs were rated as moderate severity ( $\mathrm{n}=11$, $2.5 \%$ ) and severe or life threatening ( $n=10,2.3 \%$ ). Of 10 severe ADEs, nine resulted in emergency hospital admission. No recorded ADE resulted in death. The main medication classes associated with ADEs and the main adverse effects reported by patients are presented in Table 4-12.

Table 4-12: Main medication classes (frequency of patients with ADE $\mathbf{\geq 5 \%}$ ) associated with ADEs and the main adverse effects reported

| Medication class (ATC code) | Patients with $\geq 1$ associated ADE N(\%) | Total number of ADEs <br> N (\%) | Main medications associated with ADEs | Patients prescribed this medication reporting ADE N (\%) | Adverse effects for this medication class | N (\%), of this medication class |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Antithrombotic agents (B01) | 243 (41) | 378 (19) | Aspirin | 188 (77) | Bruise easily | 191 (51) |
|  |  |  | Warfarin | 52 (21) | Difficulty stopping a small cut bleeding | 73 (19) |
|  |  |  |  |  | Indigestion/heartburn | 59 (16) |
| Diuretics (CO3) | 162 (27) | 371 (18) | Bendroflumethiazide | 73 (45) | Up at night passing urine | 124 (38) |
|  |  |  | Frusemide | 66 (41) | Passing urine more/less often | 79 (24) |
|  |  |  |  |  | Dry mouth | 49 (15) |
|  |  |  |  |  | Dizziness | 36 (11) |
| Beta-blockers (CO7) | 145 (24) | 307 (15) | Bisoprolol | 86 (59) | Fatigue | 57 (19) |
|  |  |  | Atenolol | 19 (13) | Cold hands or feet | 56 (18) |
|  |  |  | Metoprolol | 14 (10) | Dizziness | 41 (13) |
|  |  |  |  |  | Fingers painful | 35 (11) |


| Medication class (ATC code) | Patients with $\geq 1$ associated ADE N (\%) | Total number of ADEs <br> N(\%) | Main medications associated with ADEs | Patients prescribed this medication reporting ADE N (\%) | Adverse effects for this medication class | N (\%), of this medication class |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Calcium channel blockers (C08) | 94 (16) | 131 (6) | Amlodipine | 56 (60) | Ankle swelling | 61 (47) |
|  |  |  | Lercanidipine | 18 (19) | Dizziness | 24 (18) |
|  |  |  |  |  | Constipation | 20 (15) |
| Lipid modifying agents (C10) | 93 (15) | 110 (5) | Atorvastatin | 60 (65) | Muscle pain or weakness | 67 (61) |
|  |  |  | Rouvastatin | 13 (14) | Pain in lower legs | 38 (35) |
|  |  |  | Pravastatin | 7 (8) |  |  |
|  |  |  | Simvastatin | 6 (7) |  |  |
| Psycholeptics (N05) | 79 (13) | 137 (7\%) | Non benzodiazepine hypnotics | 31 (39) | Sleepier than usual | 36 (26) |
|  |  |  | Benzodiazepines used as hypnotics | 31 (39) | Fatigue | 22 (16) |
|  |  |  | Benzodiazepines used as anxiolytics | 13 (17) | Dizziness | 16 (12) |
|  |  |  |  |  | Sleeping longer and heavier | 15 (11) |
|  |  |  |  |  | Unsteady on feet | 13 (13) |
| Agents acting on the | 77 (13) | 91 (4\%) | Perindopril | 19 (25) | Cough | 44 (48) |


| Medication class (ATC code) | Patients with $\geq 1$ associated ADE N (\%) | Total number of ADEs N (\%) | Main medications associated with ADEs | Patients prescribed this medication reporting ADE N (\%) | Adverse effects for this medication class | N (\%), of this medication class |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| renin-angiotensin system (C09) |  |  |  |  |  |  |
| Analgesics (NO2) | 62 (10) | 132 (6\%) | Ramipril | 16 (21) | Dizziness | 32 (35) |
|  |  |  | Lisinopril | 8 (10) |  |  |
|  |  |  | Codeine phosphate preparations | 34 (55) | Constipation | 34 (26) |
|  |  |  | Tramadol | 13 (21) | Dizziness | 19 (14) |
|  |  |  | Buprenorphine | 7 (11) | Dry mouth | 13 (10) |
| Anti-inflammatory and anti-rheumatic agents (M01) |  |  |  |  | Sleepier more than usual | 13 (10) |
|  | 34 (6) | 43 (2\%) | Diclofenac | 18 (53) | Indigestion | 20 (47) |
|  |  |  | Ibuprofen | 10 (29) | Flatulence | 8 (19) |
| Psychoaneleptics (N06) | 33 (5) | 70 (3\%) | Antidepressants | 19 (58) | Dry mouth | 9 (13) |
|  |  |  | Amitriptyline | 12 (36) | Sleepier more than usual | 8 (11) |
|  |  |  |  |  | Dizziness | 6 (9) |
|  |  |  |  |  | Constipation | 5 (7) |


| Medication class (ATC code) | Patients with $\geq 1$ associated ADE N (\%) | Total number of ADEs <br> N (\%) | Main medications associated with ADEs | Patients prescribed this medication reporting ADE N (\%) | Adverse effects for this medication class | N (\%), of this medication class |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Urological agents (G04) |  |  |  |  | Change in sexual interest/desire | 5 (7) |
|  | 30 (5) | 41 (2\%) | Tamsulosin | 10 (33) | Erection difficulties | 17 (41) |
|  |  |  | Finasteride | 8 (27) | Dry mouth | 11 (27) |
|  |  |  |  |  | Change in sexual interest/desire | 9 (22) |

### 4.3.7.2 Persistence in patient reported ADEs between baseline and follpw ( $\mathrm{n}=591$ )

Of 591 patients who completed a baseline and follow-up ADE interview, a total of 465 (78\%) reported at least one ADE at baseline. At follow-up, 379 (82\%) participants from this group reported at least one ADE. A total of 72 (12\%) patients reported no ADE at baseline or follow-up, while 54 (9\%) patients who had no ADE at baseline reported at least one ADE at follow-up. Eighty-six participants (15\%) who had reported at least one ADE at baseline did not report any ADE at follow-up.

### 4.3.8 Multilevel logistic regression for effect of STOPP PIP on presence of at least one ADE at follow-up ( $\mathrm{n}=605$ )

Table 4-13 presents the number of participants with at least one ADE at follow-up across three levels of STOPP PIP exposure and for confounding variables. It also presents the unadjusted and adjusted analysis for the association of PIP at baseline with $\geq 1$ ADE at follow-up, accounting for confounding variables. In unadjusted analysis, $\geq 2$ STOPP PIP was associated with $\geq 1$ ADE at follow-up; unadjusted OR 5.11 ( $95 \% \mathrm{Cl}$ $2.48,10.56$ ), $\mathrm{p}<0.001$. However, following adjustment for confounding variables, $\geq 2$ STOPP PIP was not associated $\geq 1$ ADE at follow-up; adjusted OR 2.06 ( $95 \% \mathrm{CI} 0.91$, 4.66), $\mathrm{p}=0.08$. Number of drug classes and comorbidity were both independently associated with this outcome.

Table 4-13: Number and percentage of patients in a multilevel logistic regression model with unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cls}, \mathrm{p}$-value) for patients with $\geq 1$ ADE* at follow-up by exposure to STOPP PIP and patient level confounding variables measured at baseline ( $\mathrm{n}=605$ )

|  | N(\%) or <br> Patient <br> characteristics |  |  | Total <br> (N) |
| :--- | :--- | :--- | :--- | :--- |
|  | with $\geq 1$ <br> ADE | Unadjusted OR | Adjusted OR |  |
| (95\% CI), p value | (95\% CI), p value |  |  |  |


| Primary outcome |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| PIP at baseline |  | N (\%) |  |  |
| 0 | 362 | 243 (55) | 1 | 1 |
| 1 | 142 | 110 (25) | 1.60 (0.99, 2.59), p=0.06 | 0.97 (0.56, 1.68), p=0.92 |
| $\geq 2$ | 101 | 91 (20) | 5.11 (2.48, 10.56), p<0.001 | 2.06 (0.91, 4.66), p=0.08 |
| Confounding variables |  |  |  |  |
| Median (IQR) |  |  |  |  |
| Age (baseline) | 605 | $76(73,80)$ | 1.05 (1.01,1.10), p=0.03 | 1.03 (0.98 1.08), p=0.28 |
| Deprivation | 605 | $\begin{aligned} & 1.36 \text { (-0.64, } \\ & 2.88) \end{aligned}$ | 0.92 (0.84, 1.01), p=0.07 | 0.91 (0.82, 1.01), p=0.09 |
| Baseline drug classes | 605 | $6(4,8)$ | 1.33 (1.23, 1.44), p<0.001 | $\begin{aligned} & 1.25 \text { (1.13, 1.39), } \\ & \mathrm{p}<0.001 \end{aligned}$ |
| Gender |  | N (\%) |  |  |
| Male | 286 | 207 (47) | 1 | 1 |
| Female | 319 | 237 (53) | 1.12 (0.76, 1.65), p=0.56 | 0.95 (0.61, 1.50), p=0.84 |
| Social Class |  |  |  |  |
| Unskilled | 132 | 99 (22) | 1 | 1 |
| Skilled | 473 | 345 (78) | 0.86 (0.53, 1.40), p=0.55 | 0.93 (0.53, 1.61), $\mathrm{p}=0.80$ |
| Education |  |  |  |  |
| Basic | 355 | 265 (60) | 1 | 1 |
| Upper/postsecondary | 247 | 177 (40) | 0.83 (0.54, 1.26), p=0.38 | 0.96 (0.58, 1.57), p=0.86 |
| Comorbidity: Charlson weights |  |  |  |  |
| 0 | 252 | 159 (36) | 1 | 1 |
| $\geq 1$ | 353 | 285 (64) | 2.77 (1.86, 4.15), p<0.001 | 1.97 (1.24, 3.14), p=0.004 |
| Medication adherence |  |  |  |  |
| MPR < 50\% | 49 | 33 (7) | 1 | 1 |
| MPR $\leq 50 \%$ but <80\% | 136 | 92 (21) | 1.03 (0.47, 2.17), p=0.94 | 0.49 (0.21, 1.13), p=0.09 |
| MPR $\geq 80 \%$ | 391 | 305 (69) | 1.57 (0.79, 3.12), p=0.20 | 0.81 (0.37, 1.73), p=0.58 |

*ADE report was measured by patient interview and review of GP medical record. ${ }^{\text { }}$ MPR data is missing for 29 participants.

### 4.3.9 Multilevel Poisson regression for increasing number of ADEs at follow-up ( $\mathrm{n}=605$ )

In addition to examining the association of PIP, as defined by STOPP, with future ADEs, the effect of PIP on increasing numbers of ADEs at follow-up was also examined, using a multilevel Poisson regression model. In this model PIP at three levels (no PIP, one PIP, $\geq 2$ PIP) was the exposure variable and ADE count at follow-up the outcome of interest, with adjustment for relevant confounders.

Table 4-14 presents the results of the unadjusted and adjusted analyses, taking account of patient level confounding variables. In unadjusted analysis, $\geq 2$ STOPP PIP was associated with increasing numbers of ADEs at follow-up (unadjusted IRR 2.27 ( $95 \% \mathrm{Cl} 1.83,2.81$ ), $\mathrm{p}<0.001$ ) compared to no PIP and, although this association diminished with adjustment for confounders (adjusted IRR 1.29 ( $95 \% \mathrm{Cl} 1.03,1.60$ ), $\mathrm{p}=0.03$ ), it still remained significant. Number of drug classes, comorbidity and deprivation were also all independently associated with this outcome.

Table 4-14: Multilevel Poisson regression model with unadjusted and adjusted incidence rate ratios ( $95 \% \mathrm{Cls}$, p -value) for number of ADEs by exposure to STOPP PIP at baseline" and patient level confounding variables at baseline ( $n=605$ )

| Patient characteristics | Unadjusted Incidence Rate Ratio <br> (IRR) $(95 \% \mathrm{CI}), \mathrm{p}$-value | Adjusted IRR <br> (95\% CI), p-value |
| :--- | :--- | :--- |

Primary outcome
PIP at baseline
0 1

| 1 | $1.15(0.94,1.41), \mathrm{p}=0.18$ | $0.85(0.70,1.03), \mathrm{p}=0.09$ |
| :--- | :--- | :--- |
| $>2$ | $2.27(1.83,2.81), \mathrm{p}<0.001$ | $1.29(1.03,1.60), \mathrm{p}=0.03$ |

Adjusted for confounding variables

| Age at baseline | 1.02 (1.00, 1.04), p=0.05 | 1.00 (0.99, 1.02), p=0.61 |
| :---: | :---: | :---: |
| Gender |  |  |
| Male | 1 | 1 |
| Female | 1.11 (0.93, 1.32), p=0.25 | 0.99 (0.84, 1.16), p=0.88 |
| Social Class |  |  |
| Unskilled | 1 | 1 |
| Skilled | 0.92 (0.74, 1.14), p=0.46 | 0.96 (0.79, 1.16) p=0.65 |
| Deprivation | 0.96 (0.92, 1.00), p=0.04 | 0.95 (0.92, 0.99), p=0.02 |
| Education |  |  |
| Basic | 1 | 1 |
| Upper/post-secondary | 0.90 (0.74, 1.09), p=0.27 | 1.00 (0.84, 1.19), p=0.99 |
| Comorbidity: Charlson weights |  |  |
| 0 | 1 | 1 |
| $\geq 1$ | 1.61 (1.35, 1.93), p<0.001 | 1.23 (1.04, 1.46), $\mathrm{p}=0.02$ |
| Baseline drug classes | 1.16 (1.13, 1.18), p<0.001 | 1.13 (1.10, 1.66), $\mathrm{p}=<0.001$ |
| Medication adherence |  |  |
| MPR < 50\% | 1 |  |
| MPR $\leq 50 \%$ but $<80 \%$ | 1.06 (0.74, 1.50), p=0.84 | 0.75 (0.55, 1.04), $\mathrm{p}=0.09$ |
| MPR $\geq 80 \%$ | 1.42 (1.04, 1.95), p=0.30 | 0.92 (0.68, 1.23), p=0.60 |

\#Exposure to PIP was at baseline. Age and deprivation are centred. \#\# ADE was at follow-up. ${ }^{\text {§ }}$ MPR is missing for $n=29$. Over dispersion (patient level) was accounted for by an additional random effect.

### 4.3.10 Multilevel logistic regression to examine the effect of PIP as defined by the Beers $\mathbf{2 0 1 2}$ criteria on presence of ADE at follow-up ( $\mathrm{n}=605$ )

Identical analyses adjusting for the same confounders were the conducted using the Beers PIP (no PIP, one PIP, $\geq 2$ PIP) as the exposure of interest and ADE as the outcome of interest. In unadjusted analysis, $\geq 1$ Beers 2012 PIP was not associated with $\geq 1$ ADE (one Beers PIP: unadjusted OR 1.77 ( $95 \% \mathrm{Cl} 1.01,3.10$ ), p=0.05; $\geq 2$ Beers PIP: unadjusted OR 1.71 ( $95 \% \mathrm{Cl} 0.84,3.49$ ), $\mathrm{p}=0.147$ ) compared to no Beers PIP. This remained the case after adjustment for age, gender, socioeconomic status, number of drugs, comorbidity and medication adherence, (one Beers PIP: adjusted OR 1.21 (0.63, 2.31); $p=0.57$; $\geq 2$ Beers PIP; 0.73 ( $0.33,1.60$ ), $p=0.43$ ). Number of drugs and comorbidity were independently associated with $\geq 1$ ADE in this adjusted analysis. The effect of Beers 2012 PIP was the investigated in terms of increasing numbers of ADEs using Poisson regression. In unadjusted analysis, the prescription of one Beers PIP (IRR $1.23(95 \% \mathrm{Cl} 0.97,1.56), \mathrm{p}=0.09)$ was not associated with the outcome of interest but $\geq 2$ Beers PIP (IRR $1.59(95 \% \mathrm{Cl} 1.21,2.10), \mathrm{p}=0.001$ ) was associated with increasing numbers of ADEs when compared to no PIP. However, following adjustment for confounders, Beers PIP were not associated with future ADEs (one Beers PIP: IRR 0.93 ( $95 \% \mathrm{Cl} 0.75,1.15$ ), $\mathrm{p}=0.52$; $\geq 2$ Beers PIP: IRR 1.00 ( $95 \% \mathrm{Cl} 0.78,1.29$ ), $\mathrm{p}=0.98$ ) compared to no PIP. Number of drugs, comorbidity and deprivation were all independently associated with increasing numbers of future ADEs in this analysis. Appendix 11 presents the results of these unadjusted and adjusted analyses for Beers 2012 PIP across three levels (no PIP, one PIP, $\geq 2$ PIP) for the outcome of future ADE.

### 4.3.11 Secondary outcome: 1) Health related quality of life (HRQOL) ( $n=662$ )

### 4.3.11.1Descriptive statistics

A total of 673 study participants completed a postal questionnaire at follow-up, which included the EQ-5D and the EQ-5D VAS. Of 673 postal questionnaires, 11 (1.6\%) had missing data for the EQ-5D VAS component and so were excluded from the statistical analysis leaving $\mathrm{n}=662$ for analysis. The socio-demographic characteristics of the follow-up participants compared to the baseline cohort are presented in Table 4-15.

Table 4-15: Socio-demographic characteristics of study participants at baseline ( $n=904$ ) and follow-up ( $n=662$ ) for secondary outcome of HRQOL
Patient characteristic $\quad$ Baseline $(\mathrm{n}=904) \quad$ Follow-up ( $\mathrm{n}=662$ )

|  | Median (IQR) | Median (IQR) |
| :---: | :---: | :---: |
| Age | $77(74,81)$ | $79(76,83)$ |
| Deprivation | 1.49 (-0.6, 3.1) | 1.36 (-0.65, 2.88) |
| Gender | N (\%) | N (\%) |
| Male | 415 (46) | 312 (47) |
| Female | 489 (54) | 350 (53) |
| Marital status |  |  |
| Married | 403 (45) | 318 (48) |
| Separated/Divorced | 45 (5) | 33 (5) |
| Widowed | 293 (32) | 193 (29) |
| Never married/single | 162 (18) | 118 (18) |
| Living arrangements |  |  |
| Husband/Wife/Partner | 393 (44) | 308 (47) |
| Family/Relatives | 116 (13) | 80 (12) |
| Live alone | 343 (38) | 241 (36) |
| Other | 40 (5) | 33 (5) |
| Education* |  |  |
| Basic education | 555 (61) | 389 (59) |
| Upper/post-secondary | 343 (38) | 270 (41) |
| Social class |  |  |
| Unskilled | 342 (38) | 151 (22) |
| Skilled | 562 (62) | 522 (78) |
| Private Health Insurance cover |  |  |
| Yes | 509 (56) | 352 (53) |
| No | 395 (44) | 310 (47) |
| Charlson comorbidity weights ${ }^{\text {s }}$ |  |  |
| 0 | 358 (40) | 280 (42) |
| $\geq 1$ | 544 (60) | 382 (68) |

[^1]
### 4.3.11.2Multilevel linear regression model: E-QD utility ( $n=662$ )

The median EQ-5D utility at follow-up was 0.80 (IQR 0.66, 1). A multilevel linear regression model (two level, random intercept) was employed to determine if baseline PIP was associated with reduced EQ-5D utility score at follow-up, adjusting for confounding variables. Table 4-16 presents the unadjusted and adjusted coefficients for the EQ-ED utility score between baseline and follow-up by exposure to three levels of PIP (no PIP, one PIP, $\geq 2$ PIP) as defined by the STOPP criteria.

In the unadjusted analysis, increasing age, female gender, comorbidity, increasing number of drug classes and $\geq 2$ STOPP PIP were associated with lower EQ-5D utility scores. In addition, patients who reported lower levels of social support (Lubben's scale), those who screened positive for depression (as per HADS) and those who were classified as vulnerable (Vulnerable Elder's scale score $\geq 3$ ) reported lower HRQOL at follow-up. In the adjusted model, there was a statistically significant reduction in EQ5 regression co-efficient for patients with $\geq 2$ PIP of $-0.11(-0.16,-0.06), \mathrm{p}<0.001$. Other variables, which were independently associated with lower EQ-5D utility, were increasing age and vulnerability. According to one review which assessed eight prospective cohort studies encompassing eleven patient groups, the minimally important difference for the EQ-5D (i.e. the change in score that is clinically meaningful) was considered as 0.074 (ranging from -0.011 to 0.140 ).(93) This means that the association of PIP on HRQOL reported in this adjusted analysis of -0.11 is clinically significant.

Table 4-16: Multilevel linear regression model with unadjusted and adjusted coefficients ( $95 \%$ Cls, p-value) for EQ-5D score* at follow-up by exposure to PIP as defined by STOPP and patient level confounding variables at baseline ( $\mathbf{n}=662$ )

| Patient characteristics | Unadjusted coefficient (95\% CI, p value) | Adjusted coefficient (95\% CI, p value) |
| :---: | :---: | :---: |
| Primary outcome: PIP at baseline |  |  |
| 0 | 0 | 0 |
| 1 | -0.05 (-0.09, -0.01), p=0.02 | -0.002 (-0.04, 0.04), p=0.91 |
| $\geq 2$ | -0.21 (-0.25, -0.16), $\mathrm{p}<0.001$ | -0.11 (-0.16, -0.06), $\mathrm{p}<0.001$ |
| Adjusted for confounding variables |  |  |
| Age | -0.01 (-0.13, -0.006), p<0.001 | $-0.003(-0.006,-0.0009), \mathrm{p}=0.14$ |
| Gender |  |  |
| Male | 0 | 0 |
| Female | -0.05 (-0.085, -0.016), $\mathrm{p}=0.004$ | -0.015 (-0.05, 0.18), p=0.38 |
| Deprivation | $0.001(-0.007,0.009), p=0.82$ | 0.02 (-0.005, 0.009), $\mathrm{p}=0.50$ |
| Social class |  |  |
| Unskilled | 0 | 0 |
| Skilled | -0.001 (-0.04, 0.04), p=o.98 | -0.02 (-0.06, 0.16), p=0.26 |
| Education |  |  |
| Basic | 0 | 0 |
| Upper/post-secondary | 0.03 (-0.004, 0.07), p=0.08 | 0.01 (-0.02, 0.05), p=0.49 |
| Comorbidity: Charlson comorbidity weights |  |  |
| 0 | 0 | 0 |
| $\geq 1$ | -0.07 (-0.11, -0.04), p<0.001 | -0.03 (-0.06, 0.006), p=0.11 |
| Number of drug classes | -0.02 (-0.03, -0.02), $\mathrm{p}<0.001$ | -0.008 (-0.01, 0.002), p=0.10 |
| Medication adherence at baseline ${ }^{\text {\$ }}$ |  |  |
| MPR < 50\% | 0 | 0 |
| MPR $\leq 50 \%<80 \%$ | $0.04(-0.04,0.11), \mathrm{p}=0.34$ | 0.08 (0.01, 0.14$), \mathrm{p}=0.20$ |
| MPR $\geq 80 \%$ | 0.19 (-0.05, 0.09), p=0.59 | 0.08 (0.02, 0.14), p=0.01 |
| Vulnerable at baseline (VES-13 score $\geq 3$ ) |  |  |
| No | 0 | 0 |
| Yes | -0.22 (-0.25, -0.19), $\mathrm{p}<0.001$ | -0.16 (-0.20, -0.12), p<0.001 |
| Lubben's social support at baseline |  |  |
| Low | 0 | 0 |
| Moderate | 0.06 (-0.02, 0.14), p=0.15 | 0.06 (-0.006, 0.13), p=0.07 |
| High | 0.08 (0.007, 0.16), p=0.03 | 0.06 (-0.0005, 0.12), p=0.05 |
| Screened positive for depression as per HADS at baseline |  |  |
| No | 0 | 0 |
| Yes | -0.22 (-0.28, -0.15), p<0.001 | -0.10 (-0.16, -0.04), p=0.002 |

*Model was based on centred EQ-5D score at follow-up. Note: a histogram was generated to examine differences between baseline and follow-up uncentred EQ5D; 50\% didn't change, and those that did only changed slightly therefore follow-up score was used in the analysis rather than differences in EQ-5D utility score between baseline and follow-up. ${ }^{\$}$ MPR data is missing for 37 participants. Baseline age, deprivation and EQ5D were centred for the purposes of the data analysis.

### 4.3.11.3Multilevel linear regression model: E-QD-Visual Analogue Scale ( $\mathbf{n}=662$ )

The median EQ-5D VAS score at follow-up was $80(65,90)$. A second multilevel linear regression model (two level random intercept) was utilised to examine the relationship between baseline PIP as defined by the STOPP criteria and EQ-5D VAS at follow-up, adjusting for confounding variables. The unadjusted and adjusted models are presented in Table 4-17. In the unadjusted model, increasing age, female gender, number of drug classes, comorbidity, any PIP, screened positive for depression at baseline (HADS) and vulnerability were associated with lower HRQOL. In the adjusted model, $\geq 2$ PIP was associated with lower HRQOL with reported reduction in EQ-5D VAS of $-5.40(-9.34,-1.46), \mathrm{p}=0.007$. Other variables that were independently associated with lower EQ-5D VAS included vulnerability and greater number of drug classes.

Table 4-17: Multilevel linear regression model with unadjusted and adjusted regression coefficients ( $95 \%$ Cls, p-value) for EQ-5D Visual Analogue Scale* at followup by exposure to PIP and patient level confounding variables at baseline ( $\mathrm{n}=662$ )

| Patient characteristics | Unadjusted coefficient ( <br> value CI), p- | Adjusted estimated coefficient <br> $(95 \% ~ C I), ~ p-v a l u e ~$ |
| :--- | :--- | :--- |

## Primary outcome: PIP at baseline

$0 \quad 0 \quad 0$
$1-4.96(-8.07,-1.85), \mathrm{p}=0.002 \quad-1.88(-5.04,1.29), \mathrm{p}=0.25$
$\geq 2 \quad-12.61(-16.16,-9.06), \mathrm{p}<0.001 \quad-5.40(-9.34,-1.46), \mathrm{p}=0.007$
Adjusted for confounding variables

| Age | $-0.50(-0.77,-0.22), p<0.001$ | $0.007(-0.28,0.29), p=0.96$ |
| :--- | :--- | :--- |
| Gender | 0 | 0 |
| Male | $-2.66(-5.32,-0.01), p=0.05$ | $-1.89(-4.52,0.73), p=0.16$ |
| Female | 0 | 0 |
| Social class | $-1.98(-5.21,1.25), \mathrm{p}=0.23$ | $-3.44(-6.56,-0.31), \mathrm{p}=0.03$ |
| Unskilled | $-0.51(-1.08,0.05), \mathrm{p}=0.08$ | $-0.40(-0.93,0.14), \mathrm{p}=0.14$ |
| Skilled | 0 | 0 |
| Deprivation <br> Education <br> Basic | $0.1 .66(-4.47,1.14), \mathrm{p}=0.25$ |  |

## Comorbidity: Charlson weights at baseline

0
0
$\geq 1 \quad-5.47(-8.13,-2.82), \mathrm{p}<0.001$
Number of drug classes $\quad-1.59(-1.97,-1.21), p<0.001$
0
$-2.52(-5.23,0.19), p=0.07$
$-0.71(-1.20,-0.21), p<0.001$
Medication adherence at baseline ${ }^{\$}$

| MPR $<50 \%$ | 0 | 0 |
| :--- | :--- | :--- |
| $M P R>50 \%$ but $<80 \%$ | $-2.00(-7.53,3.53), p=0.48$ | $0.73(-4.46,5.92), p=0.78$ |
| $M P R \geq 80 \%$ | $-3.80(-8.83,1.25), p=0.14$ | $-0.59(-5.38,4.19), p=0.81$ |

Vulnerable at baseline (VES-13 score $\geq 3$ )
No $0 \quad 0$

Yes $\quad-12.88(-15.53,-10.23), p<0.001 \quad-10.14(-13.34,-6.97), p<0.001$
Lubben's social support at baseline

| Low | 0 | 0 |
| :--- | :--- | :--- |
| Moderate | $2.72(-3.32,8.75), \mathrm{p}=0.38$ | $4.00(-1.68,9.68), \mathrm{p}=0.17$ |
| High | $5.16(-0.45,10.76), \mathrm{p}=0.07$ | $6.13(0.88,11.38), \mathrm{p}=0.02$ |

HADS screened positive for depression at baseline
No 0

0
Yes $\quad-11.79(-16.77,-6.80), p<0.001$
0
\# Model was based on EQ-5D VAS at follow-up. Note: a histogram was generated to examine the differences between baseline and follow-up uncentred EQ-5D VAS; 50\% didn't change, and those that did only changed slightly, therefore follow-up score was utilised as the outcome of interest rather than using the change in score between baseline score and follow-up score. ${ }^{\$}$ MPR data is missing for $n=37$.

### 4.3.11.4Multilevel linear regression: Beers 201PIP and E\$D utility/EQ-5Q VAS ( $n=664$ )

A multilevel linear regression model was used to investigate if exposure to Beers 2012 PIP predicted poorer future health related quality of life. In the unadjusted analysis, both the prescription of one and $\geq 2$ Beers potentially inappropriate prescriptions were significantly associated with future reduction in EQ-5D utility score (one Beers PIP: unadjusted coefficient; -0.05 (-0.10, -0.001), $\mathrm{p}=0.04, \geq 2$ Beers PIP; unadjusted coefficient; -0.11 (-0.18, -0.06), p<0.001 compared to no PIP). However following adjustment for confounding variables, Beers PIP was not associated with future reduction in EQ-5D utility score (one Beers PIP adjusted coefficient: $0.001(-0.04,0.04)$, $\mathrm{p}=0.96$; $\geq 2$ Beers PIP adjusted coefficient: $-0.05(-0.11,0.003), \mathrm{p}=0.06$.

The median EQ-5D VAS score at follow-up was $80(65,90)$. A multilevel linear regression model (two level random intercept) was utilised to examine the relationship between baseline Beers 2012 PIP and EQ-5D VAS at follow-up, adjusting for confounding variables In unadjusted analysis, one Beers PIP was not associated with lower EQ-5D VAS at follow-up (one Beers PIP: unadjusted coefficient -2.87 (-6.47, 0.74 ), $\mathrm{p}=0.20$ ) but $\geq 2$ Beers PIP was associated with poorer EQ-5D VAS (unadjusted coefficient $-4.87(-9.41,-0.33), \mathrm{p}=0.04)$. However, following adjustment for confounding variables, Beers PIP was not associated with lower EQ-5D VAS at followup; one Beers PIP, adjusted coefficient 1.08 ( $-2.41,4.57$ ), $p=0.55$; $\geq 2$ Beers PIP, adjusted coefficient $0.70(-3.74,5.15), \mathrm{p}=0.76$. Vulnerability and increasing numbers of medications were both independently associated with lower EQ-5D VAS at follow-up. Appendix 12 presents the unadjusted and adjusted coefficients, accounting for cofounding variables, for the EQ-5D and EQ-5D VAS scores.

### 4.3.12 Secondary outcome: 2) Emergency hospital admission and A\&E visits ( $\mathrm{n}=806$ )

### 4.3.12.1Descriptive statistics

Of 904 baseline study participants, there was complete two year follow-up data available for a total of 806 for the outcomes of $A \& E$ visit and emergency admission who were included in the analysis (see Table 4-18).

Table 4-18: Socio-demographic and clinical characteristics of baseline ( $n=904$ ) and follow-up ( $\mathrm{n}=806$ ) study participants for A\&E visits and emergency admission

|  | Baseline ( $\mathrm{n}=904$ ) | Follow-up ( $\mathrm{n}=806$ ) |
| :---: | :---: | :---: |
|  | Median (IQR) | Median (IQR) |
| Age | $77(74,81)$ | $76(73,80)$ |
| Deprivation | 1.49 (-0.6, 3.2) | 1.5 (-0.6, 2.9) |
|  | N (\%) | N (\%) |
| Gender |  |  |
| Male | 415 (46) | 372 (46) |
| Female | 489 (54) | 434 (54) |
| Living arrangements ${ }^{\text {I }}$ |  |  |
| Husband/Wife/Partner | 393 (44) | 383 (44) |
| Family/Relatives | 116 (13) | 110 (13) |
| Live alone | 343 (38) | 327 (38) |
| Other | 40 (5) | 41 (5) |
| Education* |  |  |
| Basic education | 555 (61) | 493 (61) |
| Upper/post-secondary | 343 (38) | 307 (38) |
| Social class |  |  |
| Unskilled | 342 (38) | 197 (24) |
| Skilled | 562 (62) | 609 (76) |
| Charlson comorbidity weights ${ }^{\text {s }}$ |  |  |
| 0 | 358 (40) | 330 (41) |
| $\geq 1$ | 544 (60) | 476 (59) |

[^2]
### 4.3.12.2E xposure to STOPP PIP and emergency hospital attendance ( $\mathrm{n}=806$ )

A multilevel logistic regression model (two level, random intercept) was used to investigate if PIP at baseline predicted one or more A\&E visits during the two-year prospective follow-up period, adjusting for confounding variables. For this type of analysis it is not possible to account for different follow-up times so only patients with full two year follow-up data were included ( $n=806$ ). Of the 82 participants excluded from this analysis, 53 had died, 14 had moved GP practice, 12 had moved into a nursing home, and three were long-term hospital inpatients. Of the 806 study participants included in the analysis, a total of 653 patients (81\%) had no A\&E visit during two year follow-up. One hundred and twenty-three patients (15\%) attended A\&E once and 30 patients ( $4 \%$ ) had $\geq 2$ A\&E visits.

Table 4-19 presents the socio-demographic and clinical characteristics of the two groups and demonstrates that the 82 study participants excluded from logistic regression analysis were older, had more comorbidity and were taking more medications that those with full two year follow-up data. As the exclusion of these study participants may have biased the findings, all statistical analyses were repeated including patients with any follow-up healthcare utilisation data ( $\mathrm{n}=888$ ) and the results of these analyses are presented in Appendix 13. Overall, the findings were similar to the results presented below.

Table 4-19: Comparison of patients included and excluded from the logistic regression data analysis

| Patient characteristic | Included in logistic regression analysis ( $\mathrm{n}=806$ ) | Excluded from logistic regression analysis ( $\mathrm{n}=82$ ) | p-value |
| :---: | :---: | :---: | :---: |
| PIP | N (\%) | N (\%) |  |
| 0 | 469 (58) | 48 (59) |  |
| 1 | 192 (24) | 19 (24) |  |
| $\geq 2$ | 145 (18) | 15 (18) | 0.10 |
|  | Median (IQR) | Median (IQR) |  |
| Age | $76(73,80)$ | $82(77,87)$ | <0.001 |
| Deprivation | 1.5 (-0.6, 2.9) | 2.2 (-0.3, 3.4) | 0.2 |
| Baseline drug classes | $6(3,8)$ | $7(4,10)$ | 0.002 |
| Gender |  |  |  |
| Male | 372 (46) | 39 (48) |  |
| Female | 434 (54) | 43 (52) | 0.81 |
| Education* |  |  |  |
| Basic | 493 (61) | 49 (60) |  |
| Upper/post-secondary | 307 (38) | 33 (40) | 0.70 |
| Social class |  |  |  |
| Unskilled | 197 (24) | 17 (21) |  |
| Skilled | 609 (76) | 65 (79) | 0.45 |
| Comorbidity: Charlson weights |  |  |  |
| 0 | 330 (41) | 23 (28) |  |
| $\geq 1$ | 476 (59) | 59 (72) | 0.02 |
| Medication Adherence^ |  |  |  |
| MPR < $50 \%$ | 62 (8) | 9 (11) |  |
| MPR $>50 \%$ but $<80 \%$ | 176 (22) | 11 (13) |  |
| MPR $\geq 80 \%$ | 520 (65) | 61 (74) | <0.001 |

*Education data was missing for $n=6$. ^MPR data was missing for $n=37$.

Table 4-20 presents the unadjusted and adjusted $\mathrm{OR}(95 \% \mathrm{Cl}, \mathrm{p}$ value) for $\geq 1 \mathrm{~A} \& \mathrm{E}$ visit during two-year follow-up. In the unadjusted model, the number of drug classes, increasing comorbidity, one or $\geq 2$ PIP and emergency hospital attendance at baseline were associated with $\geq 1$ A\&E visit. Following adjustment for confounding variables, one PIP (adjusted OR 1.82 ( $95 \% \mathrm{Cl} 1.15,2.89$ ), $\mathrm{p}=0.01$ ) and $\geq 2$ PIP (adjusted OR 1.85 ( $95 \% \mathrm{Cl} 1.06,3.24$ ), $\mathrm{p}=0.03$ ) remained statistically significant for increasing the odds of
$\geq 1$ A\&E visit over the two-year follow-up period. Previous emergency attendance was also independently associated with future A\&E visits.

Table 4-20: Number and percentage of patients and unadjusted and adjusted odds ratios ( $95 \% \mathrm{CI}, \mathrm{p}$ value) for those with $\geq 1$ A\&E visit* by exposure to PIP at baseline as defined by STOPP and confounding variables ( $\mathrm{n}=806$ )

| Patient characteristic | Total patients (N) | N (\%) or median (IQR) with $\geq 1$ A\&E | Unadjusted Odds Ratio (OR) ( $95 \% \mathrm{Cl}$ ), p value | Adjusted OR (95\% CI), pvalue |
| :---: | :---: | :---: | :---: | :---: |


| Primary outcome: PIP at baseline |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| 0 | 469 | 66 (43) | 1 | 1 |
| 1 | 192 | 48 (31) | 2.04 (01.34, 3.10), p=0.001 | 1.82 (1.15, 2.89), p=0.01 |
| $\geq 2$ | 145 | 39 (25) | 2.21 (1.41, 3.49), p=0.001 | 1.85 (1.06, 3.24), p=0.03 |
| Adjusted for confounding variables |  | Median (IQR) |  |  |
| Age | 806 | $73(73,82)$ | 1.03 (0.99,1.06), p=0.11 | 1.01 (0.98, 1.06), $\mathrm{p}=0.47$ |
| Deprivation | 806 | 1.6 (-0.5, 3.2) | 1.02 (0.94, 1.10), p=0.63 | 1.03 (0.94, 1.12), p=0.53 |
| Baseline drug classes | 806 | $6(4,9)$ | 1.08 (1.03, 1.14), $\mathrm{p}=0.002$ | 1.02 (0.96, 1.10), p=0.50 |
| Gender |  | N(\%) |  |  |
| Male | 372 | 72 (47) | 1 | 1 |
| Female | 434 | 81 (53) | 0.93 (0.65, 1.33), p=0.70 | 0.86 (0.58, 1.29), p=0.47 |
| Social Class |  |  |  |  |
| Unskilled | 197 | 39 (25) | 1 | 1 |
| Skilled | 609 | 114 (75) | 0.94 (0.62, 1.43), p=0.79 | 0.80 (0.51, 1.26), p=0.34 |
| Education^ |  |  |  |  |
| Basic | 493 | 91 (59) | 1 | 1 |
| Upper/postsecondary | 307 | 62 (41) | 1.17 (0.80, 1.70), p=0.42 | 1.30 (0.84, 1.99), p=0.24 |
| Comorbidity: Charlson weights |  |  |  |  |
| 0 | 330 | 50 (33) | 1 | 1 |
| $\geq 1$ | 476 | 103 (67) | 1.54 (1.06, 2.23), p=0.02 | 1.26 (0.83, 1.92), p=0.28 |
| Medication adherence |  |  |  |  |
| MPR < 50\% | 62 | 16 (10) | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 176 | 26 (17) | 0.49 (0.24, 0.99), p=0.05 | 0.36 (0.17, 0.77), p=0.008 |
| MPR $\geq 80 \%$ | 520 | 105 (69) | 0.72 (0.39, 1.33), p=0.30 | 0.53 (0.28, 1.03), p=0.06 |

Vulnerable at baseline (VES-13 $\geq 3$ )

| No | 513 | $67(44)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| Yes | 293 | $86(56)$ | $1.47(1.02,2.11), p=0.04$ | $1.10(0.70,1.71), p=0.69$ |

A\&E visit or emergency admission at baseline

| No | 789 | $3(2)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| Yes | 17 | $150(98)$ | $2.31(1.39,3.83), \mathrm{p}=0.001$ | $1.88(1.10,3.22), \mathrm{p}=0.02$ |

[^3]
### 4.3.12.3Multilevel regression model: E mergency admissior=806)

A total of 199 (25\%) study participants had at least one emergency admission during two year follow-up. A total of 136 (17\%) had one emergency admission, 44 (5\%) had two and 19 (2\%) had $\geq 3$ emergency admissions. Table 4-21 presents a multilevel logistic regression model (two level, random intercept), which was used to investigate if PIP as defined by STOPP at baseline, was longitudinally associated with one or more emergency admissions during the two year prospective follow-up period, adjusting for confounding variables. In unadjusted analysis, increasing age, increasing comorbidity, $\geq 2$ PIP, baseline vulnerability as per the VES-13 and previous emergency hospital attendance were associated with $\geq 1$ emergency admissions during two year follow-up. Following adjustment for confounding variables, $\geq 2$ STOPP PIP was no longer associated with emergency admission, with adjusted ORs 1.00 ( $95 \% \mathrm{Cl} 0.63,1.61$ ), $p=0.99$. The number of drug classes at baseline, deprivation and previous emergency hospital attendance were all independently associated with emergency admission during two year follow-up.

Table 4-21: Number and percentage of patients and unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cl}, \mathrm{p}$ value) for those with $\geq 1$ emergency admission* by exposure to PIP as defined by STOPP at baseline and confounding variables ( $\mathrm{n}=806$ )

|  | Total | $\mathrm{N}(\%)$ with |  |  |
| :--- | :--- | :--- | :--- | :--- |
| Patient | (\%) <br> characteristic | patients <br> $(\mathrm{N})$ | admission | (OR) $(95 \% \mathrm{Cl}), \mathrm{p}$ value |$\quad$| Adjusted OR (95\% CI), p- |
| :--- |

Primary outcome: PIP at baseline

| 0 | 469 | $95(48)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| 1 | 192 | $50(25)$ | $1.38(0.93,2.04), \mathrm{p}=0.11$ | $0.88(0.59,1.31), \mathrm{p}=0.54$ |
| $\geq 2$ | 145 | $54(27)$ | $2.35(1.56,3.53), \mathrm{p}<0.001$ | $1.00(0.63,1.61), \mathrm{p}=0.99$ |

Adjusted for confounding variables

|  |  | Median (IQR) |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Age | 806 | $77(73,81)$ | 1.04 (1.01,1.07), p0.01 | 1.02 (0.98, 1.06), p=0.33 |
| Deprivation | 806 | $1.7(-0.2,3.4)$ | 1.06 (1.00, 1.13), p=0.06 | 1.07 (0.99, 1.14), p=0.08 |
| Baseline drug classes | 806 | $7(5,9)$ | 1.17 (1.12, 1.22), $\mathrm{p}<0.001$ | 1.13 (1.06, 1.21), $\mathrm{p}<0.001$ |
| Gender |  | N (\%) |  |  |
| Male | 372 | 88 (44) | 1 | 1 |
| Female | 434 | 111 (56) | 1.12 (0.80, 1.53), p=0.53 | 0.92 (0.64, 1.33), p=0.67 |
| Social Class |  |  |  |  |
| Unskilled | 197 | 52 (26) | 1 | 1 |
| Skilled | 609 | 147 (74) | 0.88 (0.61, 1.28), p=0.51 | 0.93 (0.61, 1.42), p=0.73 |
| Education^ |  |  |  |  |
| Basic | 493 | 123 (62) | 1 | 1 |
| Upper/postsecondary | 307 | 74 (37) | 0.95 (0.68, 1.34), p=0.78 | 1.28 (0.86, 1.90), p=0.23 |
| Comorbidity: Charlson weights |  |  |  |  |
| 0 | 330 | 60 (30) | 1 | 1 |
| $\geq 1$ | 476 | 139 (70) | 1.86 (1.31, 2.62), $\mathrm{p}<0.001$ | 1.27 (0.86, 1.88), 0.22 |
| Medication adherence ${ }^{\text {s }}$ |  |  |  |  |
| MPR < 50\% | 62 | 20 (10) | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 176 | 43 (22) | 0.68 (0.36, 1.28), p=0.23 | 0.46 (0.23, 0.92), p=0.005 |
| MPR $\geq 80 \%$ | 520 | 131 (64) | 0.71 (0.40, 1.25), p=0.23 | 0.45 (0.24, 0.84), p=0.01 |
| Vulnerable (VES-13 score $\geq 3$ ) |  |  |  |  |
| No | 513 | 103 (52) | 1 | 1 |
| Yes | 293 | 96 (48) | 1.94 (1.40, 2.69), $\mathrm{p}<0.001$ | 1.16 (0.77, 1.74), p=0.49 |

A\&E visit or inpatient admission at baseline**

| No | 789 | $192(96)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| Yes | 17 | $7(4)$ | $3.62(2.25,5.80), \mathrm{p}<0.001$ | $2.79(1.69,4.62), \mathrm{p}<0.001$ |

[^4]
### 4.3.12.4Multilevel Poissa regression: number of emergency admissions ( $\mathbf{n}=806$ )

A multilevel Poisson regression model was used to investigate if STOPP defined PIP was longitudinally associated with increasing numbers of emergency admissions during two-year follow-up, adjusting for confounding variables. Table 4-22 presents the incidence rate ratio for the unadjusted and adjusted analysis. In the unadjusted analysis, increasing age, number of baseline drug classes, increasing comorbidity, prior emergency hospital attendance, patient vulnerability and PIP were all associated with increasing numbers of emergency admission. Following adjustment for confounding variables, however, PIP was no longer associated with increasing number of emergency hospital admissions; adjusted odds ratios ( $95 \% \mathrm{CI}$ ) one PIP: OR 1.06 ( $95 \% \mathrm{Cl}$ $0.77,1.46$ ), $\mathrm{p}=0.71$; $\geq 2$ PIP: OR 1.17 ( $95 \% \mathrm{Cl} 0.81,1.68$ ), $\mathrm{p}=0.41$. Increasing number of drug classes and prior emergency hospital attendance were independently associated with repeated emergency hospital admission.

