THE DEVELOPMENT OF A PREDICTION MODEL TO ENABLE CLINICAL (HOSPITAL) PHARMACISTS TO PRIORITISE OLDER PATIENTS AT RISK OF DRUG RELATED PROBLEMS

By

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A Thesis submitted in accordance with the requirements of the University of Birmingham for

The degree of Doctor of Pharmacy

School of Pharmacy

School of Health Sciences

College of Medicine and Health

University of Birmingham

December 2024

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Dedication

I would like to dedicate this thesis to the memory of my (deceased) parents, Kathleen and Ronald (Jenkins) who both proudly saw me graduate Kings College London with my degree in Pharmacy, register as a Pharmacist and start my career working in Hospital Pharmacy. Only now, as an adult and a parent myself, am I fully appreciative of the sacrifices they made for me and my sister, Karen, and the opportunities that they gave us. I will be forever grateful to (and in awe of) them for allowing (and actively encouraging) me to make my own choices and decisions, and for their unwavering support. I hope that they are proud of me and the contribution that I am trying to make through my daily work as a Clinical Pharmacist to help patients, largely influenced by witnessing my dad's ill-health as a child and further motivated by my mum's battle with cancer. I hope that I make my own beloved children proud through my work at the hospital and through this thesis and that they realise that this (my desire to make them proud) has motivated me to complete this thesis.

Acknowledgements

I would like to acknowledge and thank my Academic Supervisors Dr Zahraa Jalal and Dr Chris Curtis for all of their support, encouragement and patience over the last few years. I feel that I was blessed to be assigned two such supportive mentors who are both experienced academics and practitioners. They have guided and supported me throughout, including during some challenging times. Their kindness was appreciated, and their support has helped me to reach this stage of thesis submission, of which I am proud. I hope that they are proud of the research that they have helped me to conduct and present .

Abstract

This thesis describes the research undertaken to develop a prioritisation tool for Clinical Pharmacists at Sligo University Hospital (SUH). The aim was to develop a tool to prioritise older (medical) patients most at risk of drug related problems (DRPs), and most likely to need Clinical Pharmacist Interventions, for early Clinical Pharmacist review.

A systematic review (SR) was conducted to identify (existing) screening tools and potential risk factors associated with DRPs (or equivalent) which would increase the need for early Clinical Pharmacist review and intervention(/s). Eight medical (/science/healthcare) literature databases were searched and a number of relevant search terms used to identify relevant published primary literature. The search of the eight databases identified 1030 titles and an additional 11 papers were identified from other sources (e.g. search of references for an included study) making a total of 1041 records. Titles, abstracts and, where deemed appropriate, full text articles were reviewed and nineteen publications met the criteria for inclusion in the SR.

From the included studies, potential risk factors for DRPs were identified; individual studies included between 3 and 38 variables. The selection of potential risk factors for the current primary research was based on the overall (collective) findings of the studies included in the SR, whilst considering the practicalities of collecting data on these variables at SUH. These potential risk factors related to patients' age, gender, number of comorbidities, number of medications taken, antimicrobial therapy (current/recent), falls, high risk medications, renal impairment, hepatic impairment and current/recent infection.

Primary research was conducted at SUH to determine if any of the potential risk factors, identified from the SR, were predictive of Clinical Pharmacist Interventions in older medical in-patients at SUH. Older patients (aged 65/+ years old) who were medically admitted during the four month study period (1st September – 31st December 2020) were prospectively identified by the Clinical Pharmacists providing Clinical Pharmacy Services to the included wards (if they met the inclusion criteria). Data on

patient demographics, the potential risk factors and the outcome (number of Clinical Pharmacist Interventions received at first Clinical Pharmacist review) were collected retrospectively by the Principal Researcher (AB), using the relevant medical notes (retrieved through the Medical Records department) and computerised laboratory results. Data collection and the sample size included were negatively impacted by a number of challenges including the COVID-19 pandemic, delays in launching a new drug kardex and changes in tracking of medical records, and this resulted in delays in data collection and the sample size being less than anticipated with data collection completed for 121 admissions.

The study outcome was the number of Clinical Pharmacist Interventions received at the time of first Clinical Pharmacist review; for the 121 patient admissions included, 246 interventions were made, equivalent to approximately 2 interventions per patient. The most common type of interventions related to medication reconciliation issues (accounting for 68.7% of interventions made) followed by those belonging to the advice/recommendation category (25.6%). The statistical program Stata was used to describe and analyse the results to determine if any of the variables appeared to be predictive for Clinical Pharmacist Interventions. Backward Poisson regression was performed to develop a risk score/model. Two risk factors were found to be predictive of (the number of) Clinical Pharmacists interventions at first review in the sample population, namely number of pre-admission medications (PAMs) taken ($p=0.000$) and gender, with the female gender found to be associated with a reduction in Clinical Pharmacist Interventions ($p=0.013$) whilst increasing the number of PAMs taken was associated with an increase in Clinical Pharmacist Interventions.

However, due to the comparatively small sample size ($n=121$) and without more specialist statistical support it was not possible to conduct internal validation of the developed score (/model) nor determine the goodness of fit of the score. Therefore, further research would need to be conducted to (internally) validate the score, determine its goodness of fit and, if necessary, refine the score before any recommendations can be made regarding its use locally at SUH. Furthermore, external validation

would need to be conducted before considering the broader application of the score outside SUH, its generalisability and its potential role in enabling Clinical Pharmacists to prioritise those older medically admitted patients most likely to benefit from early Clinical Pharmacist review.

Structure of this thesis

This DPharm thesis is presented over a series of chapters, describing the background to the topic, systematic review of relevant published studies, primary research and a comparison of the findings of the current research with the previous research findings, and drawing conclusions.

Chapter 1 – Introduction: This chapter provides background information on Clinical Pharmacy, the workload of Clinical Pharmacists and drug related problems as well as describing the healthcare system in the Republic of Ireland, and in particular Sligo (the setting for the current research). Previous researchers have referred to the target population using terms such as the elderly[1], geriatric and older people/patients and in the *Introduction* chapter, the terminology used by the previous researchers has been followed when discussing their published research.

Chapter 2 – Systematic review: This chapter contains the systematic review that was conducted to identify previous published primary research regarding screening tools used by Clinical Pharmacists to identify older patients at risk of drug related problems on hospital admission. The systematic review has been published as an 'Editor's choice' review in the international, peer-reviewed journal *Pharmacy* and is included with the publisher's consent and in the required format for that journal. Note that the term 'elderly' was used in the systematic review (subsequently, the term 'older people' or 'older patients' has been adopted in this thesis).

Chapter 3 – Methodology: The *Methodology* chapter describes the methodology adopted to conduct the current research and the rationale behind the methodological choices, such as choice of statistical program for analysis.

Chapter 4 – Results: This chapter presents the baseline characteristics of the study population and considers the number of Clinical Pharmacist Interventions (the primary outcome measure) received according to a number of potential risk factors (independent variables). Backward Poisson regression

[1] Note terms 'elderly' or 'geriatric' used in previous research/publication by author (preferred term is older people/patient)

was conducted to determine which of the (independent) variables may be predictive for the number of Clinical Pharmacist Interventions received and to develop a risk/prediction score and these findings are presented in the *Results* chapter.

Chapter 5 - Discussion: The *Discussion* chapter discusses the findings of the study and compares and contrasts them with the findings of previous related research. These comparisons are not restricted to the studies included in the systematic review, and include a number of more recent publications.

Chapter 6 – Conclusions, impact on clinical practice and future research: This final chapter draws conclusions from the findings of this current and previous research and considers the impact of these findings on clinical practice and identifies future research opportunities.

List of abbreviations used

Abbreviation used	Meaning of abbreviation in full
AAU	Acute Assessment Unit
AB	Principal Researcher, Amanda Brady
ABLF	Abnormal liver function
ABWCC	Abnormal white cell count
ACTPC	Adult Complexity Tool for Pharmaceutical Care
ADEs	Adverse drug events
ADR(/s)	Adverse drug reaction(/s)
ADRROP	Predictive tool for assessing ADR Risk in Older People
AE(/s)	Adverse events
AIC	Akaike Information Criterion
AJHP	American Journal of Health-System Pharmacy
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (also known as alanine transaminase)
ANTIMICRO	Patient taking a systemic antimicrobial therapy on admission or within a week prior to admission (treatment or prophylaxis)
ART	Assessment of Risk Tool
AST	Aspartate aminotransferase (also known as aspartate transaminase)
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
AUROC	Area under the receiver operating characteristic curve
BADRI (model)	Brighton Adverse Drug Reactions Risk (model)
BADRI (model)	Brighton Adverse Drug Reactions Risk model
BMI	Body mass index
CDR	Clinical Decision Rule
CDSS	Computerised decision support system

CEC	Academic Supervisor, Dr Chris E Curtis
CHARMS	Checklist for the critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies
CI	Confidence interval
CNS	Central nervous system
COMORB	Number of documented comorbidities
COMORBGRP	Groupings of numbers of comorbidities
COVID-19	(Disease caused by the SARS-CoV-2) Coronavirus
CPhI(/s)	Clinical Pharmacist Intervention(/s)
CPM(/s)	Clinical Prediction Model(/s)
CPRs	Clinical prediction rules
CPT[a]	Clinical Prediction Tool
CPT[b]	Clinical Prioritisation Tool
CPWPT(/s)	Clinical pharmacy work prioritisation tools
CVD	Cardiovascular disease
d.p.	Decimal point(/s)
DART	Drug-Associated Risk Tool
DCF	Data collection form
DOB	Date of birth
DRP	Drug related problem
EAHP	European Association of Hospital Pharmacists
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ENT	Ear, nose and throat
EPV	Events per variable
FALL	fall on current admission/recent fall history/ documented fall risk
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase

GIFA	Gruppo Italiano di Farmacoepidemiologia nell'Anziano
GMS	General Medical Services
GP	General Practitioner
HES	Hospital Episodes Statistics
HIPE	Hospital In-Patient Enquiry
HPC	History of presenting complaint
HRM	High risk medicines
HRPAM(/s)	High risk pre-admission medicine(/s)
HSE	Health Service Executive
ICU	Intensive Care Unit
IDAPP	International Diagnostic and Prognosis Prediction (IDAPP) group
INTERVENT	Number of interventions
IQR	Interquartile range
LDH	Lactate dehydrogenase
LFT(/s)	Liver function test(/s)
LMWH	Low molecular weight heparin
LUH	Letterkenny University Hospital
MAI	Medication Appropriateness Index
ME(/s)	Medication error(/s)
MedRec	Medication reconciliation
MERIS	Medication risk score
MESH	Medical subject headings
MMSE	Mini mental score examination
MOAT	Medicines Optimisation Assessment Tool
MPUH	Merlin Park University Hospital
MRH	Medication related harm
MRPs	Medication-related problems(s)
MSP MRP	Moderate or severe preventable medication related problems

MUH	Mayo University Hospital
N/A	Not applicable
NCCMERP	National Coordinating Council for Medication Error Reporting and Prevention
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NPSA	National Patient Safety Agency
NUI	National University of Ireland
NUPOR	Nearly Universal Prospective Order Review
PAL	Patient acuity level
PAMs	Pre-admission medicines
PAST	Pharmaceutical assessment screening tool
PCN	Unique patient identifier number for patient in SUH
PCNE	Pharmaceutical Care Network Europe
PE(/s)	Prescribing error(/s)
PhD	Doctor of Philosophy
PICOS	PICOS stands for: P Population/Patient, I Intervention, C Comparison, O Outcome, and S Study Design
PIP	Potential Inappropriate Prescribing
PMH	Previous medical history
PRISMOR	Model predicting in-hospital significant medication errors
REC	Research and Ethics Committee
ROC	Receiver operating characteristic (curve)
RUH	Roscommon University Hospital
S.D.	Standard deviation
s.f.	Significant figure(/s)
SAS	Statistical Analysis Systems
SPRM	Structured pharmacist review of medications

SPSS	Statistical Package for Social Science
SR	Systematic review
SSU	Short Stay Unit
START	Screening Tool to Alert doctors to Right Treatment
STOPP	Screening Tool of Older Person's Prescriptions
SUH	Sligo University Hospital
TDM	Therapeutic Drug Monitoring
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
UHG	University Hospital Galway
UK	United Kingdom
ULN	Upper limit of normal
UN	United Nations
UoB	University of Birmingham
US	United States
WCC	White cell count
WHO	World Health Organization
ZJ	Academic Supervisor, Dr Zahraa Jalal

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Chapter 1: Introduction

Introduction

Chapter description

This *Introduction* chapter is divided into two sections. The first section introduces terminology used in describing drug related problems (DRPs) and related synonyms, the prevalence of DRPs, and particular issues relating to DRPs in older people. The first section also addresses the broader issues of Clinical Pharmacy and the need for prioritisation of patients by Clinical Pharmacists. The second section briefly describes the health service in the Republic of Ireland which is the setting for the primary research undertaken as part of this thesis. This section considers recent and ongoing reforms in the way that public health services are being provided in Ireland and the role of private healthcare.

Introduction – Section 1

Drug Related Problems

A Drug Related Problem (DRP) has been defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"(1)(p.2). The Pharmaceutical Care Network Europe (PCNE) has developed a classification for DRPs which is validated and adapted regularly. The basic classification looks at problems (including potential problems), causes (including possible causes for potential problems), planned interventions, intervention acceptance and status of the DRPs(1).

Whilst DRPs are often caused by error(s) such as prescribing, dispensing, drug use or administration errors, this is not always the case and there may not be an error involved(2). DRPs include such medication errors as well as adverse drug reactions which have been described as "any response to a drug which is noxious and unintended"(2)(p.321) and occurs at normal doses for the "prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function"(2)(p.321-322). DRP(/s) is a broad term and "is often used interchangeably with adverse drug events (ADEs)"(3)(p.20) amongst others such as medicine-related problems or medication-related problems (MRPs), whilst referring to the same overall concept(4).

Eight major categories of DRPs were identified by Strand *et al.*; untreated indications, improper drug selection, subtherapeutic dosage, failure to receive drugs, over dosage, adverse drug reactions, drug interactions and drug use without indication(5, 6).

DRPs are "relatively common"(2)(p.322) and their outcomes can be diverse including failure to achieve desired treatment outcomes, increased morbidity and mortality, increased length of hospitalisation, increased cost of treating diseases, reduced quality of life for patients and may result in people being dissatisfied with their treatment and the healthcare system(2, 7).

DRPs can occur in primary care, intermediate care and in the hospital settings as well as at transitions of care. DRPs can occur at all stages in the hospital setting, from admission through to discharge and,

in particular, research has shown that "the secondary-primary interface is problematic with respect to DRPs"(8)(p.333). A substantial percentage of DRPs can be prevented and research has shown that incorporation of a hospital pharmacist into multi-disciplinary teams can increase the detection of DRPs(9).

Drug Related Problems and Medication Related Problems – an international issue and quantifying the extent of the problem

Medicines, taken for the prevention, treatment and management of many illnesses and health conditions, "are the most common intervention in healthcare"(10)(p.5). The World Health Organization (WHO) has estimated that 30-50% of medicines taken for long-term conditions are not taken as intended(10). Therefore, there is a significant potential for harm from medicines. In England, the Department of Health's report exploring the costs of unsafe care in the National Health Service (NHS) found that 5% to 8% of unplanned hospital admissions are due to medication issues and that preventable health care-acquired patient harm results in additional costs of £1-2.5 billion annually(10, 11).

Several researchers have looked at quantifying the extent of DRPs and their impact. The terms DRPs and medicine-related problems or medication-related problems (MRPs) are often used interchangeably and therefore it is appropriate to review the literature using these related terms. In a Spanish cross-sectional study involving hospitalised patients in medical wards, with a mean age of 72.8 years, DRPs were detected in 45% of patients and 38% of these DRPs were related to medication reconciliation(9).

There have been numerous studies conducted in Australia estimating the extent of medication-related hospital admissions (including 16 studies between 1988 and the publication of the Pharmaceutical Society of Australia's publication *Medicine Safety: Take Care*, in January 2019, referred to in the publication)(12). Research conducted in Australia has estimated that 250,000 hospital admissions annually are a result of MRPs with an additional 400,000 presentations to Emergency Departments likely to be due to MRPs(12). One Australian study estimated that 15% of hospital admissions from the Emergency Department (ED) were associated with an adverse medication event and over half of these

(54%) were avoidable(12). The annual cost of these medication-related hospital admissions in Australia was estimated at 1.4 billion dollars in the 2019 report and the research found that approximately 50% of this harm is preventable(12).

Research from Sweden has estimated that 6-16% of hospital admissions are attributed to medicines (consistent with the findings of the Australian research estimating 15% of hospital admissions from the ED were associated with adverse medication events) and estimated approximately 3000 deaths are associated with DRPs annually(12, 13). Another Scandinavian study, conducted in Norway in 2002, investigated the prevalence of DRPs in 827 patients in five general hospitals and found that the majority (81%) of patients had at least one DRP, with the most common type of DRP, non-optimal dosing, accounting for 35% of all DRPs(14).

In addition to these individual studies, a literature review that was published in 2002 incorporated data from eight retrospective and four prospective trials and looked at drug-related visits to the ED(15). The researchers found that up to 28% of all ED visits were drug-related and of these, 70% were classified as preventable and up to 24% of the visits resulted in hospital admission(15). Whilst the included trials were predominantly conducted in the United States, one was conducted in India and another in Italy making the overall findings more generalisable to settings outside the United States. Furthermore, a systematic review published (online) in 2013 found the prevalence of hospitalisation in adults aged 18/+ years old due to MRPs can be up to 12.1% (range = 4.6-12.1%)(16). The researchers found that MRPs were most prevalent in adult patients taking medicines for cardiovascular disease and diabetes and the main causes of hospitalisations due to MRPs were due to adverse drug reactions (ADRs) and noncompliance(16). It was also noted that old age and polypharmacy were “highly represented” amongst patients who were hospitalised due to MRPs(16)(p.215) .

Meanwhile, separate research has reported that between 75-96% of older people have acknowledged that they frequently make mistakes with their medicines(17). DRPs can result in adverse outcomes including increased morbidity and mortality; it has previously been estimated that in the United States up to 200,000 people may die from MRPs annually(18).

Terminology of Drug Related Problems and Synonyms

There are a number of difficulties in trying to quantify the incidence of DRPs including differences in the terminology and definitions used by different researchers. For example, this current research is focusing on the broad term DRPs whilst some studies have looked more specifically at adverse drug reactions (ADRs), adverse (drug) events (AEs/ADEs) or medication errors (MEs) making it harder to compare the findings of studies and contributing to apparent inconsistencies between the studies with respect to their reported incidence of DRPs. In practice, the terms DRPs, MRPs and medication-related harm (MRH) are often used interchangeably to describe the same concept(4). The need for the adoption and utilisation of consistent definitions for DRPs has been highlighted in the literature(19).

DRPs incorporate medication errors (including prescribing, dispensing or administration errors) and ADRs. The following figure *(Figure I1)* illustrates the relationship between some of the various definitions of adverse drug reactions and medication errors(19).

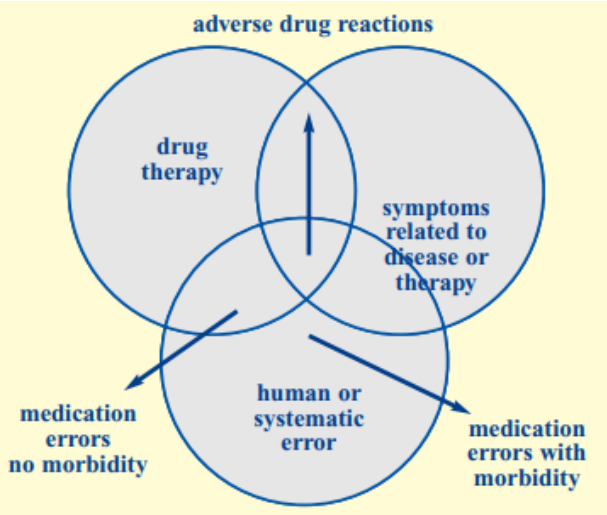


Figure I1: The relationship between various definitions of adverse drug reactions and medication errors (taken from van den Bemt P., Egberts T.)(19)(p.324).

The relationship between the definitions of drug related problems (DRPs) and adverse drug events (ADEs), medication errors (MEs), potential adverse drug events and adverse drug reactions (ADRs) not

from errors, has also been described and summarised in the following figure *(Figure I2)* by Linden-Lahti *et al.*(20).

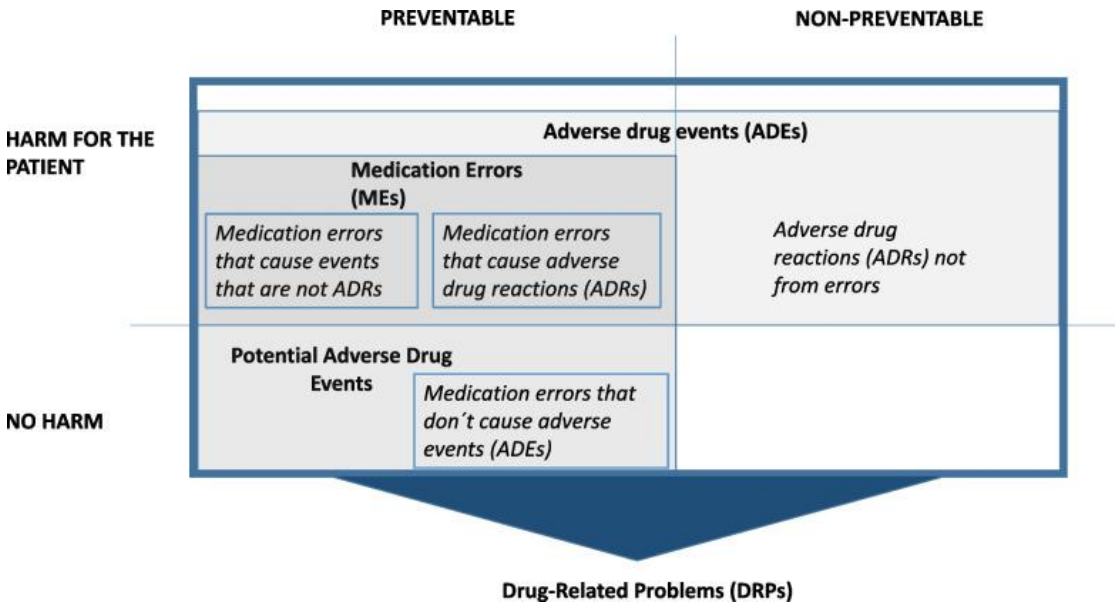


Figure I2: The relationship between DRPs, ADEs, MEs, potential ADEs and ADRs (taken from Linden-Lahti *et al.*)(20)(p.3).