Table 4-22: Number and percentage of patients and unadjusted and adjusted incidence rate ratio (IRR) ( $95 \% \mathrm{CI}, \mathrm{p}$ value) for numbers of emergency admissions* during two-year follow-up by exposure to PIP as defined by STOPP at baseline and confounding variables ( $\mathrm{n}=806$ )

| Patient <br> characteristic | Total patients <br> (N) | Incidence Rate Ratio (IRR) <br> $(95 \% \mathrm{Cl}), \mathrm{p}$ value$\quad$ Adjusted IRR (95\% CI), p-value |
| :--- | :--- | :--- |

Primary outcome: PIP at baseline

| 0 | 469 | 1 | 1 |
| :--- | :--- | :--- | :--- |
| 1 | 192 | $1.42(1,031.95), \mathrm{p}=0.03$ | $1.06(0.77,1.46), \mathrm{p}=0.71$ |
| $\geq 2$ | 145 | $2.14(1.57,2.92), \mathrm{p}<0.001$ | $1.17(0.81,1.68), \mathrm{p}=0.41$ |

Adjusted for confounding variables

| Age | 806 | $1.03(1.01,1.06), \mathrm{p}=0.007$ | $1.02(0.99,1.04), \mathrm{p}=0.21$ |
| :--- | :--- | :--- | :--- |
| Deprivation <br> Baseline drug <br> classes | 806 | 806 | $1.05(0.99,1.10), \mathrm{p}=0.09$ | | $1.04(0.99,1.09), \mathrm{p}=0.14$ |
| :--- |
| Gender |
| Male |
| Female |
| Social Class |
| Unskilled |
| Skilled |
| Education^ |
| Basic |
| Upper and post- <br> secondary |

Comorbidity: Charlson weights

| 0 | 330 | 1 | 1 |
| :---: | :---: | :---: | :---: |
| $\geq 1$ | 476 | 1.90 (1.43, 2.54), p<0.001 | 1.35 (1.01, 1.82), p=0.05 |
| Medication adherence ${ }^{\text {s }}$ |  |  |  |
| MPR < 50\% | 62 | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 176 | 0.76 (0.47, 1.25), $\mathrm{p}=0.28$ | 0.58 (0.35, 0.91), p=0.02 |
| MPR $\geq 80 \%$ | 520 | 0.71 (0.46, 1.11), $p=0.13$ | 0.50 (0.33, 0.77), p=0.002 |
| Vulnerable (VES score $\geq 3$ ) |  |  |  |
| No | 513 | 1 | 1 |
| Yes | 293 | 1.78 (1.38, 2.31), p<0.001 | 1.17 (0.87, 1.57), $\mathrm{p}=0.29$ |

Number of A\&E visits or emergency admissions at baseline**

| No | 789 | 1 |  |
| :--- | :--- | :--- | :--- |
| Yes | 17 | $1.99(1.58,2.51), \mathrm{p}<0.001$ | $1.55(1.25,1.93), \mathrm{p}<0.001$ |

[^5]
### 4.3.13 Exposure to Beers 2012 PIP and emergency hospital attendance

### 4.3.13.1Multilevel logistic regression: A\&E visit ( $\mathrm{n}=806$ )

Appendix 14 presents the number and percentage of patients who experienced at least one A\&E visit according to Beers 2012 PIP and confounding variables, and the unadjusted and adjusted logistic regression analyses for the impact of Beers 2012 PIP on subsequent A\&E visits. Following adjustment for confounding variables, Beers 2012 PIP was not associated with an increased risk of A\&E visits during the follow-up period; one Beers PIP, adjusted OR 1.07 ( $95 \% \mathrm{Cl} 0.65,1.77$ ), p=0.79; $\geq 2$ Beers PIP, adjusted OR 1.54 ( $95 \% \mathrm{Cl} 0.88,2.71$ ), $\mathrm{p}=0.13$. Previous emergency attendance was independently associated with future $A \& E$ visits.

### 4.3.13.2Multilevel logistic and Poisson regression models: Emergency admission ( $\mathrm{n}=806$ )

A logistic regression model was used to investigate if Beers 2012 were associated with one or more emergency admissions. Exposure to Beers PIP was not associated with emergency admission during follow-up in this model; one Beers PIP: adjusted OR 1.13 ( $95 \% \mathrm{Cl} 0.72,1.78$ ), $\mathrm{p}=0.60$; $\geq 2$ Beers PIP: adjusted OR 0.72 ( $95 \% \mathrm{Cl} 0.41,1.28$ ), $\mathrm{p}=0.27$. Increasing number of drug classes and prior emergency hospital attendance were independently associated with this outcome. A Poisson regression model was used to investigate if Beers 2012 PIP was associated with repeated emergency admissions. This model demonstrated that Beers PIP was not associated with repeated emergency admission during this period (one Beers PIP: adjusted IRR 1.10 ( $95 \% \mathrm{Cl} 0.80,1.51$ ), $\mathrm{p}=0.57$; $\geq 2$ Beers PIP: adjusted IRR 0.97 ( $95 \% \mathrm{Cl} 0.67,1.42$ ), $\mathrm{p}=0.89$ ). The number of baseline drug classes and previous emergency hospital attendance were both independently associated with this outcome (see Appendix 15).

### 4.4 Risk of bias of the prospective cohort study

The Cochrane risk of bias tool for non-randomised studies was used to assess the overall risk of bias of this prospective cohort study.(281) A summary is presented in Table 4-23. Overall, the risk of bias was low.

Table 4-23: Methodological quality assessment of the prospective cohort study

| Methodological quality criteria | Definitely yes | Probably yes | Probably no | Definitely no |
| :---: | :---: | :---: | :---: | :---: |
| Was selection of exposed and non-exposed cohorts drawn from the same population? | * |  |  |  |
| Can we be confident in the assessment of exposure? | * |  |  |  |
| Can we be confident that the outcome of interest was not present at start of study? | * |  |  |  |
| Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | * |  |  |  |
| Can we be confident in the assessment of the presence or absence of prognostic factors? |  | * |  |  |
| Can we be confident in the assessment of outcome? | * |  |  |  |
| Was the follow up of the cohort adequate? | * |  |  |  |
| Were co-interventions similar between groups? | * |  |  |  |

Each methodological criterion is addressed individually with the overall judgement and rationale for the judgement below.

#  population? 

## Overall judgement: Definitely yes

Rationale: Both the exposed and unexposed study participants were drawn from the same population i.e. older community-dwelling people attending 15 general practices in one geographical region.

## Can we be confident in the assessment of exposure?

Overall judgement: Definitely yes
Rationale: The risk of bias for this methodological quality criterion depends on the exposure of interest. Ascertainment of PIP was via a linked pharmacy claims database so this represents a low risk of bias.

C an we be confident that the outcome of interest was not present at start of study?

Overall judgement: Definitely yes

Rationale: The ADE exposure was ascertained at follow-up via an interview that included detailed questions regarding 74 symptoms that the patient attributed to their medication over the previous six months. In addition, the patient's GP medical record was reviewed for ADEs that were recorded in the same time period. As the patient interview was clearly delineated in terms of ADEs that had occurred in a specific sixmonth period we can be confident the ADEs reported were not present at baseline. Emergency admission was recorded from the GP medical record. This involved a review of all general practice consultations and hospital correspondence including discharge summaries, hospital alerts and outpatient correspondence. This detailed clinical record review reduces the likelihood that emergency admissions were missed. HRQOL and functional decline were recorded using a postal questionnaire administered both at baseline and follow-up. Subjectivity is an important component of these measures and in capturing the range of health outcomes that are important for older people. The repeated measurements (baseline and follow-up) reduce the risk of bias in administering these tools.

## Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust fdrese prognostic variables?

Overall judgement: Definitely yes

Rationale: Each statistical model adjusted for a range of relevant socio-economic and clinical variables. Confounding variables were chosen based on literature review and clinical relevance. This study has the advantage of being able to include a range of confounding variables not considered in previous research such as medication adherence, mental health difficulties and vulnerability. All analyses present both the unadjusted and adjusted coefficients.

Can we be confident in the assessment of the presence or absence of prognostic factors?

Overall judgement: Probably yes

Rationale: Reasons for missing data for study participants at two-year follow-up were carefully recorded and are presented in a flow diagram in Figure 4.2. GP medical record review was utilised to record medical diagnoses and healthcare utilisation for both the baseline and follow-up data collection demonstrating reproducibility and a random sample of reviews conducted at follow-up were double-checked by an independent reviewer to consolidate data accuracy.

## Can we be confident in the assessment of outcome?

Overall judgement: Definitely yes

As summarised previously the ADE interview was very comprehensive compared to previous research. It included a general question regarding side-effects to medications over the previous six months at the start of the interview then a detailed review of 74 symptoms. (See Appendix 7) After each symptom participants' were asked if they attributed the symptom to a medication and to name that medication. In addition, the participant's GP medical record was reviewed for ADEs over the same time period.

Emergency admission was recorded from the GP medical record, which included a detailed review of GP consultations; hospital correspondence and hospital attendance alerts over the two-year follow-up period. In addition, the reason for, date of each admission and length of hospital stay was recorded. All GP medical record reviews were conducted by the same researcher and a $10 \%$ random sample were double checked by an independent reviewer. However, there is a possibility that emergency admissions could have been missed using this approach, which may not be as robust as linked hospital data. However, the proportion of emergency admissions recorded in this study was very similar to the emergency admissions reported as part of a nationally representative Irish cohort study (TILDA).(306) In addition, utilising the GP medical record is less likely to introduce bias than depending on patient self-report of emergency hospital use. HRQOL and functional decline were measured using validated measures (the EQ-5D and the short functional survey) and were recorded using a
subjective assessment method of postal questionnaire, which is in keeping with previous research. This questionnaire with these measures was administered on two occasions; at baseline and follow-up, which reduces the risk of bias.

## Was the followup of the cohort adequate?

Overall judgement: Definitely yes

Rationale: Overall, follow-up for all three outcomes of interest; ADE interview, HRQOL, functional decline and emergency admission was considered high at 76.5\%.(222) This is particularly notable considering both a detailed interview and questionnaire were used as outcome measurements. Detailed reasons for missing data were collected and are summarised in Figure 4-2. There were minimal losses to follow-up for the emergency admission outcome (5\%). All emergency admission analyses were conducted on patients with any admission outcome data (including those patients who had died) and for participants who had survived to determine if there were any differences in overall results, which there was not.

## 

Overall judgement: Definitely yes

Rationale: All GP practices were treated the same in terms of feedback about the study. A generic letter was sent to all participating practices advising about the followup phase of the study and all practices were visited on several occasions by the researcher who was collecting data.

### 4.5 Examining the issue of a causal relationship between exposure (PIP) and adverse outcomes

When examining the longitudinal association between PIP, as defined by the STOPP criteria, and future ADEs, poorer HRQOL and A\&E visits, the issue of causality is particularly important. The Bradford-Hill criteria include several factors which should be present if a causal link is to be established between an exposure (PIP) and outcomes. These factors are addressed individually below.

## Temporal relationship

The measurement of the exposure of interest must precede the outcome. In this study, PIP exposure was calculated at baseline and outcomes of interest at follow-up. ADEs were ascertained over a six month time period to preclude the inclusion of historic ADEs. HRQOL was measured by the administration of the EQ-5D questionnaire at follow-up to establish HRQOL at that time point. A\&E visits were recorded prospectively from baseline.

## Strength of the association

The stronger or larger the size of the association between an exposure and outcome the more likely it is causal. Patients taking $\geq 2$ STOPP PIP were $29 \%$ more likely to report increasing counts of ADEs compared to those with no PIP which represents a modest association. The confidence interval around this estimate ranged from $3 \%$ to $60 \%(p=0.03)$ which is quite wide, and is likely due to the relatively small number of study participants taking $\geq 2$ PIP. There was a reduction of 0.11 in the EQ-5D score for patients taking $\geq 2$ STOPP PIP which is clinically meaningful. The confidence intervals around this estimate were narrower ranging from -0.16 to -0.06 ( $p<0.001$ ). Patients prescribed $\geq 2$ STOPP PIP were almost twice as likely (adjusted OR 1.85) to attend A\&E in the follow-up period compared to patients with no PIP, but confidence intervals were wide ( $95 \% \mathrm{Cl} 1.06,3.24$, p value=0.03). A very small number of patients ( $\mathrm{n}=39$ ) with $\geq 2$ PIP attended A\&E which accounts for the wide confidence intervals. Beers PIP did not impact on any adverse health outcomes indicating added value of the STOPP criteria in predicting these outcomes in this setting of care.

## Doseresponse relationship

If increasing exposure is associated with increased risk of the outcome then it is likely this represents a causal relationship. However, sometimes a threshold exposure applied beyond which the relationship is established. In this study one STOPP PIP was not associated with adverse health outcomes but $\geq 2$ PIP were. In this way there is a
threshold at which the relationship exists but it is not possible to say that a dose response relationship exists based on this study's findings.

## Consistency of the relationship

If a relationship is replicated across different studies and settings it is more likely to be causal. This is the first prospective primary care cohort study to examine the effect of PIP on adverse health outcomes so future studies are needed to ascertain if the relationship reported in this study can be replicated across different settings.

## Plausibility

This refers to a causal relationship agreeing with currently accepted understanding. For a patient to experience an ADE they must first be taking medication and previous research has examined potential links with healthcare utilisation and poorer HRQOL. Needing to take medication could reasonably be expected to have an impact on HRQOL and emergency hospital attendance based on current knowledge and understanding.

## Consideration of altemate explanations

The inclusion of a large number of confounding variables is strength of this study and sets it apart from previous research in the area. It addresses many potential alternate explanations for this study's findings. In addition, the exposure PIP was established using pharmacy claims database which is more reliable than self-report medication often used in previous studies. Important included confounders were medication adherence, number of medications, multimorbidity and several measures of socioeconomic demographics. The consideration of these variables in statistical modelling strengthens this study's findings.

## Coherence

The findings reported in this study are generally coherent with and build on the literature in this area, demonstrating an effect of PIP independent of increasing numbers of medications on relevant clinical outcomes in primary care.

## Specificity

This is established when a single putative cause is linked to the outcome. PIP does not meet this criterion but specificity is considered the least important of the Hills criteria and well established causal relationships (e.g. cigarette smoking and lung cancer) do not meet this criterion.

### 4.6 Discussion

### 4.6.1 Principal findings

This two year prospective primary care study is the first to compare explicit measures of PIP, the STOPP criteria and updated Beers 2012, in terms of their longitudinal association with future adverse health outcomes in older community-dwelling people.

The principal findings are as follows:

- The prevalence of patient reported ADES in this cohort of 605 older community-dwelling people was $74 \%$. The majority (95\%) of ADEs were classified as mild by dual independent review by an academic GP and an academic pharmacist. The most frequently reported ADEs included easy bruising, urinary frequency, ankle swelling and muscle pains. Study participants' median EQ-5D score was 0.80 (IQR 0.66, 1.00) at follow-up. A total of 153 (19\%) study participants attended A\&E at least once, and 199 (25\%) had at least one emergency admission during two-year follow-up.
- The prevalence of PIP at follow-up as defined by the STOPP criteria was 47\% compared to $42 \%$ at baseline, indicating relatively consistent levels of PIP over time.
- $\quad \geq 2$ PIP, as defined by STOPP at baseline, demonstrated a modest longitudinal association with increasing numbers of ADEs ( $\geq 2$ PIP: adjusted IRR; 1.29 (95\% CI $1.03,1.60), p=0.03)$. In the logistic regression analysis where the effect of STOPP PIP on $\geq 1$ ADE was investigated, an association was not established ( $\geq 2$ PIP: adjusted OR 2.06 ( $95 \% \mathrm{Cl} 0.91,4.66$ ), $\mathrm{p}=0.08$ ). However, Poisson modelling has the advantage of allowing inclusion of all established ADEs, rather than the
logistic model approach that categorises ADEs into no ADE versus $\geq 1$ ADE. A total of $74 \%$ of study participants reported an ADE at follow-up but the majority (59\%) reported multiple ADEs. As a result the Poisson regression model is better placed to capture any association between PIP and ADEs.
- STOPP defined PIP was also associated longitudinally with poorer HRQOL $(\geq 2$ PIP: EQ-5D score adjusted coefficient; -0.11 (95\% CI -0.16, -0.06), p<0.001; EQ5D VAS adjusted coefficient; -5.40 (95\% CI -9.34, -1.46 ), p=0.007) and an increased risk of attending A\&E ( $\geq 2$ PIP: adjusted OR 1.85 ( $95 \% \mathrm{CI} 1.06,3.24$ ), $\mathrm{p}=0.03$ ) but not with emergency hospital admission ( $\geq 2$ PIP: adjusted OR 1.00 ( $95 \% \mathrm{Cl} 0.63,1.61$ ), $\mathrm{p}=0.99$ ).
- The baseline prevalence of the Beers 2012 defined PIP in this cohort was lower at $29 \%$, but also remained relatively consistent over time with prevalence of $26 \%$ at follow-up
- PIP, as defined by the updated Beers 2012, at baseline was not associated with future ADEs ( $\geq 2$ PIP: adjusted IRR; $1.00(95 \% \mathrm{CI} 0.78,1.29) \mathrm{p}=0.98$ ), poorer HRQOL ( $\geq 2$ PIP: EQ-5D adjusted coefficient -0.05 ( $95 \% \mathrm{Cl}-0.11,0.003$ ), $\mathrm{p}=0.06$; EQ-5D VAS adjusted coefficient $0.70(95 \% \mathrm{Cl}-374,5.15) \mathrm{p}=0.76$ ) or emergency hospital attendance ( $\geq 2$ PIP: $\geq 1$ A\&E visit adjusted OR 1.54 ( $95 \% \mathrm{CI} 0.88,2.71$ ), $\mathrm{p}=0.13$; $\geq 1$ emergency admission adjusted OR 0.72 ( $95 \% \mathrm{Cl} 0.41,1.28$ ), $\mathrm{p}=0.27$ ).
- Other factors that were independently associated with ADEs in regression analysis were the number of prescribed medication classes and comorbidity. Patient vulnerability (as defined by the VES-13) and screening positive for depression or anxiety at baseline (as per the HADS) were independently associated with reduced HRQOL. Previous emergency hospital attendance and number of prescribed medications were independently associated with emergency admission.


### 4.6.2 Context of this research in comparison with previous literature

### 4.6.2.1 Explicit measures of PIP and future ADE s

This is the first prospective primary care cohort study to examine the longitudinal association of PIP measures, the STOPP criteria and updated Beers 2012 at baseline, with future ADEs in older community-dwelling adults. The limited previous communitybased research in this area has been largely conducted in the US with methodological limitations. In the logistic regression analysis where the effect of STOPP PIP on $\geq 1$ ADE was investigated an association was not established ( $\geq 2$ PIP: adjusted OR 2.06 ( $95 \% \mathrm{Cl}$ $0.91,4.66), p=0.08)$. However in Poisson regression modelling examining the association of STOPP PIP on increasing counts of ADEs at follow-up a longitudinal association was found. Poisson modelling allows inclusion of all ADEs in the model and therefore provides a richer data source. Of the $74 \%$ of study participants who reported an ADE at follow-up the majority (59\%) reported multiple ADEs. As a result the Poisson regression model is better placed to capture an association between PIP and increasing counts of ADEs.

One US primary care study ( $n=236$, aged $\geq 65$ years) used data collected during a RCT prospectively to compare Beers 2003 and the Medication Appropriateness Index (MAI) (an implicit measure of PIP) in predicting ADEs at three month follow-up. This study reported that the MAI predicted future ADEs with adjusted OR 1.13 ( $95 \% \mathrm{Cl} 1.02,1.26$ ) but the Beers 2003 criteria did not.(290) A second US population based prospective study ( $n=626, \geq 65$ years), that ascertained ADE occurrence by postal survey, reported that Beers 2003 did predict ADEs with $\geq 1$ PIP adjusted ORs 2.14 ( $95 \% \mathrm{Cl} 1.26$, 3.65).(226) However, all study participants' had established mobility disability at baseline and, therefore, were not representative of a typical community-dwelling cohort. A Taiwanese study ( $n=500, \geq 65$ years) examined the ability of the Beers 2003 criteria to predict ADEs and reported an increased relative risk (RR 15.3, 95\% CI 4.058.8) with $\geq 1$ PIP compared to no PIP.(288) However, this study was limited by the very short prospective follow-up period of one week. In summary, existing communitybased research has been largely conducted in the US and is limited by methodological
issues (e.g. retrospective study design, unrepresentative study populations and small sample sizes).

Studies comparing PIP according to the STOPP criteria versus the Beers criteria have been conducted in the hospital inpatient setting, albeit using the older iterations of the Beers (1997 and 2003). A recent Italian study ( $n=871, \geq 65$ years) reported that the prescription of $\geq 2$ PIP as per STOPP was associated with future ADEs (adjusted OR 2.36 ( $95 \%$ CI 1.10, 5.06) while the same number of Beers 2003 PIP was not (adjusted OR 2.15 ( $95 \% \mathrm{Cl} 0.90$, 5.14).(290) A second Italian study published in 2009 ( $\mathrm{n}=506, \geq 65$ years) also reported no impact of Beers 2003 PIP on the occurrence of future ADEs.(120) In Ireland, a prospective cohort study conducted in one emergency department ( $\mathrm{n}=600, \geq 65$ years) compared the measurement of PIP using the STOPP criteria compared to the 2003 Beers criteria and subsequent ADEs at a four month follow-up.(111) This study reported that the prescription of $\geq 1$ PIP as per STOPP was associated with ADEs (adjusted ORs 1.85 ( $95 \%$ CI 1.51, 2.26) while $\geq 1$ PIP Beers 2003 was not (adjusted OR 1.28 ( $95 \% \mathrm{Cl} 0.95,1.72$ ).(111) Two other European and South American inpatient studies have not reported any association between Beers identified PIP and subsequent ADEs. $(291,292)$

### 4.6.2.2 Explicit measures of PIP and future HRQOL

This is the first study to examine the prospective impact of PIP as defined by the STOPP criteria compared with the Beers 2012 on future HRQOL. There is very limited literature in this area, with a paucity of community-based research and existing studies having used other measures of PIP such as the MAI and the Beers 2003 iteration. In Ireland, a retrospective cohort study conducted by Cahir et al reported a statistically significant association between $\geq 2$ PIP, as defined by the STOPP criteria, and poorer EQ-5D scores (adjusted coefficient -0.09 (SE 0.02).(224) A retrospective US populationbased study examined the association between Beers 2003 criteria and HRQOL and found no significant association.(114) A recent Malaysian study ( $n=211, \geq 65$ years) recruited patients resident in a nursing home, applied the STOPP criteria to identify PIP and then assessed HRQOL (using the EQ-5D and EQ-5D VAS) at baseline and three-
month follow-up.(308) The authors reported no statistically significant difference in HRQOL. Another residential care study ( $\mathrm{n}=351, \geq 65$ years) examined the crosssectional association of the Beers 2003 criteria and the drugs burden index with HRQOL and reported that exposure to PIP was not associated with reduced HRQOL.(115) It can be difficult to translate changes in EQ-5D scores into clinical impact for patients. According to previous research, the impact of PIP in reducing the EQ-5D by 0.11 is considered clinically significant. Poorer HRQOL can have important implications for future health; one study that recruited 439 older people from two health systems reported that a reduction in EQ-5D of 0.05 increased the risk of death at five year follow-up.(309).

### 4.6.2.3 Explicit measures of PIP and emergency hitzp $\beta$ ttendance

This is the first primary care study to prospectively examine the impact of PIP, as defined by the STOPP criteria and the Beers 2012 criteria, on subsequent A\&E visits and emergency admission. Previous research in this area has focused on the inpatient, emergency room or nursing home settings or has used a retrospective study design.

A prospective Irish study conducted in one ED ( $\mathrm{n}=600, \geq 65$ years) with four month follow-up reported that STOPP associated ADEs were nearly three times more likely to be considered as contributing to emergency admission as Beers 2003 identified ADEs.(111) Another ED study ( $\mathrm{n}=302, \geq 65$ years) reported that $27 \%$ of ADE admissions were associated with the STOPP PIPs.(15) In a large scale US study ( $\mathrm{n}=7,594, \geq 65$ years) of patients receiving nursing home care, the one-year incidence of PIP was $42.1 \%$.(310) These patients were more likely to be hospitalised (adjusted OR 1.27; 95\% CI, 1.10, 1.46) and to die (adjusted OR $1.46 ; 95 \% \mathrm{Cl}, 1.31,1.62$ ) in the 12 months after first receiving a PIP compared to those with no PIP.(310) One Irish community-based retrospective study ( $\mathrm{n}=931$, $\geq 65$ years) has examined the association between PIP and hospital use (A\&E visits/emergency admission/OPD visits).(117) The authors reported that patients with $\geq 2$ STOPP PIP had an increased risk of hospital visits; adjusted IRR 1.32 ( $95 \%$ CI 1.14, 1.54), $\mathrm{p}<0.01$, while PIP identified by the Beers 2012 criteria were not associated with increased hospital visits.(117)

### 4.6.3 Strengths and limitations

This is the first prospective primary care study to investigate and compare the longitudinal association of PIP, identified by the STOPP and Beers 2012 criteria, with future adverse health outcomes for older people. This study was carefully conducted and adhered to the STROBE guidelines for observational research.(223) The risk of bias for the study, as assessed by the Cochrane criteria, was low. Losses to follow-up were minimal and the overall response rate for the two-year follow-up for all outcome measures: ADE interview, postal questionnaire and GP medical record review, was considered very high at 76.5\%. Use of linked national pharmacy claims data (HSE-PCRS) for dispensed medications adds to the robustness of the calculation of the exposure variable (PIP) and confounder variables, such as the number of prescribed medication classes and medication adherence calculated using the MPR. Previous studies have often relied on self-report medication use which may not be as accurate, especially in older populations.(219) A corresponding review of each study participant's GP medical record allowed for accurate recording of both medical diagnoses and healthcare utilisation.

The primary outcome of ADE was ascertained by a very detailed telephone patient interview and a corresponding review of the GP medical record. All reported ADEs were then independently reviewed by two academic GPs, who were blinded to the STOPP and Beers 2012 criteria, and then were reviewed by a different academic GP and academic pharmacist to rate ADEs in terms of severity. Secondary outcomes of EQ-5D for HRQOL were measured using a postal questionnaire and emergency attendance was ascertained by review of GP medical record, rather than depending on self-report measures of healthcare utilisation which are more likely to underestimate health service use. Confounders were carefully considered and this study was able to include several confounders that were not included in previous studies predicting ADEs such as medication adherence, comorbidity and deprivation. In addition for secondary outcomes of HRQOL and emergency attendance, measures of patient vulnerability, social support and depression/anxiety were included as confounders.

There are several limitations to this study. First, this study included 15 general practices in one region of Ireland and as such may not be generalisable to other settings. A total of 14/65 STOPP criteria and 18/53 Beers 2012 criteria could not be applied to the HSE-PCRS pharmacy claims database due to inadequate clinical information or the drug not being licensed for use in Ireland. However, this issue is common to previous studies conducted in this area. $(98,113)$ The prevalence of reported ADEs was high in this population (74\%) when compared to previous studies which ranged from $4.2 \%$ to $62 \% .(89,292)$ Previous community-based research have usually depended on patient self-report questionnaires or surveys to ascertain ADEs, rather than the detailed symptom-based interview with subsequent dual independent academic GP review conducted for this study. $(226,289)$ In addition, reported ADE prevalence at follow-up is broadly similar to that reported at baseline ADE interview (78\%), which used an identical process of outcome measurement.(112)

The vast majority (95\%) of reported ADEs were rated as mild by independent raters. However, considering the associated poorer HRQOL demonstrated in patients with PIP exposure one may argue that these types of 'low level' ADEs, such as constipation and ankle swelling, are a factor in determining overall HRQOL. EQ-5D utility values are not available for Ireland and so the UK population value set was used to calculate scores. An assumption was made that the UK and Irish populations are similar for this measure. The focus of this study was on PIP, rather than prescribing omissions, which may also be associated with increased morbidity. $(311,312)$ Finally, as new evidence emerges medications that were once considered potentially inappropriate may no longer be, highlighting the importance of revising prescribing indicators sets regularly to ensure they reflect the most up to date evidence.

### 4.6.4 Clinical and future research implications

This study adds to the relatively limited evidence base on the role of explicit measures of PIP in determining health outcomes for older people in primary care. Older people are particularly vulnerable to medication-related harm and with increasing multimorbidity and associated polypharmacy; optimising safe prescribing will be a key
challenge for prescribers into the future. This study indicates that PIP has an independent association, beyond that of polypharmacy alone, with adverse health outcomes for older people.

The concept of deprescribing (the tapering or cessation of a medication) has emerged in recent times but clinicians often find this process challenging.(46) One difficulty is the lack of evidence-based guidance to support this process, and the issue of clinical guidelines adopting a 'single disease' focus that do not take the realities of multimorbidity and polypharmacy into account. $(308,313)$ Other barriers include concern about stopping medications started by different clinicians, limited knowledge about which medications should be prioritised for cessation, and concern about medication withdrawal effects.(46) Explicit prescribing criteria such as STOPP that are linked to future adverse health outcomes offer a useful and evidence-based tool for clinicians to support medication reviews and deprescribing decisions. There is some RCT evidence to support this approach. A recent Irish primary care trial ( $\mathrm{n}=196$ patients aged $\geq 70$ years), the OPTI-SCRIPT study, used the STOPP criteria to identify PIP and then implemented a multifaceted intervention involving academic detailing by a pharmacist and GP-led medication review of PIP supported by a web-based algorithm. This intervention successfully reduced PIP at six month follow-up (\% with no PIP; intervention arm 47.5\% vs. control arm 22.7\%: OR 3.1 95\% CI 1.4, 6.5, NNT=4).(314) However, the reduction in PIP in this trial was largely driven by a dose reduction in proton pump inhibitor prescriptions which, arguably, are easier medications to target clinically. A larger scale definitive trial is currently underway by the same study group focusing on higher-risk medications such as long-term NSAIDs.

A Norwegian cluster RCT ( $\mathrm{n}=465 \mathrm{GPs}$ ) selected 13 PIPs and reported that peer academic detailing with audit and feedback produced a $10 \%(95 \% \mathrm{Cl} 5.9,15.0)$ relative reduction in PIP compared to baseline for older people aged $\geq 70$ years.(45) Primary care research in this area however remains limited and further RCTs are needed to define the role of explicit prescribing criteria in informing targeted medication reviews to reduce PIP in primary care and to measure the impact of this process on relevant
patient outcomes. The current study supports the use of the STOPP criteria as an explicit prescribing measure of choice in planning future Irish primary care trials.

### 4.6.5 Healthcare policy implications

Recognising and reducing PIP offers significant potential to improve prescribing quality and patient outcomes. Prescribed medications represent a significant cost for the healthcare service. One large scale Irish population based study examined the potential cost savings in relation to optimising proton pump inhibitor prescribing and estimated that over $€ 36$ million could be saved annually by use of generic substitution and over $€ 40$ million with dose reduction in line with clinical guidelines. (284) In Ireland, the HSE (Pricing and Medical Goods) Act 2013 recently introduced a legal framework for generic substitution and reference pricing of medications and the Medicines Management programme has launched preferred drugs for certain drug classes such as statins, SSRIs and PPIs.(315)

These legislative changes occur on a backdrop of considerable change within the Irish healthcare system. The current government plans to introduce GP care that is free of charge for all and, to date, this has been introduced for children aged <6 years and very recently for all older people aged $\geq 70$ years. The Irish GP contract is also currently under negotiation. These system changes, though at times challenging, do offer unprecedented scope to influence contractual changes that prioritise the optimisation of quality prescribing practices. The STOPP criteria may be a useful tool for use in primary care to support this process.

### 4.7 Conclusion

Explicit prescribing criteria are designed to identify medications that are potentially inappropriate and are not intended to substitute clinical judgement. This study indicates that the STOPP PIP criteria are associated with future mild ADEs, poorer health related quality of life and A\&E visits in older community-dwelling people. While there will be a clinical indication for a proportion of medications identified as potentially inappropriate by the STOPP criteria, they do offer an evidence-based
support for GPs in conducting medication reviews and promoting deprescribing for older people.

Chapter 5 Comparison of measures of multimorbidity and vulnerability in predicting emergency hospital admission and functional decline in older community-dwelling adults

### 5.1 Introduction

Characterising the impact of multimorbidity and vulnerability in predicting health outcomes in older people have emerged as important concepts in the last decade. This chapter focuses on comparing the predictive accuracy of five different count measures of multimorbidity and a measure of vulnerability in predicting emergency admission and functional decline in older community-dwelling adults.

### 5.2 Count measures of multimorbidity

A recent systematic review indicated that simple disease counts, the Charlson comorbidity index and the Adjusted Clinical Groups (ACG) system are the most commonly utilised measures of multimorbidity in the primary care and community settings.(28) However, research comparing different multimorbidity measures for relevant patient outcomes is relatively limited as discussed in Section 2.3.1.(28) Existing morbidity indexes, such as the Charlson index, that weight diagnoses in terms of their impact seem to offer more scope for considering patient outcomes.(28) However research that has validated different measures concludes that simple disease counts and medication counts appear to be as accurate in predicting mortality and healthcare expenditure, than more complex measures, and are simpler to apply.(121, 122) A recent systematic review concluded that diagnosis-based measures (e.g. ACG system) perform best in predicting mortality outcomes while medication-based indices (e.g. RxRisk) demonstrated better predictive accuracy for health care utilisation.(29) However, these results are largely based on the validation of measures in different populations rather than direct comparison of different measures in the same population.(29)

To date there is little consensus regarding which chronic medical conditions to include in diagnosis-based measures of multimorbidity, largely due to studies not specifying criteria for inclusion of chronic conditions.(124) Three factors are considered important: (i) the prevalence of the condition; (ii) chronic conditions associated with an increased mortality rate; and (iii) the impact of the condition on function or need for intensified management. A recent large-scale Scottish study by Barnett et al has
adopted this approach and developed a set of 40 medical conditions based on condition prevalence and impact on health outcomes.(23)

Utilising a count-based approach in measuring multimorbidity has several advantages. First it is reasonably simple to apply, particularly important for routinely collected data. Second, it is easier to replicate which has important implications for achieving consistent definitions of multimorbidity across different research studies. Third, having a clearer understanding of the advantages of using one of the multimorbidity measures preferentially may be helpful for researchers in defining multimorbidity when designing interventions designed to target community-dwelling older people.

Primary care research comparing different measures of multimorbidity in predicting health outcomes is relatively limited and has largely focussed on mortality and healthcare costs outcomes.( $60,62,122,297,316-320$ ) Existing studies have also had some methodological limitations (e.g. use of cross-sectional study design) and some studies have used a narrow definition of multimorbidity (e.g. index chronic condition plus another condition) which reduces generalisability. Very few community-based studies have investigated the performance of different multimorbidity measures in predicting other relevant outcomes such as emergency admission and functional decline (See Table 5-1).

Brilleman at al examined the association of different multimorbidity measures with primary care consultations and mortality rates in a UK cross-sectional analysis ( $\mathrm{n}=95,372$ adults) using a large GP research database.(121) This study compared several multimorbidity counts as follows: i) QOF chronic disease counts; ii) the Charlson index; iii) medication counts; and iv) the ACG system and reported that the Charlson index performed best overall.(121) Quail et al examined different multimorbidity count measures for predicting future hospital admission using a population administrative database which covers one region of Canada.(321) The best performing measure for older people ( $n=137,700$ aged $\geq 65$ years) in this study was simple disease counts but this measure had poor discrimination (c-statistic: $0.6795 \%$ $\mathrm{Cl} 0.66,0.67$ ) for predicting hospital admission.(321) The utility of multimorbidity
measures in predicting other outcomes such as functional decline has also been examined. In one prospective cohort study of older ( $\geq 65$ years) Italian communitydwelling people ( $n=688$ ) disease counts were found to predict functional decline most accurately when compared to other diagnosis-based measures such as the Charlson comorbidity index.(322)

Table 5-1: Community-based studies that compare different count-based measures of multimorbidity for adverse health outcomes

| Author, year | Study population, study design, study setting | Multimorbidity measures | Outcome(s) | Results |
| :---: | :---: | :---: | :---: | :---: |
| Brilleman, 2013(121) | $\mathrm{N}=95372$ adults, $\mathrm{n}=174$ <br> English GP practices, crosssectional | 1. Count of QOF chronic diseases <br> 2. Charlson index <br> 3. Count of prescribed drugs <br> 4. Three measures from the John Hopkins ACG software | Primary care consultations Mortality | Charlson index best predictive accuracy for both outcomes: Akaike's Information Criterion (AIC) 19226 and Bayesian Information Criterion (BIC) 19443: deviance based $\mathrm{R}_{2} 31.3 \%$ |
| Quail, 2011(321) | $\mathrm{N}=662,423$ general population aged $\geq 20$ years, subset $\mathrm{n}=137,700$ aged $\geq 65$ years Saskatchewan, Canada, retrospective cohort study using a longitudinal administrative database | 1. Disease counts <br> 2. Charlson index <br> 3. Elixhauser index <br> 4. Number of medications <br> 5. Chronic Disease score | Hospital admission <br> Mortality | In the older ( $\geq 65$ years) subset for outcome of $\geq 1$ hospital admission c-statistic ( $95 \% \mathrm{Cl}$ ): <br> Disease count: $0.668(0.664,0.671)$ <br> Charlson index: $0.613(0.610,0.616)$ <br> Elixhauser index: $0.630(0.627,0.633)$ <br> Number of medications: $0.625(0.622,0.628)$ <br> Chronic disease score: $0.604(0.601,0.607)$ <br> For outcome of mortality: the Elixhauser index had best predictive accuracy ( $0.805,95 \% \mathrm{Cl} 0.799,0.810$ ) |
| DiBari, 2006(322) | $N=688$ adults aged $\geq 65$ years in one region of Italy, prospective cohort study | 1. Disease count <br> 2. Charlson Comorbidity Index <br> 3. Index of Co-Existent Diseases Geriatric Index of Comorbidity <br> 4. Chronic Disease Score (medication based) | Functional decline Mortality | Disease count, Charlson Comorbidity Index and the Index of Co-Existent Diseases best predictive accuracy for functional decline and mortality. |


| Author, year | Study population, study design, study setting | Multimorbidity measures | Outcome(s) | Results |
| :---: | :---: | :---: | :---: | :---: |
| Fan, 2006(323) | $N=14,192$ adult veterans, US | 1. Seattle index of comorbidity <br> 2. RxRisk <br> 3. Charlson comorbidity index <br> 4. ACG software | Hospital admission <br> Mortality | All models similar discrimination (c-statistic range $0.73-0.74$ ). Adjusted Clinical Groups less accurate in predicting mortality. Administrative measures better than self-report in predicting hospitalisation. |
| Fortin, 2005(324) | $\mathrm{N}=238$ attending primary care in Canada, crosssectional | 1. Cumulative IIlness Rating Scale (CIRS) <br> 2. Charlson index <br> 3. Functional Comorbidity Index | HRQOL | CIRS negatively correlated with all scales of SF-36 except the Mental Component Summary |
| Bayliss, 2005(325) | $\mathrm{N}=157$ primary care, US, survey | 1. Disease burden (the number of conditions weighted by the degree each interfered with daily activities) <br> 2. Disease count <br> 3. Charlson Comorbidity Index <br> 4. RxRisk score (medication based) | HRQOL | Disease burden predicted poorer HRQOL best |
| Dominick, 2005(326) | $\mathrm{N}=306$ with osteoarthritis in Veterans affairs system, US, cross-sectional | 1. Charlson index <br> 2. Elixhauser comorbidity index <br> 3. RxRisk-V (medication based) | Health service use <br> Prescription medication use | RxRisk-V index best for the outcome of prescription medication use <br> Elixhauser index best for the outcome of physician visits |
| Parker, 2003(321) | $\mathrm{N}=6721 \text { acute }$ hospitalisations from Kaiser Permanente California | 1. Deyo Charlson index <br> 2. Chronic Disease score | Hospital readmission | Similar performance by both indices. CDS was a reasonable predictor of unplanned readmission (cstatistic $=0.68$ ) and Deyo measure was a reasonable predictor of all-cause readmission ( $c$-statistic $=0.63$ ) |

### 5.3 Vulnerability

The term 'vulnerable' in gerontology research relates to older people at increased risk of functional decline or death.(32) As the population of older people expands, it becomes increasingly important to have accurate methods of identifying high-risk people for appropriate intervention. The Vulnerable Elder's Survey-13 (VES-13) was designed to predict functional decline and death in older ( $\mathbf{2 6 5}$ years) US people over two years follow-up and has been successfully validated in several US studies.(32, 241, 327,328 ) One US study ( $\mathrm{n}=649, \geq 75$ years) reported that for each additional VES-13 point the odds of functional decline or death increased by almost 40\% (OR 1.37 (95\% CI 1.25, 1.50) and the model's c-statistic was 0.75 ( $95 \% \mathrm{Cl} 0.71,0.80$ ) over five-year follow-up.(241) Validation of the VES-13 in Europe has, however, been very limited. One cross-sectional Irish study ( $\mathrm{n}=2,033$ aged $\geq 65$ years) reported that people categorised as vulnerable (32\%) by the VES-13 had higher healthcare utilisation including primary care visits, A\&E visits and use of hospital services.(242)

The aim of the study presented in this chapter is to compare the performance of five different count-based measures of multimorbidity and a measure of vulnerability in predicting emergency hospital admission and functional decline in older communitydwelling adults.

### 5.4 Methods

The two year prospective cohort described in Chapter 3 was utilised to compare the predictive accuracy of different measures of multimorbidity and vulnerability in older community-dwelling adults.

### 5.4.1 Exposure of interest: 1) Measures of multimorbidity

Three diagnosis-based measures of multimorbidity and two medication-based measures were investigated. These measures were all calculated using baseline data. The measures are described in more detail below.

### 5.4.1.1 Total disease counts

This measure involves a simple count of chronic medical conditions. Chronic medical conditions were recorded from the GP electronic medical record. The definition of a chronic disease for the purposes of this study is described in Section 3.1.5.5. The ICPC2 classification system was used to record and classify conditions.(280) Multimorbidity was defined as the presence of $\geq 2$ conditions in an individual.(4)

### 5.4.1.2 Barnett conditions disease count

Barnett et al developed a set of 40 chronic medical conditions using a large primary care Scottish cohort of over 1.75 million adults.(23) In the original study chronic conditions were selected based on health impact and prevalence considering the following; i) conditions recommended for inclusion by any multimorbidity measure in a systematic review, ii) conditions in the QOF for UK general practice, and iii) long-term conditions identified as important by NHS Scotland.(23) For morbidities which have lifelong implications, such as congestive heart failure, the presence of the morbidity was on the basis of the condition ever being recorded in the GP record. However, for other conditions where lifelong remission or cure is possible, the presence of the morbidity had to be recorded in a defined period (e.g. cancer recorded in the previous five years), or in terms of the presence of relevant prescribing in the previous year (e.g. epilepsy currently treated).(23) Of note the authors were not able to take condition severity into account as the condition set was developed using a research database and information regarding condition severity was not available. A full list of the Barnett chronic conditions including definitions for inclusion is presented in Table 5-2 and the definition for multimorbidity was $\geq 2$ conditions.

Table 5-2: Barnett chronic medical conditions ranked according to prevalence with definitions for inclusion as a chronic disease(23)

| Condition | Read code definition for inclusion as a chronic disease* |
| :---: | :---: |
| Hypertension | Read code ever recorded |
| Depression | Read code recorded in last 12 months or $\geq 4$ anti-depressant prescriptions (excluding low dose TCAs) in last 12 months |
| Painful condition | $\geq 4$ prescription only analgesic prescriptions in last 12 months or $\geq 4$ specified anti-epileptics in the absence of epilepsy |
| Asthma (currently treated) | Read code ever recorded and any prescription in last 12 months |
| Coronary heart disease | Read code ever recorded |
| Treated dyspepsia | $\geq 4$ prescriptions in last 12 months BNF 0103\% excluding antacids and not ( $\geq 4$ NSAIDS OR $\geq 4$ aspirin/clopidogrel) |
| Diabetes mellitus | Read code ever recorded |
| Thyroid disorders | Read code ever recorded |
| Rheumatoid arthritis, other inflammatory polyarthropathies and systematic connective tissue disorders | Read code ever recorded |
| Hearing loss | Read code ever recorded |
| Chronic obstructive pulmonary disease | Read code ever recorded |
| Anxiety and other neurotic, stress related \& somatoform disorders | Read code in last 12 months or $\geq 4$ anxiolytic/hypnotic prescriptions in last 12 months or $\geq 410 / 25 \mathrm{mg}$ amitriptyline in last 12 months \& do not meet the criteria for 'Pain' |
| Irritable bowel syndrome | Read code ever recorded or $\geq 4$ prescription only medicine antispasmodic prescription in last 12 months |
| New diagnosis of cancer in last five years | Read code first recorded in last 5 years |
| Alcohol problems | Read code ever recorded |
| Other psychoactive substance misuse | Read code ever recorded |


| Condition | Read code definition for inclusion as a chronic disease* |
| :--- | :--- |
| Treated constipation | $\geq 4$ laxative prescriptions in last year |
| Stroke \& transient ischaemic attack | Read code ever recorded |
| Chronic kidney disease | Read code ever recorded |
| Diverticular disease of intestine | Read code ever recorded |
| Atrial fibrillation | Read code ever recorded |
| Peripheral vascular disease | Read code ever recorded |
| Heart failure | Read code ever recorded |
| Prostate disorders | Read code ever recorded |
| Glaucoma | Read code ever recorded and antiepileptic prescription in last 12 months |
| Epilepsy (currently treated) | Read code ever recorded |
| Dementia | Read code ever recorded/recorded in last 12 months (code dependent) or Lithium prescribed in last 168 days |
| Schizophrenia (and related non-organic |  |
| psychosis) or bipolar disorder | Read code ever recorded AND $\geq 4$ related prescriptions in last 12 months (excluding simple emollients) |
| Psoriasis or eczema | Read code ever recorded |
| Inflammatory bowel disease | $\geq 4$ prescription only medicine anti-migraine prescriptions in last year |
| Migraine | Read code ever recorded |
| Blindness \& low vision | Read code ever recorded |
| Chronic sinusitis | Read code ever recorded |
| Learning disability | Read code ever recorded |
| Anorexia or bulimia | Read code ever recorded |
| Bronchiectasis |  |


| Condition | Read code definition for inclusion as a chronic disease* |
| :--- | :--- |
| Parkinson's disease | Read code ever recorded |
| Multiple sclerosis | Read code ever recorded |
| Viral Hepatitis | Read code ever recorded |
| Chronic liver disease | Read code ever recorded |

* Read codes are the standard clinical terminology system used in general practice in the UK. It supports detailed clinical coding of multiple patient phenomena including: occupation; social circumstances; ethnicity; clinical signs, symptoms and observations; laboratory tests and results; diagnoses; diagnostic, therapeutic or surgical procedures performed; and a variety of administrative items.


### 5.4.1.3 C harlson comorbidity index

The Charlson comorbidity index has been described in Section 3.1.5.5. In brief, this measure was developed in an inpatient US population to predict mortality and includes 19 conditions that have been selected and weighted in relation to their association with mortality risk. $(263,264)$ (See Figure 5-1) Medical conditions recorded from the GP record were reviewed and each study participant was assigned a score based on the components of the Charlson index. (Emma Wallace)

| Condition | Weighted score |
| :--- | :---: |
| Myocardial infarction | I |
| Biventricular heart failure | I |
| Peripheral vascular disease | I |
| Cerebrovascular disease | I |
| Dementia | I |
| Chronic pulmonary disease | I |
| Connective tissue disease | I |
| Peptic ulcer disease | I |
| Mild liver disease | I |
| Diabetes with no end-organ damage | 1 |
| Hemiplegia from any cause | 2 |
| Moderate/severe renal disease | 2 |
| Diabetes with end-organ damage | 2 |
| Any tumor | 2 |
| Leukemia | 2 |
| Lymphoma | 2 |
| Moderate or severe liver disease | 3 |
| Metastatic solid tumor | 6 |
| AIDS | 6 |

Figure 5-1: Medical conditions included as part of the Charlson index and their weighted scores(263)

### 5.4.1.4 Number of dispensed medications

This measure was a simple count of the number of participants' dispensed medication classes. Medications were recorded from the linked HSE-PCRS pharmacy claims database as described in Chapter 3. Polypharmacy is usually defined as the concurrent prescription of four or more medications but there is also increasing interest in the risk associated with very
high levels of medication counts usually defined as $\geq 10$ medications (high-risk polypharmacy). $(9,55)$ For the purposes of data analysis number of medications was considered as a continuous variable.

### 5.4.1.5 RxR isK

The RxRisk-V has been described in Section 3.1.5.5. This measure was developed specifically for older people and classifies patients' chronic medical conditions based on the WHO-ATC medication classification system of their dispensed medications.(266) In validation studies the RxRisk-V has demonstrated both criterion validity and reliability when compared to patients' medical diagnoses.(28) The RxRisk-V was calculated using the linked HSE-PCRS pharmacy claims data and included in data analysis as a continuous variable.

### 5.4.2 Exposure of interest: 2) Vulnerability

Vulnerability was assessed using the Vulnerable Elder's Survey (VES-13) described in Section 3.1.4.3. Developed in 1993 in an older US Medicare population ( $n=6,205$ ) to predict functional decline and death over two-year follow-up, it has been validated to predict functional decline over five years follow-up. $(32,241)$ The VES-13 was developed through a methodologically robust process whereby variables with potential predictive power were identified from the Medicare database and then different models tested for outcome of functional decline and death.(32) The final VES-13 model includes items relating to patient age, self-rated health, ability to perform six physical tasks (e.g. writing or handing small objects, walking quarter of a mile, lifting) and five items relating to function (e.g. bathing, managing finances, light housework).(32) A score of $\geq 3$ is considered high-risk of experiencing future functional decline. This survey was administered via postal questionnaire at baseline and again at follow-up.(32) (See Appendix 5)

### 5.4.3 Outcomes of interest

### 5.4.3.1 Emergency admission

The definition of emergency admission used for the purposes of this study is presented in Section 3.1.4.8. As previously described emergency admission was recorded from review of
the participant's GP electronic medical record. The numbers of emergency admissions, reason for admission, length of hospital stay and date of admission and discharge was recorded over two years of follow-up. In addition, ACS admissions were identified. As described in Section 2.4.5, these are a subset of all emergency admissions that occur due to select medical conditions (e.g. COPD, congestive heart failure (CHF) and cellulitis) that are considered more amenable to prevention through primary care management.(329) A list of ACS conditions is provided in Table 5-3. Reasons for emergency admissions were reviewed and those resulting from any one of the ACS conditions listed in Table 5-3 were coded as an ACS admission.

Table 5-3: Ambulatory care sensitive conditions as defined by the Australian Victoria State Health Department

| Acute conditions | Chronic conditions | Other and vaccine- <br> preventable conditions |
| :--- | :--- | :--- |
| Cellulitis | Angina | Influenza |
| Dehydration | Asthma | Pneumonia |
| Dental conditions | COPD | Other vaccine-preventable |
| Ear, nose and throat infections | Congestive heart failure |  |
| Gangrene | Convulsions and epilepsy |  |
| Gastroenteritis | Diabetes complications |  |
| Nutritional deficiencies | Hypertension |  |
| Pelvic inflammatory disease | Iron deficiency anaemia |  |
| Perforated/bleeding ulcer |  |  |

### 5.4.3.2 Functional decline

The short functional survey, a subset of the VES-13, was used as the measure of functional status (See Appendix 5). This five-item measure has been used in previous cohort studies of older community-dwelling people and has reported similar accuracy in predicting physical functional decline as the use of a longer 12-item Activities of Daily Living scale. $(241,298)$ These five questions are;

Because of your health or a physical condition do you have any difficulty?
a) Shopping for personal items (like toilet items or medicines)
b) Managing money (like keeping track of expenses or paying bills)
c) Walking across the room (use of a cane or walker is ok)
d) Doing light housework (like washing dishes, straightening up, light cleaning)
e) Bathing or showering

Disability in the activity was defined as 'having difficulty and receiving help to perform the activity' or 'not doing the activity due to their health'. Functional ability was assumed for all other possible responses to the questions ('no difficulty', 'difficulty but does not receive help' or 'not doing the activity but for reasons other than health'). Disability in each item was awarded a score of one so a person unable to complete all five tasks was scored five. Functional decline over the two year period was defined as a reduction in the short functional survey score by at least one point between baseline and follow-up. This was calculated by subtracting the baseline ability score from the follow-up score.(298) In addition, any study participant who entered a nursing home during the follow-up period was also considered to have functionally declined.(298) This approach has been used in previous studies investigating functional decline in older community-dwelling adults.(241, 298)

### 5.4.4 Confounding variables

Each multimorbidity measure was adjusted for three confounding variables; age, gender and deprivation. This is in keeping with previous studies examining the predictive ability of these count measures on health outcomes. $(317,321,322)$ Age and gender were determined from the GP medical record. Each patient's address was geocoded according to electoral division and patient deprivation was estimated from the deprivation score of the patient's address as described in Section 3.1.5.4. In brief, electoral division deprivation level was based on the Small Area Health Research Unit (SAHRU), which shares similarities with the Townsend and Carstairs deprivation indices widely used in the UK.(330)

### 5.4.5 Statistical analysis

Baseline descriptive statistics of the cohort are described. The performance of each measure was assessed initially by investigating the discrimination which is equivalent to the area under the receiving operating curve (AUC). This score ranges from 0 to 1 where a value of 0.5 represents the same performance as chance and a value of 0.5-0.7 represents poor model discrimination. Values between $0.7-0.9$ represent reasonable predictive accuracy while a value of $\geq 0.9$ represents excellent model discrimination.(331) Discrimination was assessed using the non-parametric method by calculating a c-statistic with $95 \%$ confidence intervals for each multimorbidity measure (e.g. disease count, medication count), and the VES-13 score considered as continuous variables.

For the multimorbidity count measures analysis, different cut-off points within the same measure were examined to see which offered optimal discrimination for the outcome of interest (e.g. 0 conditions vs. 1 condition, $0-1$ conditions vs. 2 conditions, $0-2$ conditions vs. 3 conditions, $0-3$ conditions vs. 4 conditions etc.). Once the optimal cut-off point was established for each measure, all five multimorbidity measures were compared to examine which offered the best discrimination for each of the outcomes of interest (i.e. emergency admission, ACS admission and functional decline). These measures were then adjusted for age, gender and deprivation to see how this impacted overall predictive accuracy. A series of receiver operating curves (ROC) plots were generated to examine visually the differences between the various measures in predicting the outcomes of interest. Model goodness of fit was assessed using the Hosmer-Lemeshow statistic. All analyses were conducted using Stata Version 13.(304) The 'rocreg'command was used to generate c-statistics and the 'rocreg plot' command to generate ROC curves. These commands incorporate bootstrapping in order to obtain the standard error of the c -statistic and the $95 \%$ confidence intervals.

### 5.5 Results

### 5.5.1 Emergency admission outcome

### 5.5.1.1 Baseline characteristics

Of 904 baseline study participants, a total of 862 (95\%) were included in this two year follow-up study. Participants were excluded if there was incomplete hospital admission data for the follow-up period. The reasons for exclusion were: 19 moved GP practice; 14 moved to a nursing home; and 9 GP medical record reviews were missing. A sensitivity analysis was conducted, excluding participants who had died during follow-up ( $n=53$ ), which made no appreciable difference to the overall results. The baseline characteristics of the study participants are presented in Table 5-4.

Table 5-4: Baseline characteristics of study participants' ( $n=862$ )

| Patient characteristic | Median (IQR) |
| :--- | :--- |
| Age | $77(73,81)$ |
| Deprivation | $1.33(-0.64,3.04)$ |
| Gender |  |
| Male |  |
| Female | $404(47)$ |
| Marital status~ | $458(53)$ |
| Married |  |
| Separated/Divorced | $393(45)$ |
| Widowed | $42(5)$ |
| Never married/single | $278(32)$ |
| Living arrangements ${ }^{\prime \prime}$ | $148(17)$ |
| Husband/Wife/Partner | $383(44)$ |
| Family/Relatives | $110(13)$ |
| Live alone | $327(38)$ |
| Other | $42(5)$ |
| Education* | $536(62)$ |
| Basic education | $325(38)$ |
| Upper and post-secondary |  |
| Social class | $326(38)$ |
| Unskilled |  |

$\sim$ Marital status was missing for $n=1$. *Education was missing for $n=6$.

### 5.5.1.2 Multimorbidity measures

The number and proportion of study participants according to their number of chronic medical conditions as defined by each of the five multimorbidity measures are presented in Table 5-5. For the diagnosis-based measures a total of 626 study participants (73\%) met the definition for multimorbidity according to the total disease counts measure and 484 study participants' (56\%) according to the Barnett condition count measure. Three hundred and fourteen study participants (37\%) scored $\geq 2$ using the Charlson index. For the medication count measures, a total of 789 study participants ( $91 \%$ ) had $\geq 2$ chronic conditions according to the RxRisk-V and 73\% ( $n=632$ ) met the definition for polypharmacy ( $\geq 4$ medications) with $13 \%(n=119)$ prescribed 10 or more medications (high-risk polypharmacy).

Table 5-5: Number and percentage of study participants with medication-based and diagnosis-based measures of multimorbidity ( $\mathrm{n}=862$ )

| RxRisk $-\mathrm{V}$ | N (\%) | Number of medication classes | N (\%) | Total disease counts | N (\%) | Barnett conditio ns count | N (\%) | Charlson index score | N (\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 0 | 13 (2) | 0 | 37 (4) | 0 | 52 (6) | 0 | 149 (17) | 0 | 340 (39) |
| 1 | 60 (7) | 1 | 41 (5) | 1 | 184 (21) | 1 | 229 (27) | 1 | 208 (24) |
| $\geq 2$ | 789 (91) | $\geq 2$ | 789 (91) | $\geq 2$ | 626 (73) | $\geq 2$ | 484 (56) | $\geq 2$ | 314 (37) |
| 2 | 96 (11) | 2 | 75 (9) | 2 | 208 (24) | 2 | 213 (25) | 2 | 159 (19) |
| 3 | 125 (15) | 3 | 77 (9) | 3 | 157 (18) | 3 | 134 (16) | 3 | 85 (10) |
| 4 | 131 (15) | 4 | 95 (11) | 4 | 102 (12) | 4 | 79 (9) | 4 | 36 (4) |
| 5 | 114 (13) | 5 | 88 (10) | 5 | 79 (9) | 5 | 35 (4) | 5 | 17 (2) |
| 6 | 101 (12) | 6 | 116 (14) | 6 | 49 (6) | $\geq 6$ | 23 (2) | $\geq 6$ | 17 (2) |
| 7 | 78 (9) | 7 | 88 (10) | 7 | 17 (2) |  |  |  |  |
| 8 | 57 (7) | 8 | 62 (7) | $\geq 8$ | 14 (2) |  |  |  |  |
| 9 | 37 (4) | 9 | 64 (7) |  |  |  |  |  |  |
| $\geq 10$ | 50 (5) | $\geq 10$ | 119 (13) |  |  |  |  |  |  |

### 5.5.1.3 Vulnerable Elders S urvel3 (VE S13)

A total of 673 study participants who completed the baseline VES-13 also returned the postal questionnaire at follow-up and therefore functional decline could be calculated. Of this group 223 participants ( $33 \%$ ) were categorised as vulnerable (score $\geq 3$ ) on the VES-13 at baseline.

### 5.5.1.4 Emergency admission

A total of 246 study participants (29\%) were admitted as an emergency at least once during two-year follow-up. Of these 159 (18\%) were admitted once, 56 (7\%) were admitted twice and 31 (4\%) were admitted $\geq 3$ times. A total of 110 study participants ( $13 \%$ ) had an ACS emergency admission. Fifty-three study participants (6\%) died during follow-up. Statistical analysis was carried out for the outcome of emergency admission or death ( $\mathrm{n}=862$ ) and then a sensitivity analysis was conducted for the outcome of emergency admission alone.

All multimorbidity measures were examined in unadjusted analysis for the outcomes of $\geq 1$ emergency admission and $\geq 1$ ACS admission. The Hosmer-Lemeshow statistic was not statistically significant for any of the adjusted models indicating that model fit was adequate. For the outcome of emergency admission, all multimorbidity measures had very similar predictive accuracy (c-statistic range: 0.62 to 0.65 ). In unadjusted analysis, while all measures had poor discrimination, the models with greatest predictive accuracy were the RxRisk-V and number of medications. Following adjustment for age, gender and deprivation the Barnett condition count (c-statistic: 0.63 ( $95 \% \mathrm{Cl} 0.57,0.69$ )) and the RxRisk-V (cstatistic: 0.63 ( $95 \% \mathrm{Cl} 0.56,0.69$ )) were best of the five models for the outcome of emergency admission.

For the outcome of ACS admission overall performance was marginally better (c statistic range: 0.63-0.68). In unadjusted analysis the RxRisk-V and number of medications performed best. Following adjustment for age, gender and deprivation the Charlson index (c statistic: 0.67 ( $95 \% \mathrm{Cl} 0.58,0.75$ ), RxRisk-V (c statistic: 0.67 ( $95 \% \mathrm{Cl} 0.61,0.73$ ) and medication count (c-statistic: $0.67(95 \% \mathrm{Cl} 0.59,0.75)$ all demonstrated very similar poor predictive accuracy for ACS admission. The VES-13 demonstrated very poor discrimination
for the outcome of emergency admission (c statistic: 0.57 ( $95 \% \mathrm{Cl} 0.53,0.61$ )) and improved, though still poor, discrimination for the outcome of ACS admission (c statistic: $0.64(95 \% \mathrm{Cl}$ $0.60,0.68)$ ).

Table 5-6: Multimorbidity and vulnerability measures comparison for outcomes of $\geq 1$ emergency admission and $\geq 1$ ACS admission during two-year follow-up ( $\mathrm{n}=862$ )

| Model* | $\geq 1$ emergency admission |  | $\geq 1$ ACS admission |  |
| :---: | :---: | :---: | :---: | :---: |
| Multimorbidity measure | c-statistic (95\% <br> CI ) unadjusted | c-statistic (95\% <br> CI) adjusted^ | c-statistic (95\% <br> CI ) unadjusted | c-statistic ( $95 \% \mathrm{Cl}$ ) adjusted^ |
| Disease count | 0.63 (0.59, 0.66) | 0.61 (0.54, 0.68) | 0.63 (0.57, 0.69) | 0.64 (0.57, 0.71) |
| Barnett conditions count | 0.63 (0.60, 0.66) | 0.63 (0.57, 0.69) | 0.65 (0.58, 0.71) | 0.66 (0.59, 0.73) |
| Charlson index | 0.62 (0.59, 0.65) | 0.58 (0.54, 0.63) | 0.67 (0.63, 0.71) | 0.67 (0.58, 0.75) |
| RxRisk-V | 0.65 (0.61, 0.69) | 0.63 (0.56, 0.69) | 0.68 (0.62, 0.73) | 0.67 (0.61, 0.73) |
| Number of medications | 0.65 (0.61, 0.69) | 0.62 (0.55, 0.68) | 0.68 (0.62, 0.74) | 0.67 (0.59, 0.75) |
| Vulnerability measure | c-statistic (95\% <br> CI) unadjusted | c-statistic (95\% <br> $\mathrm{Cl})$ adjusted | c-statistic (95\% <br> CI) unadjusted | c-statistic ( $95 \% \mathrm{Cl}$ ) adjusted |
| VES-13 | 0.57 (0.53, 0.61) | $N A^{\text {S }}$ | 0.64 (0.60, 0.68) | $N A^{\text {s }}$ |

* All measures are included as continuous variables. ^ Adjusted for age, gender and deprivation. ${ }^{\text {§ }}$ NA=Not applicable. The VES-13 is a risk score developed using multivariate analysis and consists of 13 items including age.


### 5.5.1.5 Choosing an optimal cupoint for count measures of multimorbidity

Each multimorbidity measure was then examined at different cut-points to determine the condition or medication count that demonstrated the optimal discriminative ability for the different outcomes of interest. For the diagnosis-based measures cut-off points to a maximum of $\geq 6$ were examined, and for the medication-based measures cut-off points to a maximum of $\geq 10$ were investigated. The c -statistics at different cut-points for the outcome
of emergency admission are presented in Table 5-7. The optimal count cut-points for the outcome of emergency admission were as follows: i) RxRisk-V $\geq 6$; ii) Number of medications $\geq 6$; iii) Disease count $\geq 3$; iv) Barnett condition count $\geq 2$; and v) Charlson index $\geq 1$.

Table 5-7: C-statistics ( $95 \% \mathrm{CI}$ ) for the outcome of $\geq 1$ emergency admission ( $\mathrm{n}=862$ ) by different cut-points of the multimorbidity measures

| Count cut- <br> point | RxRisk-V | Number of <br> medication <br> classes | Disease count | Barnett <br> conditions count | Charlson index |
| :--- | :--- | :--- | :--- | :--- | :--- |
|  | c-statistic (95\% | c-statistic (95\% | c-statistic (95\% | c-statistic (95\% | c-statistic (95\% CI) |
|  | CI) | CI) | CI) |  |  |
| $\mathbf{0}$ vs. $\mathbf{1}$ | $0.50(0.50,0.51)$ | $0.52(0.51,0.53)$ | $0.52(0.50,0.53)$ | $0.54(0.52,0.57)$ | $0.58(0.56,0.60)$ |
| $\mathbf{0 - 1}$ vs. $\geq \mathbf{2}$ | $0.53(0.52,0.55)$ | $0.54(0.53,0.55)$ | $0.55(0.53,0.58)$ | $0.60(0.58,0.62)$ | $0.58(0.56,0.61)$ |
| $\mathbf{0 - 2}$ vs. $\geq \mathbf{3}$ | $0.57(0.54,0.59)$ | $0.56(0.54,0.58)$ | $0.59(0.57,0.63)$ | $0.60(0.57,0.62)$ | $0.57(0.54,0.60)$ |
| $\mathbf{0 - 3}$ vs. $\geq \mathbf{4}$ | $0.59(0.56,0.61)$ | $0.56(0.54,0.59)$ | $0.59(0.55,0.62)$ | $0.57(0.53,0.59)$ | $0.57(0.55,0.59)$ |
| $\mathbf{0 - 4}$ vs. $\geq \mathbf{5}$ | $0.60(0.57,0.63)$ | $0.59(0.56,0.62)$ | $0.58(0.55,0.61)$ | $0.56(0.52,0.58)$ | $0.54(0.53,0.55)$ |
| $\mathbf{0 - 5}$ vs. $\geq \mathbf{6}$ | $0.61(0.58,0.64)$ | $0.62(0.58,0.65)$ | $0.57(0.54,0.60)$ | $0.53(0.51,0.55)$ | $0.52(0.51,0.53)$ |
| $\mathbf{0 - 6}$ vs. $\geq \mathbf{7}$ | $0.61(0.57,0.64)$ | $0.60(0.56,0.63)$ |  |  |  |
| $\mathbf{0 - 7}$ vs. $\geq \mathbf{8}$ | $0.59(0.54,0.63)$ | $0.60(0.57,0.63)$ |  |  |  |
| $\mathbf{0 - 8}$ vs. $\geq \mathbf{9}$ | $0.57(0.53,0.59)$ | $0.60(0.57,0.62)$ |  |  |  |
| $\mathbf{0 - 9}$ vs. $\geq \mathbf{1 0}$ | $0.53(0.51,0.55)$ | $0.57(0.54,0.60)$ |  |  |  |

The five multimorbidity measures, adjusted for age, gender and deprivation, at their optimal cut-points were then compared for the outcome of emergency admission (See Figure 5-2). Overall, there was no statistically significant difference between any of the five measures for predicting emergency admission ( $\mathrm{p}=0.24$ ).


Figure 5-2: Comparison of five multimorbidity measures, adjusted for age, gender and deprivation, at optimal cut-points for outcome of $\geq 1$ emergency admission: receiver operating curve plot

For the VES-13 the cut-point of $\geq 3$ denoting vulnerability was used. This cut-point was used in the derivation and validation of this model in previous studies. $(32,241)$ Discrimination for predicting emergency admission at this cut-point was poor (c-statistic: 0.59 ( $95 \% \mathrm{Cl} 0.56$, 0.63 ) (See Figure 5-3).


Figure 5-3: The VES-13 at cut-point of $\geq 3$ for predicting $\geq 1$ emergency admissions: receiver operating curve plot

The same analysis was conducted for the outcome of $\geq 1$ ACS emergency admissions and the c-statistics for the different cut-points are presented in Table 5-8. The optimal multimorbidity count cut-points for this outcome were as follows: i) RxRisk-V $\geq 5$; ii) Number of medications $\geq 6$; iii) Disease count $\geq 3$; iv) Barnett condition count $\geq 2$; and v) Charlson index $\geq 1$.

Table 5-8: Different cut-points of multimorbidity measures with c-statistics ( $95 \% \mathrm{Cl}$ ) for the outcome of $\geq 1$ ACS emergency admission ( $n=862$ )

| Count cutpoint | RxRisk-V | Number of medications | Disease count | Barnett conditions count | Charlson index |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | c-statistic (95\% <br> $\mathrm{Cl})$ | c-statistic (95\% CI) | c-statistic (95\% CI) | c-statistic (95\% <br> $\mathrm{Cl})$ | c-statistic (95\% $\mathrm{Cl})$ |
| 0 vs. $\geq 1$ | 0.51 (0.51, 0.51) | 0.52 (0.52, 0.53) | 0.53 (0.51, 0.54) | 0.54 (0.51, 0.57) | 0.63 (0.60, 0.66) |
| 0-1 vs. $\geq 2$ | 0.54 (0.52, 0.55) | 0.55 (0.54, 0.56) | 0.55 (0.52, 0.59) | 0.61 (0.56, 0.65) | 0.63 (0.60, 0.66) |
| 0-2 vs. $\geq 3$ | 0.58 (0.55, 0.60) | 0.57 (0.53, 0.60) | 0.59 (0.54, 0.64) | 0.60 (0.55, 0.65) | 0.57 (0.53, 0.61) |
| 0-3 vs. $\geq 4$ | 0.61 (0.57, 0.64) | 0.58 (0.54, 0.62) | 0.58 (0.53, 0.64) | 0.60 (0.54, 0.65) | 0.55 (0.52, 0.59) |
| $0-4$ vs. $\geq 5$ | 0.63 (0.58, 0.67) | 0.61 (0.56, 0.65) | 0.59 (0.55, 0.64) | 0.56 (0.52, 0.61) | 0.54 (0.51, 0.57) |
| 0-5 vs. $\geq 6$ | 0.62 (0.57, 0.67) | 0.63 (0.58, 0.68) | 0.57 (0.54, 0.62) | 0.53 (0.51, 0.54) | 0.52 (0.50, 0.54) |
| $0-6$ vs. $\geq 7$ | 0.62 (0.57, 0.68) | 0.62 (0.56, 0.67) |  |  |  |
| 0-7 vs. $\geq 8$ | 0.58 (0.52, 0.64) | 0.63 (0.58, 0.69) |  |  |  |
| $0-8$ vs. $\geq 9$ | 0.58 (0.53, 0.63) | 0.63 (0.57, 0.68) |  |  |  |
| 0-9 vs. $\geq 10$ | 0.53 (0.50, 0.57) | 0.58 (0.52, 0.64) |  |  |  |

The five multimorbidity measures at their optimal cut-points, adjusted for age, gender and deprivation, were then compared for the outcome of ACS admission (See Figure 5-4). Overall, there was no statistically significant difference between any of the measures for predicting ACS admission ( $\mathrm{p}=0.95$ ).


Figure 5-4: Comparison of five multimorbidity measures, adjusted for age, gender and deprivation, for the outcome of ACS emergency admission: receiver operating curve plot The ROC plot for the VES-13 at its cut-point of $\geq 3$ indicating vulnerability is presented in Figure $5-5$. Discrimination for the outcome of $\geq 1$ ACS emergency admissions was relatively poor; c-statistic: 0.63 ( $95 \% \mathrm{Cl} 0.60,0.67$ ).


Figure 5-5: The VES-13 at cut-point of $\geq 3$ for predicting $\geq 1$ ACS emergency admissions: receiver operating curve plot

### 5.5.2 Functional decline outcome ( $n=666$ )

A total of 673 study participants completed a postal questionnaire at follow-up which included the short functional survey. Of these there were 21 study participants (3\%) with missing data for one or more items of the short functional survey and these patients were excluded from the analysis. A further 14 study participants had been admitted to a nursing home during the follow-up period and were considered to have experienced a decline in function on this basis. Therefore the study sample was $n=666$. Table $5-9$ presents the differences between postal questionnaire respondents at follow-up compared to nonrespondents. Non-respondents were older, were taking a greater number of medications and were more socioeconomically deprived than those who completed the postal questionnaire at follow-up.

Table 5-9: Comparison of follow-up postal questionnaire respondents and nonrespondents

|  | Questionnaire respondents ( $\mathrm{n}=673$ ) | Questionnaire nonrespondents ( $\mathrm{n}=133$ ) | Difference between the two groups |
| :---: | :---: | :---: | :---: |
|  | Median (IQR) | Median (IQR) | p-value |
| Age | $76(73,80)$ | $78(73,82)$ | 0.02 |
| Deprivation | 1.36 (-0.64, 2.88) | 2.16 (-0.20, 3.39) | 0.04 |
| Number of medication classes | $5(3,7)$ | $6(4,9)$ | 0.001 |
| Gender | Number (\%) | Number (\%) |  |
| Male | 318 (47) | 57 (40) |  |
| Female | 355 (53) | 87 (60) | 0.16 |
| Education* |  |  |  |
| Basic education | 397 (59) | 101 (71) |  |
| Upper/post-secondary | 272 (41) | 41 (29) | 0.01 |
| Social class |  |  |  |
| Unskilled | 151 (22) | 47 (33) |  |
| Skilled | 522 (78) | 97 (67) | 0.01 |
| Charlson comorbidity weights ${ }^{\text {s }}$ |  |  |  |
| 0 | 286 (43) | 49 (34) |  |
| $\geq 1$ | 387 (57) | 95 (66) | 0.06 |

[^6]Of patients who completed the postal questionnaire at follow-up, a total of 56 study participants (8.4\%) reported a decline in at least one of the short functional survey items at follow-up compared to baseline. As previously mentioned 14 people were admitted to a nursing home so overall, a total of 70 study participants (10.5\%) were considered to have experienced a decline in function over the two year follow-up period. The multimorbidity measures were examined in unadjusted and adjusted analyses for the outcome of functional decline (see Table 5-10). In unadjusted analysis, all measures demonstrated poor discrimination (c statistic range: 0.57-0.62). Following adjustment for age, gender and deprivation the best measure for this outcome was the RxRisk-V (c statistic: 0.61 ( $95 \% \mathrm{Cl}$ $0.55,0.67)$ ). In contrast, the VES-13 demonstrated reasonable predictive accuracy for functional decline; c-statistic: 0.74 ( $95 \% \mathrm{Cl} 0.69,0.80$ ).

Table 5-10: Multimorbidity and vulnerability measures comparison for outcomes of functional decline during two-year follow-up ( $\mathrm{n}=666$ )

| Model* | Functional decline |  |
| :--- | :--- | :--- |
| Multimorbidity measure | c-statistic (95\% CI), unadjusted | c-statistic (95\% CI), adjusted |
| Disease count | $0.59(0.52,0.66)$ | $0.55(0.49,0.60)$ |
| Barnett conditions count | $0.57(0.52,0.63)$ | $0.55(0.50,0.59)$ |
| Charlson index | $0.60(0.53,0.68)$ | $0.60(0.53,0.67)$ |
| RxRisk-V | $0.62(0.55,0.69)$ | $0.61(0.55,0.67)$ |
| Number of medications | $0.61(0.52,0.70)$ | $0.57(0.48,0.66)$ |
| Vulnerability measure |  |  |
| VES-13 | $0.74(0.69,0.80)$ | $\mathrm{NA}^{\varsigma}$ |

\$NA=Not applicable. The VES-13 is a risk score developed using multivariate analysis and consists of 13 items including age.

Each measure of multimorbidity was then examined at different cut-points to determine the condition or medication count that demonstrated the best discriminative ability for functional decline. The c-statistics at different cut-points for the outcome of functional decline are presented in Table 5-11. Discrimination was poor overall but the count cutpoints with most predictive accuracy were as follows; i) RxRisk-V $\geq 5$, ii) Number of medications $\geq 5$, iii) Disease count $\geq 3$, iv) Barnett condition count $\geq 3$ and v) Charlson index $\geq 3$.

Table 5-11: Different cut-points of multimorbidity measures with c-statistics ( $95 \% \mathrm{CI}$ ) for the outcome of functional decline ( $\mathrm{n}=666$ )

| Count cutpoint | RxRisk-V | Number of medications | Disease count | Barnett conditions count | Charlson index |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | c-statistic (95\% <br> $\mathrm{Cl})$ | c-statistic (95\% CI) | c-statistic (95\% $\mathrm{Cl})$ | c-statistic (95\% <br> Cl | c-statistic (95\% CI) |
| 0 vs. $\geq 1$ | 0.51 (0.50, 0.51) | 0.51 (0.49, 0.53) | 0.51 (0.47, 0.55) | 0.51 (0.48, 0.55) | 0.57 (0.52, 0.62) |
| 0-1 vs. $\geq 2$ | 0.54 (0.53, 0.55) | 0.53 (0.50, 0.55) | 0.55 (0.51, 0.59) | 0.55 (0.51, 0.59) | 0.57 (0.50, 0.64) |
| 0-2 vs. $\geq 3$ | 0.54 (0.50, 0.57) | 0.53 (0.48, 0.58) | 0.56 (0.51, 0.62) | 0.57 (0.52, 0.62) | 0.59 (0.52, 0.66) |
| 0-3 vs. $\geq 4$ | 0.55 (0.50, 0.60) | 0.55 (0.52, 0.59) | 0.55 (0.50, 0.60) | 0.53 (0.49, 0.58) | 0.53 (0.49, 0.56) |
| 0-4 vs. $\geq 5$ | 0.61 (0.56, 0.65) | 0.58 (0.54, 0.62) | 0.56 (0.51, 0.62) | 0.54 (0.51, 0.57) | 0.51 (0.47, 0.54) |
| 0-5 vs. $\geq 6$ | 0.60 (0.54, 0.67) | 0.57 (0.51, 0.62) | 0.52 (0.47, 0.56) | 0.52 (0.49, 0.55) | 0.51 (0.49, 0.53) |
| 0-6 vs. $\geq 7$ | 0.56 (0.50, 0.62) | 0.59 (0.50, 0.67) |  |  |  |
| 0-7 vs. $\geq 8$ | 0.55 (0.48, 0.61) | 0.59 (0.51, 0.66) |  |  |  |
| $0-8 \mathrm{vs}$. $\geq 9$ | 0.55 (0.50, 0.60) | 0.56 (0.50, 0.63) |  |  |  |
| 0-9 vs. $\geq 10$ | 0.51 (0.47, 0.55) | 0.54 (0.49, 0.60) |  |  |  |

The five multimorbidity measures at their optimal cut-points, adjusted for age, gender and deprivation, were then compared for the outcome of functional decline (See Figure 5-6). There was no statistically significant difference between any of the measures for predicting functional decline ( $p=0.40$ ).


Figure 5-6: Comparison of five multimorbidity measures, adjusted for age, gender and deprivation, at optimal cut-points for the outcome of functional decline: receiver operating curve plot

The ROC plot for the VES-13 at the cut-point of $\geq 3$ for the outcome of functional decline is presented in Figure 5-7. Discrimination at this cut-point was reasonable; c-statistic 0.69 ( $95 \% \mathrm{Cl} 0.61,0.76$ ).


Figure 5-7: The VES-13 at cut-point of $\geq 3$ for predicting functional decline: receiver operating curve plot

### 5.6 Discussion

### 5.6.1 Principal findings

This is the first prospective primary care study to compare count-based measures of multimorbidity with a measure of vulnerability for the outcomes of emergency admission and functional decline in older community-dwelling adults.

The main findings of this study are as follows;

- For the diagnosis based multimorbidity measures a total of 626 study participants ( $73 \%$ ) met the definition for multimorbidity ( $\geq 2$ conditions in an individual) by the total disease counts measure and 484 study participants' (56\%) according to the Barnett condition count measure. Three hundred and fourteen (37\%) had two or more of the Charlson comorbidity index conditions. For the medication count measures, a total of 789 study participants ( $91 \%$ ) had $\geq 2$ chronic conditions according to the RxRisk-V and 73\% ( $\mathrm{n}=632$ ) met the definition for polypharmacy ( $\geq 4$ medications) with $13 \%$ ( $\mathrm{n}=119$ ) prescribed 10 or more medications (high-risk polypharmacy).
- This indicates that multimorbidity prevalence in this older primary care cohort varies considerably depending on the measure selected to define it. If using the traditional cut-off count of two or more for the medication measures, then the vast majority of the cohort (91\%) would meet this definition, whereas utilising a measure such as the Charlson comorbidity index identifies a smaller proportion (37\%).
- At baseline a total of 223 (33\%) were categorised as vulnerable according to the VES13 (score $\geq 3$ ). This is almost identical to the proportion of older people identified as vulnerable in previous validation studies in the US and Ireland.
- Overall, following adjustment for age, gender and deprivation, the five measures of multimorbidity had similarly poor discrimination for the outcome of emergency admission. The best performing measure in this study was the RxRisk-V (c-statistic: $0.63)$. Predictive accuracy for the outcome of ACS admission was marginally better and three measures of multimorbidity (RxRisk-V, number of medications and

Charlson index) had very similar predictive accuracy (c-statistic 0.67 ) for this outcome, following adjustment for confounding variables.

- The VES-13 was not a useful predictor of emergency admissions (c-statistic 0.57 ) or ACS admissions (c-statistic 0.64).
- All multimorbidity measures demonstrated poor discrimination for the outcome of functional decline over two year follow-up (c-statistic range: $0.55,0.61$ ). However, the VES-13 demonstrated reasonable discrimination for this outcome (c-statistic: 0.74 ) and may be a useful tool in identifying older people at risk of functional decline.


### 5.6.2 Comparison with existing literature

### 5.6.2.1 C ount measures of multimorbidity for predicting patient outcomes

This study indicates that the choice of measure for multimorbidity will have implications in terms of prevalence. Using the traditional cut-off point of $\geq 2$ for the RxRisk-V measure would result in almost the entire study population categorised as multimorbid (91\%), while using the Barnett condition list would result in a much smaller proportion (56\%) identified as having multimorbidity. This has clinical and research implications. Existing multimorbidity intervention studies have largely used diagnosis-based inclusion criteria (i.e. $\geq 2$ chronic medical conditions), with a smaller number of studies using this approach in combination with medication count (e.g. $\geq 4$ prescribed medications).(159) An example is the OPTIMAL primary care study that recruited patients with $\geq 2$ chronic medical conditions prescribed $\geq 4$ medications for a self-management intervention that was successful in improving activity participation.(332) Using this approach seems pragmatic and should ensure patients with more complex multimorbidity are included in future studies aiming to develop effective interventions for this patient group.

There have been few studies that have compared the performance of different multimorbidity measures for the outcomes of emergency admission. Two population-based US studies reported that the RxRisk-V predicted future healthcare use best when compared with diagnosis based measures. $(266,333)$ A large scale UK cross-sectional study reported
that the number of prescribed medications was the most powerful predictor of future primary care consultations.(121) The current study adds to the literature in this area and suggests that while all measures demonstrated relatively poor discrimination the medication-based measures, such as the RxRisk-V, performed marginally better than diagnosis-based measures in predicting emergency and ACS admissions. These measures have several advantages as they can be applied to pharmacy claims databases, rather than requiring medical record review which is more time-consuming, and simple medication counts are easy to conduct in clinical practice. It is important to highlight that emergency admission is an inherently difficult outcome to predict accurately.(334) Existing admission risk prediction models, that include a variety of clinical, socio-economic and prior healthcare utilisation variables, rarely achieve model discrimination of $\geq 0.8$, so the performance of the various multimorbidity measures should be judged in this context.(303)

There has been very limited research comparing the performance of different measures of multimorbidity in predicting functional decline. One Italian study ( $n=633$ ) measured incident basic activities of daily living (BADL) disability in older people ( $\geq 65$ years) over five year follow-up.(322) Functional status was assessed using a modified version of the Guralnik's lower physical performance battery and a total of $9.6 \%$ had developed incident disability. Disease count had the highest predictive value (c statistic 0.85 , no Cls presented).(322) However, all study participants had an index condition of congestive heart failure which limits the generalisability of this study to typical primary care populations.

### 5.6.2.2 Measures of vulnerability used to préct patient outcomes

This is the first prospective study examining the predictive ability of the VES-13 for the outcome of emergency admission. The VES-13 has previously been tested in a crosssectional Irish study ( $n=2,033$, aged $\geq 65$ years) where it was found to be associated with increased self-reported healthcare use including primary care visits and inpatient stay.(242) Other measures largely comprising of functional status items have been used to predict future admission with varying results. A US study ( $n=6,465$, aged $\geq 65$ years) examined the value of a different measure of functional status, the Functional Status Indicator (FSI), in predicting future hospital admission.(335) Though all reported poor discrimination, the FSI
was as good as multimorbidity measures (the Charlson comorbidity index and Chronic Disease Score) in predicting this outcome (c-statistic 0.68 (no Cls reported)).(335) However, this study presented a secondary analysis of data collected for the purposes of a RCT which is a methodological limitation. A one-year prospective Dutch primary care study ( $n=430, \geq 70$ years) tested the performance of three measures of frailty, the Groningen Frailty Indicator, the Tilburg Frailty Indicator and the Sherbrooke Postal Questionnaire, in predicting admission.(336) Reported c-statistics for the three measures were poor overall; c-statistic 0.54 ( $95 \% \mathrm{Cl} 0.46,0.61$ ), $0.60(95 \% \mathrm{Cl} 0.52,0.67)$ and $0.60(95 \% \mathrm{Cl} 0.53,0.67)$ respectively.(336) The current study builds on this previous research and indicates that the VES-13 is also not a good measure of future emergency admission. This suggests that poorer physical functioning in older community-dwelling people does not, in itself, determine admission risk. However, measures based largely on physical functioning may well have a role when considered in conjunction with other important risk factors, such as previous healthcare utilisation, in developing risk prediction models to predict future emergency admission.

The VES-13 demonstrated reasonable model performance in predicting functional decline and may have a role in identifying older people at high-risk of this outcome. In contrast, the five measures of multimorbidity tested in the current study did not reliably discriminate this outcome of interest. This indicates that morbidity burden alone is not adequate to predict functional decline and other factors included in the VES-13 such as self-rated health and physical functioning are more powerful predictors of this outcome. A recent systematic review examined the concept of multimorbidity in predicting functional decline.(43) Of the nine prospective cohort studies included in this review, eight concluded that increasing morbidity burden was a predictor of functional decline over time. Of note there was significant variation in the definition of multimorbidity used across included studies and the measure of functional status administered. However, multimorbidity is only one part of the complex interplay of factors that result in functional decline over time.

### 5.6.3 Strengths and limitations

This is the first prospective primary care study to compare different count-based measures of multimorbidity and a measure of vulnerability in predicting adverse health outcomes for older community-dwelling people. The study population was not selected based on the presence of any one particular index condition which improves the generalisability of the findings. The robustness of the calculation of the multimorbidity measures is enhanced by condition measurement using GP medical record review for the diagnosis-based measures and use of a linked pharmacy claims database for the medication-based measures. The outcomes of emergency admission and ACS admission were recorded from review of the GP medical record. Examining ACS admissions as an outcome of interest is novel. This subset of emergency admissions are becoming increasingly of interest due to their perceived preventability through primary care interventions. However, to date only a limited number of risk prediction models have been developed specifically to identify ACS admissions.(303) Understanding the role of multimorbidity and vulnerability in predicting this outcome is important and adds to the limited literature in this area.

There are some study limitations. The sample size is relatively small which may affect the power of the sample to answer the study questions. However, results were largely similar to previous studies using larger sample sizes and the proportion of patients with the outcomes of interest were adequate; 29\% for emergency admission, 13\% for ACS admission and 10.5\% for functional decline respectively. Accuracy of diagnosis information was dependent on accurate recording of information taken from the GP medical record. All GP medical record data was recorded by the same researcher. As described in Section 3.1.7, a random sample of $10 \%$ of all data was double checked by an independent reviewer and extensive data cleaning was undertaken to ensure accuracy, therefore reducing the likelihood of misclassification bias. A total of 21 study participants (3\%) had some missing data for the outcome measure of functional decline and were excluded. However this proportion of missing data is very small when compared to similar prospective studies. $(53,322)$

### 5.6.4 Clinical, research and policy implications

A recently published systematic review examined the types of multimorbidity measures included in risk prediction models designed to predict future hospital admission and readmission.(337) Of the 21 studies that included a measure of multimorbidity, a total of 15 (71\%) used the Charlson Comorbidity index (or adapted version). Only two studies used a medication based measure of multimorbidity.(337) The current study indicates that medication-based measures of multimorbidity are marginally better than diagnosis-based measures for predicting future emergency admission and therefore may be considered preferentially for measuring multimorbidity in prediction models for this outcome of interest. However, the traditional cut-point of $\geq 2$ chronic medical conditions in defining multimorbidity is not sufficient for these medication based measures. Higher cut-off points ( $\geq 5$ for the RxRisk-V, $\geq 6$ for medication counts) are needed to achieve optimal discrimination. Medication-based measures have pragmatic advantages in general practice where they may be easier to apply than more complicated diagnosis-based measures. Additionally it would be interesting to examine the concept of 'complex multimorbidity' in predicting adverse health outcomes. Recently this has been defined as three or more chronic conditions affecting at least three body systems.(30) Conceptualising multimorbidity in this way may have added value in identifying older people who are more likely to experience poorer health outcomes in the future.