The US National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) has defined medication errors (MEs) as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer"(21)(para.1). Whilst there is no consensus definition of a medication error, the Council (NCCMERP) "urges medication errors researchers, software developers, and institutions to use this standard definition to identify errors"(21)(para.1) and their definition has been included in a number of publications and international guidelines(22).

Research conducted in England (published in 2021) focusing on just MEs (by definition, just one component of DRPs) estimates that 237 million MEs occur "at some point in the medication process in England"(23)(p.96) each year with just over 38% occurring in primary care; 72% of these MEs have little or no potential for harm whilst 66 million MEs annually are potentially clinically significant(23). The impact of these MEs is considerable and significant both to the individual patients and their outcomes and in terms of healthcare costs; "Definitely avoidable ADEs are estimated to cost the NHS £98 462 582

per year, consuming 181 626 bed-days, and causing/contributing to 1708 deaths. This comprises primary care ADEs leading to hospital admission (£83.7 million; causing 627 deaths), and secondary care ADEs leading to longer hospital stay (£14.8 million; causing or contributing to 1081 deaths"(23)(p.96). Previous estimates attributed to the National Patient Safety Agency (NPSA) in 2007 suggested that preventable harm from medication could cost England over £750 million annually(23).

Predictive tools to identify Drug Related Problems

Research has looked at identifying risk factors for patients developing DRPs and trying to identify particular groups of patients who might be most vulnerable. In recent years, a number of predictive scoring tools have been developed in an attempt to identify patients at the highest risk of developing DRPs. There have been limitations to these developed tools with performance being 'moderate' at best and the scoring tools not being easily applicable or transferable to other settings(24). Different tools have incorporated different parameters/risk factors, although some tools may overlap with certain factors. These limitations highlight the need to develop, identify and externally validate the overall predictive scoring tool if it is to be utilised in more than one setting.

A systematic review (SR) looking at predictive scoring tools for DRPs in hospital in-patients included 14 studies meeting its inclusion criteria that identified a total of 844 candidate risk factors(24). The authors commented on the heterogeneity of the combinations of risk factors included in the risk scores as well as variations in the definitions of these risk factors between the different studies. The authors identified five "easily ascertainable"(24)(p.19) risk factors that may aid in the identification of patients at risk of DRPs regardless of whether they are incorporated in a scoring system/tool(24). These five risk factors were number of drugs taken (polypharmacy), drugs belonging to the Anatomical Therapeutic Chemical (ATC) N (nervous system) class, co-morbidities, renal function and patients' age(24). The researchers found that more than half of the authors who included 'number of drugs' as a risk factor in their respective scoring tool considered a number above eight drugs to increase the risk of DRPs(24). Drugs belonging to the Anatomical Therapeutic Chemical (ATC) N (nervous system) class were included in six of the final scoring systems. The ATC N class contains anti-epileptics, antipsychotics, and

antidepressants as well as opioids and many of the medications included in this class are prone to drug interactions, some have a narrow therapeutic index/window and, along with the fact that many "interact with a broad spectrum of different receptors"(24)(p.17), this increases the risk of adverse events in patients taking them(24). The researchers found that although co-morbidities were included as a risk factor in final scoring tools, there was disagreement between authors about which specific disease(/s)should be included in final scoring tools and even how co-morbidities were assessed. As a result, the researchers concluded that "comorbidities as a whole, rather than a specific disease, might be more relevant to estimate the risk of the occurrence of a DRP in patients"(24)(p.18). Renal function was investigated in 12 of the 14 studies, and glomerular filtration rate (GFR) was used to access renal function in nine of these studies. The thresholds for GFR in the final screening tools differed leaving the researchers conducting this SR unable "to give a defined threshold for the GFR to assess in future scoring tools"(24)(p.18) but commenting that it is well known that "a GFR below 30 mL/min might interfere with the elimination of drugs more commonly than a GFR below 60–30 mL/min"(24)(p.18). Patients' age was studied in all of the 14 studies included in their SR but the thresholds for patients' age differed throughout the studies. Patients' age was included in six of the 14 final scoring tools. It was also highlighted that age may be related to other factors such as declining renal function and that "possible multicollinearity should be taken into account while considering "age" as a risk factor"(24)(p.18). The following figure *(Figure I3)* taken from the systemic review writeup by Jung-Poppe *et al.* summarises these five risk factors that might help in the identification of patients at risk of DRPs with the "typical cut-off values"(24)(p.17) quoted.

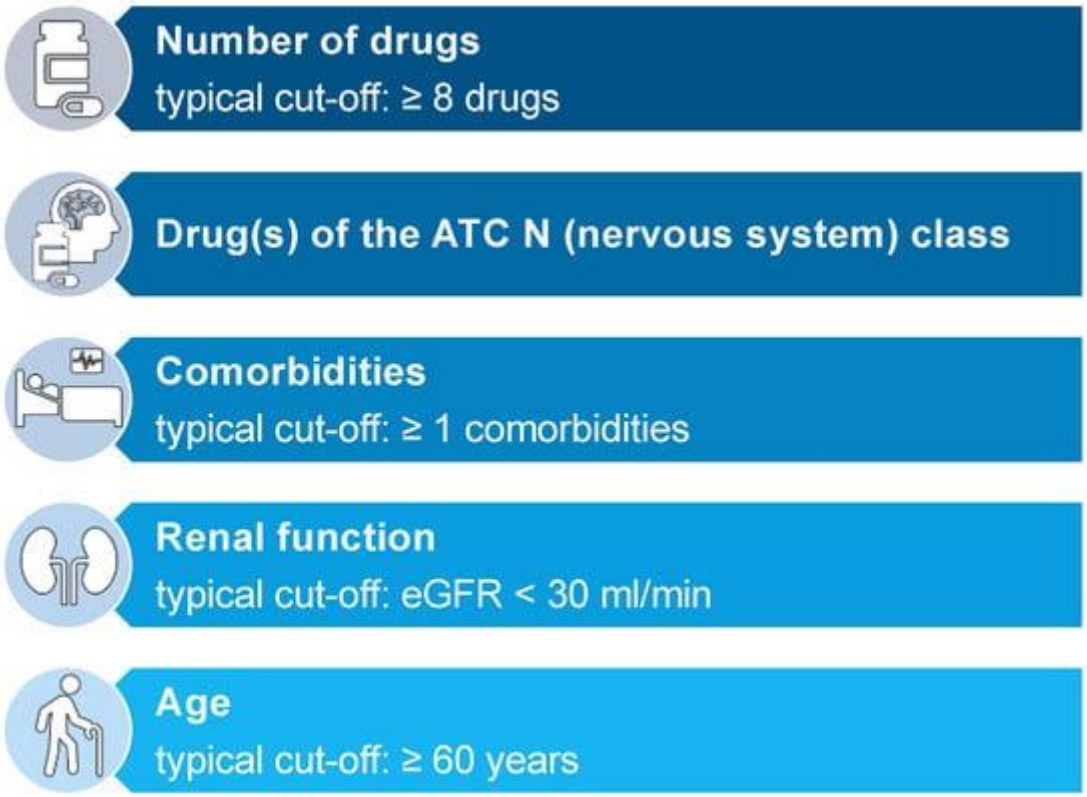


Figure I3: The risk factors that might help to identify patients at risk of DRPs (taken from Jung-Poppe *et al.*)(24)(p.17).

Drug Related Problems (DRPs) in older people

DRPs are common in older adults and can manifest as drug ineffectiveness, underdosage, overdosage, adverse drug effects, inappropriate treatment, poor adherence, inadequate monitoring and drug interactions(25). DRPs are associated with an increased risk of hospital readmissions, morbidity, and mortality in older patients with comorbidities who are using multiple drugs(26). Adverse drug effects are "effects that are unwanted, uncomfortable, or dangerous"(25)(para.3) and commonly include oversedation, confusion, hallucinations, falls, and bleeding(25). Adverse drug effects occur at a rate of approximately 50 events per 1000 person-years amongst ambulatory older patients (aged 65/+ years old) and hospitalisation rates for older patients due to adverse drug effects are approximately four times higher for older patients (17%) compared to younger patients (4%)(25). Warfarin, insulin, oral antiplatelet drugs and oral hypoglycaemic drugs are the main drug classes responsible for 66% of these hospitalisations in older patients(25).

Age “is the most frequently mentioned factor for drug related hospital admission”(27)(p.345), with the potential for DRPs and ADRs increasing with age(28). However, whilst it is generally accepted that DRPs are “prevalent in elderly[1] patients”(29)(p.375), quantification of the prevalence seems somewhat elusive and the results of studies in this topic somewhat inconsistent(30). A UK study published in 1997 reported an incidence of 14.2% for DRPs in elderly[1] patients aged over 65 years and commented on the sparsity of literature on this topic(29). The use of different terms such as DRPs, MRPs, ADRs and MRH by different researchers and even differences in the definitions of the same term used by different researchers (non-standardised definitions) as well as different study populations has made comparisons between or combining the results of studies difficult. A recently published systematic review and meta-analysis (first published online in October 2023) looked at drug-related readmissions in older adults acknowledging that “older adults are at an increased risk of drug-related problems, especially following discharge from hospital”(30)(p.1) and the burden of drug-related readmissions on the patient and healthcare system(30). The authors reported a pooled prevalence of 9% for drug-related readmissions across the included studies and concluded that approximately one fifth of these readmissions were preventable(30).

Possible reasons contributing to the comparatively high risk of older patients developing DRPs include multi-morbidity (namely the presence of multiple chronic diseases and conditions), polypharmacy (both the number and types of medications taken being important), age-related physiological changes and pharmacokinetic and pharmacodynamic alterations(18, 31, 32). Physiological changes that occur include the fact that older patients (tend to) have “lower physiologic reserves in most organs compared to younger adults, and with aging, they possess negatively affecting homeostatic mechanisms”(28)(p.1) which, along with the changes in pharmacodynamics and pharmacokinetics associated with ageing, increases their risk of ADRs(28). This is of relevance in the context of the rapidly ageing global population, with many countries described as ‘superaged societies’ whereby >20% of inhabitants are aged over 65 years old; women compromise the majority of the population of older people at a percentage that increases with age(33).

Multimorbidity, defined as the coexistence of two or more chronic conditions, is prevalent in older people, occurring in approximately 70% of the older adult population with prevalence shown to increase with age(9, 34). One study found that in those aged under 65 years of age, the prevalence of multimorbidity was 50% which rose to 62% for those aged 65-74 years and 81.5% for those aged 85/+ years of age and these findings were consistent with those of a previous systematic review which reported median prevalence of 63% of multimorbidity in older adults(34). Given the fact that many older people may be experiencing multimorbidity, some will be taking more than one or indeed several different medicines making them more susceptible to adverse drug effects.

Polypharmacy means 'many medicines' and there are many different definitions used in the literature to describe polypharmacy but no (definitive) consensus definition(35). The World Health Organization (WHO) defines polypharmacy as four or more medicines (taken concurrently by one person), whilst academia tends to use five or more medicines in its definition(/s) of polypharmacy(36). Polypharmacy, using a definition of four or five medicines, occurs in 40% of adults aged over 65 years old and the prevalence of polypharmacy reaches up to 90% of adults aged over 75 years old at the time of hospital admission(9). Elderly[1] patients use approximately three times more drugs than younger patients for the treatment of chronic diseases/conditions, thus increasing their risk of experiencing DRPs(26). Polypharmacy "increases the risk of inappropriate and unsafe prescribing for older people"(33)(p.e290) resulting in older adults, and particularly older women, being at "the greatest risk for drug-related harm"(33)(p.e290). Inappropriate medication use in older people can contribute to a range of adverse consequences including geriatric syndromes such as falls, cognitive decline and urinary incontinence, and hospitalisation(32).

Recognition of the widespread scale of harm from polypharmacy led to the WHO identifying *Medication Without Harm* as the Third International Global Patient Safety Challenge. This initiative, which was launched in 2017, aimed to reduce avoidable medication related harm (MRH) globally by 50% over five years(37). The WHO has identified three key target areas to reduce the risk of MRH to patients namely polypharmacy, high-risk situations and transitions of care(37).

Adverse drug effects in older people are thought to be preventable in at least 25% of cases and drug classes commonly involved (in causing adverse drug effects) are antipsychotics, warfarin, antiplatelet agents, hypoglycaemic drugs, insulin, antidepressants and sedative-hypnotics(25).

The need for prioritisation of Clinical Pharmacist workload

Traditionally, ward Pharmacy services in UK (National Health Service, NHS) hospitals were provided by pharmacists undertaking daily visits to their allocated ward(s) often for a specified period of the day (e.g. a couple of hours), reviewing drug kardexes for all patients and, during these ward visits, pharmacists would identify and/or discuss medication-related issues and make recommendations (often referred to as 'interventions') to medical, nursing, other healthcare professionals and patients as appropriate(38, 39). The practice widely adopted by the Pharmacy profession of conducting Nearly Universal Prospective Order Review (NUPOR) has resulted in (hospital) Clinical Pharmacists conducting prospective order review, with exemptions only in certain situations, e.g. emergency orders, without evidence of patient outcome improvement and taking up a substantial amount of the hospital pharmacist's working time(40). Whilst there is no universally adopted definition of prospective order review, it has been defined as "the pharmacists' intentional, prospective examinations of the details of medication orders with regard to their safety, anticipated efficacy, and appropriateness for the patient"(40)(p.668) and described as fulfilling a "gatekeeping function intended to safeguard patients, improve the effectiveness of drug therapies, and save costs"(40)(p.668).

The first of the European Association of Hospital Pharmacists (EAHP) Hospital Pharmacy Statements adopted in 2014 (statement 1.1) defines the overarching goal of the hospital pharmacy service as being "to optimise patient outcomes through working collaboratively within multidisciplinary teams in order to achieve the responsible use of medicines across all settings"(41)(p.256). The limited resources of health systems are identified in these European statements, and the need for these resources to "be used responsibly to optimise outcomes for patients. Hospital pharmacists should develop, in collaboration with other stakeholders, criteria and measurements to enable the prioritisation of hospital pharmacy activities"(41)(p.256). One of the recommendations made by Lord Carter in a review

of (acute) NHS hospital efficiency in England (published in 2016) was that more than 80% of (the Trust's) pharmacists' time is spent on clinical activities including direct medicines optimisation activities, medicines governance and safety remits(39).

Research has showed the benefit of incorporation of hospital pharmacists on consultant-led ward rounds, with pharmacists making more interventions and more timely interventions than with the traditional daily ward visit alone. Guidance issued by the Royal College of Physicians (and endorsed by other professional groups including the Royal Pharmaceutical Society) on modern ward rounds has recognised the beneficial role of the hospital pharmacist in multidisciplinary ward rounds (in the UK)(38, 42).

These examples illustrate the desire and need to develop an objective prioritisation tool to help (hospital) pharmacists "plan their interventions more efficiently"(43)(p.295) whilst recognising that pharmacists are an expensive, limited resource(43) . This is not a problem unique to the UK, Ireland or indeed Europe, with the need for pharmacists to "effectively prioritize their clinical pharmacy tasks to optimize both job satisfaction and work performance"(44)(p.1123) also identified in the United States and in Australia, against a background of decreasing budgets, increasing workload and need for increased efficiency(44, 45). There has been increasing interest in developing and implementing novel tools for prioritising pharmacist workload including clinical pharmacy work prioritisation tools (CPWPTs), most of which have been built into existing electronic health record platforms, to help "classify patients according to the degree to which they need clinical pharmacy services"(44)(p.1123) with no known standards identified for prioritising clinical pharmacy tasks(44).

Risk stratification and risk prediction models

In healthcare, "risk stratification aims to identify patients who are at high risk of an adverse event so that these people can be offered preventive care today aimed at averting costly, unpleasant health problems tomorrow"(46)(p.8). The use of risk stratification tries to improve the quality of care for patients whilst reducing costs but there are potential problems associated with the use of risk stratification including:

* Modest predictive accuracy of many risk stratification tools – the accuracy of risk stratification tools can be described by statisticians, e.g. the c-statistic gives an indication of the distribution of false positive and false negative results.

* Some strategies used to improve the impact of risk stratification programmes could potentially worsen health care inequalities.

* Many of the preventive interventions offered in risk stratification programmes appear to increase rather than reduce total costs(46).

Risk stratification is a systematic process(47). Risk stratification databases and tools have been developed and used within the NHS for some time, with the Department of Health commissioning the King's Fund (during 2005-2007) to develop software and predictive tools to identify people who were at high risk of readmission to hospital resulting in the development of the PARR++ and Combined Predictive Model tools(47). Following on from this, a number of products have been developed by commercial or academic providers resulting in a dramatic increase in the use of risk stratification databases and tools within the NHS(47).

Clinical Prediction Models (CPMs) are useful in clinical/medical practice, public health and for research purposes(48). CPMs "have become fundamental for risk stratification across healthcare"(49)(p.1), with clinicians increasingly using CPMs to guide decision-making and large numbers of CPMs are developed and published in medical literature every year(50). Prediction models are also known as risk scores, prognostic indices or prognostic scores(51). Most CPMs are developed using a regression framework e.g. logistic and cox regression(51).

CPMs may help clinicians estimate the probability of a patient having a particular diagnosis, disease or condition(48, 50). CPMs may help guide therapeutic decision-making, to help target treatment or interventions to those most likely to benefit from them(48). In public health, CPMs can be useful in targeting preventative interventions to individuals at relatively high risk of having or developing a disease/condition, e.g. the Framingham outcomes model and risk score could be used to classify patients and then target those at high risk of cardiovascular disease (CVD) for statin therapy(48, 52). In

research, prediction models can serve several purposes including help in the design of interventional studies, analysis of randomised trials and to control for confounding variables in observational research(48).

Risk stratification and CPMs have applications in Pharmacy, with CPMs being increasingly utilised in hospital pharmacy. It has been identified that "risk assessment forms the foundation of clinical pharmacy resource prioritisation"(53)(para.9) and that "specific patients have higher clinical pharmaceutical need which can be identified by the presence of specific risk factors"(53)(para.9). Accurate information is regarded as essential in ensuring effective prioritisation which therefore means that it may be "better suited to focus resources post-medicines reconciliation when an accurate list of a patient's usual medicines is available"(53)(para.9). Examples of CPMs being utilised in the context of hospital pharmacy include the "development of a multivariable predication model for identification of patients at risk for medication transfer errors at ICU discharge"(54)(p.1) and, similar to the aims of this current research, prognostic prediction models and clinical tools to identify patients at high risk of adverse medication-related outcomes for targeted clinical pharmacy services(55). Other models have looked at incorporating pharmacy-specific predictors on 30-day readmission risk prediction models(43). These examples illustrate the desire and need to develop an objective prioritisation tool to help (hospital) pharmacists "plan their interventions more efficiently"(43)(p.295) and recognises that pharmacists are an expensive, limited resource(43). The American Journal of Health-System Pharmacy (AJHP) has a dedicated thematic collection *AJHP Predictive Modeling Collection* that "captures articles on the use of predictive modeling to identify patients who would benefit from pharmacist-provided comprehensive medication management and those who are at greatest risk for experiencing adverse drug events"(56)(para.1). The development of such a thematic collection by a leading peer-reviewed Pharmacy publication highlights the growing level of interest in the area of prioritising pharmacist input.

Introduction – Section 2

Background to healthcare in the Republic of Ireland

The primary research undertaken as part of this thesis was conducted in a public hospital located in Sligo, the Republic of Ireland. In the Republic of Ireland, healthcare is provided via a comprehensive public health service which is (primarily) funded by the government and a private healthcare system(57). In 2024, the Health Service Executive (HSE) is in the process of undergoing reorganisation into six new health regions, providing integrated health and social care services for people in those areas and replacing the previous Hospital Groups (six) and Community Healthcare Organisations (nine)(58).

Individuals who are defined as being ordinarily resident in Ireland for a minimum of one year (or who can demonstrate their intention to remain in Ireland for at least one year) are entitled to receive healthcare via the public healthcare service which is managed by the HSE(57, 59). Individuals entitled to public healthcare may be subdivided into having full or limited eligibility for healthcare services (Category One and Category Two, respectively) (57).

Individuals with full eligibility (Category One) are in receipt of a Medical Card (also known as a General Medical Services (GMS) Card), entitling them to a wide range of health services, free of charge (at the point of use) including:

- General Practitioner (GP) services
- Public hospital services
- Specific dental, optical and aural services
- Maternity and infant care services
- Community care and personal social services,

and may be eligible for prescription medicines for free or at a minimal prescription charge (which is capped for the individual/family in receipt of the Medical Card)(57) . The application for a Medical Card is (generally) means tested, with some exceptions(60).

Certain individuals may be eligible for a Medical Card without means testing and there are mechanisms for discretionary and emergency Medical Cards(61, 62, 63). Following the outbreak of war in Ukraine in 2022 following invasion by Russia, all Ukrainian refugees who arrived in Ireland seeking refuge under the Temporary Protection Directive are entitled to access the public healthcare services in Ireland and arrangements have been established regarding Medical Card entitlement(64, 65).

Some individuals who are not eligible for a full Medical Card may be eligible for a GP Visit Card which allows them to visit a GP participating in the scheme for free. The criteria for eligibility for a GP Visit Card was extended in the Budget 2023 to include people on or below the median income and extending the GP Visit Card to children aged 6 to 7 years old(66). Overall, figures show that the percentage of the population with a full Medical Card fell from 40.4% in 2012 to 30.8% in 2021, although that decrease may be attributed (at least in part) to the introduction of free GP Visit Cards for children under 6 years of age and those aged over 70 years of age, in 2015(67). In 2012, 2.9% of the population had a GP Visit Card and this significantly increased to 10.6% of the population in 2022(67).