A systematic review and meta-analysis reported that the strongest predictors of US nursing home admission were $\geq 3$ activities of daily living dependencies (summary odds ratio (OR)=3.25; 95\% CI, 2.56, 4.09), cognitive impairment (OR=2.54; 95\% CI, 1.44, 4.51), and prior nursing home use (OR=3.47; 95\% CI, 1.89, 6.37).(338) The current study suggests that the VES-13 may have a role in predicting functional decline and may have a role in identifying community-dwelling people at higher risk of this important outcome. An ageing population requires novel and innovative approaches in identifying and managing older people who are more likely to require intensive homecare and/or nursing home admission in the future. The VES-13 can be easily administered in approximately five minutes and calculating the patient's score is straightforward. It has, therefore, good practical utility and could be used
by both GPs and allied health professionals to help prioritise care needs for older community-dwelling people.

### 5.7 Chapter summary

Multimorbidity and vulnerability are predictors of future adverse health outcomes for older community-dwelling people. This study adds to the limited existing primary care literature comparing different measures for important patient outcomes of emergency admission and functional decline. This study indicates that though all multimorbidity measures demonstrate poor discrimination, medication-based measures perform equally as well as diagnosis-based measures in predicting emergency admission and that the VES-13 may have a role in identifying older people at higher risk of functional decline.

Chapter 6 Predicting emergency admission in older community-dwelling adults

### 6.1 Introduction

This chapter presents the findings of: 1) a systematic review of risk prediction models developed to predict future emergency hospital admission; 2) a systematic review and meta-analysis of one of these risk prediction models, the Probability of repeated admissions (Pra) model; 3) an external validation study of the Pra model in a cohort of older community-dwelling people; and 4) a critical analysis of recently introduced healthcare policy in the UK directed at reducing emergency admissions through community-initiated identification of high risk people and intervention. The Pra model was selected to systematically review and externally validate as it was developed specifically for use in older people, is the longest established admission risk model, with several previous validation studies, and is relatively simple to administer and calculate, which is important for clinical applicability.

### 6.2 Risk prediction models to predict emergency hospital admission in older community-dwelling adults: a systematic review

### 6.2.1 Introduction

An expanding older population places capacity and financial pressure on healthcare systems. Currently, Ireland has a relatively young population with one in ten aged over 65 years. This is set to change considerably in coming years and by 2036, one in four will be over 65 years.(288) Older patients bear the greatest burden of illness and as a result account for the greatest proportion of prescribed medication and so this demographic shift will result in substantial capacity and financial pressure for the health service.

Emergency hospital admissions account for a large proportion of health care expenditure and have high personal costs for affected individuals. There is increasing interest internationally in reducing emergency admissions both as a measure of quality of care and in containing spiralling healthcare expenditure. In the UK, these episodes of care account for a significant proportion of healthcare expenditure; in 2012 alone emergency admissions cost the NHS $£ 12.5$ billion.(193) Emergency or unplanned admissions account for approximately $35 \%$ of all hospitalisations in the UK.(193) In the US almost one-third of all
healthcare spending is for inpatient services and average hospital costs increased 2\% per year from 2003-2013.(195) US rehospitalisations alone are estimated to cost $€ 12$ billion each year.(339)

Irish data indicates that people aged over 85 years are eight times more likely to be in hospital.(47) The reasons for this are twofold; first, this group are up to four times more likely to be admitted to hospital and second, when admitted their average length of hospital stay is twice as long.(47) As a result of this escalating expenditure, reducing emergency admissions is a priority for healthcare policy-makers.(340) For patients, unplanned hospitalisations may be distressing and older people in particular are at increased risk of related adverse events such as hospital-acquired infections, loss of functional independence and falls.(341)

One way of reducing emergency admissions is to identify people at higher risk who can then be prioritised for a community-based intervention to reduce this risk. Risk prediction models developed for this purpose for use in community settings have the advantage of broader applicability and can include a wider range of predictor variables, such as functional status compared to using clinical judgement alone. It has also been argued that focusing on specific high risk groups, such as those recently discharged from hospital, may not be the best approach to take in targeting emergency admissions. This is due, in part, to the concept of 'regression to the mean' which means that patients with a history of multiple admissions will on average have fewer admissions in the future than they had in the past. $(202,342)$

Three main types of data sources are utilised to derive risk models for predicting emergency admission.(340) The first is self-report data collected through patient questionnaire or interview with the advantage of being able to include non-medical variables such as functional status and social supports. The second is routine data collected for the purposes of administrative databases or population registries. The third incorporates data collated from the clinical record or other primary data sources with the advantage of being able to include larger number of variables and without the response biases associated with selfreport. There is a widely accepted methodology for the development such risk scores.(50) Derivation is followed by internal and external validation before finally testing the impact of
use on clinical outcomes. These steps require cumulative levels of evidence to answer the relevant research and clinical questions. $(343,344)$

The aim of this study was to perform a systematic review of validated risk prediction models for predicting emergency hospital admission in community-dwelling adults. Specific objectives were: 1) To examine the variables included in risk prediction models; 2) To summarise the performance of risk prediction models in derivation and validation cohorts; and 3) To compare the predictive accuracy of risk models externally validated in the same setting.

### 6.2.2 Methods

The protocol for this systematic review has been published on PROSPERO (PROSPERO2013:CRD42013004390). The PRISMA guidelines for the conduct and reporting of systematic reviews were utilised in undertaking this systematic review.(318)

### 6.2.2.1 Search strategy

A systematic literature search was carried out in September 2013 and updated in February 2014 using the following search engines; PubMed, EMBASE, CINAHL, the Cochrane Library and Google scholar. Additional databases were also searched; the US Agency for Healthcare Research and Quality (AHRQ), the John Hopkins Adjusted Clinical Groupings (ACG) publications, the UK Nuffield Trust and the King's fund. The search was supplemented by hand searching references of relevant articles and contacting study authors where necessary. No restrictions were placed on language or year of publication. A combination of MeSH terms and keywords were used to capture studies of interest. The PubMed database search terms are outlined below (search terms were amended accordingly for other databases).

1. Emergency admission
(("patient admission"[MeSH Terms] OR "patient readmission"[MeSH Terms]) OR ((l(()(l(l(l(l(()unplanned[All Fields] AND admission[All Fields]) OR (un[All Fields] AND planned[All Fields] AND admission[All Fields])) OR (nonelective[All Fields] AND admission[All Fields])) OR (non[All

Fields] AND elective[All Fields] AND admissions[All Fields])) OR (unexpected[All Fields] AND admission[All Fields])) OR (unscheduled[All Fields] AND admission[All Fields])) OR (non[All Fields] AND planned[All Fields] AND admissions[All Fields])) OR (non[All Fields] AND planned[All Fields] AND admissions[All Fields])) OR (("emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields]) AND ("hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields]) AND admission[All Fields])) OR (("emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields]) AND medical[All Fields] AND admission[All Fields])) OR (("emergency treatment"[MeSH Terms] OR ("emergency"[All Fields] AND "treatment"[All Fields]) OR "emergency treatment"[All Fields] OR ("emergency"[All Fields] AND "care"[All Fields]) OR "emergency care"[All Fields] OR "emergency medical services"[MeSH Terms] OR ("emergency"[All Fields] AND "medical"[All Fields] AND "services"[All Fields]) OR "emergency medical services"[All Fields] OR ("emergency"[All Fields] AND "care"[All Fields])) AND admission[All Fields])) OR (("emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields]) AND room[All Fields] AND admission[All Fields])) OR (unplanned[All Fields] AND ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields]))) OR (("emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields]) AND ("hospitalisation"[All Fields] OR "hospitalization"[MeSH Terms] OR "hospitalization"[All Fields]))) OR (unanticipated[All Fields] AND admission[All Fields])) OR (("emergencies"[MeSH Terms] OR "emergencies"[All Fields] OR "emergency"[All Fields]) AND ("referral and consultation"[MeSH Terms] OR ("referral"[All Fields]

AND

## 2. Risk prediction model

"consultation"[All Fields]) OR "referral and consultation"[All Fields] OR "referral"[All Fields])))) AND ((("risk assessment/methods"[Mesh Terms] OR "models, statistical"[MeSH Terms]) OR "forecasting"[MeSH Terms]) OR ((((("risk"[MeSH Terms] OR "risk"[All Fields]) AND score[All Fields]) OR ("risk"[MeSH Terms] OR "risk"[All Fields])) OR ("risk"[MeSH Terms] OR "risk"[All Fields])) OR ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields])))

### 6.2.2.2 Study selection

Studies were included if they met the following criteria:

1) Population: Community-dwelling adults (aged $\geq 18$ years).
2) Risk: Risk prediction models, which were not contingent on an index hospital admission, with a derivation and at least one validation (either internal or external) cohort. Models were subdivided according to the data used to develop the model as follows: i) Self-report; ii) Administrative or clinical record data.
3) Outcome: Primary outcome of emergency hospital admission (defined as unplanned overnight stay in hospital). Studies which had emergency admission as part of their outcome of interest (e.g. combined end-points) were also included.
4) Study design: Retrospective or prospective cohort studies.

The following studies were excluded:

Primary population of interest focussed on paediatrics, obstetrics, surgery, mental illness or patients enrolled in managed care programmes; readmission risk prediction models (models contingent on an index hospital admission); models where the primary outcome of interest was elective hospital admissions, models developed for use in emergency rooms, for specific diagnoses e.g. congestive heart failure, for a different primary outcome e.g. mortality and risk adjustment models (models to compare provider performance to inform pay and healthcare financing). Studies that reported risk factors only and did not develop a model were also excluded.

### 6.2.2.3 Data extraction

Two reviewers (Emma Wallace, Ellen Stuart) read the titles and/or abstracts of the identified records in duplicate and eliminated irrelevant studies. Studies that were considered eligible for inclusion were read fully in duplicate and their suitability for inclusion determined. Disagreements were managed by consensus and if consensus could not be reached then by third review (Susan Smith). Additional data was sought from authors where necessary. Data was extracted using a standardised data extraction form.

### 6.2.2.4 Statistical analysis

Meta-analysis was not possible due to risk prediction model heterogeneity so a narrative approach was utilised and each unique risk prediction model was summarised under the following headings:

- The model's derivation cohort study setting, participants and population studied.
- Type of validation cohort i.e. internal/external.
- Type of data used to derive the model.
- Model discrimination was assessed using the c-statistic with $95 \%$ Cls where available. A c-statistic of 0.5 indicates that the model performs no better than chance, a score of 0.5-0.7 indicates poor discrimination, 0.7-0.9 represents reasonable discrimination and a score of $\geq 0.9$ indicates excellent discrimination. $(331,345)$ Where the c -statistic was not presented, positive predictive values, sensitivity and specificity are presented.
- Variables evaluated and considered for inclusion.
- Variables included in the final model.


### 6.2.2.5 Methodological Quality Assessment

Methodological quality assessment of included studies was independently performed in duplicate (Ellen Stuart, Niall Vaughan) using the McGinn checklist for the methodological assessment of clinical prediction rule studies.(343) The McGinn criteria include a total of eight criteria to assess the internal and external validity of derivation studies (See Table 6-1). For validation studies, a total of five criteria were used (See Table 6-2). Detailed guidance notes were also developed in-house to accompany the derivation and validation methodological criteria. Disagreements were solved by consensus or by an adjudicating third reviewer (Emma Wallace).

Table 6-1: McGinn methodological quality standards for derivation of a clinical prediction rule

|  | Yes | No | Not <br> reported |
| :--- | :--- | :--- | :--- |

## Internal Validity

1. Were those assessing the outcome event blinded to presence of predictors?
2. Were those assessing the presence of predictors blinded to the outcome event?
3. Adequate sample size? (including outcome events)
4. Clinically sensible?

## External validity

1. Were all important predictors included in the derivation process?
2. All important predictors present in a significant proportion of the study population?
3. (a) All predictors clearly defined?
(b) All outcome events clearly defined?

Table 6-2: McGinn methodological quality standards for validation of a clinical prediction rule

|  |
| :--- |
| Internal validity |
| 1. Were those assessing the outcome event blinded to presence of |
| predictors? |
| 2. Were those assessing the presence of predictors blinded to the |
| outcome event? |
| 3. Was there $\geq 80 \%$ follow-up of those enrolled?* |
| External validity |
| 1. Were patients selected in an unbiased fashion? |
| 2. Do patients represent a wide spectrum of severity of disease? |

[^7]
### 6.2.3 Results

### 6.2.3.1 Study identification

A flow diagram of the search strategy is presented in Figure 6-1. The electronic databases search strategy yielded 20,666 papers. A further 20 articles were retrieved from searches of other resources. Following removal of duplicates, a total of 18,983 articles were screened via title and abstract of which 163 studies were reviewed in full text and 27 unique risk prediction models met the inclusion criteria.

Figure 6-1: PRISMA flow diagram of included risk prediction models

### 6.2.3.2 Description of included risk prediction models

Of 27 unique models included, 11 were developed in the UK, 11 in the US, three in Italy, one in Spain and one in Canada. Nine models were developed using self-report data or a combination of self-report and administrative or routine data and the remainder ( $\mathrm{n}=18$ ) utilised routine or primary data alone. A total of 13 models were developed specifically for use in older people ( $\geq 60$ years). Total sample sizes ranged from 96 to 4.7 million participants. The majority of models ( $n=18,67 \%$ ) were developed to predict emergency hospital admission at 12 month follow-up (range 90 days to 4 years). Of these, three models focussed on ACS emergency admissions, for chronic conditions amenable to prevention through intensified primary care management, as a primary outcome measure.(317, 346, 347) Two models predicted any hospitalisation and two predicted occupied bed days over specific time periods. $(317,326,348,349)$ A further three models used the end-point of emergency admission ED visit and two used combined hospitalisation/death.(350-354)

### 6.2.3.3 Data sources used to develop risk prediction models

The nine models developed with self-report data are presented in Table 6-3 and used: (i) literature review; (ii) medical record review; and (iii) questionnaire pilot in the development of their model. Table 6-4 presents the 18 models developed using routine or clinical record data. Of these ten (55.6\%) were developed using a combination of administrative and clinical record data. A further eight (44.4\%) were developed using administrative data alone. Eleven models included general/family practice clinical record data in their final model.

Table 6-3: Risk prediction models developed using self-report data primarily ( $\mathrm{n}=9$ )

| Author, Year, Risk model name | Population and setting | Study sample size | Data used to develop final model | Primary Outcome (emergency admission unless otherwise specified) | Number of emergency admissions (\%), c-statistic ( $95 \% \mathrm{Cl}$ where available) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| United Kingdom |  |  |  |  |  |
| Walker, 2005 (352) <br> Sherbrooke questionnaire (derivation) | Aged $\geq 75$, general practice, London, UK, 2000-2002 | Derivation 2,307 | Postal questionnaire, six items;1) Living alone; 2) Takes $\geq 3$ medications; 3) Uses a walking aid; 4) Problem with sight; 5) Problem with hearing; | 24 months (ER visit or emergency admission) | Derivation: 342 (15.5\%), NR |
| Daniels, 2012 <br> (336) <br> Sherbrooke questionnaire (validation) | Aged $\geq 70$, general practice, <br> Netherlands, 2008- <br> 2010 | Validation 532 | 6) Problem with memory | 12 months (emergency admission) | Validation: 75 (17\%) (430 participants included in final analysis) 0.60 (0.530.67) |
| Lyon, 2006, EARLI (355) | Patients aged $\geq 75 y$ <br> UK general practice, 2002-2003 | Derivation 3,032 | Pilot study and review of literature to identify predictor variables. | 12 months | 696 (23\%) $\geq 1$ emergency admission |
|  |  |  | Final model: Postal questionnaire with six yes/no items; 1) Heart problems; 2) Leg ulcers; 3) Problems with memory and get confused; 4) Go out of the house without help; 5) Admitted to hospital as an emergency in the last 12 months; 6) Rate general state of health as good. |  | Derivation= |
|  |  | Validation |  |  | 0.70 (0.67, 072) |
|  |  | $500$ |  |  | Validation: |
|  |  | (bootstrap and |  |  | Bootstrap=0.69 (no Cls) |
|  |  | split samples) |  |  | Split sample $=0.67$ (0.63, 0.71) |


| Author, Year, <br> Risk model <br> name | Population and <br> setting | Study sample <br> size | Data used to develop final <br> model | Primary Outcome <br> (emergency admission <br> unless otherwise specified) | Number of emergency admissions <br> (\%), c-statistic (95\% Cl where <br> available) |
| :--- | :--- | :--- | :--- | :--- | :--- |
| United States |  |  |  |  |  |


| Author, Year, Risk model name | Population and setting | Study sample size | Data used to develop final model | Primary Outcome (emergency admission unless otherwise specified) | Number of emergency admissions (\%), c-statistic ( $95 \% \mathrm{Cl}$ where available) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Reuben, 2002 (349) | Patients aged $\geq 71 y$ US Medicare community dwelling, 1988-1992 | Derivation <br> 5,138 <br> $50 \%$ of total <br> sample (split <br> sample) used for derivation <br> i.e. 2,569 <br> Validation <br> 5,138 <br> 50\% of total sample used for validation <br> i.e. 2,569 | Data Epidemiologic Studies of the Elderly-1988 wave for East Boston, New Haven and Iowa used as baseline. Three models developed; 1) Prior hospitalisation only; 2) Selfreport items only; 3) Selfreport and physical exam and laboratory values. 10 selfreport variables: 1) Gender; 2) Self-rated health; 3) Infrequent religious participation; 4) Help needed bathing; 5) Ability to walk 0.5 miles; 6) Diagnosis of diabetes; 7) Taking loop diuretics; 8) Not working; 9) Hospitalisation in previous year; 10) Hospitalisation in year before that. | 11 or more hospital days within 36 months | $1243 \text { (24.2\%) }$ <br> Self-report variables model; 0.68 for $\geq 2$ admissions over 3 years |
| Damush, 2004 (50) | Patients aged $\geq 50$ with prespecified chronic medical conditions and all aged $>\geq 75 y$ <br> US academic primary care (one practice) | Derivation <br> 1,041 <br> Validation <br> 1000 <br> (bootstrap <br> sample) | Data included from literature review, medical record and patient interviews. Final model: Questionnaire (via interview) five self-report items and two physical exam/lab items. Selfreport items: 1) Diagnosis of congestive heart failure; 2) Diagnosis of diabetes mellitus; 3) Number of medications; 4) Health related quality of life (physical functioning); 5) ER visits in the previous year. | 12 months | $216(20.7 \%) \geq 1$ emergency admission <br> Derivation $=0.73$ <br> Validation $=0.74$ |


| Author, Year, Risk model name | Population and setting | Study sample size | Data used to develop final model | Primary Outcome (emergency admission unless otherwise specified) | Number of emergency admissions (\%), c-statistic ( $95 \% \mathrm{Cl}$ where available) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Shelton, 2000, Community Assessment Risk Screen (CARS) (351) | Aged $\geq 65$ US <br> Medicare with $\geq 1$ <br> defined co- <br> morbidities and psychosocial factors, <br> 1993-1995 | Derivation <br> 411 <br> Validation <br> 1,054 | Data included from interview and postal questionnaire. Final model: Postal questionnaire, three items: 1) $\geq 2$ co-morbidities of a predefined list of conditions (Heart disease, Diabetes, Myocardial infarction, Stroke, COPD, and Cancer); 2) Taking $\geq 5$ medications; 3) Hospitalisation or ER encounter in previous 12 months. | 12 months <br> (admission or ER visit) | Derivation=89 (22\%) <br> Validation=180 (17\%) <br> CARS score $\geq 4=0.67$ for composite endpoint <br> NR for admissions only |
| Freedman, 1996 (358) | Aged $\geq 81 \mathrm{y}$ in Colorado, US primary care (Kaiser Permanente health plan members), 1993 | Derivation <br> 1,873 <br> Validation <br> 1,872 <br> (random split sample) | Postal questionnaire informed by literature and new items (148 questions). Final Model: Postal questionnaire, four items: 1) Presence of heart disease; 2) Presence of diabetes; 3) Need help preparing meals; 4) Require help of person or mechanical aid to get around. | 4.5 months | NR <br> Derivation=0.69 <br> Validation=0.63 |
| Italy |  |  |  |  |  |
| Mazzaglia, 2007(354) | Primary care in Florence, Italy, aged $\geq 65 y, 2003-2004$ | Derivation <br> 2,470 <br> Validation <br> 2,926 | Questionnaire (seven items) as screening test then local registry data (administrative). <br> Self-report items:1) ADLs); 2) Instrumental ADLs; 3) Poor vision; 4) Poor hearing; 5) Recent unintentional weight loss; 6) Use of homecare services; 7) Income | 15 months <br> (emergency hospitalisation or death) | Derivation: 445/2470 (18\%); 0.68(0.660.71 ) <br> Validation:509/2926 (17\%); 0.67(0.650.70) |

$N R=$ Not recorded, ER=Emergency room visit)

Table 6-4: Risk prediction models developed using administrative or clinical record data ( $\mathrm{n}=18$ )

| Author, Year, Risk model name | Study population and setting | Derivation and validation ( n ) | Data used to develop model | Outcome(s) | Number (\%) admitted to hospital | c-statistic ((95\% CIs)* |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| United Kingdom |  |  |  |  |  |  |
| Hippsley Cox 2013, Qadmissions (359) | Aged $\geq 18-100 y$ registered in UK general practice, 2010-2011 | Derivation <br> 2,849,381 <br> Two validation cohorts: <br> Qresearch 1.3m <br> CPRD 2.4 m | Developed using linked computerised GP and hospital inpatient data; final model 30 variables | 24 months (first emergency admission) | 265,573 (9\%) derivation cohort <br> Qresearch validation 132,723 (10\%) <br> CPRD validation 234,204 (9\%) | Qresearch validation 0.773 (0.771-0.774) women 0.776 (0.7740.778 ) men <br> CPRD validation 0.771 (0.770-0.773) women 0.772(0.771-0.774) men |
| Billings, 2013(360) | Aged $\geq 18 \mathrm{y}$ registered in UK general practice (5 primary care teams), 20072010, compared four models in same population | Derivation <br> 1,836,099 <br> Validation <br> NR | 4 prediction models developed to compare advantage of addition of different datasets; <br> 1) Inpatient (Inpt) only; 2) Inpt/A\&E; <br> 3) Inpt/A\&E/OPD; 4) <br> Inpt/A\&E/OPD/GP | 12 months <br> emergency admission | Risk threshold 50\%+:Inpt only <br> 52.9\%; Inpt/A\&E 53.1\%; <br> Inpt/A\&E/OPD <br> 52.3\%;Inpt/A\&E/OPD/GP53.8\% <br> Risk threshold top 1\%; <br> Inpt/A\&E/OPD 45.8\%; <br> Inpt/A\&E/OPD/GP 47.5\% | Risk threshold=50\%; <br> Inpt/A\&E/OPD/GP <br> model; <br> 0.780 <br> Inpt only model:0.731 |
| Chenore, 2013, Devon Predictive Model (361) | Patients aged $\geq 65 y$, UK General practice in Devon, (105 practices), 2007-2011 | Derivation: 80\% of total sample 722,383 i.e. <br> 577,906 <br> Validation: 20\% of total sample 722,383 i.e. 144,477 | NHS Secondary Uses Service database-inpt, OPD, A\&E <br> Local GP practice data in Devon (combined CPM variables with local variables), computerised 89 variable model | 12 months emergency admission | 65,892 (9.1\%) | $\begin{aligned} & \text { Risk threshold=50\% } \\ & 0.781 \text { (0.778-0.783) } \end{aligned}$ |


| Author, Year, Risk model name | Study population and setting | Derivation and validation ( n ) | Data used to develop model | Outcome(s) | Number (\%) admitted to hospital | c-statistic ((95\% Cls)* |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| NHS/Information Services Division Scotland, 2012, Scottish Patients At Risk of ReAdmission (SPARRA)-Version 3 (362) | Patients aged $\geq 16 y$ in population in Scotland 20062010 | Derivation <br> 3,506,796 <br> Validation <br> NR | 3 different models; 1) Frail elderly Aged>75, 2) Long term conditions, Aged 16-74, 3) Younger A\&E, Aged 16-55 with $\geq 1$ A\&E visit in last year <br> Hospital in-patient admissions data, community dispensed prescriptions, A\&E attendances, new out-patient attendances, psychiatric in-patient admissions | 12 months emergency admission | 309,783 (8.8\%) | Risk thresholds; 30\%-PPV 59.8\%, 40\%-PPV 52.2\%, 50\%-PPV 59.8\%, Sensitivity at threshold 50\%=10.5\% |
| Baker, 2012 (348) | Patients aged 40$98 y$ registered to Lodgehill clinic general practice in Nairn, Scotland** | Derivation $96^{* * *}$ <br> Validation $96^{* * *}$ | Data from one general practice in Nairn, Scotland and inpatient data (NHS Highland Patient Administration System) | Occupied bed days over 12 months*** | 105 (54.7\%) | Derivation 0.794 |
| Sussex Key Events Predictor tool, 2009 (346) | All ages in the population of East Sussex and Brighton, UK** | ```Total sample=823,000 80% derivation*** 20% validation***``` | Inpatient, outpatient, ER and community data*** | 12 months <br> Emergency <br> chronic <br> admission (Any <br> of; COPD, <br> Asthma, <br> Diabetes, <br> Dementia, Ischaemic Heart <br> Disease, <br> Respiratory <br> disease or <br> stroke)*** | NR | 0.82** |


| Author, Year, Risk model name | Study population and setting | Derivation and validation ( n ) | Data used to develop model | Outcome(s) | Number (\%) admitted to hospital | c-statistic ( ${ }^{\text {a }}$ ( $\mathrm{Cls}^{*}$ * |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Donnan, 2008, PEONY (363) | Patients aged $\geq 40$ <br> $y$ in general <br> practice in <br> Tayside, Scotland, 1996-2004 | Derivation 90,522 <br> Validation <br> 90,879 | Computerised model data from all general practices in Tayside, Scotland used record linked primary and secondary data via unique pt ID numbers (includes all health encounters)-previous admissions, number bed days, LOS mean, demographics, receipt of drugs and number. <br> Final model contains 35 variables. | 12 months emergency admission | 6793 (7.5\%) in derivation cohort | Derivation 0.80 Validation 0.79 |
| Health Dialog UK, 2008, <br> Welsh Predictive Model (WPM) (364) | All ages ( $0-100 y$ ) in general practice in Wales (51 practices), 20042007 $\text { ( } n=10,247 \text { were }$ aged <15y) | Total sample 298,077 <br> 50\% derivation, $25 \%$ validation of variables and $25 \%$ predictive testing <br> Derivation <br> 149,038 <br> Validation <br> 74,114 | Used GP data from 51 Welsh general practices, Welsh index of multiple deprivation, hospital records and GP data (no A\&E visit data), compared accuracy with CPM in same population. Compared Combined Predictive Model vs. Wales model in same population | 12 months emergency admission | NR | Risk thresholds; <br> Top 1\%; PPV=44.3\%, <br> Sensitivity 6.6\%, <br> Top 5\%; PPV=28.0\%, <br> Sensitivity=20.7\% |
| Health Dialog UK, 2006, <br> Combined Predictive Model (CPM) (365) | All ages ( $0-100 y$ ) in two UK primary care teams, 20022005 | Derivation <br> 280,000 (random <br> split sample) <br> Validation <br> 280,000, (random <br> split sample) | Data from two primary care trustsincludes inpt, OPD and A\&E data) plus primary care data (lab, diagnosis and encounter information). Limited pharmacy and social services data. Top 0.5\% considered very high risk | 12 months emergency admission | NR | Risk threshold top 1\%; <br> PPV 40.5\%, sensitivity $6 \%$ <br> (recorded in WPM report, NR in CPM report) |


| Author, Year, Risk <br> model name | Study population <br> and setting | Derivation and <br> validation ( $\mathbf{n})$ | Data used to develop model | Outcome(s) | Number (\%) admitted to <br> hospital |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| United States and Canada |  |  |  |  |  |


| Author, Year, Risk model name | Study population and setting | Derivation and validation ( n ) | Data used to develop model | Outcome(s) | Number (\%) admitted to hospital | c-statistic ((95\% CIs)* |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Lemke 2012, Adjusted Clinical Groupings (ACG) (366) | Aged < 65 y in employer health plans, $\geq 65 y$ in managed care plans in US insurance databases, 20052007, compared 3 models in same population | Derivation 4.63 million <br> Validation <br> 4.7 million | US Health Plan insurance claims administrative database <br> Several models developed and compared; <br> 1) Prior hospitalisation model <br> 2) Charlson comorbidity hospitalisation model (Combined model of hospitalisation, other healthcare utilisation and Charlson comorbidity index) <br> 3) Four ACG models | 1) Acute hospitalisation within 12 months <br> 2) ICU/CCU admission within 12 months <br> 3) Extended inpatient care for $\geq 12$ days within 12 mo | 150,417 (3.2\%) Derivation 149,843 (3.2\%) Validation | Validation cohorts; <br> 1. Prior hospitalisation $=0.75$ <br> 2. Charlson hospitalisation model $=0.78$ <br> 3. ACG inpatient hospitalisation $=0.80$ |
| Versisk Health, 2012, DxCG Likelihood of Hospitalization (367) | All ages in one US insurance database (Versisk Health) | NR | Demographics and administrative claims data from OPD and inpatient | 6 months <br> emergency <br> admission | NR | Risk threshold; Top 1\% PPV 24.2\% |
| Crane, 2010, Elders Risk Assessment Index (350) | Patients aged $\geq$ $60 y$, US primary care clinics in one hospital, 20032006 | Derivation 12,650 <br> Validation 450 (bootstrap samples) | Electronic medical record and administrative databases from primary care clinics in one hospital, computerised model, 10 items, Scored as 5 quartiles, $>16$ highest risk | 24 months (admissions or ER visits) | 5,785 (45.7\%) admitted or ER visit | Combined admission/ <br> ER visit 0.678 <br> Admission only 0.705 |
| Inouye, 2008 (316) | Patients aged $\geq 70 y$ in two US primary care clinics, 20032005 | Derivation <br> 1,932 <br> Validation <br> 1,987 | Computerised model Administrative database, inpatient and OPD visits, demographics, billing diagnoses, radiological procedures and lab results. 5 item score, $\geq 3=$ high risk | 12 months | 299 (15\%) | Derivation 0.72 <br> Validation 0.73 |


| Author, Year, Risk <br> model name | Study population <br> and setting | Derivation and <br> validation ( $\mathbf{n}$ ) | Data used to develop model | Outcome(s) | Number (\%) admitted to <br> hospital | c-statistic ((95\% CIs)* |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |

*If c-statistics are not presented then Positive Predictive Values (PPVs), sensitivity and specificity (where available) are recorded. **Author correspondence, NR=Not recorded.

### 6.2.3.4 R isk prediction model variables

Seven studies presented their final risk model only and not all variables considered for inclusion. One study used locally available data to create a risk prediction model specifically for a named population so the variables considered for inclusion vary. Each of the variables considered for and included in each of the 27 models is presented in Table 6-5. The most frequently included predictor variables in final risk models were: 1) named medical diagnoses ( 23 models); 2) age ( 23 models); 3) prior emergency admission ( 22 models) and 4) gender ( 18 models). Other healthcare utilisation variables commonly included were prior A\&E and OPD visits (14 and 13 models respectively). Twelve models included measures of multimorbidity, most commonly the Charlson index and simple disease counts. Polypharmacy was considered as a predictor variable in 14 models and included in eleven final models. Five models included a specific measure of socio-economic status and a further three used either employment history or income as proxy measures for this variable.

Overall, a smaller number of models ( $n=11$ ) included non-medical factors. These variables were largely included in self-report data models. Of those that included functional status as a predictor variable, most considered either activities of daily living, mobility and/or a history of falls. Four questionnaires included measures of selfrated health and one included health related quality of life. Two questionnaires included the social support measure of caregiver availability. Three models developed using administrative or clinical record data included non-medical variables; these included a history of falls as a predictor variable, social supports and living arrangements and a disability rating variable respectively.

Table 6-5: Predictor variables in risk prediction models ( $\mathrm{n}=2 \mathbf{2 6}^{*}$ ) for predicting emergency hospital admissions

| Predictor variable | Included in final model ( n ) | Excluded following evaluation (n)** |
| :---: | :---: | :---: |
| Medical history |  |  |
| Specific medical diagnoses | $23^{(50,203,316,317,326,347-351, ~ 353, ~ 355, ~ 356, ~ 358-362, ~ 364-368) ~}$ | 0 |
| Multimorbidity | $12^{(316, ~ 317,326, ~ 347, ~ 351, ~ 353, ~ 360, ~ 361, ~ 364-366, ~ 368) ~}$ | $1^{(349)}$ |
| ACS conditions | $2^{(360,366)}$ | $1{ }^{(50)}$ |
| Mental illness | $12^{(317,326,347,348,353,359, ~ 360, ~ 362, ~ 364-367) ~}$ | $5^{(50,349,351,355,356)}$ |
| Cognitive impairment | $7{ }^{(326,350,352,353, ~ 355, ~ 360, ~ 362) ~}$ | $3^{(203, ~ 349, ~ 364) ~}$ |
| Alcohol or substance misuse | $7{ }^{(326,359-362,365,366)}$ | $2^{(349,358)}$ |
| Clinical and laboratory findings |  |  |
| Clinical examination findings | $3^{(50,326,360)}$ | $6^{(317,349,359, ~ 361, ~ 365)}$ |
| Laboratory findings | $7{ }^{(50,326,349,359-361,365)}$ | $3^{(316,317,364)}$ |
| Medications |  |  |
| Prescribed specific medications | $9^{(317,326,359-365)}$ | 0 |
| Polypharmacy | $11^{(50,351-354,360, ~ 361, ~ 363-365, ~ 368) ~}$ | $3^{(317,355,358)}$ |
| PIP | $1^{(317)}$ | 0 |
| Healthcare utilisation |  |  |
| Prior emergency admission | $22^{(203,316,326, ~ 347-351, ~ 353-356, ~ 359-368) ~}$ | $4^{(50,317,352,358)}$ |
| Prior elective admission | $3^{(360,364,368)}$ | 0 |
| Prior ACS admission | $2^{(361,365)}$ | $1^{(356)}$ |
| Prior A\&E visits | $14^{(50,326,347, ~ 351, ~ 353, ~ 359-362, ~ 364-368) ~}$ | $2^{(352,358)}$ |
| Prior OPD visits | $13^{(203,326,347,348,356,360-362,364-368)}$ | $4^{(50,316,317,358)}$ |
| Prior GP visits | $8^{(203, ~ 316, ~ 326, ~ 347, ~ 356, ~ 360, ~ 366, ~ 368) ~}$ | $2^{(317,364)}$ |
| Duration of GP registration | $3^{(360-362)}$ | 0 |
| Number of previous bed days | $5^{(326,350,356,362,363)}$ | $1^{(203)}$ |
| Demographics |  |  |
| Age | $23^{(50,203,316,317,326,347, ~ 348, ~ 350, ~ 352-356, ~ 359-368) ~}$ | $3^{(349,351,358)}$ |
| Gender | $18^{(203,326,347-349, ~ 352-356, ~ 359-361, ~ 363-366, ~ 368) ~}$ | $5^{(50,316,317,350,351)}$ |
| Race/Ethnicity | $2{ }^{(353,359)}$ | $5^{(50,203,316,350, ~ 351)}$ |
| Marital status | $6^{(316,326,347,350,353,356)}$ | $4^{(50,349,351,364)}$ |
| Socioeconomic status | $8^{(347,349,354,359,360,362-364)}$ | $3^{(50,203,317)}$ |
| Health insurance | $2^{(347,356)}$ | $2^{(50,316)}$ |
| Functional status |  |  |


| Predictor variable | Included in final model (n) | Excluded following <br> evaluation (n)** |
| :--- | :--- | :--- |
| Activities of daily living | $4^{(347,349,354,358)}$ | $3^{(203,351,355)}$ |
| Mobility | $5^{(349,352,354,355,358)}$ | $2^{(326,356)}$ |
| History of falls or hip fracture | $2^{(359,361)}$ | $5^{(203,350,352,355,358)}$ |
| Self-rated health | $4^{(203,349,355,356)}$ | $3^{(50,351,358)}$ |
| HRQOL | $1^{(50)}$ | 0 |
| Social supports | $3^{(352-354)}$ | $7^{(50,203,349,351,355,356,358)}$ |
| Lives alone | $2^{(203,354)}$ | $2^{(50,355)}$ |
| Caregiver availability | $4^{(354,360,366,368)}$ | $1^{(203)}$ |
| Community nurse visits | $2^{(353,354)}$ | $1^{(349)}$ |
| Use of other social supports |  | $2^{(355,358)}$ |
| Other | 0 |  |
| Recent stressful life event |  |  |


#### Abstract

*One risk model (The Sussex Key Events Predictor tool) creates customised models using a combination of inpatient, outpatient, ED and community data relevant to the population of interest and was excluded here. **Seven models presented the final model only and did not present all variables considered for inclusion.


### 6.2.3.5 Predictive accuracy of risk prediction models

Eighteen models presented c-statistics for the outcome of emergency admission ranging from 0.61-0.83. Six models reported $c$-statistics of $>0.8$ indicating reasonably good model discrimination.(317, 326, 346, 347, 363, 366) Some similarities were noted amongst these models; all included prior healthcare utilisation variables, multimorbidity or polypharmacy measures and named medical diagnoses or named prescribed medications variables. Three of these six models utilised ACS admission as a primary outcome. $(317,346,347)$ Seven risk prediction models reported c-statistics of between 0.7 and 0.8 representing reasonable model performance.

Of nine models developed using self-report data primarily, eight were designed for use in older people only. In contrast, only five of the 18 models developed using administrative or clinical record data were derived specifically for use in older people. The remainder were developed for use in general populations aged over 18 years. Overall, models developed primarily using administrative or clinical record data
performed better than those developed using self-report data with reported cstatistics ranging from $0.68-0.83$ vs. $0.61-0.74$ respectively.

### 6.2.3.6 Comparison of risk prediction models performance within and across populations

Three studies developed several prediction models in one population, using different datasets and then compared their performance. Billings et al developed four models in the UK using: 1) inpatient data alone; 2) combined inpatient and A\&E data; 3) combined inpatient, A\&E and OPD data; and 4) combined inpatient/A\&E/OPD/general/family practice data.(30) This was undertaken to determine if the addition of general/family practice data improved overall model performance. In the test sample of over 1.8 million people the OPD/A\&E/GP/inpatient model performed best (c statistic 0.78 vs. 0.73 for inpatient model).(360) Similarly Lemke and colleagues in the US examined various models using the ACG classification and compared these with models using prior hospitalisation only using a data source of 4.7 million medical insurance claims. The model using ACG groupings plus prior healthcare utilisation performed best overall (c-statistic 0.8 vs. 0.75).(366) Reuben and colleagues compared models developed using prior admission only; self-report data only and a model using a combination of self-report variables and laboratory values. The model with greatest predictive accuracy used a combination of self-report and laboratory variables. (c-statistic 0.69)(349)

Two studies directly compared different validated models in the same population. The UK Combined Predictive Model (CPM) was developed to be nationally representative.(365) It was compared to two other UK risk models, the Wales predictive model and the Devon predictive model. $(361,364)$ In primary care the Wales model was found to have superior predictive ability when compared to the CPM in correctly identifying those who were subsequently admitted. The Devon predictive model included many of the same variables as the CPM but also local data variables and was found to have greater predictive accuracy when compared to the CPM. The authors argued that the addition of local factors, for example, the participant's
duration of family practitioner registration as a proxy for continuity of care, were integral to improved performance.

### 6.2.3.7 Methodological quality assessment of included studies

Overall the methodological quality of included studies was good using the McGinn checklist. For derivation, the majority of studies reported all checklist items with the exception of items pertaining to blinding of outcome assessors, blinding of those assessing the presence of predictors and reporting of the proportion of the population with important predictors. For validation the majority of studies reported all checklist items with underreporting of blinding of those assessing the outcome event (see Figure 6-2a and Figure 6-2b).


6-2a: Methodological quality assessment: Derivation studies (number of studies on the x -axis)


6-2b: Methodological quality assessment: Validation studies (number of studies on the x axis)

Figure 6-2: Methodological quality assessment of included risk prediction models ( $n=26, n=1$, model customised depending on population it is intended for)

### 6.2.4 Discussion

### 6.2.4.1 Summary of findings

This systematic review identified 27 unique risk models for predicting hospital admission. Less than half were developed specifically for older people with the rest designed for use in an adult population. Overall, models developed using administrative or clinical record data and developed on large datasets tended to have greater predictive ability than self-report questionnaires. Risk prediction models that examined the added benefit of general/family practice clinical record data in increasing predictive accuracy reported improved performance when this data source was included.

### 6.2.4.2 Variables included in risk prediction models

Overall, almost all risk models in this review included age, prior hospitalisation and specified medical diagnoses and the majority included gender. However, less than half considered a specific measurement of multimorbidity, which is surprising considering the impact the presence of multiple conditions has been shown to have on healthcare utilisation.(39) Similarly, less than half of included models considered polypharmacy and only eight included a measure for socio-economic status in their development. In this review the six risk prediction models that demonstrated greatest predictive accuracy (based on reported c-statistics) included similar variables namely; prior healthcare utilisation, multimorbidity or polypharmacy measures and named medical diagnoses or named prescribed medications predictor variables. Three of the six focussed on ACS admissions.

Overall, non-medical factors such as functional status, social supports and self-rated health were included in approximately one-third of risk models. These factors have been highlighted as potentially contributing to emergency hospitalisation. One US study of qualitative interviews with patients identified by a risk prediction model as high-risk found that the majority had poor self-rated health, precarious housing status, lived alone and reported high levels of social isolation.(369)

### 6.2.4.3 R isk prediction models performance in new settings

In two studies, a nationally developed risk prediction model was applied to new populations in the same country and its performance compared to adapted models which included local factors. $(361,364)$ In both studies the locally adapted models performed better in predicting future emergency hospitalisation. One UK risk score developer designs customised risk models for a specified population using locally available data to ensure that the model created is fit for purpose.(346) This approach seems sensible as local factors may well differ within countries and differences in population demographics may mean that a risk model should be applied differently.

### 6.2.4.4 Comparison with previous research

This is the first systematic review of risk prediction models for emergency admission in community dwelling adults. Previous systematic reviews have focused on readmission risk models and risk factors for emergency admission. Kansagara and colleagues found that of 26 retrieved readmission risk models only six reported a c-statistic greater than 0.7.(48) They concluded that most readmission models perform poorly and suggested that the additional variables available through the medical record or patient self-report may improve performance. This systematic review supports this suggestion with models developed using clinical record data demonstrating improved predictive accuracy overall.

Garcia-Perez et al reported that the risk factors of chronic disease status and functional disability were the most important predictors, followed by prior healthcare utilisation in predicting future emergency admission.(370) While medical diagnoses and prior healthcare utilisation were included in almost all risk prediction models in this review far fewer included functional status. This may be related to the type of data available in the development phase, especially those that utilise administrative or clinical record data only. Functional status variables have tended to be included in selfreport questionnaires which may be more prone to response bias for the reporting of other important predictors such as medical diagnoses and previous healthcare
utilisation. Future research needs to consider how best to capture non-medical factors, such as functional status, to determine if their inclusion into predictive models improves performance.

### 6.2.4.5 C linical andresearch implications

In 2011, a US based heritage provider group offered a $\$ 3$ million prize to any group who could develop a risk prediction model to identify people at higher risk of admission so that resources could be directed at reducing their risk.(323) However, to date, the evidence for case management for higher risk community dwelling people is mixed and has not reduced emergency admissions.(371) For instance, the Guided Care model aims to reduce hospital admissions through the provision of primary care that includes comprehensive geriatric assessment, case management, self-management support and caregiver support provided by a team that includes a specially trained care coordinator. Patients were targeted using age and multimorbidity as risk stratification criteria. In a 32 centre randomised control trial, this intervention was found to improve participants' chronic care, reduce caregiver strain and resulted in high levels of healthcare professional satisfaction.(214) However, apart from one subgroup, compared to usual care, participants utilised similar levels of healthcare at 20 month follow-up, with the exception of home health care which was significantly reduced.(49)

Another consideration relates to the choice of outcome measure. Most risk models in this review used emergency admission for any cause as their primary outcome. Only three chose ACS emergency admissions as a study end-point. A further three models considered ACS conditions in their development process. This is interesting as a proportion of all emergency admissions will not be preventable even with intensified care. $(202,372)$ As described in Section 2.4.5, ACS admissions result from chronic medical conditions for which it may be possible to prevent acute exacerbations, therefore, reducing the need for emergency admission through management in primary care. $(373,374)$ In the UK, it's estimated that approximately $16 \%$ of all emergency admissions for all age groups occur as a result of these conditions and up to $30 \%$ of admissions for those aged over 75 years. $(207,208)$ Community-based
interventions should target conditions for which up-scaling primary care management can really impact on preventing subsequent admissions. In the US, risk prediction model developers have started testing models which aim to focus resources not necessarily on patients at highest risk of emergency admission, but those with conditions or characteristics (such as prior treatment adherence) most likely to benefit from increased preventative care.(372) In this way resources can be focused where impact is more likely to be realised.

### 6.2.4.6 Strengths and Limitations

This review is timely considering the increased interest in risk stratification to identify community-dwelling people at higher risk of future emergency admission. However, there are some limitations. Risk prediction models developed in one population or healthcare setting may not be transferable to another and care must be taken in comparing models. Furthermore, risk prediction models need frequent updating to remain relevant and some of the older models described in this review are now obsolete. Seven of the included models presented their final risk model only and not all variables considered for inclusion.

### 6.2.5 Conclusions

Choosing a robust method of risk stratification is an essential first step in attempting to reduce emergency hospital admissions. This review identified 27 validated risk prediction models developed for use in the community. Local factors and choice of outcome are important considerations in choosing a model. Capturing non-medical factors, such as functional status, may have a role in improving predictive accuracy.

### 6.3 The Probability of repeated admission (Pra) risk model for predicting emergency admission: a systematic review and meta-analysis

### 6.3.1 Introduction

One risk model identified in the previous systematic review and broadly validated for identifying older people at higher risk of hospital admission is the Probability of Repeated Admission (Pra) score.(203) As described in Section 2.4.3, the Pra score was originally derived in 1993 in an elderly ( $\geq 70$ years) community-dwelling US population. The score is calculated using a logistic equation with a resulting value of between 0 and 1 and a score of 0.5 indicates a $50 \%$ likelihood of readmission within a four-year period.(203) The model has subsequently been validated to predict hospital admissions over a one-year follow-up period and to predict other outcomes such as emergency room visits and health care costs. $(375,376)$ Screening questions include; age; gender; presence of chronic conditions; previous admissions to hospital; previous physician visits; and availability of an informal caregiver.

The original Pra score was calculated using a postal questionnaire administered to patients. However, the tool has subsequently been validated using administrative databases which excluded the self-report questions of self-rated health and caregiver availability and substituted these questions with a measure of multimorbidity, the Chronic Disease score or the Deyo-Charlson index. $(263,333)$ The Chronic Disease score was developed in 1992 and uses pharmacy claims data to estimate morbidity.(333) This measure was used to develop the RxRisk-V specifically for older people which classifies prescribed medications into 45 chronic disease categories based on the ATC classification system.(377) The RxRisk-V has been validated to predict health outcomes including costs of care and healthcare utilisation. $(59,320)$

The aim of this systematic review and meta-analysis of the validation studies of the Pra risk score was to assess its performance in predicting emergency hospital admission in community-dwelling adults over one year.

### 6.3.2 Methods

### 6.3.2.1 Data sources and search strategy

The PRISMA guidelines for the conduct and reporting of systematic reviews and metaanalysis were adhered to in the conduct of this systematic review.(318) The original computerised literature search was performed including PubMed, Embase, Cinahl and the Cochrane library databases from January 1990 to the end of April 2012 and was limited to publications in English. This electronic search was then updated in September 2015. The databases were searched using a combination of terms including "probability of repeated admission", "Pra", "Pra score", "Pra instrument" and "Pra questionnaire". This electronic search was supplemented by hand searches of the references of retrieved full-text articles.

### 6.3.2.2 Study selection and data extraction

Criteria for inclusion were as follows;

1) Study design: prospective or retrospective cohort studies; 2) Patient population: patients $\geq 18$ years of age (although the Pra score was designed for use in older people this age cut-off was chosen to ensure all validation studies were captured in the search); 3) Explanatory variables: Pra score calculated; 4) Setting of care: Primary care and community settings, 5) Primary outcome; emergency hospital admission at oneyear follow-up, Secondary outcomes; mortality, days in hospital, direct hospital costs, nursing home admissions and home visits.

All articles identified by the electronic search were independently screened by title and abstract by two researchers (Emma Wallace, Susan Smith). Full texts of potentially eligible studies were then screened. Disagreements were managed by consensus or be a third reviewer (Tim Hinchey). Data was extracted from included studies by three authors (Emma Wallace, Susan Smith, Tim Hinchey) using a standardised data collection form.

### 6.3.2.3 Methodological Quality Assessment

Methodological quality assessment was independently performed by two researchers following the modified methodological standards of McGinn for validation studies of clinical prediction rules.(343) The McGinn criteria have previously been described in detail (see Section 6.2.2.5) and were used in this systematic review to assess the internal and external validity of included studies.

### 6.3.2.4 Data synthesis and analysis

All retrieved studies meeting inclusion criteria were included in the narrative synthesis. Meta-analysis was conducted on studies that used a Pra score cut-off of $\geq 0.5$ as denoting high-risk (similar to the derivation study), reported emergency hospital admission at one-year follow-up and where adequate data was available.

### 6.3.3 Statistical methods

A $2 \times 2$ table was constructed to extract the numbers of true positives, false positives, true negatives and false negatives for the Pra score from each validation study using a cut-off point of $\geq 0.5$ to identify those at high risk. The discrimination performance of the Pra score was assessed by performing a pooled ROC analysis, fitting a symmetrical, summary ROC curve using the DerSimonian-Laird random-effects model and estimating the c-statistic, its standard error (SE) and 95\% confidence intervals.(378)

To further confirm these results a bivariate random-effects model was used to construct and analyse a hierarchical summary ROC curve with its corresponding $95 \%$ confidence interval regions.(379) This model was used to estimate summary estimates of sensitivity and specificity and their corresponding $95 \%$ confidence intervals. This approach preserves the two-dimensional nature of the original data and takes into account both study size and heterogeneity.(380) In addition, the bivariate model estimates and incorporates the negative correlation, which may arise between the sensitivity and specificity as a result of differences in reference standards used in different studies.

Sensitivity (true positive) refers to the proportion of people admitted to hospital classified as high risk by the Pra. Specificity refers to the number of those not admitted to hospital correctly classified as low risk (true negative). Individual and summary estimates of sensitivity and specificity for the Pra were plotted in a hierarchical summary receiver operating curve (HSROC) graph, plotting sensitivity (true positive) on the $y$ axis against 1-specificity (false negative) on the $x$ axis.(381) The $95 \%$ confidence region and $95 \%$ prediction region around the pooled estimates were also plotted to illustrate the precision with which the pooled values were estimated (confidence ellipse around the mean value) and to illustrate the amount of between study variation (prediction ellipse).

The c-statistic ( $95 \% \mathrm{Cls}$ ), was also estimated to describe model discrimination. As previously outlined in Section 5.2.5, the c-statistic ranges from 0.5 (no discrimination) to a maximum of 1 (perfect discrimination), where a value $<0.7$ represents poor model discrimination, 0.7-0.9 reasonable discrimination and $\geq 0.9$ excellent model discrimination. $(331,345)$ Heterogeneity was assessed visually using the summary ROC plots and statistically by using the variance of logit transformed sensitivity and specificity, with smaller values indicating less heterogeneity among studies. All analyses were conducted using Stata version 13.(304)

### 6.3.4 Results

### 6.3.4.1 Identification of studies

A flow diagram of the search strategy is presented in Figure 6-3. The electronic literature search retrieved 4,484 titles and 18 potentially eligible papers were reviewed in full, leading to the identification of ten Pra validation studies describing twelve cohorts of patients. $(148,382-392)$ Five cohorts of patients from three studies ( $\mathrm{n}=8,843$ ) met the inclusion criteria for meta-analysis.


Figure 6-3: PRISMA Flow diagram of identification of studies for inclusion in Pra systematic review

### 6.3.4.2 Description of included studies

Details of included studies are presented in Table 6-6. The majority of studies ( $n=8$ ) were conducted in North America, one was carried out in South America and one study examined three European cohorts (UK, Germany and Switzerland).(389) The study cohorts ranged in size from 306 to 17,469 participants and included a total of 36,140 patients. Patient characteristics varied across all cohorts and are described in Table 6-7. As expected, the vast majority of studies focused on older people with all studies except one using either age $\geq 65$ or $\geq 70$ years as an inclusion criterion. There was variation in the reporting of the proportion of 'high-risk' patients according to Pra across different studies ranging from $2.5 \%$ to $25 \%$. This variation was, in part, due to the different Pra score cut-off points used to define 'high-risk' groups, with some studies using cut-off points of $\geq 0.3$ or $\geq 0.4$, rather than the recommended cut-point of $\geq 0.5$. Of 12 validation cohorts, a total of seven used the original $\geq 0.5$ Pra cut-off to indicate high-risk.

All studies considered hospital admission as their primary outcome although this varied in how it was reported. The original Pra derivation study reported the risk of repeated hospital admission over a four year period but subsequent studies have examined risk of admission over shorter follow-up periods usually one year. Secondary outcomes included mortality, length of hospital stay, functional decline, other service use and costs. The response rates across the studies that used the Pra postal questionnaires ranged from $40 \%$ to $70 \%$. Two US validation studies examined the use of administrative databases to calculate the Pra score. $(384,387)$ These two studies excluded the self-report items of self-rated health status and caregiver availability and reported similar predictive accuracy to the postal questionnaire in predicting admissions at one year follow-up. $(384,388)$ Both studies used a measure of multimorbidity instead of the self-rated health status item, the Chronic Disease score and Deyo-Charlson index respectively.

## Table 6-6: Characteristics of studies included in Pra systematic review ( $\mathrm{n}=10$ )

| Author, Year | Participants, study design, study setting | Primary Outcome | Secondary outcomes | Notes |
| :---: | :---: | :---: | :---: | :---: |
| Boult 1993(203) | 5876 of multistage probability sample of all noninstitutionalised US citizens aged $\geq 70$ years <br> Split-sample with second half used to internally validate score derived from first half | Number with $\geq 2$ admissions in 4 years | Mortality; <br> Hospital days; <br> Hospital costs | Derivation and internal validation study <br> Defined high risk as $\geq 0.5$ |
| Boult 1995 (383) <br> Pacala 1995(148) <br> Note same study population | 306 of all local low-income (Medicaid enrollees) in three counties in Minnesota, US; 61\% response rate. | Admissions in 1 year (Mean number per person-year survived) | Mortality; Hospital days; Pharmacy payments; Total payments | Boult 95:Also pilot study to assess Pra scores ability to identify individuals suitable for RCT intervention <br> Pacala 95same population with additional secondary outcomes reported |
| Pacala 1997(376) | 6,802 enrollees aged $\geq 65$ in Medicare Plan, California US | Admissions in 1 year | Claims; ER visits; Nursing home admissions; Home visits |  |
| Coleman 1998(384) | 2,174 of 5,240 randomly selected enrollees aged $\geq 65$ of a HMO in Washington State, US | Number with $\geq 2$ admissions in 4 years | Functional decline at 4 years | Comparison of self-report and administrative data |
| Jensen 2001(391) | 386 enrollees aged $\geq 65$ in Medicare managed-risk Health Plan in Pennsylvania State, US | Admissions in 1 year | NA | Compares Pra score with Level II Nutrition screen. <br> Pra $\geq 0.3$ considered high risk |
| Vojta 2001(388) | 296 of 558 enrollees aged $\geq 65$ in Medicare HMO in | Admissions in 6 months (sensitivity and | Total claims over 6 | Compared Pra score to database Derived score used as |


| Author, Year | Participants, study design, study setting | Primary Outcome | Secondary outcomes | Notes |
| :---: | :---: | :---: | :---: | :---: |
|  | Philadelphia, also Medicaid eligible; response rate 54\%. | specificity for Pra at different cut-points; $\geq 0.5, \geq 0.45$ and $\geq 0.4$ ) | month period | administrative proxy |
| Sidorov 2002(387) | 17,469 of 24947 enrolees of Medicare Plan in Pennsylvania State; Mean age 71.2 years; $70 \%$ response rate. | Admissions in 1 year (mean) | Mean number hospital days; Claims | Also reported variation in utilisation between different primary care sites within the plan |
| Wagner 2006(389) | 6,924 community-dwelling people aged $\geq 65$ from initial | Admissions in 1 year |  |  |
| Three separate cohorts: Germany, UK, Switzerland | sample of 18,932 potentially eligible patients identified by GPs; only those with follow-up data included. |  | $\geq 6$ physician visits in 1 year | Data from PRO-AGE RCT |
|  | 1,783 of 4,506 new enrolees in United Health Group |  |  | Compares Pra score with |
| Mosley 2009(390) | Secure Horizons Medicare Advantage Plan in Alabama, Florida or Ohio, US; response rate 45\% | Admissions in 1 year | NA | Hierarchical Condition Model (HCC score) |
| Dutra 2011(392) | 515 of 551 enrolees non-institutionalised adults $\geq 60$ years in Southern Brazil | Admissions in 6 months | NA | Pra $\geq 0.5$ high risk |

NA=Not applicable

Table 6-7: Comparison of study population characteristics of studies included in Pra systematic review ( $\mathrm{n}=10$ )

| Study | \% high risk (definition of high risk used in the study) | Gender <br> \% male | Age in years | Self-rated health fair or poor | $\geq 1$ hospital admission in previous year | > 6 physician visits in previous year |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Boult 1993(203) (Derivation) | 8\% high risk (Pra >0.5) | 42\% | 9\% >85 | 32\% | 21\% | 21\% |
| Boult 1995/ Pacala 1995(148, 383) | 21\% high risk (Pra >0.5) | 12\% | 10\% > 85 | 57\% |  | 36\% |
| Pacala 1997(393) | 25\% high risk (Pra >0.3), 2.5\% had Pra $>0.5$ | 42\% | 6\% >85 | 18\% | described as younger he | Ithier cohort overall |
| Coleman 1998(384) | 14\% high risk (Pra >0.5) | 39\% | $35 \%>75$ | 39\% | 14\% | $44 \%>3$ visits in last year |
| Jensen 2001(391) | NR* | 47\% | $3 \%>85$ | 15\% | 13\% | 14\% |
| Vojta 2001(388) | 25\% high risk (Pra >0.4) | 23\% | Mean 71 | NR | 27\% | 46\% |
| Sidorov 2002(387) | 5\% high risk ( $\mathrm{Pra}>0.5$ ) | 48\% | Mean 72 | 20\% | 19\% | 17\% |
| Wagner 2006 (389) Germany | 7\% high risk (Pra >0.5) | 37\% | 6\% >85 | 38\% | 23\% | 51\% |
| Wagner 2006 UK | $4 \%$ high risk (Pra $>0.5$ ) | 45\% | $6 \%>85$ | 24\% | 14\% | 23\% |
| Wagner 2006 Switzerland | 5\% high risk (Pra >0.5) | 44\% | 5\% >85 | 21\% | 19\% | 25\% |
| Mosley 2009(390) | 5\% high risk (Pra >0.3) | NR | NR (Medicare) | NR | NR | NR |
| Dutra 2011(392) | 7\% high risk (Pra>0.5) | 44\% | 77\% 60-74 | 21\% | 27\% | 18\% |

[^8]
### 6.3.4.3 Methodological quality assessment of included studies

Overall, external validity was good with any potential bias in patient selection resulting from the response rates to the original mailed questionnaires and these are described in Table 6-6. The main shortcomings in relation to internal validity related to blinding and no study specifically reported whether the outcome assessors were blinded to the original Pra score of participants. However, the outcomes were generally collected from automated data sets such as Medicare claims databases, so the quality of outcome assessment depended in part on the availability of claims data.

### 6.3.4.4 Discrimination of the Pra model

A meta-analysis of the Pra score was carried out for the five eligible cohorts ( $n=8,843$ ). This analysis indicated that Pra discrimination performance was reasonable; $c$-statistic=0.70 (SE 0.028 ) (See Figure 6-4). The pooled sensitivity was low ( $12 \%, 95 \%$ Cl $10.5 \%, 13.6 \%$ ), but the pooled specificity was high ( $96 \%, 95 \% \mathrm{Cl} 95.8 \%, 96.7 \%$ ). The variance of logit transformed was $0.25(95 \% \mathrm{Cl} 0.05,1.28)$ for sensitivity and $0.33(95 \% \mathrm{Cl} 0.08,1.48)$ for specificity, and the $95 \%$ prediction regions (amount of variation between studies) on the Hierarchical Summary Receiver Operating Characteristic Curve (HSROC) graph were wide, indicating heterogeneity between studies (See Figure 6-5).


Figure 6-4: Summary receiver operating characteristic (SROC) curve Pra discrimination meta-analysis for predicting emergency admission over one year follow-up


Figure 6-5: Hierarchical Summary Receiver Operating Characteristic Curve (HSROC) with 95\% confidence prediction region for studies included in Pra meta-analysis

### 6.3.4.5 Secondary outcomes

Secondary outcomes were examined in seven studies and included costs of care, length of inpatient stay, mortality and other healthcare utilisation such as primary care visits. (See Table 6-6) It was not possible to conduct meta-analysis for secondary outcomes due to significant heterogeneity but overall the narrative synthesis indicates that the Pra score may have a role in predicting higher future healthcare utilisation and healthcare costs.

### 6.3.5 Discussion

### 6.3.5.1 Statement of principal findings

This systematic review indicates that the Pra risk score is a reasonable predictor of future hospital admission in high-risk individuals (Pra score $\geq 0.5$ ) with a pooled discrimination c-
 Pra score of $\geq 0.5$ effectively 'rules in' the likelihood of hospital admission over the next year.

### 6.3.5.2 C urrent context and futureresearch implications

This review indicates that it is reasonable to use administrative or chart data to gather the information required for calculating the Pra score which may be more practical and have higher response rates than traditional postal questionnaires thus augmenting the potential of the score in healthcare planning. However, completeness and availability of administrative or chart data may be an issue so a combination of self-reporting with use of administrative data may produce the most complete data.(384) Another interesting development is the increasing recognition of the impact of multimorbidity and polypharmacy on high healthcare utilisation and hospital admissions. $(24,394,395)$ A multimorbidity measure was included in two validation studies included in this review instead of self-rated health status Pra item and predictive accuracy was similar when compared to the original Pra. $(384,388)$

### 6.3.5.3 Study limitations

There are also some limitations to this systematic review. There have been a limited number of Pra validation studies and many of these were performed more than ten years ago. This has made it difficult to obtain additional data from authors and limited the number of studies that could be included in the meta-analysis. In addition, the study authors have used different cut-off points for the Pra score to define 'high-risk' groups and different follow-up periods. There is variation across the included studies in terms of participant characteristics but this is to be expected and it could be argued that such variation adds to the external validity of the findings.

### 6.3.5.4 Conclusions

This systematic review suggests that the Pra is a risk score that is reasonably useful when trying to identify older people living in the community at increased risk of future hospital admission. However, very low pooled sensitivity indicates that hospital admission in those stratified as low risk by then score cannot be reliably ruled out. Despite its potential, there are still a relatively limited number of validation studies. Further studies are warranted in
populations of patients with broad risk of hospital admission to better determine the validity of the Pra score in different populations and to enhance its generalisability.

### 6.4 Validation of the Pra risk score in a prospective cohort of older communitydwelling people

### 6.4.1 Introduction

In applying a risk prediction model to a new setting there is always a risk that performance will diminish, largely due to differences in the study population (e.g. socioeconomic demographics), local factors (e.g. availability of hospital beds) or healthcare setting (e.g. physician payment, access to GP care).(343) It is therefore critically important that models for predicting emergency admission are tested before widespread use in a new setting. The systematic review and meta-analysis of the Pra risk model indicated that it had a high summary specificity (pooled specificity $95 \%, 95 \% \mathrm{Cl} 95.8 \%, 96.7 \%$ ) and a summary c-statistic of 0.70 , indicating reasonable pooled model discrimination.

The Pra systematic review identified some important amendments both to the administration and use of the tool since its development in 1993. First, this model was originally designed as a postal questionnaire but it has been validated successfully using data extracted from health administrative databases and the clinical record.(384) These studies excluded the Pra items relating to self-rated health and care-giver availability and instead substituted a measure of multimorbidity, the Chronic Disease Score and the DeyoCharlson index respectively. Second, while the Pra was originally derived to predict $\geq 2$ emergency admissions over four year follow-up, it has been validated successfully in several studies to predict $\geq 1$ emergency admissions over one year follow-up. This shorter follow-up time has pragmatic advantages for evaluating the usefulness of the Pra, for example as a risk stratification tool in trials of interventions aiming to reduce emergency admissions. In addition it would be possible to utilise the Pra tool on GP research databases if the selfreport items were not essential for predictive accuracy. However, the majority of validation studies identified as part of the Pra systematic review were conducted in the US over 10
years ago. To enable use of the Pra tool in Ireland would require a new validation study to determine the predictive accuracy of the score in this setting.

The aims of this study were: i) To externally validate the Pra risk model to predict future emergency hospital admission over one year in an Irish cohort of older ( $\geq 70$ years) community-dwelling people; and ii) to externally validate the modified Pra risk model (that excludes self-report items of care-giver availability and self-rated health status, substituting a measure of multimorbidity) in the same study setting and compare the predictive accuracy with the original Pra model.

### 6.4.2 Methods

The two year prospective cohort described in Chapter 3 was utilised to externally validate the Pra risk model in older Irish community-dwelling adults.

### 6.4.2.1 R isk prediction models methodological considerations

Risk prediction models should go through a defined methodological process in their development.(343) The first stage is derivation where factors with predictive ability are identified (e.g. through literature review) and then tested until a final model is developed consisting of variables with the greatest predictive accuracy for the outcome of interest. The next stage is internal validation where the model is tested in a similar setting to that in which it was developed to test the model's performance. Next, is external validation where the model should be tested in a new setting (e.g. a different country) and performance measured to ensure comparable predictive accuracy. Finally, risk prediction models with established predictive accuracy and acceptability may then be tested in terms of effectiveness, usually through a RCT, to examine if use of the model improves patient outcomes or reduces cost when compared to usual care. Specific methodological considerations are necessary in conducting external validation studies of risk prediction models. A set of reporting guidelines has recently been published to support this process called the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement. These guidelines were adhered to in the conduct of this external validation study.

### 6.4.2.2 Exposure: calculation of the Pra score

As previously described in Section 2.4.3, the Pra model was developed in the US in 1993 in a cohort of older ( $\geq 70$ years) community-dwelling people and comprises eight questions used that risk stratify patients according to the probability of experiencing a future emergency admission. These questions are: 1) age; 2) gender; 3) presence of diabetes mellitus; 4) presence of coronary heart disease; 5) hospital admission in previous year; 6) $>6$ physician visits in previous year; 7) self-rated health; and 8) availability of an informal caregiver. Each of these questions is assigned a score and then entered into a logistic formula which produces a score from 0 to 1 (See Figure 6-6). Patients allocated a score of $\geq 0.5$ are considered high-risk of future admission. This score was calculated for all patients and is referred to as the original Pra score.

In addition, a second version of the Pra was calculated. This modified Pra model has been tested previously in two US studies and substitutes the questions relating to self-rated health and availability of an informal caregiver for a measure of multimorbidity. The RxRiskV was used as the measure of multimorbidity in this instance. This score is useful in terms of application to routine databases and therefore has more potential for a population health planning and policy perspective. Therefore the modified Pra comprised of seven questions; 1) age, 2) gender, 3) presence of diabetes mellitus, 4) presence of coronary heart disease, 5) hospital admission in the previous year, 6) $>6$ physician visits in previous year and 7) RxRiskV score. This version is referred to as modified Pra score. The data source for each of the Pra risk model items (original and modified) is outlined in Table 6-8.

Table 6-8: Data source for each item of the original and modified Pra score

| Pra item | Original Pra score | Modified Pra score |
| :--- | :--- | :--- |
| Age | GP record | GP record |
| Gender | GP record | GP record |
| Presence of diabetes mellitus | GP record | GP record |
| Presence of coronary heart <br> disease | GP record | GP record |
| Self-rated health Postal questionnaire | Excluded |  |
| Formal care-giver availability | Postal questionnaire (proxy of high <br> social support on Lubben's social <br> network scale) | Excluded |
| >6 physician visits over previous <br> year <br> Emergency hospital admission <br> previous year | GP record | GP record record |
| Multimorbidity measure: RxRisk- | Excluded | GP record |
| V | Linked pharmacy claims |  |

### 6.4.2.3 Primary outcome: emergency hospital admission

Emergency admission was recorded from GP medical record review over one year prospectively. The reason for admission, date of admission and length of inpatient stay was recorded from the GP medical record review on a patient basis.

### 6.4.2.4 Statistical methods

Baseline characteristics of study participants are presented using descriptive statistics. Two aspects of the Pra model were examined in this validation study, discrimination and calibration. Discrimination refers to the ability of the Pra to distinguish correctly the patients with and without the outcome of interest i.e. hospital admission.(331) The c-statistic with 95\% Cls was estimated using non-parametric ROC curve analysis. Calibration refers to how closely predicted outcomes agree with observed outcomes and therefore is concerned with the number of emergency admissions predicted to occur by the Pra risk score versus the number of admissions actually observed during the one year prediction period. The HosmerLemeshow goodness of fit statistic was used to estimate the calibration of the Pra score across the three risk strata (low, moderate, high-risk).(396) The original Pra score was calculated for each patient using a logistic formula provided in the derivation study (see

Figure 6-6).(203) A cut-off score of $\geq 0.5$ was used to indicate high risk of future emergency hospital admission as per the Pra derivation study.(203)

$$
\operatorname{Pra}=\quad \frac{\mathrm{e}^{\mathrm{BX}}}{1+\mathrm{e}^{\mathrm{BX}}}
$$

Figure 6-6: Logistic formula for estimating the original Pra score(203)

Where;
$\mathbf{e}^{1}=2.718$ or e is the exponential
$B X=-1.802+0.327 X_{1}+0.340 X_{2}+0.552 X_{3}+0.770 X_{4}+0.390 X_{5}+0.545 X_{6}$ $+0.318 X_{7}-0.738 X_{8}+0.255 X_{9} 0.327 X_{10}+0.559 X_{11}+0.257 X_{12}+0.319 X_{13}$

Predictor variables: $0=$ absent $1=$ present ( $X_{1}$ very good general health, $X_{2}$ good general health, $X_{3}$ fair general health, $X_{4}$ poor general health, $X_{5}$ presence of coronary artery disease, $X_{6}$ any hospital admission in the past year, $X_{7}>6$ physician visits in the past year, $X_{8}$ no informal caregiver available, $X_{9}$ age 75-79 years, $X_{10}$ age 80-84 years, $X_{11}$ age 85+ years, $X_{12}$ male sex, $X_{13}$ presence of diabetes)

The modified Pra score was calculated using an amended logistic formula reported in a US validation study conducted by Coleman and colleagues (see Figure 6-7).(384) A cut-off score of $\geq 0.5$ was used to denote high-risk.

$$
P=\frac{e^{1}}{1+e^{1}}
$$

Figure 6-7: Logistic formula for estimating the modified Pra score(384)
Where:
$\mathbf{P}=$ Probability of repeated admissions ( $\geq 2$ hospitalisations over 4 years)
$\mathbf{e}=$ Natural logarithm
$\mathbf{I}=\mathbf{B}_{\mathbf{0}}+\mathbf{2}, \mathbf{B}_{\mathbf{y}} \mathbf{X}_{\mathbf{y}},\left(\mathbf{B}_{\mathbf{0}}=-1.73\right.$, a constant from the logistic regression equation; $\mathbf{X}_{\mathbf{y}}=0$ or $\mathbf{1}$, according to the presence or absence of the risk factor; $\mathbf{B}_{\mathbf{y}}=$ the regression coefficient (log adjOR) of the risk factor detailed overleaf).

| Predictor variable | $B_{y}(\log$ adjOR) | Adjusted Odds Ratio (95\% $\mathrm{Cl})$ |
| :---: | :---: | :---: |
| Age 75-79* | 0.441 | 1.55 (1.23, 1.96) |
| Age 80-84* | 0.664 | 1.94 (1.43, 2.64) |
| Age 85 and above* | 1.020 | 2.77 (1.71, 4.49) |
| Male gender | 0.185 | 1.20 (0.99, 1.46) |
| Hospitalised in past year | 0.168 | 1.18 (0.91, 1.54) |
| Six or more doctor visits | 0.554 | 1.74 (1.40, 2.15$)$ |
| Included in diabetes registry | 0.330 | 1.39 (1.00, 1.94) |
| Included in coronary heart disease registry | 0.058 | 1.06, 0.81, 1.39) |
| RxRisk-V Score 1-2 ${ }^{\text {\# }}$ | 0.413 | 1.51 (1.17, 1.95) |
| RxRisk-V Score 3-4 ${ }^{\text {\# }}$ | 0.586 | 1.80 (1.35, 2.38) |
| RxRisk-V score > $\mathbf{4}^{\text {\#S }}$ | 1.032 | 2.81 (2.06, 3.83) |

*Dummy variable, reference category is age 70-74. \#Dummy variable, reference category is RxRisk-V Score of $0 .{ }^{\$}$ The Chronic Disease score which is a precursor of the RxRisk-V was used in the original validation study.

All data analysis was conducted using Stata version 13.(304) As the Pra model is under copyright, a no-fee study licence was applied for and granted by the Pra developers to allow use of the Pra logistic formula for the purposes of this study. (See Appendix 16) Detailed guidance notes regarding the calculation of the Pra score were provided as part of this study licence.

### 6.4.3 Results

### 6.4.3.1 Baseline characteristics

Of 904 baseline study participants a total of 862 (95\%) participants were included in this study. Participants were excluded if there was incomplete hospital admission data for the prediction year. The reasons for exclusion were as follows: 19 moved GP practice, 14 moved to a nursing home and 9 GP medical record reviews were missing. Patients who died during the prediction year were included in this data analysis. The baseline characteristics of the study participants with follow-up data available for the prediction year, according to the items used in the original and modified Pra scores are summarised in Table 6-9. The
proportion of patients at high risk ( $\geq 0.5$ ) according to the original Pra was $7 \%$ ( $n=63$ ) compared to 45\% ( $n=391$ ) for the modified Pra. This higher proportion was largely due to the higher number of patients with $\geq 5$ RxRisk-V conditions ( $n=433$ ) using the modified Pra, compared to patients who reported poor or fair health status ( $n=158$ ) and lack of an informal caregiver ( $n=49$ ) applying the original Pra.

Table 6-9: Baseline characteristics of study participants by the original or modified Pra

| Patient characteristic | Original Pra ( $\mathrm{n}=858$ ) | Modified Pra ( $\mathrm{n}=862$ ) |
| :---: | :---: | :---: |
|  | N (\%) | N (\%) |
| Pra score $\mathbf{\geq 0 . 5}$ (high risk) | 63 (7) | 391 (45\%) |
| Male | 404 (47\%) | 404 (47\%) |
| Age |  |  |
| 70-74 | 325 (38) | 325 (38) |
| 75-79 | 290 (34) | 290 (34) |
| 80-84 | 157 (18) | 157 (18) |
| $\geq 85$ | 86 (10) | 86 (10) |
| Coronary artery disease | 148 (17) | 148 (17) |
| Diabetes mellitus | 101 (12) | 101 (12) |
| >6 doctor visits previous year | 484 (56) | 484 (56) |
| $\geq 1$ emergency admission previous year | 139 (16) | 139 (16) |
| Poor or fair self-rated health | 158 (18) | NA |
| No informal caregiver availability* | 49 (6\%) | NA |
| RxRisk-V number of conditions |  |  |
| 0 | NA | 13 (2) |
| 1-2 | NA | 156 (18) |
| 3-4 | NA | 256 (30) |
| $\geq 5$ | NA | 433 (50) |

NA=Not applicable. * Social support was missing for four study participants.

### 6.4.3.2 Performance of the Pra score: discrimination

The performance of the two versions of the Pra score in predicting hospital admission over the next year is presented in Table 6-10. The c-statistic for the original Pra was 0.63 ( $95 \% \mathrm{Cl}$ $0.58,0.68)$ compared to $0.64(95 \% \mathrm{Cl} 0.60,0.68)$ for the modified Pra. A total of $41 \%(n=26)$
of patients identified as high risk by the original Pra were subsequently admitted to hospital while $26 \%$ ( $n=103$ ) of those stratified as high risk using the modified Pra were subsequently admitted.

Table 6-10: Prediction of $\geq 1$ emergency admission(s) during one year of follow-up by two versions of the Pra score (original and modified)

|  | Original Pra (n=858) | Modified Pra (n=862) |
| :--- | :--- | :--- |
| Prediction of $\geq 1$ emergency <br> admission in follow-up year | c-statistic (95\% CI) | c-statistic (95\% Cl) |
|  | $0.63(0.58,0.68)$ | $\mathbf{N ( \% )}$ |
| Total study participants with $\geq 1$ <br> emergency admission | $154(18)$ | $154(18)$ |
| Patients classified as high risk <br> according to Pra score ( $\geq 0.5)$ <br> High-risk patients (Pra score $\geq 0.5)$ <br> with $\geq 1$ emergency admission (\% of <br> all high risk) | $26(41)$ | $391(46)$ |

Figure 6-8 and Figure 6-9 present the ROC, a graph of the sensitivity (y-axis) and the specificity (x-axis), for the original Pra (c-statistic $0.63,95 \% \mathrm{CI} 0.58,0.68$ ) and the modified Pra (c-statistic $0.64,95 \% \mathrm{Cl} 0.60,0.68$ ) respectively. Both models demonstrated poor model discrimination for the outcome for emergency admission during the one year follow-up period.


Figure 6-8: Receiver operating curve for the original Pra validation cohort


Figure 6-9: Receiver operating curve for modified Pra validation cohort

### 6.4.3.3 Performance of the Pra score: calibration

The calibration performance of the Pra score estimates how reliably the two versions of the Pra score predicted future hospital admission. The sensitivity and specificity of the original and modified versions of the Pra at the low, moderate and high risk cut-off points are presented in Table 6-11. The original Pra at a cut-off point of $\geq 0.5$ had high specificity of $95 \%$ but low sensitivity of $17 \%$. The modified Pra reported lower specificity of $59 \%$ at the same cut-off of $\geq 0.5$ but higher sensitivity ( $67 \%$ ).

Table 6-11: Sensitivity and specificity at different Pra cut-off points for the original and modified versions of the score

| Number of study |  |  |  |
| :--- | :--- | :--- | :--- |
| participants ( n ) | Sensitivity (\%) | Specificity (\%) | Correctly <br> classified (\%) |


| Original Pra cut-point |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
| Low risk ( $\geq 0.35$ ) | 569 | 100 | 0 | 18 |
| Moderate risk ( $\geq 0.35,<0.5$ ) | 226 | 53 | 71 | 67 |
| High risk ( $\geq 0.5$ ) | 63 | 17 | 95 | 81 |
| Modified Pra cut-point |  |  |  |  |
| Low risk $(\geq 0.35)$ | 198 | 100 | 0 | 18 |
| Moderate risk ( $\geq 0.35,<0.5$ ) | 273 | 88 | 25 | 37 |
| High risk ( $\geq 0.5$ ) | 391 | 67 | 59 | 61 |

Both the original and modified versions of the Pra score over-estimated the number of hospital admissions in this study population across the three levels of risk in the one year prediction period. The calibration performance of the original and modified Pra models is presented graphically in Figure 6-10 and Figure 6-11 respectively. The Hosmer-lemeshow goodness of fit statistic demonstrated a significant difference between observed and predicted admissions for both the original Pra ( $\mathrm{X} 2 \mathrm{HL}: 84.67, \mathrm{p}$-value: $<0.001$ ) and the modified Pra ( $\chi 2 \mathrm{HL}: 330.23$, p-value: $<0.001$ ).


Figure 6-10: Calibration performance of the original Pra score at three different Pra cut-off points


Figure 6-11: Calibration performance of the modified Pra score at three different Pra cutoff points

### 6.4.4 Discussion

### 6.4.4.1 Statement of principal findings

This is the first European validation study to compare the predictive accuracy of the original Pra tool and a modified version of the Pra, substituting two self-report items with a measure of multimorbidity, in predicting future hospital admission in older community-dwelling adults.

The principal findings are as follows:

- The original Pra score demonstrated relatively poor discrimination performance with a c-statistic of 0.63 ( $95 \% \mathrm{Cl} 0.58,0.68$ ). The original Pra identified a relatively small number of people as high risk ( $n=63,7 \%$ ). Of those identified as high-risk more than one-third ( $n=26$ ) were admitted to hospital in the outcome year.
- The modified Pra demonstrated similar discrimination performance with reported cstatistic 0.64 ( $95 \% \mathrm{Cl} 0.60,0.68$ ). However, the modified version of the Pra identified a much higher number of people as high-risk ( $n=391,46 \%$ ) of whom less than onethird were subsequently admitted ( $n=103,26 \%$ ).
- Both the original and modified Pra risk models significantly over-predicted future hospital admissions in this validation study, with fewer observed emergency admissions compared to predicted admissions across all three strata of risk (low, moderate, and high). However, the specificity of the original Pra at the cut-point of $\geq 0.5$ (high-risk) was $95 \%$ compared to $59 \%$ for the modified Pra.


### 6.4.4.2 Comparison with existing literature

In the systematic review and meta-analysis of the original Pra described earlier in this chapter the summary c-statistic was 0.70 (SE 0.28) with pooled specificity of $96 \% ~(95 \% \mathrm{Cl}$ $95.8 \%, 96.7 \%)$. The current external validation of the Pra had poorer discrimination but the specificity was similar in this new setting of care.

Previous validation studies have been largely conducted in the US and many studies were conducted over 10 years ago.(357) One previous study published in 2006 examined the
performance of the original Pra in three European countries (UK, Switzerland and Germany) and reported similar proportions of patients identified as high risk ranging from 4\% to 7\% with similar predictive accuracy; combined sites c-statistic 0.64 ( $95 \% \mathrm{Cl} 0.62,0.66$ ).(389) Two US community-based studies have examined the predictive accuracy of modifying the Pra, substituting self-report items (care giver availability and self-rated health status) for a measure of multimorbidity. One study compared the predictive accuracy of the original Pra with a modified version using the Deyo-Charlson index as a multimorbidity measure in a cohort of 296 older community-dwelling people ( $\geq 65$ years) for the primary outcome of healthcare costs over six month follow-up.(388) This study was limited by a poor response rate to the Pra questionnaire (53\%) but did report similar performance between the two approaches. The original Pra at a cut-point of $\geq 0.5$ reported specificity of $90 \%$ and sensitivity of $48 \%$ for the outcome of inpatient stay over 6 months and the modified Pra reported specificity of $92 \%$ and sensitivity of $27 \%$ for the same outcome. A second comparative study in a cohort of 2,174 US older community-dwelling people used the chronic disease score as a substitute for self-report health status and caregiver availability and reported similar predictive accuracy using either model (original Pra: 0.69 , modified Pra: 0.69 ) and similar proportions of patients identified as high risk ( $14 \%$ and $16 \%$ respectively for original and modified Pra).(384) However, as this study was published in 1998 and based in one US state, the generalisability of its findings to current practice and other healthcare settings is somewhat limited.

The Pra performs similarly to other models based on self-report and designed for use in primary care. Examples include the Sherbrooke questionnaire and the Emergency Admission Risk Likelihood Index (EARLI) which include similar items relating to previous healthcare use, self-rated health and medical diagnoses and have reported similar predictive accuracy. (336, 355)The Sherbrooke questionnaire reported a c-statistic of $0.60(95 \% \mathrm{Cl} 0.53,0.67)$ and the EARLI reported a c-statistic of $0.67(95 \% \mathrm{Cl} 0.63,0.70)$ in external validation studies. Other risk prediction models designed using routine datasets or clinical record review data only tend to include much larger numbers of variables and often require the availability of linked datasets (e.g. inpatient/OPD/primary care) for application. For example the UK QAdmissions model was developed using linked computerised GP and hospital inpatient data and
includes 30 variables (c-statistic 0.77 ( $95 \% \mathrm{Cl} 0.771,0.774$ ).(359) The predictive accuracy of these types of models tends to be higher overall but their application depends largely on the datasets available in healthcare systems. For instance, currently in Ireland there is no data source that links primary care and hospital utilisation data so applying a model such as the QAdmissions at a population level for risk stratification would be very difficult.

### 6.4.4.3 Clinica and research implications

Even for models demonstrating reasonable model performance the majority of people experiencing future admissions will not be identified. In addition, difficulty arises with limited evidence to support primary care interventions proven to reduce future admissions. These issues will be considered in more detail in the next section of this chapter.

The Pra score has been used to identify older people within a RCT of an intervention for those at increased risk of functional decline.(397) Patients who completed the Pra were eligible to participate in the study which involved a complex intervention including training of health professionals, administration of the Health Risk Appraisal for Older persons questionnaire, group education sessions for participants, additional personal reinforcement, two home visits by a specially trained nurse with detailed feedback and discussion with the geriatric team and written feedback to the participants GP. This intervention had consistently moderately favourable effects on primary outcomes of preventative care use (uptake of vaccinations) and health behavior (physical activity and diet).(398) The Pra has also been used in a similar context to identify high risk patients for inclusion in a RCT to measure the effects of an outpatient geriatric evaluation and management plan on the primary outcome of functional decline.(399) Intention-to-treat analysis showed that patients in the intervention group were significantly less likely than the controls to lose functional ability (adjusted odds ratio $=0.67,95 \% \mathrm{Cl} 0.47,0.99$ ) during the 12 to 18 months after randomisation. However, other outcomes such as mortality, use of most health services (with the exception of home health services), and total healthcare costs did not differ significantly between the two groups.

Based on the findings of the current study, use of the original Pra seems more feasible for the purpose of identifying higher risk patients for enrolment in an Irish RCT, as it identified a much smaller number of patients as high risk and demonstrated similar predictive accuracy and better calibration than the modified Pra score.

### 6.4.4.4 Study limitations

The items of the Pra score relating to presence of diabetes, coronary artery disease and previous healthcare use were recorded from the GP record rather than the patient questionnaire as per the original Pra. However, it may be argued that this is a more accurate representation of these items as self-report is more prone to response bias. In addition, the outcome of interest, emergency admission in the follow-up year was also recorded from the GP medical record. Previous studies have used different approaches in ascertaining future admission including survey and medical record review.

### 6.4.4.5 Conclusions

The original Pra score demonstrated poorer discrimination but similar specificity in this external validation study compared to previous validation studies. It identified a relatively small proportion of high risk patients as high risk. This study does not support any advantage to using the modified Pra score in this setting as it identified a large proportion of high risk individuals, the majority of whom did not experience a future admission. The original Pra may have a role in identifying older people for inclusion in future trials aiming to improve outcomes for older community-dwelling people.

### 6.5 Critical analysis of recent UK healthcare policy that advocates use of risk prediction and community-based case management as part of pay for performance for UK GPs to reduce emergency admissions

### 6.5.1 Introduction

With health systems under increasing pressure to curb escalating healthcare expenditure, emergency admissions are increasingly targeted as part of policies hoping to curtail costs and improve patient outcomes. In this section recent policy changes in the UK are used to illustrate how risk stratification and community-based case-management for higher-risk people may not be the most effective approach to reduce overall admission rates.

### 6.5.2 Emergency admission as a performance measure of quality of care

Identifying community-dwelling people at high risk of a future emergency admission and targeting this group for an intervention to reduce this risk seems like a logical, sensible endeavour and has been widely adopted by policymakers. Recent US legislative changes enacted by the Patient Protection and Affordable Care Act recommend the development of Accountable Care organisations.(199) This initiative provides incentives for healthcare providers to work collaboratively to provide high quality care while reducing costs. Quality is measured by pre-specified performance measures including emergency admissions for three chronic medical conditions where patients are judged to be at high risk of admission: COPD, congestive heart failure (CHF) and asthma.(200)

UK policymakers have taken a step further. In 2014 the QOF, a pay for performance scheme for UK GPs, was expanded to include risk stratification for emergency admissions.(201) In order to receive remuneration, GPs are required to identify, as a minimum, $2 \%$ of their practice population considered to be at highest risk of a future emergency admission. Identified patients should then be targeted for community-based case management. This policy represents a significant shift for UK GPs who must now consider how best to identify those at highest risk and then implement the required individualised case management plan.