People with limited eligibility to healthcare services (Category Two, namely individuals without Medical Cards) can still access a wide range of community and hospital health services, either free of charge or at reduced cost at the point of use. These individuals may have to pay hospital charges if they attend the hospital as a public patient. There are a number of different hospital charges including Emergency Department (ED) charges (unless referred to the ED by a GP), outpatient charges and long-term stay charges, whilst previous (daily) in-patient and day services charges were removed effective from 17th April 2023(68).

Private healthcare in Ireland

In Ireland, approximately 47% of the population have private health insurance with an average annual premium cost of 1,448 Euro (as per figures quoted by the Health Insurance Authority, for 2022)(69).

Funding of public health services in Ireland

The public health service in Ireland is largely funded by the government with the remainder funded by voluntary health care payments and out-of-pocket payments(70). In Budget 2023, the relevant Ministers announced an investment of €23.4 billion in Ireland's Health and Social Care Service(71). The overlap between the public and private funding and delivery of healthcare in Ireland has been criticised by some and it is has been noted that "some services are publicly funded and publicly delivered, some are publicly funded and privately delivered, some are privately funded and publicly delivered, and some are privately funded and privately delivered"(70)(p.56).

The majority of hospitals in Ireland are operated directly by the HSE. However, many are run under a voluntary basis by public funding ('voluntary public hospitals'), as teaching hospitals, in conjunction with a religious ethos or as private hospitals(72). Private (independently funded) hospitals account for approximately one third of the acute hospitals in Ireland and receive no State funding(73, 74). Public health services are provided to patients at HSE and voluntary public hospitals. Whilst most of these hospitals also provide private healthcare, they need to differentiate between private and public beds(74). Private patients who are treated in a public hospital are 'a private patient' of the treating consultant and must pay for all consultant services provided to them as well as an in-patient 'overnight' charge depending on the type of room occupied (single versus multiple occupancy) and whether the hospital is included in Schedule 5 or 6 of the relevant legislation which determines the level of fee payable(74).

Sligo University Hospital as part of the Saolta University Health Care Group

Prior to the reorganisation of the HSE into six health regions (currently underway) and at the time this research was undertaken, Sligo University Hospital (SUH) was part of the Saolta University Health Care Group (the 'Saolta Group'). The Saolta Group provided acute and specialist hospital services to the West and North West of Ireland, namely to counties Galway, Mayo, Roscommon, Sligo, Leitrim, Donegal and adjoining counties. Saolta Group was comprised of six hospitals spread over seven sites (with services being provided at two hospitals in Galway, as part of Galway University Hospitals) as follows:

Letterkenny University Hospital (LUH),

Mayo University Hospital (MUH),

Merlin Park University Hospital (MPUH), part of Galway University Hospitals,

Portiuncula University Hospital (PUH),

Roscommon University Hospital (RUH,)

Sligo University Hospital (SUH),

University Hospital Galway (UHG), part of Galway University Hospitals.

The Group served a population in the region of 830,000 people in Galway, Donegal, Leitrim, Sligo, Mayo, Roscommon and adjoining areas(75, 76). The Saolta Group was partnered with the National University of Ireland Galway (NUI Galway) in education, research and training across each of the hospitals within the Group and the inclusion of 'University' within the hospital's titles reflects this close collaboration(75, 76).

Sligo is located within the new HSE West and North West region along with Donegal, Leitrim, Roscommon, Mayo and Galway(58)

Sligo University Hospital structure and services provided

Sligo University Hospital (SUH) is a model 3 acute teaching hospital providing acute inpatient, outpatient and day services in addition to Regional speciality services in ophthalmology and ear, nose and throat (ENT) services. At the time that the Saolta Strategy (2019-2023) was published, SUH had 324 beds and provided governance to patients at Our Lady's Hospital in Manorhamilton and St John's Hospital, Sligo(76). The hospital provides healthcare to the population of Sligo, Leitrim, South Donegal and West Cavan of approximately 100,000 with a catchment area of approximately 213,000 people for specialist Regional services(77). Prior to the reconfiguration of wards and departments due to the worldwide Coronavirus (COVID-19) pandemic (including designated areas and/or wards for patients presenting with symptoms of COVID-19 infection), SUH was composed of the following wards providing

in-patient beds: Acute Assessment Unit (AAU), Coronary Care Unit (CCU), Haematology & Oncology ('Medical Oncology Ward'), Intensive Care Unit (ICU), Left Wing Orthopaedic, Maternity, Medical 5, Medical 7, Medical North, Medical Short Stay (Short Stay Unit, SSU), Medical South, Neonatal Intensive Care (NICU), Paediatrics, Surgical North and Surgical South (Gynaecology).

Sligo University Hospital during COVID-19 Pandemic 2020-2021

The first confirmed case of COVID-19 infection detected in the Republic of Ireland was announced on the 29th February 2020(78). In response to the COVID-19 pandemic and similar to other hospitals within the country, Europe and further afield, SUH adapted and reconfigured services and wards to manage patient flow. Designated COVID-19 pathways were developed e.g. through the Emergency Department and electively, and, where possible, designated COVID-19 wards were created to separate possibly infected patients from (known) COVID-19 negative patients(79). Research has shown that Emergency Department attendances appear to have been significantly reduced both in Ireland and more generally during the early part of the pandemic (early to mid-2020)(78).

The timing of the (first wave of the) COVID-19 pandemic in Ireland coincided with the intended study period for this research resulting in a delay of several months before the study could commence. Additionally, the subsequent changes in services and wards with the creation of designated COVID-19 pathways and wards/clinical areas impacted upon the provision of Clinical Pharmacy services during this time, particularly mindful of infection control. The impact of the COVID-19 pandemic on this study is discussed in more detail in the *Methodology* (Chapter 3).

Chapter summary

This *Introduction* chapter described drug related problems (DRPs), Clinical Pharmacy and prioritisation of Clinical Pharmacist's workload. The *Introduction* also described health service provision in Ireland and more specifically in Sligo University Hospital and the impact of COVID-19 on these.

The next chapter (Chapter 2) is comprised of the systematic review that was conducted as part of this thesis to identify published primary research looking at screening tools used by Clinical Pharmacists used to identify older (medical) patients at risk of DRPs.

Chapter 2: Systematic Review

The content for this chapter has been published as:

Brady A, Curtis CE, Jalal Z. Screening Tools Used by Clinical Pharmacists to Identify Elderly Patients at Risk of Drug-Related Problems on Hospital Admission: A Systematic Review. Pharmacy (Basel). 2020 Apr 10;8(2):64. doi: 10.3390/pharmacy8020064. PMID: 32290347; PMCID: PMC7355869

The content of this publication was co-authored by the Academic Supervisors for this thesis, Chris E Curtis and Zahraa Jalal.

The formatting of this Chapter is as per publication.

Chapter description

This chapter is composed of a systematic review (SR) of the published literature looking at screening tools used by Clinical Pharmacists to identify those older medical patients most likely to be at risk of drug related problems (DRPs), and related research(80). The SR was conducted to identify potential risk factors for DRPs that could be incorporated into primary research undertaken as part of this thesis. The SR was co-authored by the Academic Supervisors for this thesis, Dr Chris E Curtis (CEC) and Dr Zahraa Jalal (ZJ), and has been published in *Pharmacy (Basel)* from whom consent has been obtained to include the published SR in this thesis. The formatting of (and use of the term 'elderly[1]' in) this Chapter is as per publication.

The following describes the contribution of the authors in conducting and writing this SR:

"**Author Contributions:** Conceptualization, A.B., C.E.C., and Z.J.; methodology, A.B., C.E.C., and Z.J.; validation, A.B., C.E.C., and Z.J.; formal analysis, A.B.; data curation, A.B.; writing—original draft preparation, A.B.; writing—review and editing, C.E.C. and Z.J.; supervision, C.E.C. and Z.J. All authors have read and agreed to the published version of the manuscript"(80).

pharmacy

MDPI

Review

Screening Tools Used by Clinical Pharmacists to Identify Elderly Patients at Risk of Drug-Related Problems on Hospital Admission: A Systematic Review

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Received: 26 February 2020; Accepted: 8 April 2020; Published: 10 April 2020



Abstract: In recent years, a number of studies have examined tools to identify elderly patients who are at increased risk of drug-related problems (DRPs). There has been interest in developing tools to prioritise patients for clinical pharmacist (CP) review. This systematic review (SR) aimed to identify published primary research in this area and critically evaluate the quality of prediction tools to identify elderly patients at increased risk of DRPs and/or likely to need CP intervention. The PubMed, EMBASE, OVID HMIC, Cochrane Library, PsychInfo, CINAHL PLUS, Web of Science and ProQuest databases were searched. Keeping up to date with research and citations, the reference lists of included articles were also searched to identify relevant studies. The studies involved the development, utilisation and/or validation of a prediction tool. The protocol for this SR, CRD42019115673, was registered on PROSPERO. Data were extracted and systematically assessed for quality by considering the four key stages involved in accurate risk prediction models—development, validation, impact and implementation—and following the Checklist for the critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS). Nineteen studies met the inclusion criteria. Variations in study design, participant characteristics and outcomes made meta-analysis unsuitable. The tools varied in complexity. Most studies reported the sensitivity, specificity and/or discriminatory ability of the tool. Only four studies included external validation of the tool(s), namely of the BADRI model and the GerontoNet ADR Risk Score. The BADRI score demonstrated acceptable goodness of fit and good discrimination performance, whilst the GerontoNet ADR Risk Score showed poor reliability in external validation. None of the models met the four key stages required to create a quality risk prediction model. Further research is needed to either refine the tools developed to date or develop new ones that have good performance and have been externally validated before considering the potential impact and implementation of such tools.

Keywords: clinical pharmacy; risk assessment tools; frail elderly; hospital care

1. Introduction

A drug-related problem (DRP) has been defined as 'an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcome' [1]. DRPs can cause serious harm, hospital admissions, increased health care costs and even death and are known to be prevalent in elderly patients both in the community and in the hospital setting [2]. DRPs include medication errors, adverse drug reactions (ADRs), and adverse drug events (ADEs) [3]. Elderly (or older)

people, defined as those aged 65 years and over [4,5] with multiple co-morbidities receiving multiple medicines for management/treatment of long-term illness are prone to adverse drug reactions and are likely to be more susceptible to adverse drug events in general [2]. The "oldest-old" are a subgroup of elderly people, defined by the WHO as those aged 80 years and older [5]. The reported percentages of ADRs for all hospitalized patients vary between 2.4% and 10.9% [6], with a higher incidence of ADRs in older people, as they are prescribed significantly more drugs than younger individuals, and older people are nearly seven-times more likely to be hospitalized due to an ADR compared to younger people [6,7]. A number of studies have aimed to determine the risk factors associated with ADEs, ADRs and/or DRPs which may help to identify patients at risk of such events and prioritise these (high risk) patients for intervention [7,8]. The authors of a previous systematic review (SR) concluded that failure to consider risk prediction in a clinical setting can result in poor care and many guidelines have recommended incorporating life expectancy into clinical decisions to help target services to those who might benefit the most [9], such as in decisions to discontinue breast, colon and prostate cancer screening based on age and life expectancy [10–12].

A simplistic definition of inappropriate prescribing is that it is "The practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist" [13]. Inappropriate prescribing encompasses potentially inappropriate medications (PIMs) (misprescribing and overprescribing) and potential prescribing omissions (PPOs) or underprescribing [14,15]. Inappropriate prescribing is highly associated with an increased risk of adverse drug events especially in older patients with poly pharmacy who are more vulnerable [15]. In their review of inappropriate prescribing, O'Connor et al. commented that "given the complexity of prescribing decisions in the elderly a more holistic definition of inappropriate prescribing should encompass the assessment of older persons' prescription medications in the context of their multiple co-morbidities, complex medication regimes, functional and cognitive status, treatment goals and life expectancy" [14]. Whilst not exclusive to the elderly, the prescribing of potentially inappropriate medications to older people has been shown to be highly prevalent, with rates ranging from 12% for community-dwelling elderly to 40% in nursing home residents [16]. Inappropriate prescribing is associated with adverse drug events [16]. A number of tools have been developed to measure and assess medication appropriateness in older people which can be measured and assessed by using, for example, the Medication Appropriateness Index (MAI). In addition, inappropriate prescribing criteria sets such as the STOPP/START criteria can be applied to medication lists. However, these tools can be time consuming to utilise, which currently limits their use in routine clinical practice [17].

It is well recognised both within Europe and internationally that there is a need to prioritise pharmaceutical care [18,19]. Hospital clinical pharmacists are a limited and expensive resource, making routine screening of all Emergency Department patients by pharmacists unsustainable [20]. Within the National Health Service (NHS) in the United Kingdom, it is recognised that "Clinical pharmacists cannot review all patients every day" [19] and that "to allocate clinical pharmacist resource where it is most needed, patients' pharmaceutical care needs must be assessed and prioritised accordingly" [19]. In America, a $0.5 million research grant was awarded by the American Society of Health-System Pharmacists to develop and validate a pharmaceutical complexity scoring tool [18]. Pharmacists cannot identify and manage all drug-related problems but need to prioritise and "identify those drug-related problems for which management or prevention would result in the greatest benefit for as many patients as possible" [21]. In a recently published article looking at prioritising pharmaceutical care, the authors commented that there is an "urgent need for pharmacy departments to prioritise which patients need direct pharmaceutical care on a daily basis" [18].

There is limited published literature about the current imperfect use of pharmaceutical care priority screening tools in UK hospitals [18]. In recent years, a number of researchers have looked at identifying risk factors for drug-related problems (DRPs) and developing screening and acuity tools to help prioritise clinical pharmacist workflow, and research continues to develop such tools both in the UK and abroad [18,22]. A SR published in 2016 found 38 studies (that met their inclusion criteria)

that identified measurable risk factors associated with adult hospital inpatients that potentially lead to a pharmaceutical intervention [23]. Stevenson et al. conducted a SR of risk prediction models used to predict ADRs in older adults [7]. They included studies that developed and validated an ADR prediction model for use in patients over 65 years old, using a multivariable approach in the design and analysis; only four studies met the inclusion criteria for the SR, emphasising the deficit in published research on this topic in this subgroup of patients (hospital inpatients aged over 65 years) [7]. Stevenson et al.'s SR included only four studies, and additional studies have been published since 2014. Furthermore, a quality assessment of studies could not be generated in Stevenson et al. [7]. This paucity of evidence was the driver to carry out a systematic review of the literature to (1) identify any existing primary research that involves the development and/or utilisation and/or validation of a prediction tool or risk score system to identify those patients most likely to experience DRPs and/or benefit from hospital pharmacist intervention, and (2) critically evaluate the quality of the identified research. In particular, this SR aimed to identify and focus on any research that includes or is specific to elderly patients (aged over 65 years old).

2. Materials and Methods

2.1. Data Resources

A systematic search of research articles published in peer-reviewed health care-related journals was performed. The following databases were searched from inception until April–May 2018 with no date restrictions applied: PubMed, Embase, OVID HMIC, Cochrane Library, Psychinfo, CINAHL PLUS, Web of Science, and ProQuest.

These databases were selected based on previous SRs conducted by pharmacist researchers with similar aims. The titles of all papers (n=1030) were screened and, if the title suggested that the paper might be relevant to the topic (prediction tools and/or risk factors for DRPs), the abstracts (where available from search databases) were reviewed by the principal researcher (AB). Following this review of titles and abstracts, full-text publications were accessed for all potentially relevant papers and evaluated through intensive reading by the principal researcher. Details of all sourced full-text articles were tabulated to allow validation of a final list of citations and for a final list of included papers to be drawn up. Details of any articles for which there were queries were also tabulated and were referred to two independent reviewers (CC and ZJ). The reviewers considered the queries separately and then the three researchers discussed each individual query paper and reached consensus on whether it should be included in the SR. From the search of the eight databases, eight papers were identified that met the inclusion criteria.

A number of additional papers (11 further papers) were identified for inclusion in this SR (these papers were found in the initial scoping search and in the databases, and duplicates were removed). An internet search using the search engine Google Scholar was used as part of a scoping exercise when the principal researcher was initially considering conducting research in this area in order to gauge the amount of published research on this topic. From this search, a relevant systematic review published in 2014 was identified assessing the use of risk prediction models to predict adverse drug reactions in older people [7]. The systematic review (which was not itself included in this SR, as it did not meet the inclusion criteria) identified four relevant papers; these four papers were sourced and reviewed to determine whether they were relevant for inclusion in this systematic review.

An additional paper was also identified whilst trying to locate the full-text article of one of the papers included in the aforementioned SR, namely a paper by Tangiisuran B. [24], which led to the identification of another paper by Tangiisuran B. et al. [25] reporting the same research, namely the BADRI risk prediction model; these two papers describe the same research and have been considered as a single piece of research in this SR.

Another four papers were identified having been referenced or mentioned in one of the 8 papers from the search of the medical databases. Three further papers were identified through keeping up to date with research publications and from a review of relevant conference proceedings.
A total of 19 papers were identified and included in the SR through the systematic search of eight medical databases and other methods described as summarised in Figure 1.

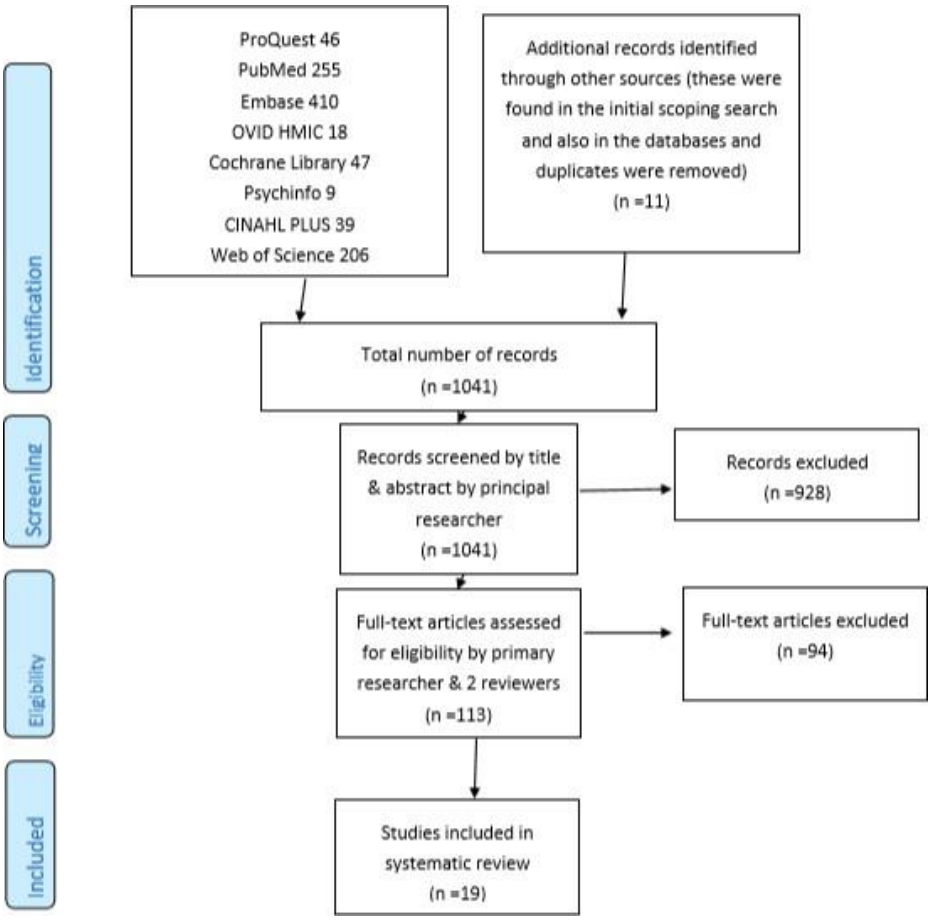


Figure 1. PRISMA flow diagram.

2.2. *Data Extraction*

Results were extracted and tabulated according to the papers included in the SR, population characteristics, sample size, study setting, whether the study examined at development, utilisation and/or validation of prediction tool, study outcomes, risk tools and performance of risk tools.

2.3. *Search Terms and Search Strategy*

PICOS is a framework designed to make the process of defining and designing a research question easier, where PICOS stands for: P Population/Patient, I Intervention, C Comparison, O Outcome, and S Study Design [26]. The author referred to the principles of the PICOS method to formulate a search strategy and select keywords relevant to the current research.
In view of the structural and content-related differences between the databases, particularly between the indexing and thesauri/controlled vocabulary used by PubMed (Medical Subject Headings, MeSH) and EMBASE (Emtree) a number of different search terms and combinations of terms were used. A combination of MeSH/Emtree and free-text search terms were used. The search terms included synonyms and various combinations of the following keywords “elderly”, “pharmacist”,

"hospital", "risk", "risk factor" and "risk assessment," with the combinations used reflecting the specific search capabilities of the different databases. For example, for those databases identifying a comparatively large number of articles from a search using the terms "elderly", "pharmacist" and "hospital", additional terms relating to risk were added to narrow the search to focus upon more relevant articles. Keywords not listed as MeSH or Map Terms were searched as phrases using the free-text search mode. A further list of search terms was generated by referring to a previous review with similar aims [7]. The reference list of relevant papers was also searched in order to identify any additional studies. Duplicate articles were removed if they were found in the different databases.
The search strategy appears in File S1, PubMed search strategy. This was supported by use of a checklist File S2 PRISMA 2009 checklist to ensure that PRISMA principles were followed during the process.
The following combination of search terms was used when conducting the scoping exercise (already described) on Google Scholar: +risk tool +elderly +drug-related problems.
Figure 1 summarises the number of potentially relevant papers that were identified and the final number included in the SR, based on (a simplified version of) the PRISMA flow diagram.

2.4. Inclusion and Exclusion Criteria

2.4.1. Paper Inclusion Criteria

Inclusion criteria for the SR included studies published in the English language, primary research/studies including (but not exclusively) patients aged 65 years and over, inpatients in secondary or tertiary care centres (hospitals), medically admitted patients, where interventions take place in the hospital setting, all primary research and research for which the full-text article was available for review.