### 6.5.3 Identifying community-dwelling people at high risk of future emergency admission: limited potential for reducing overall admissions

Risk prediction models are increasingly advocated as a way of identifying people at risk of emergency hospital admission. $(205,206)$ These tools may include a variety of clinical, demographic, prior healthcare utilisation and non-medical (e.g. functional status) variables and should provide clinically meaningful risk stratification.(48) This facilitates targeting of those identified as high risk for community-based intervention to prevent future emergency admission. A recent systematic review identified 27 separate models developed to predict future emergency admission in community-dwelling adults.(303) The six best-performing models in this review reported acceptable model discrimination for the outcome of future emergency admission (c-statistics 0.79-0.83).(303)

In this section, the maximum impact of identifying high risk patients in the UK could have on overall emergency admissions is estimated. Examples of risk prediction models identified in the risk models systematic review outlined earlier in this chapter include the Scottish Patients at Risk of Readmissions and Admission (SPARRA) model and the UK Nuffield trust model. $(204,360)$ SPARRA (Version 3) was developed in Scotland in a cohort of over 3.5 million people to predict emergency admission over the next year.(204) The Nuffield trust model was developed in a cohort of over 1.8 million people across five primary care trusts in England to predict emergency admission in the following year.(360) Both of these models are suitable tools for GPs to identify the required $2 \%$ at highest risk in their practice population, and here we use their validation cohorts as worked examples to estimate the likely impact of using such tools on emergency admissions. Consider applying the SPARRA model at a population level in Scotland; 2\% of this population equates to 65,084 people which corresponds to the risk band of $\geq 50$ (the top $1.6 \%$ of the population) (See Table 6-12). This group is responsible for 31,775 emergency admissions ( $10.7 \%$ of total emergency admissions). To capture a greater proportion of patients, the risk band below ( $\geq 40$ ) could be included: these would represent $3.1 \%$ of the population and $17.7 \%$ of emergency admissions. Therefore, depending on the risk band chosen, the maximum possible reduction for a $100 \%$ effective intervention would be $10.7 \%$ or $17.7 \%$ of all emergency admissions.

Table 6-12: Number of people predicted by SPARRA to have $\geq 1$ emergency admission to an acute hospital in Scotland versus the actual observed number who had $\geq 1$ emergency admission to an acute hospital during (1st April 2012-31st March 2013)

| SPARRA <br> risk band | Number of people per risk <br> band | $\mathbf{N}^{*}$ predicted by SPARRA to <br> have $\mathbf{\geq 1}$ emergency admission | $\mathbf{N}^{*}$ observed to have $\mathbf{\geq 1}$ <br> emergency admission |
| :--- | :--- | :--- | :--- |
| $\mathbf{0 - 9}$ | $2,437,645$ | 105,070 | 110,183 |
| $\geq 10-19$ | 454,702 | 61,399 | 63,116 |
| $\geq \mathbf{2 0 - 2 9}$ | 173,071 | 41,353 | 42,476 |
| $\geq 30-39$ | 87,190 | 29,621 | 29,460 |
| $\geq 40-49$ | 48,213 | 21,231 | 20,965 |
| $\geq 50-59$ | 26,815 | 14,483 | 13,972 |
| $\geq 60-69$ | 14,523 | 9,301 | 8,908 |
| $\geq \mathbf{7 0 - 7 9}$ | 8,227 | 6,083 | 5,823 |
| $\mathbf{\geq 8 0 - 8 9}$ | 3,479 | 2,907 | 2,770 |
| $\geq 90-99$ | 350 | 320 | 302 |
| Total | $\mathbf{3 , 2 5 4 , 2 1 5}$ | $\mathbf{2 9 1 , 7 6 8}$ | $\mathbf{2 9 7}$ |

*Number of study participants. Notes: People aged $\geq 16$ years and living in Scotland. The following emergency admissions to hospital are excluded: Emergency admissions to dental hospitals); emergency admissions to a special care baby unit, and emergency admissions by geriatric long stay patients.

Similarly, applying the Nuffield model; $2 \%$ of this population equates to 36,722 people. (See Table 6-13) This corresponds to a risk band of $\geq 0.3$ which represents the top $1.7 \%$ of the population; alternatively, choosing a lower cut-off of $\geq 0.2$ would identify 63,588 people (3.5\% of the total population). These two respective groups are responsible for $13.4 \%$ and 22.2\% of all observed admissions. In summary, using the higher bands of both models to identify the 1.6-1.7\% most at risk, would target either $10.7 \%$ or $13.4 \%$ of all emergency admissions.

Table 6-13: Nuffield Trust 'Inpatient/A\&E/Outpatient/GP' risk prediction model to predict emergency admission over next year

| Risk band (0 = $\mathbf{0}$ to $\mathbf{0 . 1} \mathbf{)}$ | $\mathbf{N}^{*}$ per risk band | $\mathbf{N}^{*}$ with an emergency admission in the <br> future year |
| :--- | :--- | :--- |
| $\mathbf{0}$ | $1,656,294$ | 55,367 |
| $\mathbf{0 . 1}$ | 116,217 | 18,299 |
| $\mathbf{0 . 2}$ | 32,583 | 8,310 |
| $\mathbf{0 . 3}$ | 13,759 | 4,583 |
| $\mathbf{0 . 4}$ | 6,926 | 2,664 |
| $\mathbf{0 . 5}$ | 4,099 | 1,832 |
| $\mathbf{0 . 6}$ | 2,424 | 1,238 |
| $\mathbf{0 . 7}$ | 1,636 | 931 |
| $\mathbf{0 . 8}$ | 1,099 | 690 |
| $\mathbf{0 . 9}$ | $\mathbf{1 , 0 6 2}$ | 778 |
| Total | $\mathbf{1 , 8 3 6}$ | $\mathbf{9 4 , 6 9 2}$ |

* Number of study participants. Notes: Only 18 to 95 year olds included. The future year does not start immediately after the variable calculation period. A 60 day gap is built in so predicting admissions in the 3rd to 14th month inclusive.

To fulfil QOF requirements applying the SPARRA risk model, a typical GP population of 10,000 patients would expect 920 emergency admissions annually (based on the proportion of patients admitted in the validation cohort, see Table 6-12) and identifying 1.6\% of the population equates to 160 patients. Applying the $\geq 50$ risk band to this group we would expect approximately 95 of those predicted to be admitted to actually experience an emergency hospital admission over the next year.

### 6.5.4 Which emergency admissions are preventable?

Of course in reality many emergency admissions, such as acute appendicitis, are unavoidable. There is, therefore, increasing interest in ACS admissions, previously described in Section 2.4.5. These account for approximately $20 \%$ of all emergency admissions and over half occur in older people aged $\geq 65$ years. $(207,208)$ Definitions of what constitutes an ACS condition vary internationally but the Australian Victoria State Health Department condition list is a good example and is commonly used in the UK NHS.(209) While the data
presented so far has focused on the policy objective which aims to reduce all emergency admissions, it may be argued that focusing on ambulatory care sensitive admissions is more appropriate, particularly for community-based interventions.

If ACS admissions were to be targeted then the impact on avoidable admissions can be quantified; of the $1.6 \%$ of the SPARRA population at highest risk of future emergency admission (responsible for $10.7 \%$ of all emergency admissions), we could expect to prevent approximately one in five, that is $2.1 \%$ of all emergency admissions (this figure may vary depending on the patient demographics of the practice population). A typical GP practice having identified and proactively managed 160 patients can therefore expect to prevent approximately 19 emergency admissions annually (as only 95 patients predicted to be admitted will actually experience an emergency hospital admission as presented in Figure 6-12). No intervention for these admissions will be $100 \%$ effective and the limited literature in this area indicates that up to $18 \%$ of ACS admissions could be prevented based on each local health authority performing at the level of the best performing quintile.(208) This would result in the prevention of four emergency admissions annually.


Figure 6-12: Application of a risk prediction model to a hypothetical GP practice population of $\mathbf{1 0 , 0 0 0}$ patients to identify the top $\mathbf{1 . 6 \%}$ most at risk of emergency admission over the next year

### 6.5.5 Community-initiated case management as an intervention for emergency admission avoidance: limited evidence of effectiveness

As part of the recently introduced UK emergency admission avoidance policy, case management of patients identified as high risk is now a requirement for QOF.(201) GPs are expected to create a written personalised care plan for these patients to detail how ongoing care will be delivered in order to reduce each patient's risk of future emergency admission. In addition, practices are expected to provide timely telephone access for higher risk patients and all patients discharged from hospital should be contacted within three days to facilitate enhanced coordination of care.

Case management may be defined as a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available
resources to promote quality, cost-effective outcomes.(210) It typically includes a case finding mechanism, assessment, individualised care plans for those stratified as high risk, care co-ordination and multidisciplinary team involvement.(211) Existing evidence supports the role of case management in increasing patient satisfaction with care received, promoting high levels of professional satisfaction and reducing caregiver strain(49, 212215), but systematic reviews of community-based case management RCTs have not demonstrated an impact on reducing future emergency admissions.(216-218). A recent systematic review and meta-analysis of case management for adults with long term condition(s) in primary care ( $\mathrm{n}=36$ studies) reported that case management had a small significant effect on patient satisfaction, both short term (standardised mean difference $0.26,95 \% \mathrm{Cl} 0.16,0.36$ ) and long term (standardised mean difference $0.35,95 \% \mathrm{Cl} 0.04$, $0.66)$, but was not effective in reducing primary or secondary care utilisation or costs of care.(400) The authors highlighted the need for a consistent definition of multimorbidity in conducting these studies and noted in subgroup analysis a small non-significant effect of case management delivered by a multidisciplinary team with social worker involvement for reducing short-term secondary care utilisation which may merit further investigation.(400)

A second systematic review which included five community-based case management RCTs reported that four of the five trials demonstrated no benefit of case management when compared to usual care.(217) Three of these studies were included in a meta-analysis of case management in older populations ( $n=728$ ) versus usual care $(n=688)$ and demonstrated a mean difference in subsequent rate of emergency admissions of $0.05(95 \% \mathrm{Cl}-0.04$, 0.15).(217) A third systematic review ( $n=7$ RCTs) focussing on older patients with multimorbidity examined the US concept of 'patient centred medical home', an intervention with similar components to case management, and reported no reduction in hospital admissions (RR $0.96,95 \% \mathrm{Cl} 0.84,1.10$ ).(218) In summary, current evidence does not support case management as an effective intervention for reducing emergency admission despite the significant time and energy it requires on behalf of the primary care team.

### 6.5.6 Time for a shift in focus?

There are several issues to consider in targeting people identified as being at high risk of future emergency admission in the community. First, those who have experienced multiple admissions in the past are likely to be identified as high risk using risk prediction models for future emergency admission. However, this group are actually less likely to experience emergency admissions in future years, a concept known as 'regression to the mean', as emergency admissions will naturally decrease over time. $(202,401)$ This underlines the importance of including a comparison group when considering the effectiveness of any interventions aiming to reduce emergency admission rates. Second, in targeting those at highest risk we neglect the fact that in absolute terms the great majority of emergency admissions come from those stratified as lower risk as demonstrated in Table 6-12 and Table 6-13.

So what is the best approach in tackling emergency admissions? Virtual wards, which use the same staffing and processes of a hospital ward but patients stay at home, held considerable promise as a community-based intervention to reduce emergency admissions.(402) However evaluations of this model both in the UK and US have found that it did not achieve anticipated reductions in emergency admissions, even for ACS conditions. $(402,403)$ However, while evidence is limited several other approaches merit consideration. First, as previously mentioned, ACS conditions account for approximately $20 \%$ of all emergency admissions and in the UK five conditions account for more than $50 \%$ of all ACS admissions so targeting these admissions may prove beneficial. These include urinary tract infection (UTI)/pyelonephritis, COPD and pneumonia (accounting for 16\%, 12\% and $10 \%$ of admissions respectively and largely affecting older people) and ENT infections and convulsions/epilepsy, (accounting for 9\% and 7\% of admissions respectively and largely affecting children).(207) There is some existing evidence to support this approach; for example, a recent Cochrane review which included seven RCTs for the outcome of respiratory emergency admissions reported that integrated disease management for COPD successfully reduced these admissions.(219) Integrated disease management included several components including patient education, self-management, structured follow-up and exercise.(219) Taking a broader approach, a recent study found that the introduction of
the QOF primary care national pay for performance scheme in England was associated with a decrease in emergency admissions for incentivised ambulatory care sensitive conditions such as epilepsy and CHF compared with non-incentivised ambulatory care sensitive conditions such as cellulitis and UTI/pyelonephritis.(404) Previous research has also demonstrated reductions in emergency admissions for incentivised conditions in primary care such as diabetes mellitus and ischaemic heart disease. $(405,406)$

Second, hospital care at home for certain conditions (e.g. Infective exacerbation of COPD) may have an impact on emergency admissions. $(377,407)$ A systematic review of 10 RCTs reported that hospital care at home as an alternative to emergency admission yielded similar outcomes in terms of mortality and subsequent admission to hospital when compared to inpatient care with higher patient satisfaction rates.(407) However, only three of these trials recruited patients directly from primary care, and the majority focused on single specific conditions which limits generalisability but does merit further research. Targeting end of life care may also have an impact and the effectiveness of home based care has been evaluated in a large retrospective analysis.(301) This study included 29,538 UK adults who received home-based nursing care delivered by the Marie Curie Nursing Service with matched controls and this formal home-based care group were significantly more likely to die at home and less likely to die in hospital than the matched controls (unadjusted OR $6.16,95 \% \mathrm{Cl} 5.94,6.38, \mathrm{p}<0.001) .(301)$ Emergency admissions were also significantly lower among intervention than matched control patients (emergency admissions: 0.14 vs .0 .44 admissions per person per year, $p<0.001$ ).(301)

Third, it's important to acknowledge the impact of variation in medical practice on emergency admissions. Factors influencing GP referrals include individual tolerance of clinical uncertainty and access to ambulatory care services (especially out of hours).(408, 409) A recent qualitative study, which examined GPs' referral decisions for ambulatory care sensitive conditions, found that they involved a complex interplay of clinician (e.g. access to services), patient (e.g. delayed help-seeking) and social (e.g. lack of social support) factors.(410) However, the extent to which variation in referral patterns impact upon overall rates of emergency admission remains largely unknown. Variation is also an issue in
secondary care internationally with significant differences across hospitals in emergency admission rates for ambulatory care sensitive conditions. $(408,411,412)$ In the UK, an analysis of emergency admission rates between 2008-2011 demonstrated a threefold variation in admissions for 14 ambulatory care sensitive conditions across 129 hospitals, largely explained by the socio-economic deprivation of the population served. $(408,411)$ Concentrating admission avoidance efforts in more deprived areas known to have higher levels of multimorbidty may be beneficial in reducing overall emergency admission rates.(23)

Lastly, interventions in the emergency department and the inpatient setting may have a role to play in reducing emergency admissions. To date, RCTs in the emergency department setting aimed at reducing re-attendance and admissions have largely focussed on older patients targeted through risk screening for focused geriatric assessment with post discharge follow-up with mixed results. $(413,414)$ A recent systematic review and metaanalysis which included 42 RCTs reported that interventions aimed at medical and surgical inpatients to reduce their risk of 30-day readmission were successful overall (pooled relative risk $0.82(95 \% \mathrm{Cl} 0.73,0.91)$ ).(221) Successful interventions were usually comprehensive, involving five or more components designed to address patient factors including the impact of multimorbidity, functional capacity, socio-economic factors, self-care as well as caregiver capabilities.(221) Typically these complex interventions were co-ordinated across the inpatient to outpatient transition by at least two healthcare providers who made regular contact with the patient including home visits.(221) A second systematic review which included 26 RCTs of inpatients with chronic conditions reported that transitional care interventions, initiated during hospital admission and continued after discharge through home visits or telephone follow-up for a minimum of one month, were effective in reducing readmissions longer term both at 180 days (pooled odds ratio $=0.77$ ( $95 \% \mathrm{Cl} \mathrm{0.62}, \mathrm{0.96))} \mathrm{and}$ up to 365 days (pooled odds ratio=0.58 ( $95 \% \mathrm{Cl} 0.46,0.75$ )).(415)

### 6.6 Summary: reducing emergency admissions through community-initiated identification and intervention

With healthcare expenditure of increasing concern, policymakers must ensure that health policy and clinical practice recommendations in relation to prevention of emergency admissions reflect current best evidence and account for the considerable uncertainties that exist around identification and best preventative management. Risk stratification has inherent limitations in terms of opportunity costs, and may also result in the overmedicalisation of community-dwelling people with the potential for iatrogenic harm. Inherent in any risk-stratification approach is the fact that, at best, only a minority of patients who subsequently experience an emergency hospital admission will be identified. Risk modelling may improve in the future with the development and validation of more complex models that can include person level data including factors such as medication adherence, mood, social interaction and lifestyle factors.

Current evidence does not support community-initiated case management in reducing emergency admissions, while the impact of incentivising ACS conditions and other interventions such as hospital at home and initiatives to reduce 30-day readmissions require consideration of overlap and coherence in approach. Consideration should also be given to the context of individual patient circumstances, particularly in relation to multimorbidity and the care trajectory for each patient (curative or palliative). Lastly, the realities of medical practice variation in relation to emergency hospital admissions needs to be acknowledged and contextualised to local circumstances and national healthcare systems. It is important that these uncertainties are reflected in health policy recommendations and financial incentives that aim to reduce emergency admissions.

Chapter 7 Overall Discussion

### 7.1 Introduction

This discussion chapter will present an overview of the thesis main findings, a consideration of the impact of the thesis in terms of research, policy, health service and society and how this research informs future research and clinical practice.

This thesis aimed to examine different measures of predicting future adverse health outcomes in older community-dwelling adults and was underpinned by a conceptual framework (see Figure 2-1) relating to how relationships between conditions, psychosocial factors and healthcare use and delivery, all interact and evolve over time and impact upon adverse health outcomes for older people. There were five objectives;
i. To determine if PIP, as defined by the STOPP and Beers 2012 criteria, has a longitudinal association with adverse health outcomes including ADEs, poorer HRQOL and increased emergency hospital attendance in a cohort of older ( $\geq 70$ years) community-dwelling adults followed up for two years.
ii. To assess the performance of different count measures of multimorbidity and a measure of vulnerability in older people ( $\geq 70$ years) in predicting emergency admission and functional decline at two year follow-up.
iii. To conduct a systematic review of risk prediction models developed for use in community-dwelling adults to predict future emergency hospital admission.
iv. To conduct a systematic review and meta-analysis of the validation studies of the Pra risk model to predict future emergency admission.
v. To externally validate the Pra risk model in a cohort of older ( $\geq 70$ years) communitydwelling adults in predicting emergency hospital admission over the following year.

### 7.2 Explicit measures of PIP and adverse health outcomes

Chapter 4 presents the results of this two year prospective cohort study which is the first to compare the association of explicit measures of PIP, the STOPP criteria and the Beers 2012, with future adverse health outcomes in an older primary care population. The Cochrane risk of bias tool for non-randomised studies was used to assess the overall risk of bias of this
prospective cohort study.(281) Overall, the risk of bias for this prospective cohort study was low (see Table 4-23).

The prevalence of PIP, as defined by the STOPP criteria, was $42 \%$ at baseline and $47 \%$ at follow-up, while PIP as per the Beers 2012 criteria was $29 \%$ at baseline and $26 \%$ at followup, indicating relatively consistent levels of PIP over time. There was very little overlap between the most prevalent PIP indicators, as defined by the STOPP compared to the Beers 2012 criteria. The most prevalent STOPP indicators were: 1) PPI at a maximum therapeutic dose for $>8$ weeks; 2 ) aspirin prescribed for primary prevention and prescribed for patients with history of peptic ulcer disease without concomitant gastro protection; and 3) calcium channel blockers or opiate analgesics prescribed for patients with chronic constipation. The most frequent Beers 2012 indicators were: 1) benzodiazepines; 2) non-COX NSAIDs; 3) antipsychotics; and, 4) patients with chronic constipation prescribed oral antimuscarinics, diltiazem, veramapil, first generation antihistamines and anticholinergic antispasmodics. Overall, the prevalence of PIP as defined by the Beers 2012 criteria was lower compared to the STOPP criteria, but fewer Beers indicators could be applied due to differences in drug licencing between the US and Ireland and varying therapeutic indications between the two care settings. Therefore, it is important to acknowledge that the Beers 2012 may perform differently in settings of care where all indicators are applicable.

The primary outcome of interest of the current study was patient-reported ADEs. Seventyfour per cent of study participants reported one or more ADEs over the previous six-month period, the majority ( $95 \%$ ) of which were classified as mild by dual independent academic review. The most frequently reported ADEs were easy bruising, urinary frequency, ankle swelling and muscle pains. Following multilevel regression modelling, adjusting for relevant confounders the receipt of $\geq 2$ PIP, as defined by STOPP, was modestly associated with increasing numbers of ADEs (adjusted IRR; 1.29 ( $95 \% \mathrm{Cl} 1.03,1.60$ ), $\mathrm{p}=0.03$ ). This association was demonstrated following adjustment for a number of confounders, including the number of prescribed medication classes and comorbidity, both of which were independently associated with increasing numbers of ADEs.

PIP, identified by STOPP, also demonstrated a longitudinal association with poorer HRQOL ( $\geq 2$ PIP: EQ-5D adjusted coefficient; -0.11 ( $95 \% \mathrm{Cl}-0.16,-0.06$ ), $\mathrm{p}<0.001$ ) which is considered clinically significant. This suggests that PIP and ADEs judged as clinically mild, may well have an impact on a patient's overall HRQOL. Identifying and addressing milder ADEs, therefore, may have potential in improving overall HRQOL for older people. STOPP identified PIP were also associated with an increased risk of attending A\&E over the follow-up period ( $\geq 2$ PIP: adjusted OR 1.85 ( $1.06,3.24$ ), $\mathrm{p}=0.03$ ), but there was no association with emergency admission ( $\geq 2$ PIP: adjusted OR 1.00 ( $95 \% \mathrm{Cl} 0.63,1.61$ ), $\mathrm{p}=0.99$ ). This may be due to the small proportion of ADEs in this study that were judged as severe or life-threatening (2.3\%), and it would be interesting to investigate PIP and emergency admissions in a larger sample of older patients with a higher proportion of severe ADEs. In contrast, PIP identified by the Beers 2012 criteria were not associated with any of the outcomes under investigation in this study, indicating that the STOPP prescribing indicators should be used preferentially for identifying PIP in this setting of care.

The current study's findings may have implications for designing interventions to improve the quality and safety of prescribing in primary care. As summarised in section 4.4.4, a recent Irish primary care RCT used the STOPP criteria to identify patients with PIP and then implemented a multifaceted intervention (academic detailing by a pharmacist, GP feedback, patient information leaflets) to reduce PIP and encourage deprescribing.(314) This intervention successfully reduced PIP, but it is important to note that PIP reduction was largely driven by the dose reduction and cessation of inappropriate proton pump inhibitors. The concept of deprescribing is gaining momentum as part of a broader shift against the over medicalisation of older people and includes ceasing PIP, but also addressing medications that are not inappropriate but ineffective or poorly adhered to by patients. As outlined in section 4.4.4, clinicians often find deprescribing decisions challenging. This is due in part to a lack of evidence-based guidance to support the process, concerns about ceasing medications started by another clinician and a knowledge gap regarding which medications should be prioritised for cessation in primary care. Prescribing indicators, such as STOPP, have been criticised for not incorporating patient preference or shared decision making into their development and application, but this research indicates that these indicators do have
an impact on patient centred outcomes such as ADEs and HRQOL. In addition, these indicators are designed to identify medications that are 'potentially inappropriate' only, so in certain cases there may be clinical indications for a patient to be prescribed one or more of these indicators. Notwithstanding these criticisms, the STOPP criteria do offer an evidence-based approach for clinicians to use as part of medication reviews with patients' in primary care and could have a valuable role in assisting deprescribing decisions.

Recently updated and expanded versions of the STOPP and Beers prescribing indicators have been published. $(416,417)$ From a clinical perspective ensuring the criteria are up to date and relevant is essential. Practically speaking if STOPP indicators are to be implemented in clinical practice, then they would need to be incorporated into GP software systems to facilitate application at the point of patient care.

### 7.3 Use of measures of multimorbidity and vulnerability to predict future emergency admission and functional decline over time

Emergency admission has received a lot of attention as an outcome that is important both for patients and healthcare systems but is a difficult outcome to predict accurately as outlined in section 5.4.2.1. It is well established that higher levels of multimorbidity are associated with an increased risk of emergency admission. However, as the literature regarding the definition and measurement of multimorbidity varies considerably, it can be very difficult to decide which measure of multimorbidity should be included in admission risk prediction models or in recruiting patients to RCTs. Chapter 5 examined the performance of different measures of multimorbidity and vulnerability in predicting adverse health outcomes. The current study indicates that while all multimorbidity measures demonstrated similar poor discrimination for future emergency admission, those that are calculated based on prescribed medications are marginally more accurate than diagnosisbased measures. This is important as medication-based measures of multimorbidity can be calculated using pharmacy claims databases, and may be easier to apply than measures requiring clinical record review. However, the optimal discrimination of these counts is not at the traditional definition of multimorbidity as $\geq 2$ condition counts. In the current study,
the RxRisk-V required a cut-off of $\geq 5$ and simple medication counts a cut-off of $\geq 6$ medications to optimise discrimination for the outcome of future emergency admission.

Combining the traditional condition count definition of multimorbidity (i.e. $\geq 2$ conditions) with a medication count (e.g. $\geq 5$ prescribed medications) may offer the best compromise in capturing patients with more complex health needs for the purposes of multimorbidity RCTs. The Cochrane review of multimorbidty interventions indicates that the majority of existing studies use either condition count or medication count to define eligibility for inclusion for patients with multimorbidity.(418) Many admission risk prediction models use the Charlson comorbidity index for identifying multimorbidity, which was initially developed to predict mortality in an inpatient US setting and therefore may not be the best measure of future emergency admission in primary care. The current study indicates that using a single measure alone has poor predictive ability and therefore adopting an approach of a simple condition count supplemented with a medication count may offer more scope for identifying higher risk older people.

The concept of vulnerability has emerged in the gerontology literature over the past decade and refers to older people who are at higher risk of functional decline over time. This study is the first prospective European validation of the VES-13, a risk prediction tool designed to identify community-dwelling older people at risk of functional decline and comprised of items relating to patient physical functioning, activities of daily living, age and self-rated health. This tool classified $33 \%$ of study participants as vulnerable which is very similar to the proportion of people risk stratified as vulnerable in previous validation studies. The VES13 demonstrated acceptable performance in predicting functional decline in this new setting, and may have a role in identifying older people who will need increased community supports in the future. This tool has practical advantages as it can be administered quickly (approximately five minutes) by any healthcare professional, and is easy to score. However, identification of higher-risk people is only the first step, and there is a need to develop and test community-based interventions that aim to improve functioning for older people living in the community.

### 7.4 Predicting emergency admission in community-dwelling older people

Chapter 6 presented the findings of a systematic review of risk prediction models designed to identify community-dwelling people at highest risk of future emergency admission. Overall, the 27 validated models identified as part of this review demonstrated reasonable to poor model discrimination, with only six models reporting a c -statistic of $\geq 0.8$. The better performing models did share similarities as all included: 1) variables relating to previous healthcare utilisation; 2) a measure of multimorbidity or polypharmacy; and 3) specific medical diagnoses or medications. Interestingly, three of the six models better performing models predicted ACS admissions. Focusing prediction efforts on ACS admissions seems sensible as these are the admissions for which community-initiated interventions are most likely to have impact. Overall, non-medical factors, such as functional status, were generally poorly represented in models with only one-third including any non-medical factor. These factors have been previously highlighted as risk factors for emergency admission, but are more difficult to capture.(370) Models developed using clinical record review and linked datasets (including inpatient/OPD/A\&E/primary care utilisation and pharmacy claims data) tended to perform better than models developed using self-report questionnaires but were more difficult to apply in clinical practice.

A second systematic review and meta-analysis focussed on the Pra risk prediction model. This tool has been validated for use in older people in the US and Europe but the most recent community-based validation was 10 years ago and it has never been validated in Ireland. The systematic review identified 10 relevant studies and meta-analysis reported that the Pra demonstrates reasonable discrimination (pooled c-statistic 0.70 ) in predicting admission over the next year for those identified as high-risk (score $\geq 0.5$ ). The Pra demonstrated high specificity of $95 \%$ ( $95 \% \mathrm{Cl} 95.8 \%, 96.7 \%$ ) but low sensitivity of $12 \%$ ( $95 \%$ CI $10.5 \%, 13.6 \%)$. However, the meta-analysis was limited by the fact that only five cohorts could be included. This was due to studies using different cut-off points for denoting high risk (e.g. 0.3, 0.4), different prediction time periods and difficulty in obtaining additional data from authors of older studies. The systematic review found that two studies had substituted two self-report Pra items (self-rated health and caregiver availability) for a measure of multimorbidity with similar predictive accuracy. This is interesting as if the Pra
could be applied to a research database rather than needing to administer a questionnaire to capture self-report items this could have implications for its practical use in clinical practice.

The Pra tool was then externally validated using the Irish prospective cohort described in Chapter 3. The original Pra was tested and compared to the modified Pra, described above, which substituted the self-report items for a measure of multimorbidity (RxRisk-V). Overall, the original Pra identified 63 study participants (7\%) as high risk (score $\geq 0.5$ ), of whom 26 (41\%) were admitted as an emergency over the next year. The modified Pra identified a higher proportion of people as high risk ( $n=391,45 \%$ ) of whom 103 (26\%) were subsequently admitted. Model discrimination for both models was similar; original Pra: cstatistic 0.63 ( $95 \% \mathrm{Cl} 0.58,0.68$ ) and modified Pra: c-statistic 0.64 ( $95 \% \mathrm{Cl} 0.60,0.68$ ). Both models significantly over-predicted admissions, but the calibration performance of the original Pra was better than the modified Pra. Overall in this external validation, the original Pra demonstrated better clinical and research utility as it identified a much smaller number of people as high risk of whom $41 \%$ were subsequently admitted. In practice this tool could be used to identify community-dwelling people for trials testing the effectiveness of interventions aiming to reduce their admission risk.

However, as summarised in section 6.5, risk stratification and community-based intervention as a policy to reduce emergency admissions is not without its challenges. Emergency admissions are a popular target for healthcare policymakers trying to curb escalating expenditure but are an inherently difficult outcome to predict reliably. In addition, the majority of healthcare policy initiatives focus on all-cause emergency admissions, many of which are not preventable. Any risk stratification approach will have opportunity costs and at best only a minority of people who experience a future emergency admission will be identified using this approach. It is important that these issues and challenges are recognised when introducing policy that aims to reduce emergency admissions.

### 7.5 Strengths and limitations of this thesis

This thesis utilised a two year prospective cohort with very rich data sources. Each participant's GP medical record data was linked to the national pharmacy database which allowed accurate ascertainment of dispensed medications over this time period. In addition participating patients completed a detailed questionnaire and ADE interview. As a result several potential confounding variables were considered in regression analysis that previous studies were not able to include. In addition the overall risk of bias was low and losses to follow up were minimised in comparison with previous studies. The use of self-report ADEs may be raised as a limitation but this approach has been used in previous similar studies and all patient-reported ADEs were reviewed in duplicate by two academic GPs who determined the likelihood of the reported symptom being an ADE. Only ADEs where both reviewers agreed an ADE was likely were included as ADEs for the purposes of analysis. A larger sample size may have been preferable for examining different measures of multimorbidity. However this study's findings are broadly in line with previous studies which have examined different medication and diagnosis-based measures of multimorbidity in predicting adverse health outcomes.

### 7.6 Considering the impact of this thesis

A research impact framework developed by Kuruvilla in 2006 identified four key areas where research can impact upon health.(419) These are: i) Research related impact; ii) Policy impact; iii) Health service impact; and iv) Societal impact. This thesis is considered under each of these headings below.

### 7.6.1 Research related impact

This thesis reports several novel findings. First, is that PIP, as defined by STOPP, has a longitudinal association with future ADEs, poorer HRQOL and A\&E visits. This is the first primary care study to link PIP with these outcome using a prospective cohort study design. Second, this study indicates that the VES-13 may be a useful tool in identifying older people at risk of future functional decline, which may help target community-dwelling people for interventions to reduce this risk. Third, two systematic reviews have quantified the
prevalence of validated risk prediction models designed for use in primary care to predict future emergency hospital admission. Fourth, one of these tools, the Pra was externally validated and its discrimination was found to be relatively poor in Irish primary care but it demonstrated high specificity and identified a relatively small proportion of patients as high risk. This eight -item tool has advantages in terms of ease of administration and could be used to identify older people at higher risk of emergency admission.

This thesis was based on a prospective primary care cohort with two year follow-up. Plans are in place to continue following up this cohort which will offer further insights into the impact of PIP on adverse health outcomes over time. This research has also resulted in four high impact peer reviewed publications to date, with further publications planned, and has been presented at both national and international health services research and primary care conferences. This is important in terms of disseminating this research and increasing its impact.

### 7.6.2 Policy impact

There is increasing recognition of the need to restructure healthcare for the people who use it most i.e. patients with multimorbidity and the importance of a generalist approach in managing this patient group. The current single disease focus of clinical guidelines means that applying evidence-based medicine for this patient group is at best difficult and at worst hazardous due to often conflicting and sometimes impractical recommendations. These patients are often prescribed several medications from different prescribers increasing their risk of PIP and ADEs. The risk: benefit ratio of additional medications becomes more tenuous with increasing numbers due to risks associated with drug-drug and drug-disease interactions. From a policy perspective, understanding the importance of protected clinical time for medication reviews with patients and the need for robust information systems to support prescribing is essential. Prescribing indicators, such as STOPP, may have a role to play in supporting clinical prescribing decisions and improving the overall, quality of prescribing. I am currently a committee member the National Advisory group for Medicines in Older People, which was established by the HSE to inform policy aiming to improve prescribing for older people. I plan on disseminating the results of this thesis to this group.

In Chapter 6, a critical analysis of recently introduced UK healthcare policy hoping to reduce emergency admissions through identification and community-initiated interventions for people regarded risk stratified as high-risk was presented. This critical analysis details how at times healthcare policy which seems both logical and sensible may be misguided if it is not based on the best available evidence. Emergency admissions are a difficult outcome to predict reliably, and there is currently little evidence to support community-based interventions, in particular case management, in reducing emergency admission. This critical analysis aims to garner debate on how best to target emergency admissions through healthcare policy which requires a multifaceted approach.

### 7.6.3 Health service impact

This thesis provides evidence that PIP is linked with future increasing numbers of ADEs, reduced HRQOL and A\&E visits and strengthens the underpinning for interventions that use the STOPP prescribing indicators in future RCTs aiming to improve prescribing quality. Future research needs to focus on how best to incorporate prescribing indicators at the point of clinical care, ideally through computerised clinical decision support systems. Reducing PIP could have both clinical and cost saving implications for patients and the health service. This thesis also compares the predictive accuracy of different diagnosis and medication-based measures of multimorbidity, and found all have similar poor discrimination for the outcome of emergency admission. This is not surprising considering that admission risk models, that include a large number of clinical and socio-economic variables, have at best reasonable model discrimination. The current study indicates that using a diagnosis count measure at the traditional $\geq 2$ cut-off count is reasonable but that medication counts require higher cut-off points of $\geq 5$ or $\geq 6$ to achieve optimal discrimination. Practically speaking, including both a diagnosis measure and a polypharmacy measure may be the best approach in identifying more complex multimorbidity patients for RCTs and admission prediction models. Finally, this thesis summarises the existing risk prediction tools designed to predict emergency admission in community-dwelling adults, and some of the challenges that risk stratification presents. These challenges need to be considered and addressed when evaluating and implementing health service initiatives aimed at reducing emergency admissions.

### 7.6.4 Societal impact

This research may have potential for promoting improved health status in patients taking prescribed medication, largely through the improvement of HRQOL and reduction of ADEs associated with PIP. In addition there is potentially significant cost savings to be realised through the reduction of certain PIP e.g. reduction in dose or cessation of proton pump inhibitors. Critically analysing current healthcare policy regarding the targeting of higher risk community-dwelling people for interventions is essential, as this process has opportunity costs, and may lead to the over medicalisation of older people. Identifying older people at risk of functional decline is important as it prioritises the physical functioning and the person remaining in their own home for as long as possible. This is an essential component of person-centred, holistic care which has important implications for society as a whole.

### 7.7 Clinical and research implications

### 7.7.1 Clinical implications

This study links PIP, as defined by STOPP, to poorer health outcomes over time. The next essential step is to test the effectiveness of this tool in improving prescribing in clinical practice. If patient safety is the primary driver, then targeting a smaller number of higher risk medications (e.g. NSAIDs, warfarin, and ACE inhibitors) is a good approach. However, if the objective is to improve overall prescribing quality, then the application of the STOPP criteria is a good tool to implement to support this process. From a clinical perspective, focussing efforts on higher-risk prescribing that is more likely to impact upon patient safety (e.g. chronic NSAID use, long term benzodiazepines) may offer a greater driver for prescribing change.

Another issue to consider is how best to identify and record ADEs. The majority of ADEs in this study were rated as clinically mild, but PIP was also associated with poorer quality of life. It may be that ADEs considered as mild clinically are impacting significantly upon older people's quality of life and that more emphasis is required in capturing and addressing these events. If reducing ADE-related emergency admissions is of most interest, then targeting high-risk medications is more likely to be effective. However it may be argued that targeting
lower level ADEs, commonly encountered in general practice, also has a role to play in promoting better quality of life for patients. Therefore placing more emphasis on asking patients about milder ADEs during routine medication reviews and making medication changes accordingly may have an impact on improving overall health related quality of life.

Emergency admission is a difficult outcome to predict reliability. Risk stratification approaches have inherent limitations and applying these models on a population basis means that inevitably only a small proportion of people who experience future admissions will be identified. In addition, for any risk stratification approach to be effective in reducing an outcome of interest there must be an effective intervention available to implement. Current policy efforts to reduce all-cause emergency admissions are unlikely to be successful as many admissions are simply not preventable. The best chance of reducing emergency admissions through community-based intervention lies in recognising this, and focussing policy efforts on ACS admissions where impact is most likely to be realised.

### 7.7.2 Research implications

Future research is needed to develop and test computerised clinical decision support systems that would facilitate dissemination of these indicators at the point of care. In addition a larger study with a higher proportion of severe ADEs is needed to determine if PIP has a longitudinal association with these types of events. Comparing different measures of multimorbidity indicates that medication counts and disease counts perform similarly in predicting emergency admission. Practically speaking, when considering how best to identify patients with multimorbidity for recruitment to RCTs, it may be more useful to combine a count measure of conditions with a polypharmacy measure. This approach should mean that patients with more complex multimorbidity are identified rather than patients with less impactful combinations of conditions (e.g. hypertension and hypercholesterolemia). From a RCT recruitment perspective, simple counts of multimorbidity are easier to apply and this study indicates that using count measures is a reasonable approach. For emergency admission, further research is needed on interventions targeting ACS admissions and the impact of unwarranted practice variation, both in terms of the impact of GP referral patterns and the impact of deprivation on emergency admissions.

### 7.8 Conclusions

The current shift in population demographics means that the proportion of older community-dwelling people is set to expand significantly over the next decade and beyond. Identifying which older people are more likely to experience future adverse health outcomes is an important component of care planning. This thesis adds to the literature in this area by examining several measures of prescribing, multimorbidity and vulnerability that can be used to identify people at higher risk of ADEs, poorer HRQOL, functional decline and emergency hospital attendance.

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Appendices

## Appendix 1: STROBE checklist for prospective cohort studies

|  | Item No | Recommendation | Thesis page |
| :---: | :---: | :---: | :---: |
| Title and abstract | 1 | (a) I n di c a t e the commonly used term in the title or the abstract |  |
|  |  | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 22-23 |
| Introduction |  |  |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 29-38 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 36-38 |
| Methods |  |  |  |
| Study design | 4 | Present key elements of study design early in the paper | 74 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 74-80 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 75 |
|  |  | (b) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 81-107 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). <br> Describe comparability of assessment methods if there is more than one group | 81-107 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 108, 164-171 |
| Study size | 10 | Explain how the study size was | 77 |


|  |  | arrived at |  |
| :---: | :---: | :---: | :---: |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 81-107 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding | $\begin{aligned} & 108,119-124,196, \\ & 260-265 \end{aligned}$ |
|  |  | (b) Describe any methods used to examine subgroups and interactions | 119-124 |
|  |  | (c) Explain how missing data were addressed | 157-158, 197, 206 |
|  |  | (d) If applicable, explain how loss to follow-up was addressed | 168 |
|  |  | (e) Describe any sensitivity analyses | 258, Appendix 13 |
| Results |  |  |  |
| Participants | 13* | (a) Report numbers of individuals at each stage of studyò eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 126-131 |
|  |  | (b) Give reasons for non-participation at each stage | 126-127 |
|  |  | (c) Consider use of a flow diagram | 126 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 128, 135-139 |
|  |  | (b) Indicate number of participants with missing data for each variable of interest | 126-127, as footnotes for all tables |
|  |  | (c) Summarise follow-up time (eg, average and total amount) | 78 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | $\begin{aligned} & 139-144,149-150, \\ & 156 \end{aligned}$ |
| 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 | All regression analysis tables |
|  |  | (b) Report category boundaries when continuous variables were categorized | All regression analysis tables |


|  |  | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| :---: | :---: | :---: | :---: |
| Other analyses | 17 | Report other analyses doneò eg analyses of subgroups and interactions, and sensitivity analyses | Appendices 12 and 13 |
| Discussion |  |  |  |
| Key results | 18 | Summarise key results with reference to study objectives | 210, 265-271 |
| 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 | $\begin{aligned} & 172-178,210-214 \\ & 271-273 \end{aligned}$ |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | $\begin{aligned} & 176-77,215-16, \\ & 274 \end{aligned}$ |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 177 |
| 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 | Acknowledgements page |

*Give information separately for exposed and unexposed groups.

## Appendix 2: Ethical approval for cohort follow-up



Dear Dr Emma Wallace,
Thank you for your amendment to Research Ethics Committee (REC) application REC462b. We are pleased to advise that ethical approval has been granted by the committee for this amendment.

## Content of Amendment:

1. Change in named Principal Investigator.

Extension of 1 year.
3. Minor amendments to 'GP data collection form' \& 'Patient questionnaire'.

Therefore the research ethics approval for this study will expire on $26^{\text {th }}$ March, 2013. Where data collection is necessary beyond this point, approval for an extension must be sought from the Research Ethics Committee.

This ethical approval is given on the understanding that:

- All personnel listed in the approved application have read, understand and are thoroughly farniliar with all aspects of the study.
* Any significant change which occurs in connection with this study and/or which may alter its ethital consideration, must be reported immediately to the REC, and an ethical amendment submitted where appropriate.
- As per the original approval, a form of global feedback is to be prowided to each participating GP practice on the outcome(s) of the study research, at the end of each of the participating GP practice study analysis.
- Please submit a final report to the REC upon completion of your project.

We wish you all the best with your research.
Yours sincerely,


PP Ms. Stephanie O'Connor (Convenor)
Dr David 5mith (Acting Chair)

Royal College of Surgeons in Ireland
The Research Ethics Committee
121 St. Stephens Green, Dublin 2, Ireland.
Tel: +35314022373 Fax: +35314022449 Email: recadmingircsi.ie
Dr. David Smith, Acting Chair
Ms. Stephanie O'Connor, Convenar cole istr mbor NA masteh in birien
$7^{\text {th }}$ January, 2013
Dr Emma Wallace,
Division of Population Health Sciences,
Royal College of Surgeons in Ireland,
Beaux Lane House,
Mercer Street Lower,
Dublin 2

| Ethics Reference No: | REC462bbb |
| ---: | :--- |
| Project Title: | Study 1: Prescribing in primary care patients aged 70 years <br> or older. |
| Researchers Name: | Dr Emma Wallace |
| Other Individuals Involved: | Professor Tom Fahey, Dept of General Practice, RCSI. <br> Ms Caitriona Cahir, HRB PhD Scholar in Health Services <br> Research, RCSI. <br> Dr Kathleen Bennett, Dept of Pharmacology and <br> Therapeutics, Trinity College Dublin. <br> Dr Conor Teljeur, Dept of Public Health and Primary Care, <br> Trinity College Dublin. |

Dear Dr Emma Wallace,
Thank you for your amendment to Research Ethics Committee (REC) application REC452bb. We are pleased to advise that ethical approval has been grar ted by the committee for this amendment.

Content of Amendment:

1. Time extension of 9 months.

Therefore the research ethics approval for this study will expire on $26^{\text {t/ }}$ December, 2013. Where data collection is necessary beyond this point, approval for an extension must be sought from the Research Ethics Committee.

This ethical approval is given on the understanding that:

- All personnel listed in the approwed application have read, understand ard are thoroughly familiar with all aspects of the study.
- Any significant change which occurs in connection with this study and/or which may alter its ethical consideration, must be reported immediately to the REC, and an ethical amendment submitted where appropriate.
- As per the original approval, a form of global feedback is to be provided :o each participating GP practice on the outcome(s) of the study research, at the end of each of the participating GP practice study analysis.
- Please submit a final report to the REC upon completion of your project.

We wish you all the best with your research.

```
Yours sincerely,
    <
PP Ms. Stephanie O'Connor (Convenor)
Dr David Smith (Acting Chair)
```


# Appendix 3: Letter regarding follow-up of cohort to GP 



## 7* June 2012

## Studv title: Prescribing in primary care patients aged 70 vears or older

Dear Dr,
We would like to thank you and your pratice staff for recently reviewing the list of study paticipants from your practice Those who you have indicated are no longer eligible to take part will be exchded from follow-up.

We are now at the stage for sending postal questiomaires to study particip ants. Participants have aleady consented to this follow up. Before sending the postal questionnaire to patients we wanted to share with you what will be sent to patients (please see letter and questionnaire attached).