2.4.2. Paper Exclusion Criteria

Exclusion criteria for the SR included systematic reviews; literature reviews; meta-analyses; summary articles; discussion articles; conference proceedings; editorials; surgically admitted patients; studies solely in patients in specialist care settings, e.g., intensive care or psychiatry (but not geriatric/older persons wards); studies looking at specific areas, e.g., blood glucose or HbA1c control or dementia; studies conducted in community pharmacy, primary care settings, outpatients or attending outpatient clinics (e.g., diabetes, heart failure clinics), those in ambulatory care and patients (solely) aged
<65 years; studies where one or more of the interventions took place in the home/community setting; studies that focussed solely on interventions at the point of or following hospital discharge/transition. The SR excluded proposals for research (e.g., published research protocols) for which results had not been published (in journals included in the selected databases)/were not available through the databases used and research where only the abstract was available for review. In addition, studies using a set of arbitrary or predetermined factors incorporated in a tool/scoring system that were not developed or tested with any statistical analysis methods (such as regression analysis) to determine relevance of the variables were excluded.

2.4.3. Critical Appraisal and Data Extraction for Included Studies

The studies identified via the searches were initially reviewed by the principal researcher considering the four key stages involved in accurate risk prediction models—development, validation, impact and implementation—as described by Petrovic M. [27]. To assess the bias and quality of the included studies in a systematic manner, the Checklist for the critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) was used by the principal researcher to critically appraise the studies. The items extracted using the checklist were then tabulated into Excel spreadsheets—the format of which was influenced by the tabulated results included in a recently published systematic review relevant to this topic by Falconer N. et al. [28].
The protocol for this SR, CRD42019115673, was registered on PROSPERO [29].

3. Results

Nineteen papers were included in the SR, and the citations are included in Table 1.

Table 1. Table showing the papers included in this systematic review (SR).

Author	Tool
Tangiisuran B. et al. [25] (note: this research was also reported in PhD thesis [24] but only counted as one piece of research in this SR)	BADRI model
Onder G. et al. [30]	GerontoNet ADR Risk Score
Trivalle C. et al. [31]	A geriatric score
O'Connor M.N. et al. [32]	GerontoNet ADR Risk Score
Alassaad A. et al. [33]	The 80+ score
Suggett E. [34]	Risk scores to identify patients who were at high risk of (hospital) pharmacist intervention (no specific name for score stated by authors)
Hohl C.M. et al. (2017) [35]	Clinical decision rules
Hohl C.M. et al. (2012) [20]	Clinical decision rules
Bonnerup D.K. et al. [36]	MERIS score
Kaufmann C.P. et al. (2018) [37]	Drug-Associated Risk Tool (DART)
Falconer N. et al. (2014) [38]	Assessment of Risk Tool (ART)
Falconer N. et al. (2017) [39]	Assessment of Risk Tool (ART),
McAuliffe L. et al. [40]	MEDCOINS score
McElnay J.C. et al. [41]	A predictive model for adverse drug events (ADEs) in elderly patients (no specific name for model stated by authors)
Urbina O. et al. [3]	A score that quantifies the risk of a DRP during hospital admission (no specific name for score stated by authors)
Hickson R.P. et al. [18]	Pharmaceutical assessment screening tool (PAST)
Saedder E.A. et al. [42]	MERIS score
Petrovic M. et al. [43]	GerontoNet ADR Risk Score
O'Mahony D. et al. [44]	The adverse drug reaction risk in older persons (ADRROP) prediction scale

3.1. Included Papers

Full details of the data extracted from the included studies are included in the Supporting Information, Table S1.

3.2. Population Characteristics: Age

All of the studies were conducted in the hospital setting and, as per inclusion criteria, in adult patients. Seven of the studies were carried out exclusively in elderly patients (aged 65 years and over) [25,30–32,41,43,44] and only the very elderly (aged 80 years and over) were represented in a further study [33]. Two studies [18,38] did not report the age demographics of the study participants (although participants were adults). The remaining studies were conducted in adult patients (including but not exclusively elderly patients) [3,20,34–37,39,40,42]. The majority of the studies presented either the mean or median age for participants, with the mean age of participants

varying from 51.4 years [20] to 86.7 years [33], showing significant variations between the participants of the various studies.

3.3. Population Characteristics: Gender

There were significant differences in the gender profiles for participants in the differing studies, with four studies [18,30,38,42] not reporting this characteristic; in the remaining fifteen studies, female participants represented 46%–72% of the sample populations, so there were significant differences between the study populations with regard to this, with differences also observed between those included in the development and individual validation studies carried out by the same researchers, e.g., females accounted for 49% of participants in the first validation study conducted by Kaufmann et al. in 2018, compared to 61% of participants in the second validation study after the questionnaire was revised [37].

3.4. Population Characteristics: Ethnicity

Ethnicity was only reported in two of the studies [25,38], with 88% white-British ethnicity reported in one study [38] and 51.1% European, 23% Pacific Island decent, Maori and 13.6% 'others' (25) in the second study.

The other study was conducted in New Zealand and the population that the hospital served was described as being "an ethnically diverse population largely consisting of people of Maori and Pacific descent, with a high proportion of the population living in the most socio-economically deprived communities" [38]. This highlights significant differences between the populations where the two studies that reported participant ethnicity were conducted (Brighton, UK compared to New Zealand).

3.5. Population Characteristics: Number of Study Participants

The number of participants included in each study varied significantly from 35 patients [18] to 10,807 [35].

3.6. Development/Modelling, Utilisation or Validation of Assessment Tools

Different studies examined the development/modelling, utilisation or validation of an assessment tool and combinations of these phases. Validation of the majority of studies was internal, whilst four provided external validation [20,30,32,43], and one of these studies included both internal and external validation [25]. The majority of studies used separate populations to develop and subsequently validate their tools, whilst two studies [31,33] used the same populations and used bootstrapping techniques to test the developed tool and a third used internal cross validation methods [40]. Overall, nine of the studies involved the development (or adaptation of a draft version of a tool) and internal validation of the assessment tool [3,18,31,34,40–42,44]. One study involved the development and external validation of a tool [30], whilst another involved the development, internal and external validation of a tool [25]. One study [20] only described the development of an assessment tool (which was subsequently utilised in a further study; see below [35]); another study described the development and subsequent utilisation (rather than validation) of a tool [38], four studies described the utilisation or internal validation of a previously developed tool [35–37,39], and two studies provided external validation (only) of the previously developed GerontoNet ADR Risk Score [32,43].

3.7. Study Setting (Country/Countries)

The majority of the studies (74%) were conducted in European centres [3,18,25,30–34,36,37,41–44], and the remaining studies were conducted in New Zealand [38,39], Canada [20,35] and the US [40]. In two of the European-based studies [25,30], the development phase took place in Europe and the developed tools were then externally validated within centres in four European countries (and also internally validated in one of the studies [25]). The GerontoNet ADR Risk Score was developed and

externally validated in Europe [30] and subsequently externally validated in two further European studies [32,43].

3.8. Primary Outcomes of the Studies

The primary outcomes for the studies varied significantly. Five studies assessed the incidence (or rate) of ADRs [25,30,32,43,44] and another three studies looked at the incidence (or rate) of ADEs [20,31,41]. There were also subtle differences between studies with the same broad primary outcomes with respect to definitions/interpretations—for example, one study looked at the incidence of "non-trivial ADRs" [44] and another specified that their primary outcomes were ADEs that required a change in medical therapy, diagnostic testing, consultation, or hospital admission [20]. The primary outcomes for the remaining studies were more specific/individual to each study and included the incidence of medication errors per patient [42], prescribing errors (PEs) [36], medication discrepancies on medication reconciliation at admission and Pes [39], time to rehospitalisation or death during the year following discharge [33], the number of DRPs per admission [3], the rate of potentially avoidable hospital readmission at 30 days [40] and the rate of pharmacist interventions [34]. These variations in the primary outcomes (and even differences in the exact definitions included within these primary outcomes) made it difficult to compare or collate the results and findings of the different studies, as they were not measuring the same parameters.

3.9. Number of Risk Factors Included in Risk Scores/Tools

The number of risk factors identified by and included in the risk scores/tools ranged from three [36,40,42] to thirty eight [38]. One study described the development of two clinical decision rules (CDRs) containing seven and four risk factors respectively [20]; in a subsequent study by the same researchers, a modified ADE CDR was used which was composed of five risk factors [35]. One study identified thirty eight flags for inclusion as part of an Assessment Risk Tool (ART) [38]; in the subsequent validation study reported in 2017, twenty five of these ART flags were included—four of which were found to be significantly associated with at least one unintentional medication discrepancy [39].

3.10. Identification of Risk Factors

The risk factors included in the various studies and tools/scores were identified via a number of methods—these included clinical judgement, from literature review (alone), patient characteristics/variables and by combinations of methods. For example, one study identified possible risk factors from available study data (demographic and clinical details) and previously established risk factors from published reports [44]. In another study, five consecutive steps (literature search, Delphi process, construction of algorithm, calibration of algorithm, and prospective pilot study) were used to develop the algorithm [42].

3.11. Statistical Analysis

Statistical analysis was conducted and reported to determine the performance of the various tools/models in seventeen of the nineteen studies [3,18,20,25,30–34,36,37,39–44], but there was variation in the extent and types of statistical analyses conducted. In the other two studies [35,38], the development of a tool was described but validation of the tool was not conducted (38); statistical analysis was conducted to determine the value of medication review by pharmacists of patients identified by the CDR but not to evaluate the performance of the CDR itself [35].

3.12. Methodologies for Development of Point Scores

Different methods were used in the various studies to develop the point scores for the tools/models described. In 15 of the studies, the methodology described the weighting system used for the different variables included in the scores—of which, 14 were individualised for the different variables [3,30–34,36,38–44], whilst one assigned arbitrary weighting to the variables [25]. Four of the

14 studies with individualised weighting were based on theoretical weighting [36,42] or determined via group consensus [38,39]; the exact methodology used for determining weighting was unclear in one study [41] (although odds ratios and beta coefficients were calculated and included in the write up). In the remaining nine (of the 14) studies, the methodologies described the calculation and use of odds ratios, beta coefficients and regression coefficients to determine weightings of individual variables. Four studies did not report on the calculation of weightings of variables in risk scores; in one study, no score was calculated [37], whilst the levels of risk were assigned by meeting set criteria for following an algorithm in the remaining three studies [18,20,35].

3.13. Performance of Risk Score/Tool/Model: Sensitivity, Specificity and/or Discriminatory Ability

The majority of the studies reported on the sensitivity, specificity and/or discriminatory ability of the risk score/tool/model. Sensitivity and specificity were reported in six of the studies [20,25,30,37,41,42], and discriminatory ability (including AUC/AUROC/AUCROC, C-statistics) or overall accuracy was reported in thirteen of the studies [3,25,30–34,39–44] including four studies, where sensitivity, specificity and discriminatory ability were all reported [25,30,41,42]. There were four studies which did not report sensitivity, specificity or discriminatory ability/overall accuracy of the scores/tools [18,35,36,38]. These results are summarised in Table 2.

3.14. Sample Size and Power of Study

The events per variable (EPV) ratio is often used to assess the adequacy of the sample size when developing a risk model. The EPV ratio "is calculated by using the number of outcomes divided by the number of candidate predictor variables in the development cohort" and a minimum EPV ratio of 10 is usually recommended {28]. The results show that only two studies had adequate sample sizes using the EPV ratio>10 rule [3,30]. The remaining studies that involved the development of a risk model/tool either did not contain an adequate sample size [25,33] or the details were unclear or not reported in these studies. In the case of one study [38], the tool consisting of 38 variables or risk factors was developed from consensus opinion rather than modelling methods and so the EPV ratio was regarded as not applicable in this instance.

In the validation studies, only four studies [3,32,35,39] were sufficiently powered (with >100 events), and the remaining validation studies were either underpowered or there was not sufficient information to accurately assess this parameter [28].

3.15. Quality of Included Studies

Six (32%) of the included studies described how missing data were handled [20,25,35,37,40,43]. In the remaining studies, it was either unclear or not reported how missing data were handled. From the papers describing the studies, study outcomes were assessed blinded in six studies [18,20,35,36,39,42]. It was either unclear or not reported whether study outcomes were assessed blinded in the remaining studies. Only two of the studies [3,30] that included the development of a tool using modelling methods (excluding, for example, the development of a tool by consensus methods rather than modelling [18]) reported a sufficient sample size using the "rule of thumb" of the EPV ratio>10 that is commonly adhered to by researchers when developing prediction tools [28]. In the validation studies or those studies with a separate validation arm, only four [3,32,35,39] reported a sufficient event rate to suggest that the (validation) study was adequately powered (with >100 events reported). In the remaining studies, the sample size or powering was either insufficient or not clearly reported.

Table 2. Table showing the reported sensitivity, specificity, discriminatory ability and overall accuracy of the risk scores/tools used in each study.

Author	Sensitivity	Specificity	Other			
			Discriminatory Ability: AUROC/AUCROC	**Discriminatory Ability: C-statistic**	**Overall Accuracy**	**Other**
Tangiisuran B. et al.	80.0% for internal validation; 84% for external validation	55.0% for internal validation; 43% for external validation	0.74 (95%CI = 0.68–0.79) for internal validation; 0.73 (95%CI = 0.66–0.80) for external validation			
Onder et al.	68% (development)	65% (development)	0.71 (95% CI = 0.68–0.73) (development) 0.70 (95% CI = 0.63–0.78) (validation)			
Trivalle et al.	n/r	n/r	0.70 (95% CI = 0.635–0.74)			
O'Connor et al.	n/r	n/r	0.62 (95% CI = 0.57–0.68) on admission (lower on subsequent days, days 5 & 10 post-admission)			
Alassaad A. (&et al)	n/r	n/r		0.71		
Suggett E.	n/r	n/r	0.607 for main data; 0.616 for validation data			
Hohl et al (2017)	n/r	n/r	n/r	n/r	n/r	
Hohl et al (2012)	1) More sensitive rule (ADE rule) 96.7% (95%CI = 91.8–98.6%)	1) 40 3%				
	2) More specific rule (Adverse Drug Reaction Rule) 90.8% (95%CI = 81.4–95.7%)	2) 59.1%				
Bonnerup et al.	n/r	n/r	n/r	n/r	n/r	
Kaufmann et al.	67% average (range = 21–100)	88% average (range = 27–100)	n/r			
Falconer et al. (2014)	n/r	n/r	n/r	n/r	n/r	
Falconer et al. (2017)	n/r	n/r	0.72 (95%CI = 0.66–0.78) to predict at least one unintended medication discrepancy; from score from 2 flags (>8 regular admission medicines and readmission within 30 days of discharge)			

Table 2. *Cont.*

Author	Sensitivity	Specificity	Other			
			Discriminatory Ability: AUROC/AUCROC	**Discriminatory Ability: C-statistic**	**Overall Accuracy**	**Other**
McAuliffe et al.	n/r	n/r		0.65 (95%CI = 0.60–0.70)		Hosmer-Lemeshow goodness-of-fit = 0.99
McElnay et al.	41% (validation)	69% (validation)			63%	
Urbina et al.	n/r	n/r	0.778 (95% CI = 0.768–0.789) (training set); 0.776 (95%CI = 0.759–0.792) (validation set)			Hosmer-Lemeshow goodness-of-fit = non-significant (p = 0.13) (validation set)
Hickson et al.	n/r	n/r	n/r	n/r	n/r	n/r
Saedder et al.	0.64 (for final version of MERIS)	0.75 (for final version of MERIS)	0.76, 0.87, 0.74, 0.66 for final MERIS score in different populations within study			
Petrovic et al.	n/r	n/r	0.64 (95%CI = 0.55–0.74) to predict ADRs probably or definitely related to drug use; 0.69 (95%CI = 0.60–0.77) for predicting Type A ADRs; subgroup analysis: AUC = 0.70–0.79 and 0.80–0.89			
O'Mahony et al.	n/r	n/r	0.623 (95% CI = 0.598–0.665) (derivation cohort); 0.592 (95%CI = 0.532–0.652) (vallidation cohort)			

n/r = not relevant.

4. Discussion

The population characteristics, methodologies, primary outcomes and presentation of results of the nineteen studies included in this SR vary significantly, making quantitative synthesis of their findings and meta-analysis unsuitable for this review. Instead, narrative synthesis of the findings was conducted and presented.

The results of this SR do not currently support the use of any of the models identified in routine clinical practice, similar to the findings of a previous SR [7]. Only four of the nineteen studies included any external validation [25,30,32,43]. External validation would provide confidence that a particular model's predictive ability is reliable across different populations and settings. Even in the four studies which incorporated external validation, there were limitations to usefulness of the models/scores involved as outlined below

The sensitivity of a predictive model measures the ability of the model to correctly predict (identify) individuals who will experience the outcome (e.g., who have an ADR) (true positive), whilst specificity is a measure of the true negative rate of the model, measuring the ability of the model to correctly predict those individuals who will not experience the outcome (e.g., an ADR). Whilst a satisfactory level of sensitivity of 80% was reported for the BADRI model, its low specificity of 46% meant that "the model may incorrectly label patients 'at risk of an ADR' who will not ordinarily go on to experience such an event" [25].

The GerontoNet ADR Risk Score (developed by Onder et al.) showed comparable discriminatory ability to the BADRI model (with AUROC of 0.71 in the development phase for the GerontoNet ADR Risk Score and 0.74 for internal validation of the BADRI model) but the sensitivity for the GerontoNet ADR Risk Score was lower than that for the BADRI model (68% and 80% respectively); the specificity of both models was low but the specificity was higher for the GerontoNet ADR Risk Score (at 65%) compared to the BADRI model (at 55%) [25,30].

External validation of the GerontoNet ADR Risk Score [32] identified an AUC value of 0.62 (on admission) and also reported that the score incorrectly classified 38% of patients as being at low risk of ADRs [32], showing poor performance of the score [43].

A second published external validation for the GerontoNet ADR Risk Score [43] reported that AUC values of 0.64 and 0.69 were calculated to predict (1) ADRs probably or definitely related to drug use and (2) type A ADRs (type A (intrinsic) reactions are those that are usually predictable from the known pharmacology of a drug), respectively. From the researchers' own definitions of model performance, these AUC values show poor performance of the GerontoNet ADR Risk Score. In particular in subpopulations of older hospitalised patients, the GerontoNet ADR Risk Score was found to have fair to good diagnostic accuracy, with AUC values of 0.70–0.79 and 0.80–0.89. It was concluded that the GerontoNet ADR Risk Score could be adopted for use in older patients belonging to the specific subpopulations; these findings suggest that the GerontoNet ADR Risk Score may not be suitable for routine clinical use in the general elderly (65 years and over) hospital in-patient population for which it was originally developed [43].

Limitations

There are a number of possible limitations to this SR. The search strategy used to identify relevant studies included "pharmacist" as an essential search term. Whilst this was deemed appropriate, as the focus of the SR was prioritising patients for pharmacist review, it is possible that other research that identified risk prediction models for elderly patients experiencing DRPs could have been excluded if they did not include a pharmacist in the study methodology; such studies may have provided useful insight into factors and models to predict the likelihood of DRPs in elderly in-patients. To minimise the potential for "missing" relevant studies, the PICOS framework was used to formulate the search strategy, and all three researchers extensively discussed the choice of search terms to be used. Due to the heterogenous nature of the methodologies and patient demographics, the outcomes and reporting of results, it was not possible to conduct a meta-analysis and instead a qualitative analysis was conducted.

However, the CHARMS checklist was used to try to systematically assess the quality of the included studies and minimise subjectivity. It is recognised that it was difficult to assess bias due to the relatively small number of studies (insufficient), heterogeneity and the lack of preregistered protocols [45].

5. Conclusions

The findings from this systematic review show that a number of tools have been developed for use in the (acute) hospital setting for assessment of the risk of older people experiencing drug-related problems, including ADRs and AEs. The tools developed to date vary in their complexity, outcome measures and how their performance has been validated. There is no definitive validated assessment tool which is in widespread use for this group of patients. None of the tools identified in this SR "satisfied the four key stages in the creation of a quality risk prediction model" (7)—development, validation, impact and implementation. Whilst research to date has focused on the development and validation of such tools, further work is needed to assess the potential impact of utilising the tools and their implementation.

Supplementary Materials: The following are available online at http://www.mdpi.com/2226-4787/8/2/64/s1, File S1 PUBMED search strategy, File S2 PRISMA Checklist, and Table S1: Summary of results.

Author Contributions: Conceptualization, A.B., C.E.C., and Z.J.; methodology, A.B., C.E.C., and Z.J.; validation, A.B., C.E.C., and Z.J.; formal analysis, A.B.; data curation, A.B.; writing—original draft preparation, A.B.; writing—review and editing, C.E.C. and Z.J.; supervision, C.E.C. and Z.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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Explanation of Presentation of Figure 1: PRISMA Flow Diagram in the Systematic Review

The reasons for articles being excluded from the systematic review (SR) were diverse and, in many instances, multifactorial. As a result, the number of articles (/studies) excluded at the different stages of the screening and review process were summarised in Figure 1 of the SR but a breakdown of the specific reasons was not included. Broadly, as summarised in section 2.4.2 of the published SR, the reasons for study exclusion from the SR were that the studies either failed to meet the explicit inclusion criteria, the full paper was not available in English or the research was presented as part of Conference proceedings (rather than as a full published paper), despite using relevant search terms and criteria/limits in the relevant database search strategies. Examples of reasons for research studies failing to meet the inclusion criteria included some not describing primary research, not incorporating a screening tool/model or equivalent (to identify patients, as per the title of the SR), research relating to a specialist clinical area e.g. cardiology ward or outpatient models, and where specific risk factors for drug related problems were not studied rather (the impact of) overall pharmacist input.

Chapter summary

This chapter described a systematic review (SR) that was conducted of the published literature looking at screening tools used by Clinical Pharmacists to identify those older medical patients most likely to be at risk of drug related problems (DRPs). The SR identified a number of potential risk factors for DRPs from the included published studies.

The next chapter (Chapter 3), *Methodology*, describes the methodology adopted to conduct the primary research undertaken as part of this thesis, which is guided by the findings of the SR with respect to potential risk factors for DRPs.