The second part of this follow-mp is the review of the patient's GP record. Dr Enera Wallacewill be in contact with you shortly to arange a suitable timefora climial member of the raxeach tean to review participants GPrecords for this purpose.

Please do not hesitate to coutact Emma with any queries.
Email: emmawallace@rcaiie Office: 014028664, Mobile: 0868480037

Kind regards,

Dr Erma Wallace
Professor Susan Smith
Professor Tom Fahsy
-


## Appendix 4: Cover letter regarding study follow-up to patients

## Practice letterhead inserted here

Medicines Management in patients aged 70 years or older

Dear (Mr/Mrs/Ms Surname of patient),

Last year you kindly agreed to participate in a research study being carried out at your General Practice surgery in association with the Health Research Board Centre for Primary Care Research of the Royal College of Surgeons in Ireland (RCSI). As you may recall the study is examining prescription medications in older people and it is now one year since you filled out a questionnaire asking questions about your general health, use of healthcare services and how you manage your medication.

You may recall that we planned to ask you to fill out a questionnaire again in one yearös t i me. We would be very grateful if questionnaire. The information gathered from this research will help us understand more about medicines management in older people in General Practice.

If you have any questions about this questionnaire please contact Dr Emma Wallace at the Department of General Practice, RCSI. Tel: 01) 4028664 or 086) 8480037

Yours sincerely,
Erra wallace

Dr Emma Wallace
Dr Insert name of participant GP

Appendix 5: Postal patient questionnaire


# Medicines Management in patients aged 70 years or older 

Thank you for agreeing to participate in this study.
We would be very grateful if you could fill out this questionnaire and return it to us in the FREEPOST envelope enclosed. It will take about 20 minutes. The information that you provide will remain strictly confidential.

Please answer all questions in Section A through to Section E by ticking the boxes $\mathbf{X}$ or filling in answers when requested to. Please read the instructions for each carefully and remember that there are no "right" or "wrong" answers.

If any of the questions are unclear or if you do not understand what the question is asking please contact; Dr Emma Wallace, Department of General Practice, Royal College of Surgeons in Ireland, Dublin 2. Ph: 014028664 / 0868480037 . Please do not leave the question blank.

## Section A- Your General Health

I would like to ask you a few questions about your health. Below are five groups of statements about your health today. Please indicate which of these statements best describe your own health today by placing a tick in one box for each group.

1. Mobility

■. I have no problems in walking about I have some problems in walking about
D. 1 am confined to bed
2. Self-Care

$$
\begin{aligned}
& \text { D. I have no problems with self-care } \square \text { : I have some problems with washing or dressing } \\
& \square \text { I am unable to wash or dress myself }
\end{aligned}
$$

3. Usual activities (e.g. work, housework, family or leisure activities)
D. I have no problems with performing my usual activities
[. I have some problems with performing my usual activities
[. I am unable to perform my usual activities
4. Pain/Discomfort
D. I have no pain or discomfort
D: I have moderate pain or discomfort
[. I am unable to perform my usual activities

## 5. Anxiety/Depression

D. I am not anxious or depressed

D: I am moderately anxious or depressed
D. I am extremely anxious or depressed
6.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0 .

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state today

Best
imaginable health state


Worst imaginable health state
7. In general, compared to other people your age, would you say your health is:

| D. Poor | D: Fair | [:Good | D. Very Good | [: Excellent |
| :---: | :---: | :---: | :---: | :---: |

I would like to ask you a few questions about your ability to carry out certain tasks. Even if you have not done any of the tasks described below in the past few weeks, please tell me if you think you are able to do these tasks.
8. How much difficulty, on average, do you have with the following physical activities?

|  | No Difficulty | A little Difficulty | Some Difficulty | A lot of Difficulty | Unable to do so |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Stooping, crouching or kneeing'? | $\square$ | $\square$ | $\square$ | $\square$ | $\square:$ |
| Litting or carrying objects as heavy as 10 pounds? | $\square$ | $\square$ | $\square$ | $\square$ | D: |
| Keaching or extending arms above shoulder level? | $\square$ | $\square$ | $\square$ | $\square$ | D: |
| Writing, or handing and grasping small objects? | $\square$ | $\square$ | $\square$ | $\square$ | [: |
| WValking a quarter of a mile? | $\square$ | $\square$ | $\square$ | $\square$ | [: |
| Heavy housework such as scrubbing floors or washing windows? | $\square$ | $\square$ | $\square$ | $\square$ | ㅁ: |

9. 

9.1 Because of your health or a physical condition, do you have any difficulty shopping for personal items (like toilet items or medicines)?

| $\square$ Yes | Vo | Dan't Do |
| :--- | :--- | :--- |

y. 2 Uo you get help with shopping?
D. Yes

D: No
9.3 If you do not shop, is that because of your health? $\qquad$ D: No
9.4 Because of your health or a physical condition, do you have any difficulty managing money (like keeping track of expenses or paying bills)?

| $\square$ Yes | Vi Do | Don't Do |
| :--- | :--- | :--- |

9.5 Do you get help with managing money?
D. Yes

ㅁ: No
9.6 If you do not manage your money, is that because of your health?

9.7 Because of your health or a physical condition, do you have any difficulty walking across the room (use of cane or walker is ok)?

| $\square$ Yes | ■i No | Dent Do |
| :--- | :--- | :--- |

9.8 Do you get help with wal king?

■. Yes DiNo
9.9 If you do not walk, is that because of your health?
D. Yes DiNo

| 9.10 | Because of your health or a physical condition, do you have any difficulty doing light housework (like washing dishes, straightening up, or light cleaning)? |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | D. Yes | $\square \square_{\text {No }}$ | D. Drat Do |  |  |  |
| 9.11 | Do you | light housework? | - Yes | $\square$ No |  |  |
| 9.12 | If you do not do light housework, is that because of your health? |  |  |  | D. Yes | $\square \mathrm{D}$ No |

9.13 Because of your health or a physical condition, do you have any difficulty bathing or showering?

| $\square$ Yes | ■i No | Den't Do |
| :--- | :--- | :--- |

9.14 Do you get help with bathing or showering?

■. Yes $\quad$ I: No
9.15 If you do not bath or shower, is that because of your health? $\square$ D: No
10.

The following questions relate to how you are feeling at present. Please choose the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-outresponse.

| I feel tense or 'wound up': | I feel as if I have slowed down: |
| :---: | :---: |
| $\square$ : Most of the time | D. Nearly all the time |
| [.: A lot of the time | D: Very often |
| -. From time to time, occasionally | - Sometimes |
| ■: Not at all | D: Not at all |
| I still enjoy the things I used to enjoy: <br> Definitely as much | I get a sort of frightened feeling like 'butterflies" in my stomach: |
| - Not quite as much | D: Not at all $\square$ - Occasionally |
| ■. Only a little | $\square$ : Quite often $\square$ : Very often |
| D. Hardly at all |  |

The following questions relate to how you are feeling at present. Please choose the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

| I get a sort of frightened feeling as if something awful is about to happen: Yes definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all | I have lost interest in my appearance: <br> D: Definitely <br> D: I don't take as much care as I should <br> D. I may not take quite as much care <br> D: I take just as much care as ever |
| :---: | :---: |
| I can laugh and see the funny side of things: <br> ㅁ: As much as I always could <br> D. Not quite so much now <br> $\square$ : A little, but it doesn't worry me <br> D. Not at all | I feel restless as I have to be on the move: Very much indeed <br> D: Quite a lot <br> -. Not very much <br> ㅁ: Not at all |
| Worrying thoughts go through my mind: A great deal of the time A lot of the time From time to time but not too often Only occasionally | I look forward with enjoyment to things: <br> ㅁ: As much as ever <br> D. Rather less than I used to <br> D: Definitely less than I used to <br> D: Hardly at all |
| I feel cheerful: <br> D. Not at all <br> D. Not often <br> [. Sometimes <br> ㅁ: Most of the time | I get sudden feelings of panic: <br> $\square$ : Very often indeed <br> ㅁ. Quite often <br> -. Not very often <br> ㅁ: Not at all |
| I can sit at ease and feel relaxed: Definitely Usually Not often Not at all | I can enjoy a good book or radio or TV programme: <br> D: Often <br> ■. Sometimes <br> ©: Not often <br> [. Very seldom |

11. During the past 4 weeks to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?
D: Not at all $\quad$ I. Slightly $\quad \square$ Moderately $\quad \square$ : Quite a bit $\quad \square$. Extremely
12. During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc)?

| ■. All of the time | $\square:$ Most of the time | D: A good bit of the time |
| :--- | :--- | :--- |
| a. Some of the time | D: A little of the time | D: None of the time |

The following questions relate to general social support
13. I see myself as someone who has high self-esteem (self-worth)
$\square$. Strongly disagne $\square$ : Disagree $\square$ Neither agme nor disagree $\square$ Agree $\square$ : Strongly agree
14. I would like to ask you some questions about your family and friends

| How many relatives or triends do you see or hear from at least oncea month? | None $\square$. | One $\square$ | Two $\square$ | $3 \text { or } 4$ <br> $\square$ | 5 thru 8 $\square$. | 9 or more $\square$. |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| relative or friend with whom you have most contact? | Never <br> ㅁ: | Seldom | Sometimes $\square$ | Often $\square$ | Very often $\square$. | Always $\square$ |

15. People sometimes look to others such as friends or close relatives for companionship. help or other types of support. How often would each of the following kinds of support be available if you needed it?

|  | None of the time | A little of the time | Some of the time | Most of the time | All of the time |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Someone who makes youteel loved and appreciated | $\square$ | $\square$ | $\square$ | $\square$. | $\square$ |
| Someone whom you can contide in and who will give you advice or information | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Someone who will help you with practcal tasks like preparing meals, household chores, or shopping | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |

16. Is there a friend/relative/neighbour that would take care of you for a few days if necessary?
a) Yes

- 

b) No
-
17. Here are some statements about life in general that people feel different ways about. Please read each statement on the list and tick the box the best describes how you feel about this statement.

|  | Agree | Disagree | Unsure |
| :---: | :---: | :---: | :---: |
| As I grow older, things seem better than I thought they would be | $\square$ | $\square$ | $\square$ |
| I have got more of the breaks in life than most people I know | $\square$ | $\square$ | $\square$ |
| Ihis is the dreariest time of my lite | $\square$ | $\square$ | $\square$ |
| I am just as happy as when I was younger | $\square$ | $\square$ | $\square$ |
| My lite could be happler than it is now | $\square$ | $\square$ | $\square$ |
| I hese are the best years of my life | $\square$ | $\square$ | $\square$ |
| Most of the things I do are boring or monotonous | $\square$ | $\square$ | $\square$ |
| I expect some interesting and pleasantthings to happen to me in the future | $\square$ | $\square$ | $\square$ |
| Ihe things I do are as interesting to me as they ever were | 口 | $\square$ | $\square$ |


| Q17 - Continued | Apree | Disagree | Unsure |
| :---: | :---: | :---: | :---: |
| I teel old and somewhat tired | $\square$ | $\square$ | $\square$ |
| As I look back on my life, I am tairly well satistied | $\square$ | $\square$ | $\square$ |
| I would not change my past even it I could | $\square$ | $\square$ | $\square$ |
| Compared to other people my age, I make a good appearance | $\square$ | $\square$ | $\square$ |
| I have made plans tor things I'll be doing in a month or a year trom now | $\square$ | $\square$ | $\square$ |
| When I think backover my life, I didn't get most of the important things I wanted | $\square$ | $\square$ | $\square$ |
| Compared to other people, I get down in the dumps too otten | $\square$ | $\square$ | $\square$ |
| I got pretty much what I expected out of life | $\square$ | $\square$ | $\square$ |
| In spite of what some people say, the lot of the average man is getting worse, not better | $\square$ | $\square$ | $\square$ |

## Section B- Health Services

I would like to ask you a few questions about your use of medical services e.g. hospital, GP
18. Do you have private health insurance that covers the cost of private medical treatment (e.g. VHI, BUPA, VIVAS)?
$\square$ YES
D: NO
19. In the last 12 months, how many times have you seen your GP or visited an Outpatient clinic?

- Not at all
- 1 time
-2-3 times
-4-6 times
->6 times

20. In the last 12 months, how many times have you been admitted to hospital?
```
\squareNot at all
-1 time
\square2-3 times
\square4-6 times
\square>6 times
```

21. As part of this study, a small number of people who have been admitted to hospital in the last year will be invited to discuss their views and experiences of events leading up to hospital admission. Would you be willing to be contacted about this? If you agree and your name is selected then you will be contacted by the researcher who will explain in more detail what is involved. You would of course be free to take part or not at that time.

■. YES
$\square \mathrm{NO}$
NOT APPLICABLE (No hospital admission in the last year)
22. In the last 12 months have you used any of the following services for medical treatment? (Tick all that apply).
If you have, please advise the number of visits.
If you stayed overnight, please advise the number of nights

| List of services | YES | No. of visits (Last 12 months) | No of nights (Last 12 months) |
| :---: | :---: | :---: | :---: |
| Accident andtmergency departmert | $\square$ |  |  |
| Out of hours (Gi' services (eg. UubLIoc, ULIOC) | $\square$ |  | $\because \because \because \cdot$ |
| Hospital-Scheduled inpabert (planned overnght stay) | $\square$ |  |  |
| Hospital Uutpatert (meetwth a consultant) | $\square$ |  |  |
| Fublic Health Nurse | $\square$ |  |  |
| -hysiotherapy Services | $\square$ |  |  |
| Uccupational Iherapy | $\square$ |  |  |
| Speech Iherapy | $\square$ |  |  |
| Uletician Services | $\square$ |  |  |
| Uptician Services | $\square$ |  |  |
| Uental Services | $\square$ |  |  |
| Hearing Services | $\square$ |  |  |
| Chiropody Services | $\square$ |  |  |
| H'sychologcal Counselling | $\square$ |  |  |
| Uay Care Centre | $\square$ |  |  |
| Respite care (recever of care) | $\square$ |  |  |
| Chiropractor | $\square$ |  | $\because \because \because$ |
| Alternative therapies eg. acupuncturist, Cinnese medicine | $\square$ |  | $\cdots$ |

23. Are you currently on a waiting list for any of the following services? (Tick all that apply)

| Service | Yes |
| :---: | :---: |
| Uutpatient hosptal appoirtmert (e.g. a visitto a clinic to be seen by a consultant or specialist) | $\square$ |
| Inpatient hospital admission (e.g. for surgery requiring overnight stay) | $\square$ |
| Appointment for a day care procedure or investigation (e.g. appointment for a test or minor operation that will not need anovemight stay) | $\square$ |
| Uay care centre | $\square$ |
| -hysiotherapy I herapy | $\square$ |
| Uccupational I herapy | $\square$ |
| Speech Inerapy | $\square$ |
| F'sychological Counselling Services | $\square$ |
| Respite care (as a recever of care) | 口 |

24. In the last 12 months, did you need help from others to maintain your independence on a regular basis? (Tick all that apply)
If you have, how often did you receive help?

|  |  | How often did you receive help? |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | YES | All the time (day \& night | Most of the day | 1-2 times per day | A few times each week | Once weekly or less |
| Spouse/r'artner | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square:$ |
| Uther relative in your household | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square:$ |
| Uther relativeliving elsewhere | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square:$ |
| Neighbour | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Voluntary Urganisaton | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Fersonal care attendart | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Home Help | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Meals on Wheels | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ | $\square:$ |

25. We are interested in your journey to access healthcare services.

Please complete the following table which asks about how you travel, how far and how long it takes and how long you have to wait before being seen when you visit a healthcare setting e.g. GP surgery, hospital.
If you visit other healthcare settings, please include this information in the 'Other' category in the table.

| Question | GP Surgery | Hospital | Uther: Flease specity the healthcare setting |
| :---: | :---: | :---: | :---: |
| How many miles do you have to travel from your home to... | $\underline{\text { miles }}$ | __miles | Setting $\qquad$ $\qquad$ mies |
| How do you usually travel to your GP/HospitalOther.a. (eg. bus, car, taxi, train, walk) |  |  |  |
| How long does it usually take you to travel from your home to the... | _ minutos | $\ldots$ minutes | _ minutes |
| How long do you usually haveto wat to see the doctor or nurseor healthcare professionalafter you arrive at, | _minutes | __minutes | __minutes |

26. Is there any other information you would like to include about your use of medical and support services?

## Section C-MANAGING YOUR MEDICATION

This section of the questionnaire asks you about managing and taking your medication. There are no right or wrong answers. Please answer each question based on your own experience


We would like to ask you about your personal views about medicines prescribed for you. These are statements other people have made about their medicines. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views.

| $\cdot 28$ | Strongly Agree | Agree | Uncertain | Disagree | Strongly disagree |
| :---: | :---: | :---: | :---: | :---: | :---: |
| My heaith at present dapends on my medicines | $\square:$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Having to take medicines worrles me | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| My lfe would be impossible without my medicines | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| Without my medicinas I would be very | D: | $\square$ | $\square$ | $\square$ | $\square$ |
| I sometimes worry about long-term effects of my medicines | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |
| My medicinas are a mystery to me | D: | $\square$ | $\square$ | $\square$ | $\square$ |
| My neaith in the fiture will depend on my medicines | D: | $\square$ | $\square$ | $\square$ | $\square$ |
| My medicines disrupt my life | D: | $\square$ | $\square$ | $\square$ | $\square$ |
| 1 sometimes worry about becoming 100 depandent on my medicinas | $\square$ | $\square$ | $\square$ | $\square$ | $\square$ |


| My medicinas protect me from decoming worse | $\square_{:}$ | $\square_{i}$ | $\square_{i}$ | $\square_{i}$ | $\square$ |
| :--- | :--- | :--- | :--- | :--- | :--- |

## Section D-GENERAL QUESTIONS

This final section of the questionnaire asks you some general questions. This information is needed so we can look at the health of older people in different situations.
29. What is your ethnic or cultural background? (Tick one only)

30. What is your current marital status? (Tick one only)

31. Please could you tell me whom you live with? (Tick all that apply)

■. Husband/Wife/Partner ■: Family/Relatives ■i Flat/House share Di Live alone ■: Qther

```
Thank you very much for taking the time to complete this questionnaire. Please return
the questionnaire in the FREEPOST envelope enclosed to:
LICENCE DN 7088
DrEmma Wallace
Department of General Practice
Royal College of Surgeons in Ireland
123 St Stephens Green
Business Reply
Dublin 2
```


## Section A. Administration

Patient ID


Interviewer Name
Date $\qquad$ 1 $\qquad$ /10 Start Time $\qquad$ (24hr)

## Section B- Medical Record Information

This part of the questionnaire is to be completed by review of patient ö srecard. dhiparticular you are looking for information on repeat and acute medications, illness (morbidity), episodes of care, referrals and adverse drug events or reported side-effects in the previous 6 months

1. Pleaserecord detailsof patientösprescribed medicat previous six months into the Tables below (Repeat and Acute Medications).

## REPEAT MEDICATIONS

| Drug Name (e.g. Rosuvastatin- Crestor) | Strength (e.g. <br> 10) | Unit (e.g. <br> mg) | Quantity <br> (e.g. 28) | Frequency <br> (e.g. 1 daily) |
| :--- | :--- | :--- | :--- | :--- |
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## ACUTE MEDICATIONS- IN PAST ONE YEAR

| Drug Name (e.g. Lansoprazole- Zoton FasTab) | Strength <br> (e.g. 30) | Unit (e.g. <br> mg) | Quantity <br> (e.g. 28) | Frequency (e.g. <br> 1 daily) |
| :--- | :--- | :--- | :--- | :--- |
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2. Detailsof patientös medical conditionslillnesses

Ongoing Medical Conditions (please describe below, include morbidity code if available)

|  |
| :--- | :--- |
|  |
|  |
|  |
|  |

3. Review of patientös medical record for any specified

| Name of Drug | Brief description of reaction |  |
| :--- | :--- | :--- |
|  |  |  |
|  |  |  |
|  |  |  |

## 4. Number of GP visits in the previous 2 years

## Number of non-consultation/prescription only visits

$\square$
5. Detailsof the patientös use of any of the following years? (Tick all that apply).

Please review documents for referral discharge from hospital. If there are other services not listed below please add them to the table.

| Service Type (please tick) |  | No. of episodes <br> (Last 2 years) | No of nights <br> (Last 2 years) |
| :--- | :--- | :--- | :--- |
| Out of hours GP services (e.g. DubDoc) | $\square_{1}$ |  |  |
| Hospital - Accident \& Emergency (Casualty Department) | $\square_{1}$ |  |  |
| Hospital -Scheduled Inpatient (planned overnight stay) | $\square_{1}$ |  |  |
| Hospital- Day procedure | $\square_{1}$ |  |  |
| Hospital Outpatient (meet with a consultant, specify speciality below) | $\square_{1}$ |  |  |
| Speciality 1: | $\square_{1}$ |  |  |
| Speciality 2: | $\square_{1}$ |  |  |
| Speciality 3: | $\square_{1}$ | $\square_{1}$ |  |
| Public Health Nurse | $\square_{1}$ |  |  |
| Physiotherapy Services | $\square_{1}$ |  |  |


| Occupational Therapy | $\square_{1}$ |  |  |
| :--- | :--- | :--- | :--- |
| Psychological/Counselling | $\square_{1}$ |  |  |
| Day Care Centre | $\square_{1}$ |  |  |
| Respite care (receiver of care) | $\square_{1}$ |  |  |
|  | $\square_{1}$ |  |  |
|  | $\square_{1}$ |  |  |
|  | $\square_{1}$ |  |  |

 to say feeling dizzy and listless since started tenormin, stopped medication, review appointment.
 took.


|  | - |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\square$, No of nights | $\square_{2}$ | $\square$ | $\square \square_{2}$ YES $\square_{3}$ NO | $\square \square_{4}$ | $\square \square$ | $\square \square_{\text {。 }}$ | $\square 7$ |  |
|  | $\square$, No of nights | $\square_{2}$ | $\square$ | $\square \square_{2}$ YES $\square_{3}$ NO | $\square \square_{4}$ | $\square \square$ | $\square$ 。 | $\square 7$ |  |
|  | $\square$ No of nights | $\square_{2}$ | $\square$ | $\square \square_{2}$ YES $\square_{3}$ NO | $\square 4$ | $\square \square^{5}$ | $\square \square^{6}$ | $\square 7$ |  |

## Appendix 7: ADE patient interview template

## Section C- Medication Side-Effects

## Patient ID



Interviewer Name


Date $\qquad$ /10 Start Time $\qquad$ (24hr)

This part of the questionnaire is to be completed by patient interview. Please have a copy of $t h e \quad p a t i e$ prescribed medications for the previous 6 months in front of you (question 1) as well as details of any reported adverse drug event or side-effect (question 6). You will have agreed a time to call the patientIntroduce yourself to the patient- your name, say you are calling from the HRB Centre for Primary Care Research, RCSI and that you are calling about the study on prescribing in older people. Thank the patient for agreeing to take part in the study and for giving up their time.

Explain the process of the interview to the patients: Sample text below

I would like to get a greater understanding of how you manage your medications. I am going to ask you a couple of questions about your medications and then I am going to go through a list of symptoms with you and ask you if you have had any of these symptoms in the last 6 months. This will take about 10 minutes. Your answers are strictly confidential. As we go through the list of symptoms if there is anything that you do not understand or if anything I am asking is unclear please stop me.

## Interviewer:

Have you noticed any side effects, unwanted reactions, or other problems from your medications in the past 6 months? $\square$ GU" ő " s w g u v kPqQp" "ő;" "s"w g u v k q p " :

Interviewer: Use of prompts- examples below
It is very hard to know what symptoms are related to your medication. Is there anything at all that has been bothering you? If there is a GP report of an ADE or side-effect, use that information to probe the patient.

## Interviewer:

Ask the patient to broadly describe the side-effect
Sample Text: Please could you describe generally the side-effect or difficulty you experienced.

| System Review Side-Effects | YES | Drug Name | Start Date | Duration | Bothered? | Tell GP | YES: Did your GP do any of the following for the side-effect? NO: Did you do any of the following? |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Cardiovascular |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chest pain/pressure in chest | $\square_{1}$ |  |  |  | Not at all $\boldsymbol{\square}_{1}$ Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect $\square$ | Tests <br> $\square 6$ | Nothing $\square_{7}$ | Other describe | Hospital <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square_{1}$ | $\begin{aligned} & \hline \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |
| Palpitations/ racing heart/irregular heart beat | $\square{ }_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue口1 | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect $\square$ | Tests $\square 6$ | Nothing $\square 7$ | Other describe | Hospital <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \hline \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square$ $\square 3$ | Other describe |  |  |  |  |
| Woken at night by shortness of breath | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue口1 | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square$ | Another med for side effect $\square$ | $\begin{aligned} & \hline \text { Tests } \\ & \square_{6} \end{aligned}$ | Nothing $\square_{7}$ | Other describe | Hospital $\square$ <br> No of nights <br> $\overline{0}$ if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square_{1}$ | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |




| System Review Side－Effects | YES | Drug Name | Start Date | Duration | Bothered？ | Tell GP | YES：Did your GP do any of the following for the side－effect？ NO：Did you do any of the following？ |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Respiratory |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cough －sputum －haemoptysis （blood in sputum） | 口1 <br> $\square_{2}$ <br> $\square \square_{3}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square$口 | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change （dose， quantity） $\square_{4}$ | Another med for side effect $\square$ | Tests $\square 6$ | Nothing口7 | Other describe | Hospital <br> No of nights <br> $\overline{\text {（0 if no }}$ overnight stay） |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square_{1}$ | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |
| Short of breath | $\square{ }_{1}$ |  |  |  | Not at all $\square_{1}$ Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square$ | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change （dose， quantity） $\square$ $\square 4$ | Another med for side effect | Tests $\square 6$ | Nothing口7 | Other describe | Hospital <br> No of nights <br> $\overline{\text {（0 if no }}$ overnight stay） |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square$ | $\begin{aligned} & \hline \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |
| Wheezing | $\square 1$ |  |  |  | Not at all $\square_{1}$ Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square$ |  | change （dose， quantity） | Another med for side effect <br> $\square 5$ | Tests口6 | Nothing口7 | Other describe | Hospital <br> No of nights <br> $\overline{0} 0$ if no overnight stay） |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \hline \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |






| System Review Side-Effects | YES | Drug Name | Start Date | Duration | Bothered? | Tell GP | YES: Did your GP do any of the following for the side-effect? NO: Did you do any of the following? |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Genitourinary |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Burning, discomfort or pain when passing water | $\square{ }_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect | Tests $\square 6$ | Nothing $\square$ $\square_{7}$ | Other describe | Hospital <br> No of nights <br> $\overline{\text { (0 if no }}$ overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square_{1}$ | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square \square_{3}$ | Other describe |  |  |  |  |
| Change in colour of urine | $\square{ }_{1}$ |  |  |  | Not at all $\square_{1}$ Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square 4$ | Another med for side effect | Tests $\square$ | Nothing口7 | Other describe | Hospital $\square$ <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square \square_{3}$ | Other describe |  |  |  |  |
| Difficulty in passing water (poor stream, delayed start to passing urine, or dribbling at the end of passing urine) | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop <br> replace with another YES NO | change (dose, quantity) $\square$ 4 | Another med for side effect | Tests $\square 6$ | Nothing $\square$ | Other describe | Hospital <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |



| System Review Side-Effects | YES | Drug Name | Start Date | Duration | Bothered? | Tell GP | YES: Did your GP do any of the following for the side-effect? NO: Did you do any of the following? |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Sexual Function |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Have you experienced decreased sexual interest or sexual desire | $\square \square_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square 1$ | stop <br> replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect | Tests $\square 6$ | Nothing $\square 7$ | Other describe | Hospital <br> No of nights <br> $\overline{(0 \text { if no }}$ overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square_{1}$ | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square \square_{3}$ | Other describe |  |  |  |  |
| Have you experienced difficulty in reaching erection (males only) | $\square{ }_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square 4$ | Another med for side effect | Tests ■6 | Nothing口7 | Other describe | Hospital $\square$ <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square \square_{3}$ | Other describe |  |  |  |  |
| Do you have problems with a dry vagina (females only) | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square_{1}$ | stop <br> replace with another YES NO | change (dose, quantity) $\square$ 4 | Another med for side effect | $\begin{aligned} & \text { Tests } \\ & \square_{6} \end{aligned}$ | Nothing $\square$ | Other describe | Hospital <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |







| System Review Side-Effects | YES | Drug Name | Start Date | Duration | Bothered? | Tell GP | YES: Did your GP do any of the following for the side-effect? NO: Did you do any of the following? |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| ENT |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose bleeds | $\square \square_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square 1$ | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect | Tests $\square 6$ | Nothing $\square 7$ | Other describe | Hospital <br> No of nights <br> $\overline{(0 \text { if no }}$ overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \hline \text { stop } \\ & \square_{2} \end{aligned}$ | change <br> $\square 3$ | Other describe |  |  |  |  |
| CNS |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Headaches | $\square_{1}$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square 4$ | Another med for side effect $\square$ | Tests $\square$ | Nothing $\square$ | Other describe | Hospital <br> No of nights <br> $\overline{(0 \text { if no }}$ overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue $\square$ $\square 1$ | stop <br> $\square 2$ | change $\square$ $\square 3$ | Other describe |  |  |  |  |
| Dizziness or lightheadness | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square 1$ | stop replace with another <br> $\square_{2}$ YES <br> $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect $\square$ | Tests <br> $\square 6$ | Nothing $\square_{7}$ $\square$ | Other describe | Hospital <br> No of nights <br> $\overline{\text { (0 if no }}$ overnight stay) |




| System Review Side-Effects | YES | Drug Name | Start Date | Duration | Bothered? | Tell GP | YES: Did your GP do any of the following for the side-effect? NO: Did you do any of the following? |  |  |  |  |  |  | Hospital |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Mental Health |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Do you feel nervous, restless, tense or do you have trouble relaxing? | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square$ | stop <br> replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square$ | Another med for side effect | Tests $\square 6$ | Nothing $\square 7$ | Other describe | Hospital $\square$ <br> No of nights <br> $\overline{(0 \text { if no }}$ overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \mathrm{\square}_{2}$ | continue | stop <br> $\square 2$ | change $\square$ | Other describe |  |  |  |  |
| Do you feel low/no motivation, loss of interest in usual activities | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue $\square 1$ | stop replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect | Tests $\square 6$ | Nothing $\square_{7}$ | Other describe | Hospital $\square$ <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | $\begin{aligned} & \text { stop } \\ & \square_{2} \end{aligned}$ | change $\square 3$ | Other describe |  |  |  |  |
| Do you have any difficulties in collecting your thoughts e.g. concentration difficulties | $\square 1$ |  |  |  | Not at all $\square_{1}$ <br> Very little $\square_{2}$ <br> A little $\square_{3}$ <br> Quite a lot $\square_{4}$ <br> Very much $\square_{5}$ | YES $\square_{1}$ | continue ㅁ | stop replace with another $\square_{2}$ YES $\square_{3} \mathrm{NO}$ | change (dose, quantity) $\square_{4}$ | Another med for side effect | Tests $\square 6$ | Nothing $\square 7$ | Other describe | Hospital $\square$ <br> No of nights <br> (0 if no overnight stay) |
|  |  |  |  |  |  | $\mathrm{NO} \square_{2}$ | continue | stop $\square_{2}$ | change $\square 3$ | Other describe |  |  |  |  |







Interviewer:
6. Ask patient: Have you experience any other symptoms or problems with your medication in the last 6 months? Write a description in this box or use this box to include further detail which you thinkis r rele

7. If a patient has reported side-effects above and has not told their GP, probe them gently to explain why

8. Do you take any over the counter medications on a regular basis? An over the counter medication is a drug that is sold without a prescription e.g. paracetamol, herbal medicine (milk thistle)
$\square$ NO

If yes, please name the medications
9. Is the patient a smoker?
10. Did the patient ever smoke?
Q. 8
$\square_{2} \mathrm{NO}$ ${ }_{2} \mathrm{NO}$
11. How long is it since they last smoked?


## Interview completed

Interview not fully completed (tick reason):

Patient tired- wished to stop
No time- patient called away/had to leave
Patient refused to continue $\square$

Other (explain)


# Appendix 8: Guidance notes for independent academic reviewers of ADEs regarding severity <br> <br> Definition of an ADE 

 <br> <br> Definition of an ADE}
'An event which results in unintended harm to the patient and is related to the care and/or services provided to the patient, rather than the patient's underlying medical conditions.' Examples include ACE inhibitors and cough, NSAIDs and dyspepsia, opioids and constipation

## Background

## Cohort ADE mesurement

Each patient's medical record and medication list (repeat and acute) was retrieved from their GP record. Medical records were also reviewed for any documented allergies to medications or ADEs. This information was then used as the basis of a patient interview regarding ADEs to prescribed medication in the previous six months. This interview could be completed either by telephone or in person. The initial question was as follows; 'In the last six months have you noticed any side effects, unwanted reactions or other problems with the medications you were taking'. Questions were then asked regarding 74 symptoms categorised according to physiological system. This interview was based on previous research and included patient self-report measures of ADEs, a generic symptom report measure and a side-effect rating scale. If during the interview the patient reported a specific symptom then this triggered further questions regarding whether the patient attributed the symptom to their medication, if so the name of the medication, the date (approximately) the symptom began, the duration of the symptom, the degree to which it bothered the patient and whether or not they had discussed the symptom with their GP. If they had discussed the symptom with their GP they were then asked what the GP had done (if anything) and whether or not they attended the out-patient department or were hospitalised as a result.

If patients' had in their GP record a documented ADE they were asked about it, at the end of the interview, if it had not already been mentioned. If the patient was unaware of the documented ADE, then this was added to their interview as a symptom and that the patient did not believe it to be caused by medication. Once interviews were completed patients'
self-reported ADEs were reviewed by two academic GPs who were blinded to the STOPP prescribing criteria. These reviewers were also given a copy of the patient's medical record and prescriptions and their attendances at secondary care. Reviewers were asked to rate the likelihood of the reported ADEs. A six point scale was provided as follows; 1: little or no confidence, 2 : slight to moderate confidence, 3 : $<50 \%$ confidence, 4 : $>50 \%$ confidence but a close call, 5 : strong confidence, 6 : virtually certain. The symptom was categorised as an ADE if the confidence level was $\geq 4$. These ADEs will now be classified according to their severity.

## Taxonomy for classification of ADE severity

Several taxonomies to classify ADE severity have been developed. The taxonomy used for the purposes of this study was chosen due to ease of reproducibility (i.e. clear definitions provided for each category) and relevance to clinical practice. This taxonomy has been used in several studies to assess severity of ADEs across different countries and healthcare settings. Each ADE is classified by 2 independent reviewers (one pharmacist and one GP) who rate the ADE according to severity. Classes of severity are as follows;

## 1. Mild ADE

Definition: Laboratory abnormality or symptom not requiring treatment.

Examples include; Non urticarial rash, Fall without fracture, Over sedation, Bruising, Constipation

## 2. Moderate ADE

Laboratory abnormality or symptom requiring treatment with GP/hospital outpatients or emergency admission to hospital or ADEs resulting in nonpermanent disability

Examples include; Falls with fracture, Delirium, Haemorrhage requiring transfusion, no hypotension

## 3. Severe ADE

Definition: Laboratory abnormality or symptom that was life-threatening or resulted in permanent disability or death.

Examples include; Haemorrhage with hypotension, Hypoglycaemic encephalopathy, Acute renal failure, Liver failure

## Appendix 9: Prevalence of individual STOPP criteria ( $\mathrm{n}=51$ ) at baseline and

## follow-up ( $\mathrm{n}=605$ )

| STOPP criteria description by clinical domain | Baseline <br> study <br> participants $\mathrm{N}=904$ | Proportion \% \$ | Follow-up <br> study <br> participants $N=605$ | Proportion \% \$ |
| :---: | :---: | :---: | :---: | :---: |
| Cardiovascular |  |  |  |  |
| Digoxin > 125 $\mu \mathrm{g} /$ day (increased risk of toxicity) | 0 | 0 | 0 | 0 |
| Loop diuretic as first line monotherapy for hypertension | 10 | 2.6 | 10 | 1.9 |
| Thiazide diuretic with gout (medication as a proxy) (exacerbate gout) | 4 | 13.3 | 2 | 6.3 |
| Beta-blocker with COPD (medical condition) | 28 | 27.7 | 20 | 23.3 |
| Beta-blocker with verapamil (risk of symptomatic heart block) | 1 | <1 | 0 | 0 |
| Calcium channel blockers with chronic constipation§ (patient report) | 63 | 30 | 63 | 38.2 |
| Aspirin and warfarin without histamine H2 receptor antagonist (except cimetidine) or PPI: (high risk of gastrointestinal bleeding) | 23 | 6.2 | 19 | 76 |
| Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence of efficacy) | 1 | <1 | 0 | 0 |
| Aspirin with a past history of peptic ulcer disease without histamine H 2 receptor antagonist or PPI (risk of bleeding) | 58 | 43.6 | 55 | 41.2 |


| STOPP criteria description by clinical domain | Baseline study participants $N=904$ | Proportion \% \$ | Follow-up study participants $\mathrm{N}=605$ | Proportion \% \$ |
| :---: | :---: | :---: | :---: | :---: |
| Aspirin $\mathbf{> 1 5 0} \mathbf{m g} /$ day (increased bleeding risk) | 10 | 2.1 | 3 | 0.9 |
| Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event (not indicated) | 0 | 0 | 1 | <1 |
| Warfarin for first, uncomplicated deep vein thrombosis for longer than 6 months duration (no proven added benefit) | 0 | 0 | 0 | 0 |
| Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration (no proven benefit) | 1 | 8.3 | 1 | 8.3 |
| Central nervous system |  |  |  |  |
| TCA with dementia (medical condition) | 1 | 10 | 0 | 0 |
| TCA with glaucoma (medical condition) | 1 | 3.7 | 0 | 0 |
| TCA with cardiac conductive abnormalities (pro-arrhythmic effects) | 3 | 3.7 | 0 | 0 |
| TCA with constipation (patient report) | 16 | 7.6 | 15 | 9.1 |
| TCA with constipation (laxative medication as a proxy) (likely to worsen constipation) | 10 | 7.4 | 10 | 33.3 |
| TCA and opiate or calcium channel blockers (risk of severe constipation) | 10 | 56 | 17 | 56.7 |
| TCA with prostatism or prior history of urinary retention (risk of urinary retention) | 1 | 25 | 1 | 1.7 |


|  | Baseline |  | Follow-up |  |
| :--- | :--- | :--- | :--- | :--- |
| STOPP criteria description by clinical | study Proportion study | Proportion \% |  |  |
| domain | participants | $\% \$$ | participants | \$ |
|  | $\mathrm{N}=904$ |  | $\mathrm{~N}=605$ |  |

Long-term (i.e. > 1 month), long-acting benzodiazepines (risk of prolonged sedation, confusion, impaired balance, falls)

Long-term (i.e. > 1 month) neuroleptics (risk of confusion, hypotension, 3 extrapyramidal side- effects, falls)

Long-term (i.e. > 1 month) neuroleptics with Parkinsonism (medical condition)

Phenothiazines with epilepsy (medical condition)

Anticholinergics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)

Prolonged use (i.e. > 1 week) of firstgeneration antihistamines (risk of sedation and anti-cholinergic sideeffects)

Gastrointestinal system

Dipehoxylate, loperamide or codeine phosphate for treatment of diarrheal (medical condition) II

Dipehoxylate, loperamide or codeine phosphate for treatment of diarrhoea (patient-report) (risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognized gastroenteritis) II

| STOPP criteria description by clinical domain | Baseline study participants $\mathrm{N}=904$ | Proportion \% \$ | Follow-up study participants $N=605$ | Proportion \% \$ |
| :---: | :---: | :---: | :---: | :---: |
| Prochlorperazine/metoclopramide with Parkinsonism (medical condition) | 1 | 9.1 | 0 | 0 |
| PPI for peptic ulcer disease at maximum therapeutic dosage for $>8$ weeks (dose reduction or earlier discontinuation indicated)* | 146 | 41.7 | 127 | 52.5 |
| Anticholinergic antispasmodic drugs with chronic constipation (patient report) | 5 | 2.4 | 6 | 3.6 |
| Anticholinergic antispasmodic drugs with chronic constipation (laxative medication as a proxy) (risk of exacerbation of constipation) § | 1 | <1 | 4 | <1 |
| Respiratory system |  |  |  |  |
| Theophylline with COPD (medical condition) (risk of adverse effects due to narrow therapeutic index) | 4 | 4 | 2 | 2.4 |
| Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate/severe COPD (medical condition) | 1 | 5 | 1 | 1.2 |
| Nebulised ipratropium with glaucoma (medical condition) | 0 | 0 | 0 | 0 |
| Musculoskeletal system |  |  |  |  |
| NSAID: with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 receptor, PPI or misoprostol (risk of peptic ulcer relapse) | 26 | 24.1 | 10 | 14.7 |


| STOPP criteria description by clinical domain | Baseline study participants $\mathrm{N}=904$ | Proportion \% \$ | Follow-up study participants $N=605$ | Proportion \% \$ |
| :---: | :---: | :---: | :---: | :---: |
| NSAID with heart failure (risk of exacerbation of heart failure) | 5 | 17.2 | 1 | 3.45 |
| Long-term use of NSAID (i.e. > 3 months) for pain relief (simple analgesics preferable) | 62 | 24.9 | 27 | 22.5 |
| Warfarin and NSAID (risk of gastrointestinal bleeding) | 6 | 7 | 1 | 1.1 |
| NSAID with chronic renal failure (risk of deterioration in renal function) | 1 | 8.3 | 10 | 13.7 |
| Long-term corticosteroids (> $\mathbf{3}$ months) as monotherapy for rheumatoid arthritis or osteoarthritis (risk of major systemic corticosteroid side-effects) | 2 | 1.2 | 2 | 0.9 |
| Urogenital system |  |  |  |  |
| Antimuscarinic drugs with dementia (medical condition) | 2 | 20 | 1 | 4.6 |
| Antimuscarinic drugs with chronic glaucoma (> 3 months) (medical condition) | 2 | 7.4 | 1 | 4.2 |
| Antimuscarinic drugs with chronic constipation§ (patient report) § | 13 | 6.2 | 14 | 8.5 |
| Antimuscarinic drugs with chronic constipation (laxative medication as a proxy) (risk of exacerbation of constipation) § | 9 | 6.6 | 7 | 6.3 |
| Antimuscarinic drugs with chronic prostatism (risk of urinary retention) | 0 | 0 | 6 | 10 |
| Endocrine system |  |  |  |  |


| STOPP criteria description by clinical domain | Baseline study participants $\mathrm{N}=904$ | Proportion \% \$ | Follow-up study participants $\mathrm{N}=605$ | Proportion \% \$ |
| :---: | :---: | :---: | :---: | :---: |
| Glibenclamide or chlorpropamide with type 2 diabetes mellitus (medical condition) (risk of prolonged hypoglycemia) | 0 | 0 | 0 | 0 |
| Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence) | 1 | 5.26 | 0 | 0 |
| Oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer) | 0 | 0 | 0 | 0 |
| Drugs that adversely affect those prone to falls (at least 1 fall in the past 3 months) |  |  |  |  |
| Benzodiazepines (sedative, may cause reduced sensorium, impair balance) | 12 | 8.6 | 6 | 10 |
| Neuroleptic drugs (may cause gait dyspraxia, parkinsonism) | 7 | 5 | 5 | 8.3 |
| First generation antihistamines (sedative, may impair sensorium) | 1 | 0.7 | 2 | 3.3 |
| Analgesic drugs |  |  |  |  |
| Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives (risk of severe constipation)§ | 43 | 20.5 | 42 | 25 |
| Duplicate drug classes** |  |  |  |  |
| Two concurrent opiates | 13 | 7.7 | 6 | 3.9 |
| Two concurrent NSAIDs | 15 | 6 | 2 | 1.7 |
| Two concurrent SSRIs | 0 | 0 | 0 | 0 |


| STOPP criteria description by clinical | Baseline <br> study <br> participants <br> $\mathbf{N}=904$ | Proportion <br> $\%$ \$ | Follow-up <br> study <br> participants <br> $\mathbf{N}=605$ | Proportion \% <br> $\$$ |
| :--- | :--- | :--- | :--- | :--- |
| Two concurrent antidepressants | 2 | 8.3 | 1 | 1.4 |
| Two concurrent loop diuretics | 0 | 0 | 0 | 0 |
| Two concurrent ACE inhibitors+ | 10 | 3 | 3 | 1.2 |
| All duplicates** (optimisation of <br> monotherapy within a single drug class) | 39 | NA | 12 | NA |

Notes: \$ Proportionate prescribing per indication is the prevalence of the STOPP criteria as a proportion of the overall disease or drug prevalence e.g. thiazide diuretic with gout as a proportion of patients with gout. Medical conditions were recorded from the GP medical record. Abbreviations: COPD= Chronic Obstructive Pulmonary Disease, PPI=proton pump inhibitor, TCA=tricyclic antidepressant, NSAID=non-steroidal anti-inflammatory drug, SSRI=selective serotonin re- uptake inhibitor, ACE inhibitors=angiotensin converting enzyme inhibitors. § Prevalence was assessed using patient report of chronic constipation and by dispensed medication (laxatives) as a proxy for diagnosis. Il Prevalence was assessed using patient report of diarrhoea and by medical condition per GP record. *PPI at maximum therapeutic dose $=40 \mathrm{mg}$ daily omeprazole, pantoprazole and esomeprazole, 30 mg daily lansoprazole and 20 mg daily rabeprazole. ${ }^{* *}$ Adjusted for those receiving more than one duplicate prescription.