Chapter 3: Methodology

Methodology

Chapter description

This *Methodology* chapter describes the methodology adopted as part of the primary research undertaken for this thesis, to develop a prediction tool to identify older patients for early Clinical Pharmacist review at Sligo University Hospital. It describes the statistical analysis and modelling processes undertaken and discusses the rationale for decisions made relating to them.

The influence of the Systematic Review on the methodology of this research

The findings of the systematic review (SR) described in the previous chapter (Chapter 2) guided the methodology adopted in this current primary research (undertaken as part of this thesis) and the potential variables studied. There was much heterogeneity between the number and choice of variables included in the different models described in the prior research, with the number of variables ranging from 3 to 38. The potential variables selected for inclusion in this study were identified and chosen on the basis of their presence in (final versions of) models developed in the studies included in the SR, particularly those variables that were incorporated in more than one/several of the models described (adding confidence to their relevance). The selection of variables from the studies included in the SR was also influenced by the ability to measure the variables in the course of usual clinical practice for Clinical Pharmacists at SUH. The number of medicines taken (either pre-admission or the medicines prescribed on admission), for example, is a variable that featured in the vast majority of the (final) models described in the studies in the SR. Data on some variables included in other developed models, e.g. presence and number of STOPP (Screening Tool of Older People's Prescriptions)-criteria potentially inappropriate medications and length of stay would not be readily available to Clinical Pharmacists at SUH at the time of admission (due to limitations on information technology systems used at SUH, and the fact that information on length of stay for current admission would only be available retrospectively) and so these variables would not have been considered for inclusion in the list of potential variables to be studied in this current research. Information on the potential variables

included in the study and their incorporation in the previously developed models (as described in the SR) is summarised later in this chapter.

Conducting the SR and reviewing the papers included with respect to their methodologies influenced the methodology adopted in this current primary research. A prospective design was chosen for this current study, similar to the approach adopted by McElnay *et al.*(81). A prospective cohort design is the preferred method for model development, enabling optimal measurement of prognostic factors and outcome events(82). A number of the external validation studies for other models included in the SR also identified patients prospectively, such as the use of the CRIME cohort for external validation of the GerontoNet score(83). An alternative approach, which was adopted by some of the researchers developing and/or validating a number of the different models included in the SR, would have been to use retrospective patient populations. The use of retrospective patient populations provides advantages such as reduced time and costs associated with conducting the research, ease of access, the ability to examine long-term trends and outcomes and, in some cases, the ability to pool data from a number of different study populations (thus increasing the sample size), but can be more susceptible to sources of bias and confounding(84). The prospective cohort design was felt to be best suited to the needs of the current research, particularly as no retrospective patient population data was available at the site of the current research, SUH.

Research question

Can a tool be developed that will predict which older medical inpatients admitted to hospital are most likely to benefit from early Clinical Pharmacist review and intervention(/s)?

Aims

The overall aim of this research is to identify older (medically admitted) patients requiring Clinical Pharmacist review and interventions and potentially prioritise these patients for early Clinical Pharmacist review at Sligo University Hospital (SUH). This can be done by determining if there is an

association between potential risk factors for drug related problems (DRPs) (as identified from the earlier systematic review) and the number of Clinical Pharmacy interventions received by older medically admitted in-patients at SUH. The data will be analysed to determine whether any of these predefined risk factors can help in prioritising older patients for pharmacist review and develop a clinical prediction model/tool (CPM) for local use at SUH.

Objectives

The overall objectives of this research are to:

1) Produce a list of potential risk factors for DRPs from the systematic review and define risk factors for local interpretation and measurement at SUH.
2) Identify study population (prospectively) via Clinical Pharmacists visiting the selected wards/departments.
3) Retrospectively collect relevant data on a sample of the study population using medical records and laboratory results (computerised) on a data collection form (DCF) and enter into an Excel spreadsheet.
4) Run statistical analysis on the data collected regarding baseline characteristics of the sample population and to determine which independent variables are predictive of the outcome (the number of Clinical Pharmacist Interventions on first Clinical Pharmacist review).
5) Use statistical modelling methodology to develop Clinical Prediction Model/Tool (CPM) and, if possible, conduct internal validation of the developed CPM.

Purpose(/s) for conducting this research

The literature supports the concept of Clinical Pharmacists being a limited resource and therefore the need for prioritisation of Clinical Pharmacy Services to provide services to those most in need(43). Locally, at SUH, there is a shortage of Clinical Pharmacists available to provide these services to in-patients and as a result it is becoming more evident that evidence-based methods for prioritising

patients are essential. At the time that this research was undertaken, there were no (formal/agreed) systems in place for prioritising Clinical Pharmacist workload nor patients for review at SUH.

Methodology

Study site

The study was conducted at SUH, which was part of the Saolta University Health Care Group, and overall part of the Health Service Executive (HSE) of Ireland, at the time of the study (restructuring into HSE Health Regions commenced in February 2024). The focus of the study was looking at the care of medically admitted older patients presenting at Sligo University Hospital (SUH) for unscheduled care and so data collection was conducted on medically admitted patients in those wards and departments where these patients would typically be expected to be admitted and excluded those patients admitted as 'outliers' on other wards or departments and specialist areas. In the context of this research and the patient (sample) population, the term 'outliers' is used to refer to medical patients admitted to wards/departments other than those included in *Table M1* (see next section).

Inpatient care can broadly be defined as (1) planned (scheduled) care or (2) emergency (unscheduled) care, typically being admitted via the Emergency Department or medical assessment unit(85); this current research relates to patients presenting to the hospital for unscheduled (i.e. emergency) care.

Wards and departments included for sample population to be drawn from

Prior to the first wave of the COVID-19 pandemic and as per initial plans for implementation of this project, the designated wards and departments identified to be included in this project (from which the sample population could be drawn) were as listed below in *Table M1*.

Table M1: Included wards/departments for the study (where patients were medically admitted and met other inclusion criteria)

Ward/department	**Description of type of ward/department (where not apparent from ward name)**
Emergency department (ED)	N/A
Medical Assessment Unit (MAU)	N/A
Short Stay Unit (SSU)	N/A
Medical North (MN)	General medical ward, (predominantly) male patients
Medical South (MS)	General medical ward, (predominantly) female patients
Level 5 Medical (L5)	General medical ward, including neurology beds*
Level 7 Medical (L7)	General medical ward, including beds for stroke patients

*Excluding patients attending SUH for intravenous infusions (part of scheduled care).

Wards and departments excluded from sample population

All patients with non-medical admissions were excluded from the study population; this meant that a surgically admitted patient in one of the wards/departments listed in *Table M1* would be excluded. Patients who were medically admitted but not admitted to one of the wards/departments above were also excluded from the study population as the Principal Researcher (AB) decided from a logistical perspective to restrict the study to these principal areas and exclude outliers (defined previously) as this would require more individual Clinical Pharmacists to be educated on identifying potential patients for inclusion and completion of the relevant form. In addition, patients attending a

ward/department for scheduled care (e.g. infusions) were also excluded (even if the ward/department was included in *Table M1*). The following table, *Table M2*, summarises the rationale behind certain wards/departments being excluded from the study population.

Table M2: Rationale behind excluded wards/departments

Ward/department	**Description of type of ward/department (where not apparent from ward name)**	**Rationale for exclusion from study population**
Surgical North	Surgical ward, (predominantly) male patients	Surgical ward
Surgical South	Surgical ward, (predominantly) female patients	Surgical ward
Orthopaedics	Orthopaedic patients	Orthopaedics ward
Level 4 Medical Oncology & Haematology	(Predominantly) Oncology & haematology patients	Under care of Oncology and Haematology Teams. Many of these patients are admitted via Acute Oncology Service (Clinical Nurse Specialist) pathway or via Day Oncology/Haematology Unit – specialist pathways
Maternity and delivery	N/A	Maternity and obstetrics patients
Neonatal Unit	N/A	Patients below age for study population
Paediatrics	N/A	
Intensive Care Unit	N/A	

Coronary Care Unit	N/A	Patients admitted to these areas may not be able to have an early Clinical Pharmacist review and participate in the medication reconciliation process or may be subject to a different admission pathway.
General Day Services	N/A	These patients are attending for scheduled care (e.g. infusions or chemotherapy) rather than unscheduled care
Day Oncology/Haematology Unit	N/A	
Renal dialysis unit	N/A	These patients are attending for scheduled care (dialysis)

Effect of COVID-19 on wards included for sample population to be drawn from

Adapting to the impact of the first wave of COVID-19 infection in Ireland, services were reconfigured within SUH with different pathways for admission and patient flow for patients who were COVID-19 positive or suspected COVID-19 positive (symptomatic/close contact) compared to those who were not symptomatic of COVID-19 or COVID-19 negative on testing, with distinct, designated Emergency Department areas. Consequently, as this project was undertaken during the COVID-19 pandemic and before the immunisation program began in Ireland (vaccinations began on 29th December 2020 just as the period for identification of potential patients for the sample population was ending), only (admitted) patients who were able to be reviewed by the Clinical Pharmacist could be included in this research; during the early stages of the COVID-19 pandemic and prior to vaccination of healthcare workers, due to risk assessment for staff, it was not possible for some patients admitted via the COVID-

19 positive/suspected positive pathway to be seen face-to-face by the Clinical Pharmacists and those patients who did not receive a Clinical Pharmacist review were not included in the study population.

Identification of study population

Definition of elderly/older people for purposes of the study

A working definition, proposed in 2001 as part of the World Health Organization's MDS project, states that "Most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly[1]' or older person"(86)(p.1). However, the authors recognised that "Age classification varied between countries and over time"(86)(p.2) and, for the purposes of the MDS project, a more realistic working definition of older persons in developing countries, specifically in sub-Saharan Africa, of 50 years (and over) was proposed(86).

The United Nations (UN) uses a definition of 60 years and older for the older person in their definition of age groups whilst elsewhere 'elderly[1] persons' are defined as being aged 65 years by the UN(87, 88). The UN also recognises that "The concept of "old age" is multidimensional"(87)(p.21) and is influenced by factors including chronological, biological, psychological and social age(87). In fact, in more recent years, with a growing ageing population, the focus on chronological age for defining old age is changing and there is increasing interest in the heterogeneity of ageing and concepts such as prospective (rather than chronological) age for populations(89).

On their website, NHS England states that "Generally, someone over the age of 65 might be considered an older person"(90)(para.3) but also highlights the limitations and difficulties of applying a strict definition/criteria due to individuals biologically ageing at different rates(90). NHS England proposes the concept of 'frailty' as having a bigger impact on the likelihood of an individual to require care and support than simple chronological age(90). In Ireland, the location in which this current research was conducted, the National Clinical Programme for Older People (Part 1) defined the older person and geriatric medicine as being "mainly concerned with people over the age of 65"(91)(p.15).

Mindful of the above definitions in national (Irish), UK (English) and international guidelines and reports, the chronological age of 65 years and older was used in this project for the inclusion criteria. When the concept for this thesis was first conceived, the Principal Researcher (AB) was employed as the Senior Pharmacist to the newly established Frail Elderly Assessment Team (FEAT) at Mayo University Hospital (Ireland), which was launched at the end of 2015. As a result, the term 'elderly' was used initially in the research proposal and related documents/publications as well as in the systematic review. However, cognisant of the (negative) preconceptions, stereotypes and judgements associated with the use of certain terms, the importance of using age-inclusive language, and the preferred terminology recommended by the British Geriatrics Society (BGS), the terms older people/patients/adults/individuals have subsequently been utilised in this thesis(92). The exception to using the preferred terminology in this thesis is when discussing previously published literature (including the published SR incorporated in Chapter 2) which has used different terms e.g. elderly or geriatric, in which case the terminology used by the author has been followed. This is also consistent with the terminology used by the Health Service Executive (HSE) and Royal College of Physicians of Ireland (RCPI) in the National Clinical Programme for Older People (NCPOP)(93). Similarly, the BGS has suggested that the term 'frail' should be avoided and the preferred term "(older) person with frailty/living with frailty"(92)('Language to avoid' section) is used.

Study population

The study population was composed of older patients (defined as 65 years or older), medically admitted to SUH who were reviewed by a Clinical Pharmacist during their admission. Patients were reviewed as part of the 'normal' Clinical Pharmacy service which operates Monday to Friday (during the core hours of 8:30-4:30 or 5pm) and excludes Public Holidays; it is noted that Pharmacist cover to clinical areas may not have been provided during staff leave, e.g. for annual, sick or parental leave due to staff shortages (and particularly during the COVID-19 pandemic due to illness).

Inclusion criteria

The eligibility criteria were that patients were aged 65 years or older (at the time of the (initial) Clinical Pharmacist review), were medically admitted to SUH to one of the designated wards/departments (see *Table M1*) and had given verbal consent for being reviewed by the Clinical Pharmacist.

Exclusion criteria

Patients aged less than 65 years of age at the time of the (initial) Clinical Pharmacist review, patients who were not medically admitted or who were not admitted to one of the designated wards or departments during the study period and those who did not consent to being reviewed by a Clinical Pharmacist (or whose family member/carer did not consent) were excluded from the study population. In addition, responding to health and safety concerns for healthcare professionals, some patients were excluded due to being unable to have a comprehensive and/or face-to-face review by the Clinical Pharmacist due to local COVID-19 precautions. Patients who attended the hospital for scheduled (rather than unscheduled) care were also excluded from the study.

Study period

Duration of study period

A four-month study period was chosen by consideration of the practicalities of data collection mindful that whilst the Principal Researcher (AB) was responsible for the actual data collection from review of the patients' medical notes, the individual Clinical Pharmacists visiting the wards were being asked to undertake this additional task (when already busy) of identifying those patients they had seen who met the inclusion criteria and recording their details on the relevant form. Selection of a realistic, manageable study period would hopefully result in better 'buy in' and co-operation from colleagues than a more prolonged study period or an open ended study period if a certain quota of patients had to be included of, for example, several hundreds. Additionally, many of the reports produced annually regarding the health service in Ireland are presented as quarterly results, with each quarter equal to

a period of three months. The four-month study period exceeded a quarter (as in a quarter of a year) and the findings might be more representative of the overall situation than if a shorter time period had been selected e.g. of just one or two months which could either fall in calendar months typically busier or quieter in terms of hospital presentations.

Challenges affecting the study period for data collection

Initially, the Primary Researcher (AB) had hoped to begin data collection early in the year 2020 and had carried out a briefing session with the Clinical Pharmacists at the hospital at a meeting in December 2019/January 2020. However, at this stage, the Primary Researcher (AB) was then advised that the drug kardex (sometimes also known as the drug chart, although the terms are often used interchangeably) used at SUH was in the final stages of redesign after a comprehensive review process and consultation between relevant parties (nursing, pharmacy and medical) and the new format of drug kardex would hopefully be launched within the next couple of months. The drug kardex is essentially "the Prescription and Administration Record"(94)(p.348) used to "direct administration of medicines in a hospital setting"(94)(p.348) and is a record of the medications prescribed and their administration in the hospital. The redesign of the drug kardex was highly relevant as the new drug kardex would, for the first time, have a dedicated page for the Clinical Pharmacist to complete the medicines reconciliation process within and a communication page (back page) where any queries, discrepancies or other interventions could be documented by the Pharmacist.

Prior to this, Clinical Pharmacists at SUH had utilised Pink Intervention Notes which were stapled to the front of the drug kardex for documenting any queries, discrepancies (e.g. between prescribed medicines and pre-admission medicines as per the medicines reconciliation process) and other interventions. Each Clinical Pharmacist had their own dedicated booklet of Pink Intervention Notes which had unique page numbers and duplicate copies so that the notes were traceable (via the unique number in the top corner) to the individual book (and therefore to the individual Pharmacist) and a copy automatically kept by the Pharmacist (and subsequently stored when the book was completed)

as typically the Pink Intervention Note stapled to the drug kardex would be removed by the prescriber (or other party/ies) after it had been read. The outcome for this study was the number of Clinical Pharmacist Interventions and therefore the method of communicating and documenting these interventions was highly relevant. For the sake of consistency, the same method of communicating and documenting interventions would be needed throughout the study period. Given the imminent intended launch of the revised drug kardex it was therefore decided to wait until after the new drug kardex was launched (copies already printed and being stored ready for education sessions and launch) to begin data collection, which was anticipated by early spring 2020.

Unfortunately, the launch of the new drug kardex was delayed due to the first wave of the COVID-19 pandemic in Ireland. Additionally, with the overall disruption to healthcare services and the need for reconfiguration of services, it would not have been feasible to ask Clinical Pharmacists to identify eligible patients for inclusion in the study at this time (in early 2020) regardless of the status of the new drug kardex launch. As a result of managing the impact of the COVID-19 pandemic in the initial phase, there was a delay of several months before the new drug kardex could be launched in the hospital. Mindful of the delay in the launch of the revised drug kardex, the impact of the COVID-19 pandemic on the provision of healthcare services both nationally and locally at SUH and staffing levels for Pharmacists (with Pharmacists having to self-isolate if symptomatic of COVID-19, upon positive COVID-19 test result and/or being a close contact, as per the public health and occupational health guidance for healthcare workers that was in place at the time), the study period was delayed for several months.

Final study period (in response to challenges faced)

Following these delays due to the COVID-19 pandemic and the launch of the new drug kardex, the study period commenced on the 1st September 2020 and concluded on the 31st December 2020. During this period, the Clinical Pharmacists providing a service to the relevant wards/clinical areas

were asked to identify any suitable patients who met the inclusion criteria and who received a Clinical Pharmacist review and complete the patient's details on the relevant form.

Due to the COVID-19 pandemic, there were changes in the provision of healthcare services within SUH and additionally, there was a significant reduction in population rates of Emergency Department (ED) presentations (and non-COVID-19 related admissions)(79). A study conducted in an Irish 1000-bed university hospital found that there was a significant decrease in the number of older people presenting to the ED for unscheduled care and this included presentations for potentially time-dependent conditions such as stroke and cardiac issues(95).

The study period (1st September to 31st December 2020) was during the COVID-19 pandemic and before the COVID-19 vaccination program in Ireland was implemented. The consequence of this is that the COVID-19 pandemic is likely to have reduced the potential number of patients who would have met the inclusion criteria for the study population and potentially affected the demographic profile and indeed the type of admissions. Additionally, some patients did not receive face-to-face reviews by a Clinical Pharmacist, for example if there was a local outbreak of COVID-19 on the ward/in the department to reduce the risk of transmission of COVID-19.

Identification of patients for sample population

The Clinical Pharmacists visiting the relevant wards/departments were provided with copies of a pro-forma (specially designed and solely used) for this project for recording the details of potentially eligible patients who had been reviewed (see *Appendix M1*). In order to ensure that all of the relevant ('essential') details were provided whilst minimising the time and effort required by the individual Clinical Pharmacists, one of the small addressograph stickers (routinely printed upon the patient's registration at the Emergency Department (ED) and readily available in the patient's medical notes) containing the basic patient demographics (name, hospital number (PCN) and date of birth) could be affixed to the form; alternatively, if no sticker was available to the Clinical Pharmacist at the time that they were completing the form (e.g. if completed at the end of the day or the week from review of

their ward census sheets), this basic demographic information could be transcribed by the Clinical Pharmacist onto the pro-forma.

This basic demographic information of each patient along with details of the Clinical Pharmacist completing the form (and the reviews), the relevant ward/department name and the date, were regarded as the minimum amount of information ('essential fields') required as this would enable the Principal Researcher (AB) to identify the patient and request the medical notes from the Medical Records Department and extract the relevant information relating to the admission and review by the Clinical Pharmacist. The Clinical Pharmacist could also complete some additional ('optional') fields on the pro-forma, for example indicating if just a medication reconciliation process had been completed and/or if the patient had been transferred from another ward but, these were not essential fields.

A copy of the pro-forma used by the Clinical Pharmacists for recording potential patients for the sample population is included as *Appendix M1*.

Recognising the pressures on all staff working during the early phase of the COVID-19 pandemic and mindful that this was an additional (non-essential) task that they were being asked to complete, the Clinical Pharmacists were asked to complete the form(s) with the details of as many of the patients that they reviewed (on first review) as possible and were given flexibility to do so at the time of review or retrospectively e.g. at the end of the day or week from review of the printed ward census sheets for their ward. However, it was accepted that the Clinical Pharmacists might forget or not get the opportunity to complete the form and so some patients who might have potentially met the inclusion criteria were in fact not included due to the practicalities of the numerous demands on the Pharmacists and their workload. This may have reduced the number of patients identified during the study period for inclusion in the study population but, as described later, only a sample of the population was included for data collection and, pragmatically, this was not felt to be introducing a form of systematic sampling bias as it could have affected patients who received no interventions on first Clinical Pharmacist review equally as much as those who received numerous interventions. The

identification of patients for inclusion in the study population was recognised as an additional task that should not interrupt or distract Clinical Pharmacists' focus from their necessary tasks on the wards/departments as had been discussed by the Primary Researcher (AB) with the Chief Pharmacist at SUH prior to asking the Clinical Pharmacists to be involved in the identification of patients. In addition, as discussed later (section *Retrieval of patients' medical notes*), it was decided to automatically review the retrieved medical notes for each identified patient for the entire study period and include all relevant admissions during the period if they met the inclusion criteria, regardless of whether a pro-forma had been completed for a specific admission.

Repeat admissions for the same patient

In England, the Hospital Episodes Statistics (HES) dataset contains data for all hospital admissions, outpatient appointments and (historical) accident and emergency attendances of NHS patients in England(96). The definition of a hospital spell used by the HES is "a continuous period in hospital from admission to discharge"(96)(p.2). For the purposes of this research, it is recognised that individual patients may have multiple spells (of treatment) and each spell (from admission to discharge) will be considered separately. This is a pragmatic decision reflecting the actual presentation of patients to the hospital and the reality of repeat presentations and repeat admissions to hospital which are broadly recognised as common problems among the target population (older patients)(97). Therefore, if an individual patient presented to the hospital on multiple occasions during the study period and was reviewed by a Clinical Pharmacist on each presentation ('spell'), each of these spells could be included separately in this study. This approach is also consistent with that of previous research in this general topic where "Repeated admissions to hospital were treated as being independent; hence if a patient was discharged and readmitted, they would be included in the data once for each admission"(98)(p.132).

Study design

Older patients (aged 65 years and older) who were medically admitted to one of the eligible wards and received a first Clinical Pharmacist review during the study period were identified prospectively by the relevant Clinical Pharmacist and included in the potential study population for this cohort study. The prospective cohort study design is regarded as the preferred method for clinical prediction model development studies "as it enables optimal measurement of predictors and outcome"(82)(p.3). Due to the limitations affecting the study (due to COVID-19 restrictions and challenges involving the retrieval of medical notes, described in detail in the section *Retrieval of patients' medical notes*) the medical notes were not retrieved for all patients and instead, a sample of the potential study population (who met the inclusion criteria) was used for the purposes of full data collection and analysis. Full data collection, including data on potential risk factors such as polypharmacy, use of high risk pre-admission medications and renal and hepatic function was conducted retrospectively and manually extracted from the medical records and computerised laboratory result system (Lab73) used at SUH. A similar approach (prospective identification of study participants and retrospective retrieval of data relating to potential risk factors/candidate predictors) was utilised by previous researchers in this field(99).

The Research Proposal is included as an appendix (see *Appendix M2*) to show the rationale behind decisions made early in the design of this current study such as choice of study design (cohort, prospective) and outcome measures.

Ethical considerations

The Research and Ethics Committee (REC) at SUH was consulted regarding the need for ethical approval to conduct this study. A standard application form for ethical review of the proposed study was submitted and reviewed and it was determined by the REC that ethical approval was not needed (see *Appendix M3*).

Philosophical influences on research methodology

Research philosophy has been described as "an approach which selects an appropriate methodology to answer a research question"(100)(p.428). As observed by Winit-Watjana, the philosophy of (Pharmacy) research has remained largely unexplored(100). However, an appreciation and understanding of research philosophy is "crucial for pharmacy researchers and pharmacists, as it underpins the choice of methodology and data collection"(100)(p.428) which is fundamental to the research generated. A research paradigm is a philosophical framework or set of beliefs that guides the research process. There are four philosophical paradigms relevant to Pharmacy research namely:

- Positivism/empiricism/reductionism
- Postpositivism/realism
- Interpretivism/constructionism
- Pragmatism.

These paradigms can be considered according to the philosophical realms ontology, epistemology, axiology and logic of mind or methodology. Ontology refers to the nature of reality(101, 102). Epistemology refers to the nature of knowledge, considering what constitutes knowledge and how researchers acquire knowledge(101, 102). Axiology refers to the roles of values and ethics in the research process (101, 102). Logic of inquiry or methodology refers to the techniques utilised to conduct scientific research(102).

Like much research in the field of Pharmacy and pharmaceutical sciences, this current study adopted a positivist philosophy, focusing on explanation and prediction, conducting quantitative research and making (or trying to make) generalisations (regarding the variables/risk factors for DRPs)(100). Quantitative research methods were adopted for this research to produce objective findings and enable generalisation of the data collected to develop a clinical prediction tool/model. However, an alternative approach that could have been adopted is the pragmatist philosophy and using a mixed methods approach combining qualitative and quantitative approaches. The pragmatist paradigm

adopts a practical, problem-solving approach to conducting research(100). This could have been achieved by either:

(1) Incorporating an element of local expert opinion and consensus on variables/risk factors to include in the modelling process, similar to the Delphi approach, which aligns with the philosophical principles of pragmatism (rather than wholly focusing on published research and previous developed models to guide variable selection), or
(2) Conducting qualitative interviews with users of the developed clinical prediction tool to gain an understanding of its usefulness/utility in clinical practice, ease of use and acceptability to the user.

The following table *(Table M3)* considers the current research in the context of the philosophical realms associated with the positivist philosophy.

Table M3 Consideration of the positivist research paradigm according to the philosophical realms of ontology, epistemology, axiology and logic of inquiry in the context of the current research undertaken

Philosophical realm	**Philosophical realm in the context of the positivist research paradigm**	**Study methodology consistent with specific philosophical realm for positivist research paradigm, or not**
Ontology	There is a single reality that can be understood, identified and measured. Study of causal and explanatory factors (independent variables) and outcomes (dependent variables)	Yes (looking to develop a tool with independent variables influencing outcome)
Epistemology	Positivists believe knowledge must be developed objectively and not be	Yes (objective variables with respect to measurement and outcome)

	influenced by the researcher nor participants	
Axiology	Positivism relies on objectivity and excludes subjective data/values/experiences	Yes (objective variables with respect to measurement and outcome)
Logic of inquiry/ methodology	Positivist methodology promotes research being conducted with variables being controlled and allows examination of causal relationships between variables in the study(100)	Yes (looking to develop a tool with independent variables influencing outcome as examined via statistical methods for significance)

Potential variables included for data collection

As mentioned at the beginning of this Chapter (see section *The influence of the Systematic Review on the methodology of this research*), the findings of the systematic review (SR) (conducted by the Principal Researcher (AB) in collaboration with the Academic Supervisors [ZJ and CEC]) guided the selection of potential variables for this current study(80). The SR is incorporated into this thesis writeup (Chapter 2). Potential variables (or risk factors or candidate predictors) for DRPs were identified from the studies included in the SR and comparisons made between the risk factors/variables included in the final prediction models for the included studies. Variables included in at least one model were considered for inclusion in this project as a potential risk factor, whilst considering the feasibility and accessibility of information on these potential risk factors at the point of first Clinical Pharmacist review. For example, the parameter 'length of hospital stay' which was identified in previous research as a potential risk factor/predictor, was not included as a potential risk factor in this project as it is information that would not be available to the Clinical Pharmacist at the point of first review. Some factors such health insurance status would also not be regarded as being

as relevant in Ireland as in some other countries e.g. United States of America, and so were also not included/studied in this current research.

With respect to those potential risk factors that were included in this project, exact definitions and/or reference ranges used for determining if, for example, laboratory results were abnormal depended on local reference ranges and were intentionally pragmatic. The definitions used by previous researchers may have differed (between the researchers where the same factor was studied) or may have been vague/ambiguous or were dependent upon information (including clinician diagnoses using International Classification of Diseases, ICD, codes) that would not be readily available to Clinical Pharmacists at SUH, for example for the term 'liver disease' as a risk factor. The following table, *Table M4*, summarises the risk factors that were studied in this current research and indicates which of the final models from the studies included in the SR included each of these variables/similar variables.

Table M4: Table showing the potential variables studied in the current research and the studies from the SR that incorporated these (or similar) variables in their (final) model(/s)

Variable (broad description)	**SR papers that included variable (/related variable) in final model**
Number of medicines/pre-admission medicines	(98), (103), (104), (105), (83), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115)
Liver (dys)function/failure	(98), (104), (105), (83), (111), (116), (117)
Renal (dys)function/failure	(98), (104), (105), (83), (118), (107), (109), (110), (111), (112), (114)[11], (117)
White cell count	(103), (112)
Antimicrobial use (at the time of admission or recent use)	(98)[0], (107), (108), (117)[12]

Number of co-morbidities or having certain co-morbidities	(98), (104), (105), (83), (118)[4], (107), (108), (111), (112), (115), (113), (81)[10], (114), (116), (117)
Being on/Number of high risk medications (or specific groups of medicines e.g. anticoagulants, CNS, opiates etc.) taken	(98), (103)[1], (106)[3], (118)[5], (109)[6], (110)[7], (111), (112), (115)[8], (81)[9], (114), (117) Related variables: Inappropriate medicines: (105), (116)
Falls (current, history and/or falls risk)	(116)
Exclusively conducted in older population	(103), (104), (105), (83), (106), (118), (116)
Age as a variable/increased age found to be associated with increased risk of the outcome e.g. ADR	(98), (105)[2], (107), (108),(112), (114), (115), (116)
Gender	(98), (116)

Note

The references are not listed in numerical order (in column 3 of *Table M4*) due to adopting the order in which the different studies were reviewed and summarised in an Excel spreadsheet at the time that the SR was conducted, for logistical reasons and ease of verification of same.

(98)[0] = on IV antimicrobials (in the hospital)

(103)[1] = anti-diabetic medicines

(105)[2] = study conducted in older population however age of 75/+ years found to be associated with increased risk of ADR on analysis

(106)[3] = taking antipsychotic medication(/s) and recent initiation of anticoagulant therapy (separate variables)

(118)[4] = presence of pulmonary disease; presence of malignant disease

(118)[5] = taking medicines for PUD/GORD/GERD; opioids; non-tricyclic antidepressants

(109)[6] = MERIS score included variable looking at the number of drugs with different levels of risk of harm and/or interactions with different weightings assigned according to the levels of risk

(110)[7] = MERIS score included variable looking at the number of drugs with different levels of risk of harm and/or interactions with different weightings assigned according to the levels of risk

(115)[8] = a number of different types of specific high risk medicines were studied with diabetic medicines being a statistically significant flag

(81)[9] = prescribed digoxin and prescribed antidepressants were found to be two (separate) variables associated with adverse drug events in the study population

(81)[10] = a number of disease states: gastrointestinal disorders (nausea, vomiting, diarrhoea), chronic obstructive airways disease and angina

(114)[11] = kidney and urinary tract included as a major diagnostic category that was found to be associated with drug related problems

(117)[12] = patient with infectious disease consult; prescribed aminoglycosides, triazole antifungal and/or amphotericin B.

Table M5 shows the potential risk factors incorporated in the DCF and how they were measured in this current research.

Table M5: Table showing the potential risk factors studied in this current research and the source of information on each risk factor

Potential risk factor	**How potential risk factor is measured**	**Source of information (to complete DCF)**
Age	Age in years	From patient addressograph sticker and medical records
Gender	Gender (male or female)	From medical records
Polypharmacy	Actual number of pre-admission medicines (PAMs) taken	From documented medication reconciliation recorded on the relevant page of the new drug kardex by the Clinical Pharmacist (filed in the medical notes for the patient)
Presence of infection (current or recent) or on prophylactic systemic antimicrobials or high risk of infection	Whether patient was on systemic antimicrobial on/prior to (within 7 days of) admission (treatment or prophylaxis)	From documented medication reconciliation recorded in the new drug kardex by the Clinical Pharmacist plus review of clerking notes on (current) admission and referral letter where available (patient may have attended an out-of-hours GP service and received antibiotics/antimicrobials)
Presence of infection or inflammation (current)	**Abnormal** white cell count (WCC) and/or Neutrophil count.	Documented as part of (current) admission process (routine laboratory test results requested); where not available/unclear/for clarification purposes, the computerised laboratory results (Lab73) at SUH were consulted

Renal function	Estimated glomerular filtration rate (eGFR)	Documented as part of admission process (routine laboratory test results requested); where not available/unclear/for clarification purposes, the computerised laboratory results (Lab73) at SUH were consulted
Liver (hepatic) impairment	Documented liver impairment as part of HPC or PMH from current admission notes **and/or** Abnormal AST &/or ALT >x2 ULN	Documented liver impairment as part of HPC or PMH from current admission notes in medical notes. AST & ALT levels - Documented as part of (current) admission process (routine laboratory test results requested); where not available/unclear/for clarification purposes, the computerised laboratory results (Lab73) at SUH were consulted
Falls history	Documented fall as part of current admission presentation as per current admission notes **and/or** Documented recent fall or falls risk in Activity of Living assessment or falls risk sticker on medical notes	Documented fall as part of HPC from current admission notes in medical notes Documented recent fall (within PMH section of clerking notes for current admission) in medical notes or falls risk recorded in Activity of Living assessment (filed in current set of medical notes) or falls risk sticker on medical notes

High number of co-morbidities	Number of documented co-morbidities (or medical/surgical problems) as per **current** admission notes (clerking notes)	Documented in medical notes for current admission
Taking high risk medication	Number of high risk medications taken pre-admission (HRPAMs) (from list of HRPAMs prepared)	From review of the documented medication reconciliation recorded in relevant section of the new drug kardex by the Clinical Pharmacist (filed in the medical notes for the patient)
Outcome measure: Clinical Pharmacist Interventions (CPhI)	Actual number of Clinical Pharmacist Interventions (CPhI) on first review	Number of documented interventions made by the Clinical Pharmacist on first review as documented either in the medical notes and/or in the relevant section of the new drug kardex (back page) where the date matches the date of the first review by the Clinical Pharmacist

Abbreviations used in above table *(Table M5)*

HPC = history of presenting complaint

PMH = previous medical history

ULN = upper limit of normal

AST = aspartate aminotransferase (also known as aspartate transaminase)

ALT = alanine transaminase (also known as alanine transaminase).

Liver disease is not straightforward to define or quantify. The interpretation of liver enzyme alterations can be complex. Serum liver chemistry tests, commonly referred to as liver function tests (LFTs), encompasses a number of tests including bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), serum albumin, aspartate aminotransferase (AST), gamma glutamyl transferase (GGT) and lactate dehydrogenase (LDH)(119). These tests are actually markers of liver injury rather than liver function itself and it has been suggested, in recent years, that they should be referred to as liver blood tests as they relate to elevations of hepatobiliary liver enzymes rather than liver function(119, 120). In some of the prediction tools/models identified in the systematic review (conducted by AB, CEC and ZJ) it was found that whilst liver disease was included as a risk factor, definitions of liver disease were not included(80, 99). One researcher (of related research in this field) commented that there is no direct relationship between LFTs and the degree of liver function observed and therefore in their research they used indicators of a diagnosis of poor liver function (including ICD disease code diagnoses, patient being in the care of the liver directorate and/or declared liver interest) rather than LFTs for the purposes of defining poor liver function as a risk factor(98). Another researcher used a combination of selected LFT results (ALP, ALT and Bilirubin) and "documented liver disease" as indicators of liver impairment(99). Hepatocellular changes or abnormalities are predominantly characterised by elevations in the transaminases ALT and AST, cholestatic changes predominantly are characterised by elevations in ALP and mixed/infiltrative pattern of liver injury is characterised by elevations in both ALT/AST and ALP(119). Bilirubin can be elevated in any category of liver disease and in the benign condition Gilbert's syndrome and isolated elevations in GGT are very common resulting in many institutions opting to exclude GGT from their routine panel of LFT results(119). ALP levels can also be increased due to a number of non-hepatic causes as it is also found in bone, placenta, kidneys and the intestines(119).

The Primary Researcher (AB) opted to focus on elevations of the transaminases (ALT and/or AST) and/or a documented history of liver disease/dysfunction in the medical notes or as part of the current presenting complaint (in the notes for the current admission) for the (potential) risk factor of liver

disease(/dysfunction), in this study. This decision, made in consultation with the Academic Supervisors (ZJ and CEC) was mindful of the limitations of interpreting elevated liver blood results in isolation (i.e. without review of the previous results, past medical history and current medical condition), that the "extent of liver blood test abnormality is not necessarily a guide to clinical significance"(120)(p.6,14) and the fact that some of these so-called LFTs may be found in other tissues (e.g. ALP in bone) and hence elevations may be due to non-hepatic causes. The threshold for abnormal ALT and/or AST was defined for this study as greater than twice the upper limit of normal (>2xULN) using the reference laboratory values at SUH, recognising that liver blood tests result abnormalities are commonly observed (where >2xULN is considered equivalent to elevations of at least a moderate degree of abnormality)(121).

The groups of high-risk pre-admission medications included in the study are listed in *Table M6.*

Table M6: Table showing groups of included high-risk pre-admission medications (HRPAMs)

HRPAM group/category of medicines
Anti-coagulants (oral)
Antidiabetics (oral/parenteral)
Antiepileptic medication (used for epilepsy not pain)
Antiparkinson's disease medication
Antipsychotic
Benzodiazepine and/or Z-drug (e.g. zopiclone or zolpidem) or equivalent
Opioid use
Therapeutic heparin doses (including low molecular weight heparins)
Medications requiring therapeutic dose monitoring (TDM) including lithium, digoxin, aminophylline, theophylline, carbamazepine, sodium valproate, aminoglycosides
Methotrexate (oral or subcutaneous)[*]

Methotrexate (oral or subcutaneous)* was not included in the original prepared list of HRPAMs and is therefore not listed specifically on the relevant section of the DCF. However, when the list of PAMs for one of the included patients was reviewed and once weekly oral methotrexate was identified, the Principal Researcher (AB) felt that in her professional judgement as a Clinical Pharmacist this should be recorded as a HRPAMs and reflected that the absence of methotrexate from the list was unintentional/an omission rather than a deliberate decision. Methotrexate (oral) was the subject of National Patient Safety Agency (NPSA) Safer Practice Notices and/or Patient Safety Alerts (issued in July 2004 and reissued in June 2006) in the UK following a number of reports of serious medicines errors including fatalities(122, 123, 124). Two actions from the 2006 Patient Safety Alert remained in the NHS Improvement document entitled 'Recommendations from National Patient Safety Agency alerts that remain relevant to the Never Events list 2018'(123). In Ireland, the Irish Medication Safety Network issued a Safety Alert with recommendations to reduce the risks associated with the use of once weekly oral methotrexate(125). These alerts and notices support the decision to add (oral) methotrexate to the list of HRPAMs for this research (albeit after the initial list was composed and data collection was underway) and emphasises the high risk nature of the prescribing and administration of (oral) methotrexate. In the case of subcutaneous methotrexate, although none of the study participants were found to be receiving it, the Principal Researcher (AB) felt that it would be prudent to include it in the (revised) list of HRPAMs due to the dosing frequency (weekly) and differences in preparations and doses available and this rationale is consistent with an NHS Trust's methotrexate policy which contained recommendations to reduce the harm to patients from regular weekly methotrexate administered via the oral and subcutaneous routes(126).

Data collection form

The data collection form (DCF) was designed by consideration of the various parameters needed to determine whether particular pre-defined factors (identified from the systematic review of previous research) were predictive of the number of Clinical Pharmacist Interventions received by individual

older medical patients. In addition to the basic demographic details, information on the number and type (general types/categories) of interventions and then details relevant for those pre-defined factors e.g. number of pre-admission medications (PAMs) and number (and type) of high risk medications were included in the DCF. Some of the data collected, e.g. categories of the different type of high risk medications (HRPAMs), might not actually be separately analysed in the main body of the data analysis process but by inclusion of minimal, succinct information regarding this factor, if the number of HRPAMs by older patients was found to be significant in predicting the number of Clinical Pharmacist Interventions received, subgroup analysis could be conducted to further identify if particular types of high risk medication were more predictive of the outcome than others. By including this information on the overall DCF it reduced the potential for needing to request, access and review medical notes for individual patients more than once. However, the principles of data collection and processing in research were followed and, as much as possible, only as much data as was required to successfully answer the research question was collected.

A copy of the DCF is shown in *Figure M1*.

Patient Addressograph/details	Patient identifier

Ward code		Patient identifier				
Pharmacist identifier						
Date of Pharmacist r/v		Date of admission				
No. of PAMs		No of PAM	<5	5-7	8/+	
On systematic Antimicrobial On admission/Within 7 days	Y# ☐ or N ☐ #Treatment / prophylaxis (cross out)	**Laboratory results (1st results on presentation or within 48hr)**				
Total number of interventions made during 1st r/v (V1)		WCC		Level normal range	Y	N
Breakdown of interventions made (indicate number of interventions) during initial pharmacist review (V1)		Cr level				
		eGFR		Category		
MedRec issue		LFT: AST &/or ALT level >x2 of ULN		Y	N	
Prescribing error		Documented fall as part of /cause of current admission		Y	N	
Medication administration issue		Documented fall within last 12 mths		Y	N	
Advice/recommendation to Rxr* □		No. of documented co-morbidities				
Patient counselling*		On 1/+ high-risk medication (HRPAM)		Y	N	
Other*		No of high-risk medications (HRPAM)				
Details for interventions denoted with *		**Type of high-risk medication prior to admission**				
		Anti-coagulants (oral)				
		Antidiabetics (oral/parenteral)				
		Antiepileptic				
		Antiparkinson's disease medicine				
		Antipsychotic				
		Benzodiazepine &/or Z-drug or equivalent (regularly or taken twice or more weekly))				
		Opioid use (regularly or, taken twice or more weekly))				
		Therapeutic heparin (inc. LMWH)				
		TDM medicines (lithium, digoxin, theophylline, aminophylline, carbamazepine, valproate, aminoglycoside)				
		Details				

Figure M1: DCF: **Pharmacist Intervention Prioritisation Tool for Elderly Patients**

Completion of the data collection form

It was decided early in the design of this study that data collection would solely be conducted by the Principal Researcher (AB). There were several reasons for this decision including trying to minimise additional workload/responsibilities on the relevant Clinical Pharmacists mindful of the existing demands on their time and this was particularly relevant during the incredibly stressful time of working during the early stages of the COVID-19 pandemic. Additionally, it was felt that a single person completing the data collection forms (DCFs) for all patients would reduce the inevitable variations between individuals and result in improved consistency in how the different criteria and definitions were interpreted. For example, early in the process of data collection, it was decided by the Principal Researcher (AB) and Academic Supervisors (ZJ and CEC) that medicinal products containing two or more ingredients e.g. Sinemet® containing co-careldopa which is composed of levodopa and carbidopa would be counted as a single PAM, after much consideration. The rationale behind this decision was to provide consistency and also cognisant of how, when a junior doctor would be clerking a patient as part of the admission process, the doctor would likely record the proprietary (brand) name Sinemet® or as the generic co-careldopa in their medication history (or drug history) and effectively count it as a single medication (when writing a list of medicines taken) rather than consciously document and count the two separate ingredients (e.g. levodopa and carbidopa in the case of Sinemet® or co-careldopa) . This approach was applied with other multi-constituent medicinal products e.g. inhalers containing two or more active ingredients were counted as a single (pre-admission) medicinal product (PAM) rather than counting the number of separate active ingredients, for the sake of consistency. Such a decision could be implemented relatively easily and consistently (once the decision was made by the Researchers AB, ZJ and CEC) as only one individual (the Principal Researcher, AB) was actually collecting the data. If each individual Clinical Pharmacist had been asked to record the number of PAMs taken by any of the patients that they reviewed, there is the possibility that the counting of PAMs could have been interpreted differently by different Pharmacists despite defining what a PAM was in the context of this study.