| Organ System or Therapeutic Category or Drug | Baseline ( $\mathrm{n}=605$ ) |  | Follow-up ( $\mathrm{n}=605$ ) |  |
| :---: | :---: | :---: | :---: | :---: |
|  | N | Proportion (\%) | N | Proportion (\%) |
| 9. Spironolactone $>25$ $\mathrm{mg} / \mathrm{d}$ | 1 | 0.2 | 1 | 0.2 |
| 10. Central nervous system |  |  |  |  |
| Tertiary TCAs, alone or in combination e.g. Amitriptyline | 17 | 2.9 | 25 | 4.7 |
| 11. Antipsychotics, first (conventional) and second (atypical) generation | 31 | 5.2 | 29 | 5.0 |
| 12. Barbiturates e.g. Phenobarbital | 1 | 0.2 | 1 | 0.2 |
| 13. Benzodiazepines |  |  |  |  |
| Short and intermediate acting: e.g. Alprazolam Lorazepam | 41 | 6.8 | 36 | 6.8 |
| Long acting: e.g. <br> Clonazepam Diazepam Flurazepam |  |  |  |  |
| 14. Nonbenzodiazepine hypnotics e.g. Zolpidem | 8 | 1.3 | 8 | 1.5 |
| Endocrine |  |  |  |  |
| 15. Oestrogens with or without progestins | 5 | 0.8 | 5 | 0.9 |
| 16. Sulfonylureas, long duration e.g. Chlorpropamide, Glyburide | 0 | 0 | 0 | 0 |
| G astrointestinal |  |  |  |  |
| 17. Metoclopramide | 3 | 0.5 | 3 | 0.5 |
| Pain |  |  |  |  |


| Organ System or <br> Therapeutic Category <br> or Drug | Baseline (n=605) | Follow-up (n=605) | Proportion (\%) |  |
| :--- | :--- | :--- | :--- | :--- |
| 18. Meperidine | N | 0.2 | $\mathbf{N}$ | 0 |
| 19. Non-COX-selective <br> NSAIDs, oral | 30 | 5.0 | 31 | 5.9 |
| 20. Indomethacin and <br> Ketorolac, includes <br> parenteral | 0 | 0 | 2 | 0.4 |

CNS = central nervous system; $\mathrm{COX}=$ cyclooxygenase $; \mathrm{CrCl}=$ creatinine clearance

Appendix 10-2: 2012 Beers Criteria due to drug-disease or drug-syndrome interactions
that may exacerbate the disease or syndrome ( $n=13$ )

| Drugs to avoid if Disease or Syndrome <br> present | Baseline <br> $(n=904)$ | Proportion (\%) | Follow-up <br> $(n=605)$ | Proportion (\%) |
| :--- | :--- | :--- | :--- | :--- |

## Cardiovascular

## 1. Heart failure

NSAIDs and COX-2 inhibitors, Nondihydropyridine CCBs (avoid only

1
0.2

2
0.4
for systolic heart failure), Diltiazem,
Verapamil, Pioglitazone, rosiglitazone

## 2. Syncope

ACEIs, Peripheral alpha blockers,
Doxazosin, Prazosin, Terazosin, Tertiary
TCAs, Chlorpromazine, olanzapine
3. Chronic seizures or epilepsy

Chlorpromazine, Clozapine, Maprotiline,
Olanzapine, Tramadol, Anticholinergics,
Benzodiazepines, Chlorpromazine,
Corticosteroids, $\mathrm{H}_{2}$-receptor antagonist, Meperidine, Sedative hypnotics

## 4. Dementia and cognitive impairment

Anticholinergics Benzodiazepines $\mathrm{H}_{2}{ }^{-}$
4
0.7

3
receptor antagonists, Zolpidem, Antipsychotics, chronic/as-needed use
5. History of falls or fractures

Anticonvulsants, Antipsychotics, Benzodiazepines, Nonbenzodiazepine hypnotics, Eszopiclone, Zaleplon, Zolpidem, TCAs, SSRIs

## 6. Insomnia

Oral decongestants, Pseudoephedrine, Phenylephrine, Stimulants,

## All antipsychotics, Antiemetics,

Metoclopramide, Prochlorperazine, Promethazine

## Gastrointestinal

## 8. Chronic constipation

Oral antimuscarinics for urinary incontinence, Fesoterodine, Oxybutynin, Solifenacin, Tolterodine, Trospium, Nondihydropyridine CCB, Diltiazem, Verapamil, First-generation antihistamines, Chlorpheniramine Dexchlorpheniramine (various) Diphenhydramine Hydroxyzine Promethazine, Anticholinergics and antispasmodics Antipsychotics Belladonna alkaloids Hyoscyamine Scopolamine, Tertiary TCAs
9. History of gastric or duodenal ulcers

Aspirin (>325 mg/d) Non-COX-2
3
selective NSAIDs
10. Chronic kidney disease Stages IV and V

NSAIDs, Triamterene (alone or in combination)
11. Lower urinary tract symptoms, benign prostatic hyperplasia

Inhaled anticholinergic agents. Strongly anticholinergic drugs, except
antimuscarinics for urinary incontinence
12. Stress or mixed urinary incontinence

0
1
0.2

Alpha blockers Doxazosin Prazosin Terazosin

Appendix 11: Unadjusted and adjusted analysis for Beers 2012 PIP exposure and outcome of ADE ( $\mathrm{n}=605$ )

Appendix 11-1: Number and percentage of patients in a multilevel logistic regression model with unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cls}, \mathrm{p}$-value) for patients with $\geq 1$ ADE at follow-up ${ }^{\# \# \prime}$ by exposure to Beers 2012 PIP and patient level confounding variables measured at baseline ( $\mathrm{n}=605$ )

| Patient characteristic s | Total (N) | N (\%) or median (IQR) with $\geq 1$ ADE | Unadjusted Odds Ratio (OR) ( $95 \% \mathrm{Cl}$ ), p value | Adjusted OR (95\% CI), p value |
| :---: | :---: | :---: | :---: | :---: |
| Primary outcome: PIP at baseline |  |  |  |  |
| 0 | 450 | 322 (73) | 1 |  |
| 1 | 96 | 75 (17) | 1.77 (1.01, 3.10), p=0.05 | 1.21 (0.63, 2.31), $\mathrm{p}=0.57$ |
| $\geq 2$ | 59 | 47 (11) | 1.71 (0.84, 3.49), $\mathrm{p}=0.14$ | 0.73 (0.33, 1.60), p=0.43 |

Adjusted for confounding variables
Median (IQR)

| Age | 605 | $76(73,80)$ | $1.05(1.01,1.10), \mathrm{p}=0.03$ | $1.02(0.971 .07), \mathrm{p}=0.37$ |
| :--- | :--- | :--- | :--- | :--- |
| Deprivation | 605 | $1.36(-0.64,2.88)$ | $0.92(0.84,1.01), \mathrm{p}=0.07$ | $0.91(0.82,1.01), \mathrm{p}=0.07$ |
| Number of <br> drug classes | 605 | $6(4,8)$ | $1.33(1.23,1.44)$, <br> $\mathrm{p}<0.001$ | $1.30(1.18,1.43), \mathrm{p}<0.001$ |
| Gender |  | $\mathrm{N}(\%)$ | 1 | 1 |
| Male | 286 | $207(47)$ | $1.12(0.76,1.65), \mathrm{p}=0.56$ | $0.96(0.61,1.51), \mathrm{p}=0.86$ |
| Female | 319 | $237(53)$ | 1 | 1 |
| Social Class |  |  | $0.86(0.53,1.40), \mathrm{p}=0.55$ | $0.96(0.55,1.67), \mathrm{p}=0.89$ |
| Unskilled | 132 | $99(22)$ | 1 | 1 |

Comorbidity: Charlson weights

| 0 | 252 | 159 (36) | 1 | 1 |
| :---: | :---: | :---: | :---: | :---: |
| $\geq 1$ | 353 | 285 (64) | $\begin{aligned} & 2.77(1.86,4.15), \\ & p<0.001 \end{aligned}$ | 1.92 (1.21, 3.05), p=0.006 |
| Medication Adherence |  |  |  |  |
| MPR < 50\% | 49 | 33 (7) | 1 | 1 |
| $\begin{aligned} & \text { MPR } \leq 50 \%<80 \\ & \% \end{aligned}$ | 136 | 92 (21) | 1.03 (0.47, 2.17), p=0.94 | 0.49 (0.21, 1.13), p=0.10 |
| MPR $\geq 80 \%$ | 391 | 305 (69) | $\begin{aligned} & 1.57(0.79,3.12), \\ & \mathrm{p}=0.20 \end{aligned}$ | 0.79 (0.36, 1.73), p=0.56 |

\#\# ADE measured by patient interview and review of GP medical record. ${ }^{\$}$ MPR data is missing $n=29$

Appendix 11-2: Multilevel Poisson regression model with unadjusted and adjusted incidence rate ratios ( $95 \%$ Cls, p-value) for number of ADEs by exposure to Beers 2012 PIP at baseline\# and patient level confounding variables at baseline ( $n=605$ )

| Patient characteristics | Unadjusted Incidence Rate Ratio | Adjusted IRR |
| :---: | :---: | :---: |
|  | (IRR) $(95 \%$ CI), p-value | (95\% CI), p-value |

## Primary outcome: PIP at baseline

| 0 | 1 |  |
| :--- | :--- | :--- |
| 1 | $1.23(0.97,1.56), p=0.09$ | $0.93(0.75,1.15), p=0.52$ |
| $\geq 2$ | $1.59(1.21,2.10), p=0.001$ | $1.00(0.78,1.29), p=0.98$ |

## Adjusted for confounding variables

Age at baseline $\quad 1.02(1.00,1.04), \mathrm{p}=0.05 \quad 1.00(0.99,1.02), \mathrm{p}=0.69$

## Gender

| Male | 1 | 1 |
| :--- | :--- | :--- |
| Female | $1.11(0.93,1.32), \mathrm{p}=0.25$ | $1.01(0.86,1.19), \mathrm{p}=0.88$ |
| Social Class | 1 | 1 |
| Unskilled <br> Skilled | $0.92(0.74,1.14), \mathrm{p}=0.46$ | $1.00(0.82,1.21) \mathrm{p}=0.98$ |
| Deprivation | $0.96(0.92,1.00), \mathrm{p}=0.04$ | $0.96(0.92,0.99), \mathrm{p}=0.02$ |
| Education | 1 | 1 |
| Baseline |  |  |
| Upper and post- <br> secondary | $0.90(0.74,1.09), \mathrm{p}=0.27$ | $0.97(0.81,1.16), \mathrm{p}=0.70$ |

## Co-morbidity: Charlson weights

| 0 | 1 | 1 |
| :--- | :--- | :--- |
| $\geq 1$ | $1.61(1.35,1.93), \mathrm{p}<0.001$ | $1.21(1.02,1.44), \mathrm{p}=0.03$ |
| Number of drug classes | $1.16(1.13,1.18), \mathrm{p}<0.001$ | $1.15(1.12,1.18), \mathrm{p}=<0.001$ |
| Medication adherence |  |  |
| MPR $<50 \%$ | 1 | $0.77(0.55,1.06), \mathrm{p}=0.11$ |
| MPR $\leq 50 \%<80 \%$ | $1.06(0.74,1.50), \mathrm{p}=0.84$ | $0.93(0.69,1.26), \mathrm{p}=0.65$ |

[^9]
## Appendix 12: Unadjusted and adjusted analysis for Beers 2012 PIP exposure and outcome of HRQOL ( $n=664$ )

Appendix 12-1: Multilevel linear regression model with unadjusted and adjusted regression coefficients (95\% Cls, p-value) for EQ-5D score\#\# at follow-up by exposure to Beers 2012 PIP\# and patient level confounding variables at baseline ( $\mathrm{n}=662$ )

| Patient <br> characteristics | Unadjusted coefficient (95\% Cl, p <br> value) | Adjusted coefficient (95\% Cl, p <br> value) |
| :--- | :---: | :---: |

Primary outcome: Beers PIP at baseline

## 0 0

1
$\geq 2 \quad-0.11(-0.18,-0.06), \mathrm{p}<0.001$

## Adjusted for confounding variables

| Age | $-0.01(-0.13,-0.006), p<0.001$ | $-0.002(-0.006,-0.002), p=0.26$ |
| :--- | :---: | :---: |
| Gender |  |  |
| Male |  |  |

secondary
0.03 (-0.004, 0.07), p=0.08

Comorbidity: Charlson weights at baseline

| 0 | 0 | 0 |
| :---: | :---: | :---: |
| $\geq 1$ | -0.07 (-0.11, -0.04), p<0.001 | -0.02 (-0.06, 0.01), p=0.17 |
| Number of drug classes | -0.02 (-0.03, -0.02), p<0.001 | -0.01 (-0.02, 0.007), p<0.001 |
| Medication adherence at baseline ${ }^{\text {s }}$ |  |  |
| MPR < $50 \%$ | 0 | 0 |
| MPR $\leq 50 \%<80 \%$ | 0.04 (-0.04, 0.11), p=0.34 | 0.07 (0.006, 0.14), p=0.03 |
| MPR $\geq 80 \%$ | 0.19 (-0.05, 0.09), p=0.59 | 0.07 (0.008, 0.13), p=0.03 |
| Vulnerable at baseline |  |  |
| No | 0 | 0 |
| Yes | -0.22 (-0.25, -0.19), p<0.001 | -0.17 (-0.21, -0.13), p<0.001 |
| Lubben's social support at baseline |  |  |
| Low | 0 | 0 |
| Moderate | 0.06 (-0.02, 0.14), p=0.15 | 0.72 (0.0007, 0.14), p=0.05 |


| Patient <br> characteristics | Unadjusted coefficient (95\% Cl, p <br> value) | Adjusted coefficient (95\% Cl, p <br> value) |
| :--- | :---: | :---: |
| High | $0.08(0.007,0.16), \mathrm{p}=0.03$ | $0.08(0.02,0.15), \mathrm{p}=0.01$ |

## Screened positive for depression as per HADS

No
0
0
Yes $\quad-0.22(-0.28,-0.15), \mathrm{p}<0.001 \quad-0.10(-0.16,-0.04), \mathrm{p}=0.002$

[^10]Appendix 12-2: Multilevel linear regression model with unadjusted and adjusted regression coefficients ( $95 \%$ Cls, p-value) for EQ-5D VAS\# at follow-up by exposure to Beers PIP and patient level confounding variables at baseline ( $n=662$ )

| Patient characteristics | Unadjusted coefficient (95\% CI), $p$-value | Adjusted estimated coefficient (95\% CI), p-value |
| :---: | :---: | :---: |
| Primary outcome: Beers PIP at baseline |  |  |
| 0 | 0 | 0 |
| 1 | -2.87 (-6.47, -0.74), p=0.20 | 1.08 (-2.41, 4.57), $\mathrm{p}=0.55$ |
| $\geq 2$ | -4.87 (-9.41, -0.33), $\mathrm{p}=0.04$ | 0.70 (-3.74, 5.15), $\mathrm{p}=0.76$ |
| Adjusted for confounding variables |  |  |
| Age | -0.50 (-0.77, -0.22), $\mathrm{p}<0.001$ | 0.03 (-0.25, 0.31), p=0.84 |
| Gender |  |  |
| Male | 0 | 0 |
| Female | $-2.66(-5.32,-0.01), \mathrm{p}=0.05$ | -1.94 (-4.58, 0.70), p=0.15 |
| Social class |  |  |
| Unskilled | 0 | 0 |
| Skilled | -1.98 (-5.21, 1.25), p=0.23 | -3.63 (-6.77, -0.49), p=0.02 |
| Deprivation | -0.51 (-1.08, 0.05), p=0.08 | -0.42 (-0.95, 0.12), p=0.13 |
| Education |  |  |
| Basic | 0 | 0 |
| Upper/post-secondary | 0.26 (-2.56, 3.08), $\mathrm{p}=0.86$ | -1.59 (-4.41, 1.22), p=0.27 |
| Comorbidity: Charlson weights at baseline |  |  |
| 0 | 0 | 0 |
| $\geq 1$ | -5.47 (-8.13, -2.82), $\mathrm{p}<0.001$ | -2.27 (-4.99, 0.46), p=0.10 |
| Number of drug classes | -1.59 (-1.97, -1.21), p<0.001 | -1.05 (-1.51, -0.59), $\mathrm{p}<0.001$ |
| Medication adherence at baseline\$ |  |  |
| MPR<50\% | 0 | 0 |
| MPR >50\%<80\% | -2.00 (-7.53, 3.53), p=0.48 | 0.41 (-4.80, 5.63), p=0.88 |
| MPR $\geq 80 \%$ | -3.80 (-8.83, 1.25), p=0.14 | -0.85 (-5.66, 3.97), p=0.73 |
| Vulnerable at baseline (VES $\geq 3$ ) |  |  |
| No | 0 | 0 |
| Yes | -12.88 (-15.53, -10.23), p<0.001 | -10.55 (-13.73, -7.37), p<0.001 |
| Lubben's social support at baseline |  |  |
| Low | 0 | 0 |
| Moderate | 2.72 (-3.32, 8.75), $\mathrm{p}=0.38$ | 3.71 (-2.01, 9.42), p=0.20 |
| High | 5.16 (-0.45, 10.76), p=0.07 | 6.04 (0.75, 11.33), p=0.03 |
| HADS screened positive for depression at baseline |  |  |
| No | 0 | 0 |
| Yes | -11.79 (-16.77, -6.80), p<0.001 | -3.91 (-8.89, 1.07), p=0.12 |

## Appendix 13: Unadjusted and adjusted analyses for STOPP and outcome of emergency hospital attendance $(\mathrm{n}=888)$

Appendix 13-1 Multilevel logistic regression model with unadjusted and adjusted odds ratios ( $95 \%$ Cls, p-value) for patients with $\geq 1$ A\&E visit at follow-up ${ }^{\# \#}$ by exposure to PIP and patient level confounding variables measured at baseline ( $\mathrm{n}=888$ )

| Patient characteristics | Total patients <br> (N) | $\geq 1$ A\&E visit | Unadjusted Odds Ratio (OR) ( $95 \% \mathrm{Cl}$ ), p value | Adjusted OR <br> (95\% CI), p-value |
| :---: | :---: | :---: | :---: | :---: |
| Primary outcome: PIP at baseline |  | Median (IQR) |  |  |
| 0 | 517 | 77 (46) | 1 | 1 |
| 1 | 211 | 52 (31) | 1.88 (01.26, 2.80), $\mathrm{p}=0.002$ | 1.67 (1.08, 2.56), $\mathrm{p}=0.02$ |
| $\geq 2$ | 160 | 40 (24) | 1.87 (1.20, 2.89), p=0.005 | 1.56 (0.92, 2.65),p=0.10 |
| Age | 888 | $77(73,82)$ | 1.01 (0.98,1.04), $\mathrm{p}=0.42$ | 1.00 (0.96 1.04), p=0.95 |
| Deprivation | 888 | $1.5(-0.3,3.2)$ | 1.01 (0.94, 1.09), $\mathrm{p}=0.62$ | 1.03 (0.95, 1.12), p=0.41 |
| Drug classes | 888 | $6(4,9)$ | 1.07 (1.02, 1.12), $\mathrm{p}=0.004$ | 1.02 (0.96, 1.09), p=0.46 |
| Gender |  | N(\%) |  |  |
| Male | 411 | 82 (49) | 1 | 1 |
| Female | 477 | 87 (51) | 0.87 (0.62, 1.22), p=0.42 | 0.84 (0.58, 1.23), p=0.38 |
| Social Class |  |  |  |  |
| Unskilled | 214 | 41 (24) | 1 | 1 |
| Skilled | 674 | 128 (76) | 1.00 (0.67, 1.50), p=0.97 | 0.91 (0.60, 1.40), p=0.69 |
| Co-morbidity: Baseline Charlson weights |  |  |  |  |
| 0 | 409 | 61 (36) | 1 | 1 |
| $\geq 1$ | 479 | 108 (64) | 1.66 (1.17, 2.35), p<0.004 | 1.25 (0.84, 1.87), p=0.27 |
| Medication adherence at baseline ${ }^{\text {s }}$ |  |  |  |  |
| MPR < 50\% | 71 | 17 (10 | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 187 | 29 (17) | 0.56 (0.28, 1.11), p=0.10 | 0.45 (0.22, 0.91), p=0.03 |
| MPR $\geq 80 \%$ | 464 | 117 (69) | 0.79 (0.44, 1.43), p=0.44 | 0.63 (0.33, 1.18),p=0.15 |

Vulnerable at baseline (VES-13 $\geq 3$ )

| No | 544 | $76(45)$ | 1 | 1 |
| :--- | :--- | :--- | :---: | :---: |
| Yes | 344 | $93(55)$ | $1.37(0.97,1.94), p=0.06$ | $1.16(0.76,1.78) p<0.50$ |

A\&E visit or inpatient admission at baseline*

| Yes | 794 | $29(17)$ | 1 | 1 |
| :--- | :--- | :--- | :---: | :---: |
| No | 93 | $140(83)$ | $2.10(1.29,3.40), p=0.003$ | $1.78(1.07,2.97), p=0.03$ |

${ }^{\text {\#\# }}$ ADE report was measured by patient interview and review of GP medical record. ${ }^{\text {§ MPR data is }}$ missing for 37 participants.* A\&E visit/inpatient data missing for one participant.

Appendix 13-2: Number and percentage of patients and unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cl}, \mathrm{p}$ value) for numbers of emergency admissions* during two-year follow-up by exposure to PIP as defined by STOPP at baseline and confounding variables ( $\mathrm{n}=888$ )

| Patient <br> characteristic | Total patients <br> (N) | Incidence Rate Ratio (IRR) <br> $(95 \% \mathrm{Cl}), \mathrm{p}$ value | Adjusted IRR (95\% CI), p- <br> value |
| :--- | :--- | :--- | :--- |

Primary outcome: PIP at baseline

| 0 | 517 | 1 |  |
| :--- | :--- | :--- | :--- |
| 1 | 211 | $1.25(0.94,1.66), p=0.12$ | $0.96(0.73,1.26), p=0.78$ |
| $\geq 2$ | 160 | $1.78(1.33,2.38), p<0.001$ | $0.96(0.70,1.32), p=0.82$ |

Adjusted for confounding variables

| Age | 888 | 1.06 (1.04,1.08), $\mathrm{p}<0.001$ | 1.03 (1.01, 1.05), p=0.007 |
| :---: | :---: | :---: | :---: |
| Deprivation | 888 | 1.04 (0.99, 1.09), p=0.09 | 1.05 (1.00, 1.10), p=0.05 |
| Number of drug classes | 888 | 1.13 (1.10, 1.16), p<0.001 | 1.09 (1.05, 1.13), p<0.001 |
| Gender |  |  |  |
| Male | 411 | 1 |  |
| Female | 477 | 0.95 (0.75, 1.20), p=0.67 | 0.83 (0.66, 1.05), p=0.12 |
| Social Class |  |  |  |
| Unskilled | 214 | 1 |  |
| Skilled | 674 | 0.91 (0.69, 1.20), p=0.52 | 0.91 (0.70, 1.18), p=0.48 |
| Education^ |  |  |  |
| Basic | 542 | 1 | 1 |
| Upper/postsecondary | 340 | 0.89 (0.69, 1.14), p=0.36 | 1.05 (0.82, 1.34), p=0.70 |

Co-morbidity: Baseline Charlson weights

| 0 | 409 | 1 |  |
| :--- | :--- | :--- | :--- |
| $\geq 1$ | 479 | $2.04(1.57,2.64), \mathrm{p}<0.001$ | $1.45(1.12,1.88), \mathrm{p}=0.005$ |

Adherence at baselines

| MPR $<50 \%$ | 71 | 1 |  |
| :--- | :--- | :--- | :--- |
| $M P R \leq 50 \%<80 \%$ | 187 | $0.71(0.45,1.10), p=0.13$ | $0.53(0.35,0.80), p=0.003$ |
| $M P R \geq 80 \%$ | 464 | $0.75(0.51,1.11), p=0.16$ | $0.52(0.36,0.75), p<0.001$ |

Vulnerable at baseline (Vulnerable Elder's scale $\geq 3$ )

| No | 544 | 1 |  |
| :--- | :--- | :--- | :--- |
| Yes | 344 | $2.01(1.59,2.54), p<0.001$ | $1.20(0.92,1.56), p=0.18$ |

Number of A\&E visits or emergency admissions at baseline**

| No | 794 | 1 |  |
| :--- | :--- | :--- | :--- |
| Yes | 93 | $1.91(1.52,2.41), p<0.001$ | $1.39(1.14,1.70), p=0.001$ |
| A\&E visits were measured by review of the participant's GP medical record. ${ }^{5}$ MPR data is missing for |  |  |  |
| $n=37 .{ }^{\wedge}$ Education data is missing $n=6 .{ }^{* *}$ A\&E visit/inpatient data missing $n=1$ |  |  |  |

## Appendix 14: Number and percentage of patients and odds ratios (95\% CI, p

 value) with $\geq 1$ A\&E visit* by exposure to Beers PIP and confounding variables ( $\mathrm{n}=806$ )| Patient characteristic | Total patients (N) | N (\%) or median (IQR) with $\geq 1$ A\&E visits | Unadjusted Odds Ratio (OR) ( $95 \% \mathrm{Cl}$ ), p value | Adjusted OR (95\% CI), $p$-value |
| :---: | :---: | :---: | :---: | :---: |
| Primary outcome: PIP at baseline |  |  |  |  |
| 0 | 577 | 99 (66) | 1 | 1 |
| 1 | 138 | 28 (18) | 1.21 (0.75, 1.93), p=0.44 | 1.07 (0.65, 1.77), $\mathrm{p}=0.79$ |
| $\geq 2$ | 91 | 25 (16) | 1.78 (1.06, 2.96), p=0.03 | 1.54 (0.88, 2.71), p=0.13 |
| Adjusted for confounding variables |  | Median (IQR) |  |  |
| Age | 806 | $73(73,82)$ | 1.03 (0.99,1.06), p= 0.11 | 1.01 (0.97, 1.05), p=0.53 |
| Deprivation | 806 | $\begin{aligned} & 1.6(-0.5, \\ & 3.2) \end{aligned}$ | 1.02 (0.94, 1.10), p=0.63 | 1.03 (0.94, 1.12), p=0.54 |
| Number of baseline drugs | 806 | $6(4,9)$ | 1.08 (1.03, 1.14), $\mathrm{p}=0.002$ | 1.05 (0.99, 1.12), p=0.12 |
| Gender |  | $N(\%)$ |  |  |
| Male | 372 | 72 (47) | 1 | 1 |
| Female | 434 | 81 (53) | 0.93 (0.65, 1.33), p=0.70 | 0.84 (0.57, 1.25), $\mathrm{p}=0.40$ |

Social Class

| Unskilled | 197 | $39(25)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| Skilled | 609 | $114(75)$ | $0.94(0.62,1.43), \mathrm{p}=0.79$ | $0.81(0.52,1.27), \mathrm{p}=0.36$ |
| Education^ | 493 | $91(59)$ | 1 | 1 |
| Basic | $62(41)$ | $1.17(0.80,1.70), \mathrm{p}=0.42$ | $1.34(0.88,2.06), \mathrm{p}=0.18$ |  |

Comorbidity: Charlson weights

| 0 | 330 | 50 (33) | 1 | 1 |
| :---: | :---: | :---: | :---: | :---: |
| $\geq 1$ | 476 | 103 (67) | 1.54 (1.06, 2.23), p=0.02 | 1.26 (0.83, 1.91), p=0.28 |
| Medication adherence |  |  |  |  |
| MPR < 50\% | 62 | 16 (10) | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 176 | 26(17) | 0.49 (0.24, 0.99), p=0.05 | 0.40 (0.19, 0.84), p=0.02 |
| MPR $\geq 80 \%$ | 520 | 105 (69) | 0.72 (0.39, 1.33), p=0.30 | 0.59 (0.31, 1.13), p=0.11 |
| Vulnerable at baseline |  |  |  |  |
| No | 513 | 67 (44) | 1 | 1 |
| Yes | 293 | 86 (56) | 1.47 (1.02, 2.11), $\mathrm{p}=0.04$ | 1.10 (0.71, 1.72), p=0.67 |

[^11]
## Appendix 15: The unadjusted and adjusted analysis for Beers 2012 and emergency admission ( $\mathrm{n}=806$ )

Appendix 15-1: Multilevel logistic regression model with unadjusted and adjusted odds ratios ( $95 \% \mathrm{Cl}, \mathrm{p}$ value) for those with $\geq 1$ emergency admission* by exposure to Beers 2012 PIP at baseline and confounding variables ( $n=806$ )

| Patient characteristic | Total patien ts (N) | $\geq 1$ emergency admission | Unadjusted Odds Ratio (OR) (95\% CI), p value | Adjusted OR (95\% CI), pvalue |
| :---: | :---: | :---: | :---: | :---: |
| Primary outcome: PIP at baseline |  | N (\%) |  |  |
| 0 | 577 | 144 (24) | 1 | 1 |
| 1 | 178 | 47 (29) | 1.60 (1.06, 2.41), p=0.02 | 1.13 (0.72, 1.78), p=0.60 |
| $\geq 2$ | 91 | 8 (22) | 1.22 (0.74, 2.03), p=0.43 | 0.72 (0.41, 1.28), p=0.27 |
| Adjusted for confounding variables |  |  |  |  |
| Median (IQR) |  |  |  |  |
| Age | 806 | $77(73,81)$ | 1.04 (1.01,1.07), p0.01 | 1.01 (0.98, 1.05), p=0.50 |
| Deprivation | 806 | $1.7(-0.2,3.4)$ | 1.06 (1.00, 1.13), p=0.06 | 1.07 (0.99, 1.14), p=0.09 |
| Drug classes | 806 | $7(5,9)$ | 1.17 (1.12, 1.22), | 1.14 (1.08, 1.22), $\mathrm{p}<0.001$ |
| Gender |  | N(\%) |  |  |
| Male | 372 | 88 (44) | 1 | 1 |
| Female | 434 | 111 (56) | 1.12 (0.80, 1.53), p=0.53 | 0.95 (0.66, 1.36), p=0.77 |
| Social Class |  |  |  |  |
| Unskilled | 197 | 52 (26) | 1 | 1 |
| Skilled | 609 | 147 (74) | 0.88 (0.61, 1.28), p=0.51 | 0.92 (0.60, 1.40), p=0.71 |
| Education^ |  |  |  |  |
| Basic | 493 | 123 (62) | 1 | 1 |
| Post-secondary | 307 | 74 (37) | 0.95 (0.68, 1.34), p=0.78 | 1.24 (0.84, 1.85), p=0.29 |
| Co-morbidity: Baseline Charlson weights |  |  |  |  |
| 0 | 409 | 60 (30) | 1 | 1 |
| $\geq 1$ | 479 | 139 (70) | 1.86 (1.31, 2.62), p<0.001 | 1.26 (0.86, 1.86), p=0.24 |
| Medication adherence at baseline ${ }^{\text {s }}$ |  |  |  |  |
| MPR < 50\% | 71 | 20 (10) | 1 | 1 |
| MPR $\leq 50 \%<80 \%$ | 187 | 43 (22) | 0.68 (0.36, 1.28), p=0.23 | 0.49 (0.25, 0.97), p=0.41 |
| MPR $\geq 80 \%$ | 464 | 131 (64) | 0.71 (0.40, 1.25), p=0.23 | 0.47 (0.25, 0.88), p=0.02 |
| Vulnerable at baseline (Vulnerable Elder's scale $\geq 3$ ) |  |  |  |  |
| No | 513 | 103 (52) | 1 | 1 |
| Yes | 293 | 96 (48) | 1.94 (1.40, 2.69), p<0.001 | 1.19 (0.79, 1.79), p=0.41 |

A\&E visit or inpatient admission at baseline**

| No | 789 | $192(96)$ | 1 | 1 |
| :--- | :--- | :--- | :--- | :--- |
| Yes | 17 | $7(4)$ | $3.62(2.25,5.80), \mathrm{p}<0.001$ | $2.89(1.75,4.77), \mathrm{p}<0.001$ |

* A\&E visits were measured by review of the participant's GP medical record. ${ }^{\text {S }}$ MPR data missing $\mathrm{n}=37 \mathrm{~s}$. $\wedge$ Education missing $\mathrm{n}=6$. ** A\&E visit/inpatient missing for $\mathrm{n}=1$ (baseline)

Appendix 15-2: Number and percentage of patients and unadjusted and adjusted incidence rate ratio (IRR) ( $95 \% \mathrm{Cl}, \mathrm{p}$ value) for numbers of emergency admissions* during two-year follow-up by exposure to Beers 2012 PIP at baseline and confounding variables ( $\mathrm{n}=806$ )

| Patient <br> characteristic | Total <br> patients <br> (N) | Incidence Rate Ratio <br> (IRR) $(95 \% ~ C I), ~ p ~ v a l u e ~$ |
| :--- | :--- | :--- | :--- |$\quad$ Adjusted IRR (95\% CI), p-value

Primary outcome: PIP at baseline

| 0 | 577 | 1 | 1 |
| :--- | :--- | :--- | :--- |
| 1 | 178 | $1.48(1.072 .05), p=0.02$ | $1.10(0.80,1.51), p=0.57$ |
| $\geq 2$ | 91 | $1.49(1.02,2.19), p=0.04$ | $0.97(0.67,1.42), \mathrm{p}=0.89$ |

Adjusted for confounding variables

| Age | 806 | $1.03(1.01,1.06), \mathrm{p}=0.007$ | $1.02(0.99,1.04), \mathrm{p}=0.21$ |
| :--- | :--- | :--- | :--- |
| Deprivation | 806 | $1.05(0.99,1.10), \mathrm{p}=0.09$ | $1.04(0.99,1.10), \mathrm{p}=0.13$ |
| Number of baseline <br> drug classes | 806 | $1.13(1.09,1.17), \mathrm{p}<0.001$ | $1.10(1.06,1.15), \mathrm{p}<0.001$ |

Gender

| Male | 372 | 1 | 1 |
| :--- | :--- | :--- | :--- |
| Female | 434 | $1.03(0.79,1.34), p=0.81$ | $0.88(0.68,1.14), \mathrm{p}=0.34$ |
| Social Class |  |  | 1 |
| Unskilled | 197 | $0.82(0.61,1.10), \mathrm{p}=0.19$ | $0.84(0.62,1.13), \mathrm{p}=0.25$ |
| Skilled | 609 | 1 | 1 |
| Education^ |  | $0.93(0.70,1.22), \mathrm{p}=0.60$ | $1.14(0.86,1.52), \mathrm{p}=0.36$ |

Co-morbidity: Baseline Charlson weights

| 0 | 330 | 1 | 1 |
| :--- | :--- | :--- | :--- |
| $\geq 1$ | 476 | $1.90(1.43,2.54), p<0.001$ | $1.35(1.01,1.82), \mathrm{p}=0.05$ |

Medication adherence at baseline ${ }^{\text {s }}$

| MPR $<50 \%$ | 62 | 1 | 1 |
| :--- | :--- | :--- | :--- |
| $M P R \leq 50 \%<80 \%$ | 176 | $0.76(0.47,1.25), p=0.28$ | $0.58(0.36,0.92), p=0.02$ |
| $M P R \geq 80 \%$ | 520 | $0.71(0.46,1.11), p=0.13$ | $0.52(0.34,0.78), p=0.002$ |

Vulnerable at baseline (Vulnerable Elder's scale $\geq 3$ )

| No | 513 | 1 | 1 |
| :--- | :---: | :---: | :---: |
| Yes | 293 | $1.78(1.38,2.31), p<0.001$ | $1.18(0.88,1.58), p=0.27$ |

[^12]
# Appendix 16: Developer no-fee licence for use of Pra risk tool 

THE JOHNS HOPKINS UNIVERSITY ("JHU")
MATERIAL TRANSFER AGREEMENT (NON-PROFIT RECIPIENT)

THIS MATERIAL TRANSFER AGREEMENT ("Agreement") is made effective as of the date of the last authorized signature hereto ("Effective Date"), and is entered into by and between The Johns Hopkins University, a Maryland not-for-profit corporation having an address at 3400 North Charles Street, Baltimore, Maryland, 21218-2695 ("JHU") and Royal College of Surgeons in Ireland, HRB Centre for Primary Care Research ("Recipient"), with an address at Lower Mercer Street, Dublin 2, Ireland on behalf of its employee Dr. Emma Wallace ("Recipient Investigator"). JHU and Recipient are referred to individually as a "Party" and collectively as the "Parties".

WHEREAS, JHU has certain Materials (described below) that is used to predict risk in older community dwelling adults;

WHEREAS, Recipient is interested in the Materials and intends to validate the Materials on a cohort of older community dwelling adults;

WHEREAS, JHU is willing to provide the Materials to for Recipient's use under the specific terms and conditions as outlined below;

NOW THEREFORE, the Parties agree as follows:

## TERMS AND CONDITIONS

1. Description of Materials \& JHU Reference Number. PraPlus ${ }^{\text {TM }}$ (JHU Case Number C01162) is a screening instrument used to identify members of older populations who are at high risk for using health services heavily in the future and to begin the process of evaluating the needs of those at risk individuals. The PraPlus ${ }^{\text {TM }}$ Materials is made up of a Questionnaire, Telephone Survey with Instruction, Scoring Formula and the PraPlus ${ }^{\text {TM }}$ Manual (collectively hereinafter "Material").
2. Research Purpose. Recipient will use the Material to conduct a systematic review of and to validate the instrument on a cohort of 904 community dwelling Irish older people.
3. Limitations on use of the Material. The Material is confidential and proprietary to JHU ("Confidential Information"). The Material shall not be used for any commercial purpose or for purposes of diagnostic testing on any human. Recipient may not disclose or distribute the Material to any other party (for-profit or non-profit) for any reason. The Material shall be used at all times under the care and supervision of the Recipient Investigator. All requests for use of the Material shall be forwarded to JHU: JHTT-Communications@ihu.edu and should reference C01162 - Pra/PraPlus ${ }^{\text {TM }}$ Materials.
4. Results and Publication. At the end of Term (defined below in Section 6) Recipient agrees to provide JHU with a summary of any results or data generated by the Recipient and Recipient Investigator's use of the Material. Should the use of the Material result in one or more scientific publication(s), Recipient shall acknowledge in the publication(s) that the Material was provided to Recipient by JHU. Recipient and Recipient Investigator agree that it will not include any of the JHU Confidential Information in any such publication.
5. Disclaimer of Warranties and Indemnification. The Material is experimental in nature and must be used with prudence and appropriate caution, since not all of its characteristics are known. The Material is provided to Recipient AS IS and with all faults. THE MATERIAL(S) IS PROVIDED

WITHOUT WARRANTY OF MERCHANTABILITY OR FTTNESS FOR A PARTICULAR PURPOSE OR ANY OTHER WARRANTY, EXPRESS OR IMPLIED. Except to the extent prohibited by law, Recipient shall assume all liability for damages, which may arise from the use, storage or disposal of the Material. JHU (including, but not limited to, its directors, trustees, officers, employees, students, and agents, as applicable) will not be liable to Recipient for any loss, claim or demand made by any other party, due to or arising from Recipient's use of the Material.
6. Term and Termination. This Agreement shall remain in effect for a period of two (2) years beginning on the Effective Date and ending on the second anniversary thereof. This Agreement may be terminated by JHU at any time if Recipient's or Recipient Investigator's use of the Materials is no longer accordance with the terms of this Agreement. Recipient may terminate this agreement before the end of the Term with thirty ( 30 ) days written notice to JHU. Upon termination, Recipient shall delete and destroy any printed and electronic copies of the Materials.
7. Miscellaneous. Recipient may not assign or otherwise transfer Materials or Recipient's rights duties or obligations hereunder to any other party, in whole or in part, without JHU's prior written consent and any attempted transfer or assignment shall be null and void and without legal effect. If any provision of this Agreement is held to be invalid, illegal or unenforceable by a court or other tribunal of competent jurisdiction, such provision shall be severed from this Agreement, but the validity, legality and enforceability of the remaining provisions hereof shall not be affected or impaired thereby in any way. Any failure or delay by JHU to enforce any right or remedy under this Agreement shall not be construed as a waiver by JHU of any future right to exercise the same or any other right or remedy. No modification or amendment to this Agreement will be valid or binding unless reduced to writing and duly executed by both parties hereto. Unless provided for under this Agreement, neither Party shall use the name of the other Party or any contraction or derivative thereof or the name(s) of the other Party's faculty members, employees, or students, as applicable, in any advertising, promotional, sales literature, or fundraising documents without the other Party's prior written consent. This Agreement constitutes the sole and entire agreement between the parties hereto with respect to the subject matter hereof and supersedes any and all prior or contemporaneous agreements, representations, understandings, and arrangements, whether written or oral, between the parties hereto concerning the subject matter hercof. The Parties may execute this Agreement in counterparts, each of which is deemed an original, but all of which together constitute one and the same agreement. Electronic signatures hereon are legal, valid and enforceable as originals.

THE JOHNS HOPKINS UNIVERSITY


RECIPIENT
TON FOMER
Authorized Signature
Name TOM FAHEY Date $23 / 4 / 2015$
Title
PROFEISER OF FEAERZAL PRATCTICE
READAND UNDERSTOOD:
$\frac{\sqrt{2} \text { ra wolle er }}{\text { Signed(Recipient Investigator) }}$


[^0]:    ~Marital status missing $n=1$ (baseline). "Living arrangements missing $n=1$ (baseline), $n=10$ (follow-up).
    *Education missing $n=3$ (follow-up). ${ }^{\text {² }}$ Charlson missing $n=2$ (baseline). ^PHI missing $n=8$ (follow-up).

[^1]:    *Education data was missing for three participants. ${ }^{\$}$ Charlson comorbidity weights are classified into two groups according to the cumulative frequency distribution of the six weights.

[^2]:    ~Marital status was missing for $n=1$ (baseline). "Living arrangements were missing for $n=1$
    (baseline).*Education data was missing for $n=6$. ${ }^{\$}$ Charlson comorbidity weights are classified into two groups according to the cumulative frequency distribution of the six weights.

[^3]:    *A\&E visits were measured by review of the participant's GP medical record. ${ }^{\$}$ MPR data is missing for $n=37$. ^Education data is missing for $n=6$. ** A\&E visit/inpatient data missing for $n=1$

[^4]:    *Emergency admissions were measured by GP medical record review. ${ }^{\$}$ MPR is missing for $n=37$.
    ${ }^{\wedge}$ Education is missing for $n=6 .{ }^{* *}$ Baseline A\&E visit/inpatient missing for $\mathrm{n}=1$. All confounders were measured at baseline.

[^5]:    *A\&E visits were measured by review of the participant's GP medical record. ${ }^{\$}$ MPR data is missing for $\mathrm{n}=37$. $\wedge$ Education data is missing for $\mathrm{n}=6$. ** Baseline $A \& E$ visit/inpatient data missing for $\mathrm{n}=1$ and was measured by GP medical record review. All confounders were measured at baseline.

[^6]:    *Education was missing for $n=6$ (baseline). \$Charlson comorbidity was missing for $n=2$ (baseline).

[^7]:    *This criterion was modified from the original publication. Notes: Following a pilot of the validation criteria, one modification was made to the McGinn criteria. Specifically, the criterion concerning ' $100 \%$ follow-up' was changed to 'adequate follow-up' and was defined as $\geq 80 \%$ follow-up of study participants.

[^8]:    *NR=Not reported

[^9]:    \# Exposure to PIP, number of drugs, Charlson co-morbidity and previous ADE count was at baseline. Age and deprivation are centred. ${ }^{\# \#}$ ADE report was at follow up. ${ }^{\text {™ }}$ MPR data is missing for 29 participants. Over dispersion at the patient level was taken account for in the model by including an additional patient level random effect.

[^10]:    \#\# Model based on EQ-5D score at follow-up. Note; a histogram was generated to examine differences between baseline and follow-up uncentred EQ5D; $50 \%$ didn't change, and those that did only changed slightly therefore follow-up score was used in the analysis rather than change in in EQ-5D score. Baseline age, deprivation and EQ-5D were centred. ${ }^{\$}$ MPR data is missing $n=37$.

[^11]:    *A\&E visits were measured by review of the participant's GP medical record. ${ }^{\text {§ }}$ MPR data missing for $\mathrm{n}=37$. ^Education data is missing for $\mathrm{n}=6$. ${ }^{* *} \mathrm{~A} \& \mathrm{E}$ visit/inpatient data missing for $\mathrm{n}=1$ (baseline).

[^12]:    *A\&E visits were measured by review of the GP medical record. ${ }^{5}$ MPR data is missing $n=37$.
    ${ }^{\wedge}$ Education data is missing for $\mathrm{n}=6 .{ }^{* *}$ A\&E visit/inpatient data missing for $\mathrm{n}=1$ (baseline)