The fields included in the DCF were manually completed by the Principal Researcher (AB) when reviewing the appropriate volume(/s) of the patient's medical notes for the relevant admission(/s) during the study period. The drug kardex from that admission and the relevant nursing records (filed separately in the medical notes, including the Activity of Living assessment completed by nursing staff and recording falls history details) were also reviewed and used to complete the DCF. All medical notes were reviewed in the Medical Records Department at SUH. For some patients, the documented laboratory results were incomplete, unclear or missing. To ensure that the correct information was collected for all patients, after the review of all the medical notes was completed, the computerised laboratory results system used at the hospital, Lab73, was used to verify the results of the (initial) laboratory results for all patients included in the study population. Clinical Pharmacists have access to the laboratory results system at SUH and routinely access the results for patients on the wards/in the departments or clinical areas that they are providing a Clinical Pharmacy service to.

Data was collected for the patients included in the study and all sections of the DCF were completed using the data available. The information recorded in the admission notes (as part of the clerking process) was used to complete the DCF and essentially 'taken at face value' with respect to information on medical history, co-morbidities and falls risk/falls history. The reason for this assumption is that it represents the information available to the Clinical Pharmacist at the point of their first review of the patient, perhaps whilst the full medical records for the patient are being tracked and retrieved, and so forms the basis upon which any prioritisation of patients would be made at that time. However, limitations of the accuracy of the clerking notes are recognised and it was observed for some included patients who had more than one admission during the study period that differing, or even conflicting, information was recorded in the clerking notes for that admission and even in the medication reconciliation. For example, not all co-morbidities may have been documented in the clerking notes from one admission. However, as the clerking notes from the current admission would be the main source of information for the Clinical Pharmacist at the time of the first Clinical Pharmacist review, it was decided to use this information primarily to complete the DCF. Given that

the falls risk/history does depend on the documented history of same, the documentation of 'falls risk' on the front of the medical notes as well as in the admission notes (clerking notes) and relevant nursing notes (including the Assessment of Living form for that admission period) were consulted for completing this part of the DCF.

Details regarding the number of PAMs and high risk PAMs (HRPAMs) were completed from the medication history documented in the drug kardex by the Clinical Pharmacist. The documented medication history, clerking notes and any referral letter were consulted to confirm whether the patient was taking systemic antimicrobial agents at the time of admission or within the previous seven days; the clerking notes and referral letter (where available) were consulted when completing this part of the DCF as it was possible that patients might have attended an emergency GP service and obtained antimicrobial agents 'out of hours' and not via their usual GP and/or Community Pharmacy and therefore details of such antimicrobial therapy might not have been provided by the GP and/or Community Pharmacy when the Clinical Pharmacist conducted the medicines reconciliation process.

Retrieval of patients' medical notes

Following the completion of the study period (which concluded on the 31st of December 2020), the Principal Researcher (AB) contacted the Medical Records Department at SUH to discuss the retrieval of medical notes for patients identified by the Clinical Pharmacists. Initially, the Medical Records Department at SUH was unable to facilitate the retrieval of any notes for non-clinical reasons (i.e. not for admission, ED attendance or out-patient appointment) due to limitations on their staffing levels partially attributed to the impact of the COVID-19 pandemic. After meeting with the relevant manager and discussing the importance of retrieving the notes for this work, efforts were made to facilitate the retrieval of medical notes for this research project where their staffing levels allowed it, which was variable/fluctuating.

A list of patient names and hospital numbers (based on the details completed on the collated pro-forma, *Appendix M1*) was provided to the Medical Records Department and notes were retrieved by

the staff by working sequentially through the list and depending upon which notes were physically available in the Medical Records Department at that time. Where notes were not available in the department, e.g. tracked by Medical Records to a ward, consultant/relevant secretary, outpatient clinic, the Medical Records staff just moved onto the next patient's name on the list and tried to retrieve that next set of medical notes. In the event, notes for all of the potential patients identified by the Clinical Pharmacists were not retrieved due to logistical issues which significantly impacted upon and delayed the process of data collection.

Some patients presented more than once during the study period and, in the early stages of data collection, notes were retrieved for some individual patients more than once as their name was listed more than once on the list provided to the Medical Records Department. Therefore, in an attempt to avoid repeat requests for the same set(s) of medical notes being requested, the Principal Researcher (AB) made the pragmatic decision to review the notes for the full study period (four month period) and complete DCFs for each relevant admission if it met the inclusion criteria, and the patient had been reviewed by a Clinical Pharmacist as documented on the relevant drug kardex, regardless of whether that specific admission was documented on a pro-forma.

The DCF was completed (essentially 'piloting' the form in case any amendments were needed for ease of completion) for an initial group of patients (16) at the end of September 2021 and the completed DCFs reviewed by the Principal Researcher (AB) and discussed with the Academic Supervisors (ZJ and CEC) in early October 2021. No amendments to the DCF were identified as being needed; these 16 records were included in the sample population and the process of medical record retrieval and data collection continued.

In addition to the previous factors impacting upon the availability of staff to retrieve notes, a new system for tracking medical records was introduced at SUH which resulted in a huge demand on staff resources and significantly reduced the ability of the Medical Records Department to retrieve any non-essential sets of medical records during this period, essentially impacting on all those requesting

medical notes for research and/or audit purposes. A period of weeks went by without any notes being retrieved and at this stage, the Principal Researcher discussed this issue and the implications of this on continuing with data collection and the timeframe of the work with the Supervisors (ZJ and CEC). The decision was made (towards the end of June 2022, in agreement with the Academic Supervisors [ZJ and CEC]) to conclude data collection and proceed with the data collected up until that point.

Excel worksheet recording raw data/results

An Excel worksheet was designed to record all the results collected with a row representing each included admission. The data was entered in a pseudonymised format, in that each DCF was allocated a sequential number (001 onwards) and a separate record of these numbers and corresponding patient identifiers (Hospital number, PCN) was saved on the hospital computer network in a password protected document. This provided the opportunity to consult the patient's medical notes and/or computerised laboratory results using the relevant hospital number (PCN) if needed after the DCF was completed, whilst allowing the data to be saved in an Excel worksheet without being able to directly identify patients from it (without access to the separate list with sequential numbers and their corresponding hospital number, PCN).

The Excel worksheet contained numerous columns representing the different parameters included in the DCF. For the purposes of data analysis, it was decided to combine some of the fields collected to avoid (or substantially reduce the likelihood of) collinearity of variables in any final Clinical Prediction Model/Tool developed. For example, data was collected on transaminase levels (ALT and AST) as well as documented liver disease or liver dysfunction. Instead of analysing these as separate variables, they were combined to give a single variable of raised ALT, raised AST and/or documented liver disease and/or dysfunction. In the event of a patient having documented liver dysfunction in their medical admission notes (clerking notes), it is highly probable that their transaminase levels would be abnormal although not every patient with raised transaminases would have a documented diagnosis of liver disease or dysfunction. Similarly, the DCF recorded details of total white cell count and

neutrophil count as an indication of inflammation and/or infection. These were combined to give a variable of abnormal (elevated or low) total white cell count and/or abnormal neutrophil count, outside the normal laboratory range at SUH. Data was collected on falls looking at fall(/s) as a cause of current admission and falls history or documented falls risk, and these were also combined for the purpose of analysis. *Table M7* summarises which variables were considered as a combined variable for the purposes of data analysis, in an attempt to reduce the possibility of collinearity of variables when developing a Clinical Prediction Model.

Table M7: Table showing variables recorded individually in the DCF and subsequently considered together for the purposes of data analysis

Individual variable measured in the DCF	**Combined/composite variable considered for data analysis**
Abnormal total white cell count	Abnormal WCC and/or neutrophil count
Abnormal neutrophil count	
Abnormal AST (>x2 ULN*)	Abnormal liver function
Abnormal ALT (>x2 ULN*)	
Documented liver impairment, dysfunction or disease as part of presenting complaint or previous medical history	
Fall as part of current admission presentation	Falls and falls risk
Documented recent fall (within previous year), falls risk (in Activity of Living assessment) or falls risk sticker on front of medical notes	

* ULN = upper limit of normal (for SUH laboratory values of AST and ALT)

Where possible, data for variables were represented as binary numerical values (e.g. male = 0 and female = 1) to make statistical analysis easier following discussion with the Statistician.

Choice of statistical software program used

There are several different statistical software programs available with commonly used programs (currently) including SPSS (Statistical Package for Social Science), SAS (Statistical Analysis Systems), R, Stata and Python. A bibliometric analysis study looking at Trends in the Usage of Statistical Software and Their Associated Study Designs in Health Sciences Research found that the most common statistical software used in the reviewed studies was SPSS (accounting for 52.1%), followed by SAS (12.9%) and Stata(12.6%)(127). In consultation with a statistician at the University of Birmingham (UoB), it was decided that Stata would be the most appropriate program to use for this research in view of its functionality. This decision was made despite the Principal Researcher (AB) having previous limited experience of using SPSS which is a package used by many healthcare researchers for statistical analysis including pharmacists. It is also of note that subsequent to the decision to use Stata, the Principal Researcher (AB) undertook a short course at the UoB entitled 'Statistical methods for risk prediction and prognostic models' which included computer practical sessions using R and/or Stata software packages. Stata version 17 was used initially for statistical analysis which was subsequently upgraded to version 18 (midway during 2023).

The Stata software package was used to describe the data and perform analyses. The tabulate command was used to present the frequency, percentage and cumulative percentage for the different values of the independent variables. The tabulate command was run using 'tab', e.g. after loading the relevant data, the command 'tab GENDER' was entered to tabulate the frequency table for the GENDER variable where the options were 0 (representing male gender) and 1 (representing the female gender) and this was repeated for the other independent variables studied.

Presentation of demographic information as mean and median values

The demographic data has been presented with mean and median values to describe the central tendency. It is generally accepted that researchers are interested in "knowing about the value to which the sample or population would centre round"(128)(p.5) and, in statistics, there are three measures of this central tendency that are commonly used, namely the mean, the median and the mode(128).

The arithmetic mean is the sum of all the observations divided by the number of observations. The median is the value (or observation) which subdivides the numerically ordered data into two equal halves. The mean value is only useful for continuous data and is regarded as a "good measure"(129)(p.7) of central tendency when the data are "fairly well distributed and do not have outliers"(129)(p.7). The median is a more useful measure of central tendency compared to the mean when the underlying population is non-symmetrical as it is less affected by single outliers(129). The mode is the observation which occurs most frequently in the dataset studied. The mode is not often used to describe central tendency (compared to the mean and median values)(128).

In addition to an indication of its central tendency, the mean can also be useful to measure the spread or variance of the data. Where the mean is used to describe the central tendency of a set of data, the spread of the data around the mean is presented as the standard deviation (S.D.) which, mathematically, is the positive square root of the variance. When the population is non-symmetrical, measures such as quartiles, deciles and percentiles can be used to define the spread of data around the average value(128). Quartiles subdivide the data set so that 25% of the values are above the upper quartile (which is the 75^{th} percentile) and 25% are below the lower quartile(129). The interquartile range (IQR) is defined as the difference between the 25^{th} and 75^{th} percentiles (also known as the first and third quartiles) and, essentially, focusses on the middle (50%) of sorted data and so does not get skewed by outliers(129).

Data derived from a count or a standard measurement have a frequency distribution and the numbers can be discrete or continuous(129). A discrete variable is characterised by the fact that only certain values are permissible within the range studied; discrete data are whole numbers (integers) and examples include number of GP visits in a year or number of children in a family(128, 129). In contrast, continuous data can take any value within the range (there is an infinite number of possible values) and examples of continuous data include height, weight and age(128, 129).

The characteristics age (in the case of this study, the age in years at time of presentation, only represented as whole integers e.g. a patient aged 74 years old and 260 days would have a recorded age of 74 years), number of pre-admission medications (PAMs), renal function (presented as eGFR up to a maximum value of 90/+ and only given whole integer values), number of documented co-morbidities (COMORB, as documented on clerking/admission notes for current admission) and number of high risk pre-admission medications (HRPAMs) are essentially treated as discrete quantitative variables (in all cases, these variables can only take on whole integer values). Therefore, the results for these variables are presented both as mean values (with standard deviation, S.D.) and median values (with the interquartile range, IQR) in the *Results* (Chapter 4) to show the distribution of the values. Whilst there are a number of statistical tests that can be conducted to test for normal distribution of data these can be easily misinterpreted and it has been recommended that these are avoided(130). Instead, histograms were plotted using the statistical software program Stata (versions 17 and 18 used during the course of data analysis due to the updated version becoming available mid-2023; see next section *Statistical software program used*) for each of these numerical variables (as correct at the time of the first Pharmacist review) to show the distributions of the variables. The recognised yet pragmatic approach of visually reviewing ('eye-balling') the general/overall shape of the resultant histograms was used to determine whether each variable was normally distributed (following a bell curve distribution shape), plotting the variable on the x-axis versus density on the y-axis(130, 131). Below is a figure (*Figure M2*) showing a standard normal distribution (taken from NHS FIFE reference, (129)(p.16)).

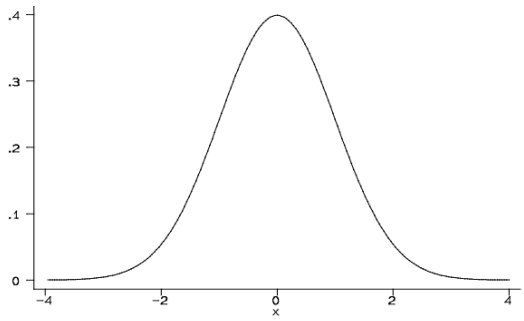


Figure M2: Figure showing Standard Normal Distribution, N (0,1). Note: Mean = 0, Standard deviation = 1 (taken from NHS FIFE reference, (129)(p.16))

68% within +/- 1 S.D., 95% within +/- 1.96 S.D., 99% within +/- 2.58 S.D. (taken from NHS FIFE reference(129).

The only one of these numerical variables in this study that appears to follow the overall pattern of a normal, bell-shaped distribution, also known as Gaussian distribution, is age and therefore, for the other numerical variables, it may be more appropriate (and indeed would be regarded as customary) to use the median and percentiles (presented as interquartile range, IQR) to summarise/describe the (non-normally distributed) data rather than using mean values(131). The rationale for this is that, as previously described, the median is less sensitive to the influence of outliers in the data. The histograms are included in the *Appendices*.

Statistical modelling and variable selection methods

Type of regression method

The choice of statistical analysis method most appropriate to the data collected and the outcome measure (the number of Clinical Pharmacist Interventions, essentially a count) was discussed with the UoB statistician providing support who advised that Poisson regression would be most appropriate with this type of outcome. Count data follow a Poisson distribution(132). Poisson regression can be used when considering which factors can predict the frequency of an event or outcome(132).

Univariate versus multivariate analyses to select variables

Univariate analysis of individual variables/predictors for statistical significance testing was not undertaken as part of this research due to limitations associated with its use. Some previous researchers have used univariate analysis in the process of developing risk prediction models/tools (in research related to this topic) to generate a potential list of variables or predictors or to essentially screen a large list of potential risk factors and create a shorter list of such factors for further analysis. For example, the researchers involved in the development of the Brighton Adverse Drug Reactions Risk (BADRI) Model (for Predicting Adverse Drug Reactions (ADRs) in Older People during Hospital Stay), used a combination of univariate analysis and multivariate binary logistic regression to identify clinical risk factors for (older patients) developing an ADR in a UK teaching hospital (103). Univariate analysis was used to "generate a framework of variables, or predictors"(103)(p.2) and from this identified 13 potential variables with statistical significance ($p<0.05$) and additional variables with p values of >0.05 but less than 0.25 that had previously been identified as being important predictors of ADRs from other studies were also included in the subsequent stage of model development(103). After testing for collinearity and discarding variables that were found to be correlated, eight variables were taken forward to the multivariate analysis stage(103). Similarly, the methodology used by another researcher (submitted as a DPharm thesis, in 2017) in the development of a risk score for 'Risk Assessment of Patients in an Acute Trust as a Means of Directing a Clinical Pharmacy Service' incorporated univariate and multivariate analyses, with univariate analyses being used to identify whether individual potential risk factors were significantly associated with the likelihood of the respective patient receiving a pharmacist intervention(98).

However, whilst exploratory univariate analysis (term used interchangeably with univariable analysis) may reveal some preliminary univariable associations with the outcome being considered, there are limitations associated with the use of univariable analysis to select predictors for inclusion in modelling and the current consensus is that univariable analyses should not be used for predictor

selection(133, 134, 135). PROBAST is a tool that was developed to assess the risk of bias and (the) applicability of prediction model studies. One of the domains considered in the PROBAST tool for studies relating to model development relates to the selection of predictors with recommendations that researchers should avoid univariable analysis methods which "can lead to incorrect predictor selection because predictors are chosen on the basis of their statistical significance as a single predictor rather than in context with other predictors"(134)(p.W21) and bias "occurs when univariable modeling results in omission of variables from the model, because some predictors are important only after adjustment for other predictors, known from previous research to be important, did not reach statistical significance in the particular development set (for example, due to small sample size)"(134)(p.W21). In addition, univariable analysis may result in predictors being "selected on the basis of a spurious (accidental) association with the outcome in the development set"(134)(p.W21).

Therefore, it was a deliberate decision in this current research to follow the current consensus opinion and not to employ univariable analysis of individual variables/predictors for statistical significance testing in this research whilst mindful that this methodology was adopted by numerous previous (published) researchers in this field.

Variable selection methodology

Variable selection (in regression) has been described as "the hardest part of model building"(136)(p.65). There are numerous different methods used for selecting the variables included in a Clinical Prediction Model/Clinical Prediction Tool (CPM/CPT[a]). These methods include fit full model (no variable selection, all are included), automatic selection procedures and penalised regression techniques. Considering the advantages and disadvantages of these different methods, and following consultation with the UoB statistician providing support, the Principal Researcher (AB) decided to utilise the backward elimination method for variable selection in this study. The different

approaches are described in the order listed above, according to increasing complexity, and the rationale for using the backward elimination approach summarised thereafter.

The fit full model approach includes all (pre-identified) candidate variables in the model, which avoids the problems of overfitting and selection bias whilst providing correct standard errors and P values. However, it is often impractical to include all candidates(137, 138).

The automatic selection procedures use statistical testing to develop the model. A series of significance tests can be conducted to determine which variables to include and which variables to remove from the model. Selection can be forward, backward or stepwise.

In forward selection, the process begins with a null model, containing no variables. After defining the criteria (significance level) for inclusion in the model, each variable is fitted and tested (individually) to determine if it improves model fit. The most significant variable is added (first) and then the model tested for a second variable. This process is repeated until no more variables are added, following a prespecified stopping rule (such as a P-value or the Akaike Information Criterion [AIC]), e.g. where the P-value exceeds the prespecified level for all other variables when added(136, 139).

In backward selection, the process starts with a full model, containing all the variables. The criteria for removal from the model (e.g. significance level, P-value or the AIC) is defined in advance. Each variable is (individually) removed in turn (from the full model) and the significance tested. From these results, the least significant of the variables (as per the testing) is removed from the (original full) model and then testing is carried out for removing another (second) variable. The process is continued, removing one variable at a time until no more variables will be removed from the model when the predefined stopping rule is satisfied, e.g. where the P-value is less than the specified level for all variables remaining in the model. Where automatic selection is used, backward selection, also called backward elimination, is preferred to forward selection(136, 138, 139).

In stepwise selection the process can begin with either a null or full model. The difference with the stepwise selection process is that it combines forward and backward elimination into the modelling process. The criteria for inclusion or removal from the model is defined (significance level). When starting with a full model, testing for removal of the variable is conducted and then testing is conducted to see if any of the variables should re-enter the model (or vice versa if starting with the null model, testing initially to add the variable, then testing if it is removed). The process stops when none of the variables in the model meet the defined criteria for exclusion and none of the variables out of the model meet the criteria for inclusion. As a result of repeated significance testing, stepwise selection procedures tend to produce an overfitting model and are not recommended(135, 140).

Penalisation techniques have been recommended by some when developing a CPM because they "address overfitting, as they shrink predictor effect estimates toward the null and reduce mean-square prediction error in new individuals"(141)(p.88). However, it has be found that these techniques "do not guarantee a reliable prediction model is developed"(141)(p.88) and that penalisation and shrinkage methods can produce unreliable CPMs especially when sample size was small(141).

Mindful of the limitations associated with these different methods of variable selection for CPM development, the decision was made to utilise the backward elimination method for variable selection in this study as using a full fit model is often unfeasible to use in practice (containing numerous variables), backward elimination is preferable to forward elimination, stepwise methods may produce an overfitting model and penalisation/shrinkage methods can produce unreliable CPMs.

Whilst the variable's (/predictor's) significance level is often set to α=0.05, as is common for hypothesis testing, simulation studies have suggested that a higher value may be appropriate, particularly in small data sets(139). Use of the AIC for selection, corresponding to a value of α=0.157 for backward elimination, may be used (using p=0.157 as a proxy, in the program Stata) which takes into account model fit whilst penalising for the number of parameters (or variables or predictors)

being estimated(139). Therefore, p=0.157 was used as a proxy for AIC for backward variable selection using Stata in this study.

Stata commands for variable selection

The relevant command for conducting backward (elimination) selection in Stata is:

stepwise, pr(#):

where the (#) denotes the significance level for removal from the model; terms with p ≥ pr() are eligible for removal from the model(142) .

(Note that whilst the command says "stepwise, pr(#)", the above command is for backward selection; the commands included for a backward stepwise selection are:

pr() pe()

using combinations of backward and forward selection(127).)

The following command was used in this study to conduct backward variable elimination (selection) in Stata using Poisson regression using a value of p=0.157 as a proxy for the AIC:

stepwise, pr (0.157): poisson INTERVENT AGE PAMS eGFR COMORB HRPAM i.GENDER i.ANTIMICRO i.ABWCC i.FALL i.ABLF

The abbreviations used for the different variables in Stata are summarised in *Table M8*.

Table M8: Table showing the abbreviations used in the Stata commands

Abbreviation used for variable in Stata	**Description**
INTERVENT	Number of interventions received (Primary outcome of study)
AGE	Age (in years)
PAMs	Number of pre-admission medications taken

eGFR	Estimated glomerular filtration rate (0-90)
COMORB	Number of co-morbidities
HRPAM	Number of high risk pre-admission medications taken
GENDER	Male or female (where Male = 0, Female =1)
ANTIMICRO	On systemic antimicrobial on/pre-admission (Yes=1, No=0)
ABWCC	Abnormal white cell count (Yes=1 or No=0)
FALL	Fall as part of current admission or history of fall/fall risk documented (Yes=1 or No=0)
ABLF	Abnormal liver function (Yes=1 or No=0)

The prefix 'i' was used for relevant categorical variables (when typing the Stata command) e.g. i.GENDER where individuals fall into one of a number of categories, in this case one of two categories being either male (Male = 0 for purposes of data entry/analysis in Excel and Stata) or female (Female = 1, for purposes of data entry/analysis in Excel and Stata).

Chapter summary

The *Methodology* chapter has described the methodology followed to develop a prediction tool to identify older patients for early Clinical Pharmacist review and the statistical analysis methods used to analyse the results.

The next chapter (Chapter 4), *Results,* will describe the results obtained from the data collection and subsequent statistical modelling and analysis methods.

Chapter 4: Results

Results

Chapter description

This chapter summarises the results of the data collected. The overall demographics and baseline characteristics of the study participants and the findings are presented together with an overview of the statistical analysis conducted and the results. Following the statistical analysis, clinical prediction modelling will be utilised to identify those independent variables that predict the outcome (Clinical Pharmacist Interventions, CPhIs) and develop a model which will then need to be validated prior to use in routine clinical practice.

Demographics and baseline characteristics

Data were available for 121 patient episodes, the demographics and baseline characteristics (at the time of presentation) of whom are reported in *Table R1* below.

Table R1: Baseline and demographic characteristics for patients

Demographic/baseline characteristic		Number (* %age of total, to 2 s.f.)		Range	Mean (S.D.) (to 2 decimal points, 2 d.p.)	Median (interquartile range, IQR)
Gender*	Male (0)	69	(57)			
	Female (1)	52	(43)			
Age				65-97	79.88 (7.21)	80 (74-85)
PAMs				0-29	11.81 (5.32)	12 (9-15)
eGFR				9-90	54.31 (22.68)	54 (36-74)
COMORB				1-15	6.58 (3.09)	6 (4-8)
HRPAM				0-6	1.60 (1.36)	1 (1-3)
ANTIMICRO*	Yes (1)	42	(35)			
	No (0)	79	(65)			
ABWCC*	Yes (1)	61	(50)			
	No (0)	60	(50)			
ABLF*	Yes (1)	7	(6)			
	No (0)	114	(94)			
FALL*	Yes (1)	57	(47)			
	No (0)	64	(53)			

Abbreviations used in Table R1:

PAMs = number of pre-admission medications

eGFR = estimated glomerular filtration rate on admission (expressed in ml/min/1.73m^2)

COMORB = number of (documented) co-morbidities/co-existing conditions as per clerking notes (on admission)

HRPAM = number of high risk pre-admission medications

ANTIMICRO = patient taking a systemic antimicrobial agent on admission or within week prior to admission (treatment or prophylaxis)

ABWCC = abnormal white cell count, as indicated by either/or total white cell count and/or neutrophil count being outside normal laboratory range for these parameters

ABLF = abnormal liver function, as indicated by either abnormal transaminase levels (ALT+/-AST) and/or documented current liver dysfunction on admission notes and/or documented previous medical history of liver dysfunction

FALL = fall documented as a contributing factor/cause of current admission, and/or recent fall within previous year documented in clerking (admission) notes, and/ or falls risk as identified and documented on admission (including in nursing assessment forms where available in notes for current admission) and/or from a FALLS RISK sticker attached to the front of the medical notes

s.f. = significant figures

S.D. = standard deviation.

Explanation of presentation of demographic information as mean and median values

As described earlier in Chapter 3, *Methodology,* the quantitative variables studied in this research namely number of interventions (outcome), age, eGFR, number of PAMS, number of HRPAM(/s) and

the number of comorbidities, are all discrete variables and the distribution plots generated on Stata (adjusted for discrete variable) generally do not follow a normal, bell-shaped distribution or are skewed or have outliers. Therefore, whilst mean values are automatically reported in Stata (e.g. using the 'tabstat' command) the relevant commands were used to report median values and interquartile range (IQR) in the results.

Measurement of independent variables and outcome

The following table *(Table R2)* summarises the format of the data included for each independent variable for analysis.

Table R2: Independent variables and outcome studied and measurement type

Parameter measured	**Factor/variable being studied**	**Measurement type (e.g. numerical or binary)**
Age	Age	Numerical value (65/+); no maximum value; whole numbers used
Gender (m/f)	Gender	Binary - Male (0) or Female (1)
PAMs = Actual number of pre-admission medicines (PAMs) taken	Polypharmacy	Numerical value, e.g. 0 upwards with no maximum value; whole numbers
On systemic antimicrobial on/prior to (within 7 days) admission (treatment or prophylaxis)	Presence of infection (current or recent) or history of recurrent infection	Binary - Yes (1) or No (0)

	necessitating prophylactic systemic antimicrobials or being at high risk of infections	
ABNORMAL White cell count (ABWCC) and/or Neutrophil count.	Presence of infection or inflammation (current)	Binary - Yes (1) or No (0) (in this instance N = 0 means that the blood results are Normal)
eGFR = a value from 0-90 (where 90 is the maximum value so essentially it measures 0 to 90/+)	Renal function	Numerical value, ranging from 0-90; whole numbers
Documented liver impairment as part of HPC or PMH from current admission notes **and/or** Abnormal AST &/or ALT >x2 ULN	Liver (hepatic) impairment	Binary - Yes (1) or No (0)
Documented fall as part of current admission presentation as per current admission notes **and/or**	Falls history	Binary - Yes (1) or No (0)

Documented recent fall and/or falls risk in Activity of Living assessment, and/or falls risk sticker on medical notes		
Number of documented co-morbidities (or medical/surgical problems) as per **current** admission notes (clerking notes)	Number of co-morbidities	Numerical value ranging from 0 upwards with no maximum value; whole numbers
HRPAM = Number of high risk medications taken as PAM (from previously identified list of high risk medications)	Taking high risk medication	Numerical value ranging from 0 upwards with no maximum value; whole numbers
Actual number of Clinical Pharmacist Interventions (CPhI)	**Outcome measure**: Clinical Pharmacist Interventions (CPhI)	Numerical value ranging from 0 upwards (no maximum value); whole numbers

Computer statistical software program used for Results analysis

In consultation with a statistician at the University of Birmingham (UoB), it was decided that Stata would be appropriate to use as the software program for conducting statistical analysis of this research; consideration of the different programs available has been previously discussed in the

Methodology chapter. Stata version 17 was used initially for statistical analysis which was subsequently upgraded to version 18 (midway during 2023).

Baseline characteristics/demographics

Gender

From the sample size of 121, 69 (57%) of patients were male whilst 52 (43%) were female. Numerical values of 0 and 1 were allocated to describe the male and female genders respectively to make analysis of the results using Stata easier.

Age

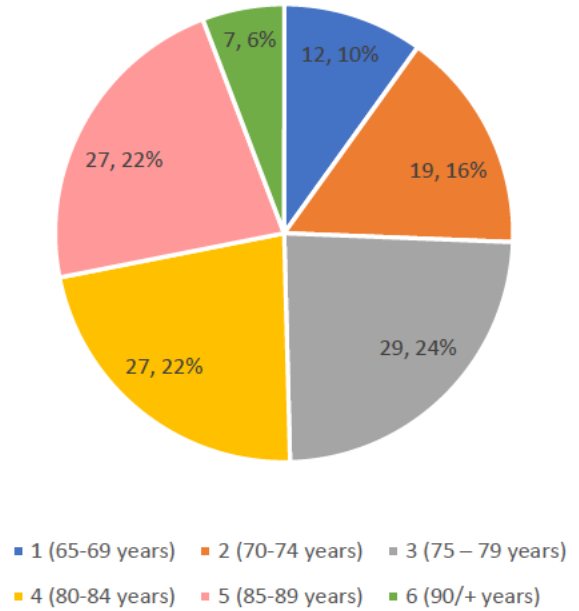
The 'tab AGE' command was used in Stata to tabulate the age demographics for the 121 patients. The full breakdown of the age demographics is included in the *Appendices (Appendix R1)*. Age was represented as a discrete variable, able to take on whole, positive values representing the patient's age in years. A patient's age was recorded as, for example, 80 years old until their 81st birthday was reached. As tabulated in *Table R1*, the ages of patients included in the sample population ranged from 65 to 97 years old, with the mean age calculated as 79.88 years (80 years corrected to 2 significant figures) (+/- 7.21 standard deviation, S.D.). The median age of the sample population was 80 years (with an interquartile range, IQR, of 74-85 years).

To get a better understanding of the distribution of the ages of included patients, Stata was used to create age groups as a separate variable (see *Appendix R2* for details of commands used in Stata), as presented in *Table R3* and *Chart R1*, below.

Table R3: The age groups and their distribution in the sample population as frequency, percentage and cumulative percentage.

Age Group	Frequency	Percentage (%)	Cumulative percentage (%)
1 (65-69 years)	12	9.92	9.92
2 (70-74 years)	19	15.70	25.62
3 (75 – 79 years)	29	23.97	49.59
4 (80-84 years)	27	22.31	71.90
5 (85-89 years)	27	22.31	94.21
6 (90/+ years)	7	5.79	100.00
Total	**121**	**100.00**	

Chart R1: Chart showing the age of patients in sample population according to age groups (frequency and percentage)



From *Table R3* and *Chart R1* it can be clearly seen that the vast majority of patients were within the age range 75-89 years old, accounting for approximately two thirds of patients (68.59%) and, in fact, 84.29% of the sample had ages between 70-89 years of age.

Histograms were generated in Stata to show the distributions of the independent variables; the shape of the histogram generated for the age variable appeared to follow a bell-shape generally consistent with a normal distribution (see *Appendix R3*).

Number of pre-admission medicines (PAMs) taken

The 'tab PAMs' command was used in Stata to tabulate the number of pre-admission medicines (PAMs) taken by the 121 patients. The full breakdown of the PAMs characteristic in the sample population is included in the *Appendices* (*Appendix R4*) and a histogram showing the distribution of PAMs taken is included (*Appendix R5*).

The number of PAMs taken was represented as a discrete variable, able to take on whole, positive values representing the number of PAMs taken as per Medication Reconciliation undertaken by the Clinical Pharmacist. The number of PAMs taken by individuals in the sample population ranged from 0 to 29, as tabulated in *Table R1*. In the sample population (n=121), the median value for PAMs was 12 with an IQR of 9 to 15 (IQR=9-15) and mean value of 11.81 (S.D. = 5.32).

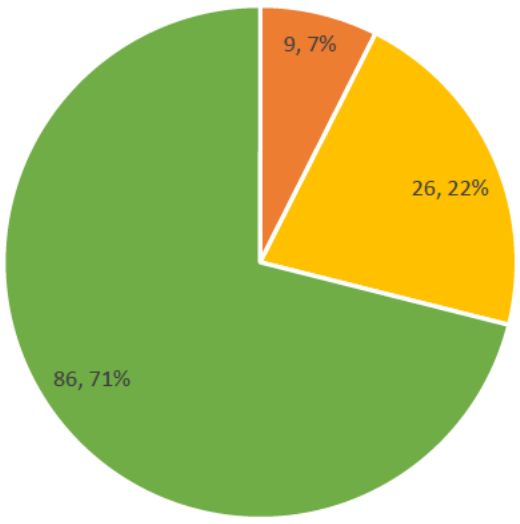
Retrospectively the distribution of PAMs has been divided into categories according to the widely accepted definitions of poly- and hyperpolypharmacy, corresponding to the use of less than five PAMs, 5-9 PAMs ('polypharmacy') and 10/+ PAMs ('hyperpolypharmacy'), by creating the relevant categories in Stata (described in *Appendix R6*). The number of PAMs taken according to these categories is described in *Table R4.*

Table R4: Groupings for the number of PAMs taken and distribution of same in the sample population as frequency, percentage and cumulative percentage.

PAMs Group	Frequency	Percentage (%)	Cumulative percentage (%)
1 (PAMs=0-4)	9	7.44	7.44
2 (PAMs = 5-9)	26	21.49	28.93
3 (PAMs = 10/+)	86	71.07	100.00
Total	**121**	**100.00**	

This table shows that the vast majority of patients (71%) were prescribed (/taking) 10 or more medications (hyperpolypharmacy) at the time of admission, and in fact almost 93% of the patients included in the sample were taking at least 5 medications. The distribution is also illustrated in the following chart, *Chart R2*.

Chart R2: Chart showing the number of PAMs taken by patients in sample population according to groups 1-3 (presented as frequency and percentage)



On systemic antimicrobial on/prior to (within 7 days) admission (treatment or prophylaxis)

In the sample population (n=121), 42 patients (35%) were taking some form of systemic antimicrobial agent (including antibacterial, antifungal and antiviral agents), used for either treatment or prophylaxis (e.g. for urinary tract infection prophylaxis) within the 7 days prior to admission/presentation to SUH. The remaining 79, 65%, of patients were not taking systemic antimicrobial therapy within this timeframe around their admission.

Abnormal white cell count (ABWCC) and/or neutrophil count

Half of the sample population (61 patients, 50%) had a total white cell count (WCC) and/or neutrophil count outside the normal laboratory reference range used at SUH (outside the normal range at the time that the result was reported) (i.e. at least one of these blood results was outside the normal range), which could have been lower or higher than the reference range. The first blood results from the presentation/admission were used for this result (as 'admission bloods') and within the first 48 hours (in the case where there was delay in these bloods being taken). For the remaining half (60 patients, 50%), neither the total WCC nor neutrophil counts were outside the normal laboratory reference range at SUH.

Renal function (on admission)

The renal function of the patients on admission (first result, taken within 48 hours of admission) was estimated(/calculated) and reported by the hospital laboratory systems using the serum creatinine value and expressed as estimated glomerular filtration rate (eGFR) (calculated and presented on the Lab73 system as this eGFR value). The eGFR is presented (and reported by the SUH laboratory) as an eGFR normalised to a body surface area of $1.73m^2$ with the units of measurement for eGFR being **$ml/min/1.73m^2$**.

The full breakdown of the demographics for renal function is included in the *Appendices* (see *Appendix R7*) and a histogram showing the distribution of renal function is included (*Appendix R8*).

Similar to the creation of groups to present the demographic, baseline characteristics of the sample population with respect to age and number of PAMs taken, the eGFR results can be presented as per the categories for eGFR from G1 to G5 (including G3a and G3b) (see *Appendix R9* for details).

Table R5: Groups for the different categories of (e)GFR (G1 to G5) and distribution of same in the sample population as frequency, percentage and cumulative percentage.

(e)GFR category	Frequency	Percentage (%)	Cumulative percentage (%)
G1	8	6.61	6.61
G2	44	36.36	42.98
G3a*	25	20.66	63.64
G3b#	28	23.14	86.78
G4	9	7.44	94.21
G5	7	5.79	100.00
Total	**121**	**100.00**	

Note:

G1 represents a GFR = 90/+ ml/min/1.73m^2

G2 = 60-89 ml/min/1.73m^2

G3a = 45-59 ml/min/1.73m^2

G3b = 30-44 ml/min/1.73m^2

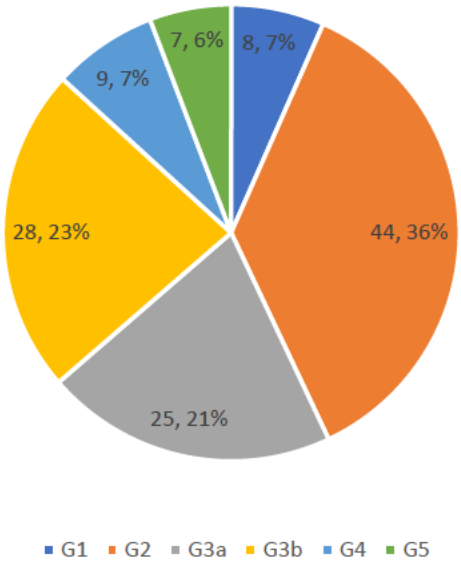
G4 = 15-29 ml/min/1.73m^2

G5 <15 ml/min/1.73m^2

Table R5 shows that the vast majority of patients (97, 80%) had an eGFR corresponding to G2-G3b (i.e. within the range 30-89ml/min/1.73m^2). In the sample population, 16 individuals (13%) had an eGFR

in category 4 or 5, equivalent to an eGFR < 30ml/min/1.73m^2. The distribution is also illustrated in the following chart, *Chart R3*.

Chart R3: Chart showing the (e)GFR of patients in sample population according to categories G1 to G5 (frequency and percentage)



Abnormal liver function (ABLF)

In the sample population (n=121), seven patients (6%) were classified as having ABLF on admission as indicated by at least one of the following:

- Abnormal (raised) transaminase levels (ALT +/- AST) on admission bloods (defined as >x2 ULN as described in *Methodology*)
- Documented current liver dysfunction on admission notes
- Documented previous medical history of liver dysfunction,

with the remaining 114 patients (94%) having no sign or documented current/history of abnormal liver function.

Falls (current/recent history of falls) and falls risk

A fall was documented as a contributing factor/cause of current admission, and/or recent fall within previous year documented in clerking (admission) notes or falls risk as identified and documented on admission (including in nursing assessment forms where available in notes for current admission) or from 'FALLS RISK' sticker attached to the front of the medical notes for 57 (47%) of patients in the sample (n=121). The remaining 64 patients (53%) did not have a fall contributing to current admission or documented recent falls history or fall risk.

Number of documented co-morbidities (COMORB)

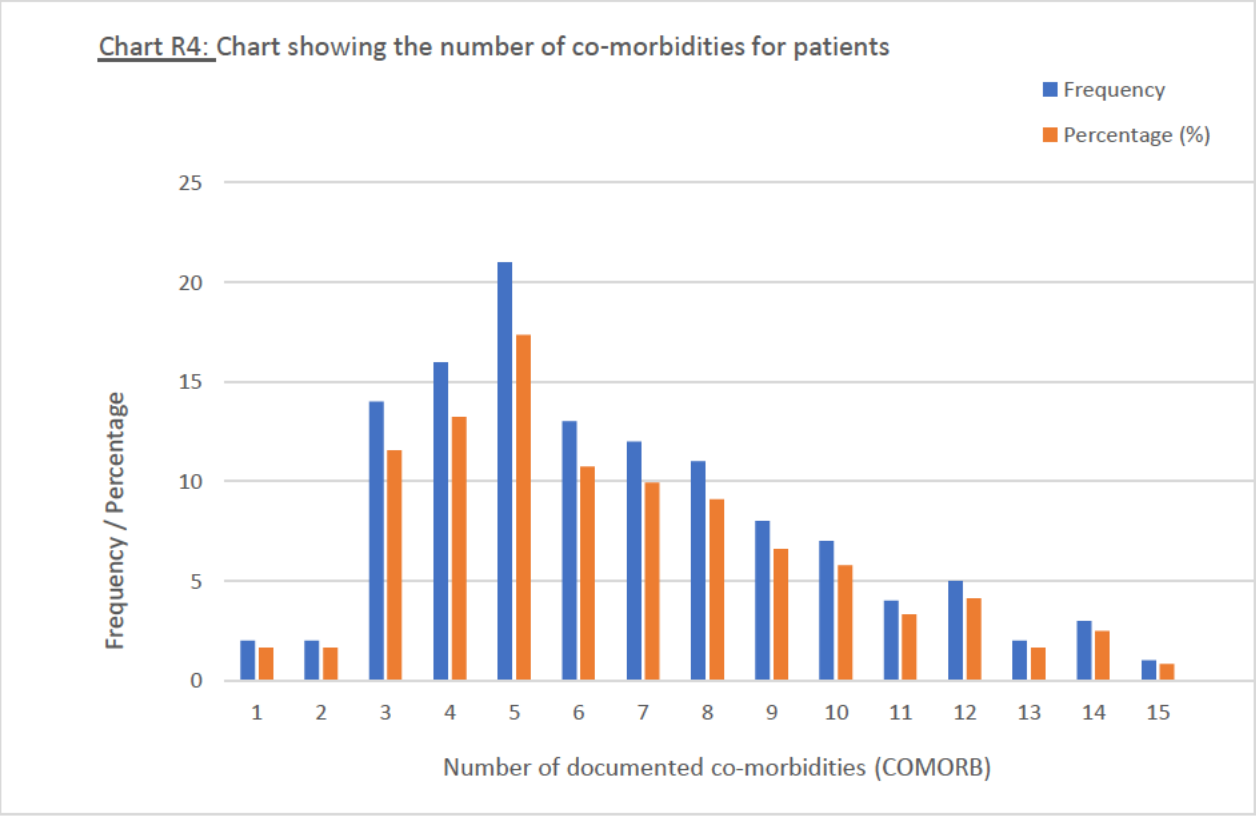
The 'tab COMORB' command was used in Stata to tabulate the number of co-morbidities/co-existing conditions documented in the clerking notes for the current admission. COMORB was represented as a discrete variable, able to take on whole, positive values. The number of documented co-morbidities in the sample population ranged from 1 to 15, as tabulated below in *Table R6*. The values for number of COMORB showed a non-normal distribution for the sample and so median values would be considered more appropriate/meaningful to describe the average value of this variable compared to the mean. In the sample population (n=121), the median value for COMORB was 6 with an IQR of 4 to 8 (IQR=4-8). The full distribution of the values of COMORB in the sample is shown in the table below, *Table R6*.

Table R6: The number of documented co-morbidities for patients in the sample

COMORB	Frequency	Percentage (%)	Cumulative percentage (%)
1	2	1.65	1.65
2	2	1.65	3.31
3	14	11.57	14.88
4	16	13.22	28.10
5	21	17.36	45.45

6	13	10.74	56.20
7	12	9.92	66.12
8	11	9.09	75.21
9	8	6.61	81.82
10	7	5.79	87.60
11	4	3.31	90.91
12	5	4.13	95.04
13	2	1.65	96.69
14	3	2.48	99.17
15	1	0.83	100.00
Total	**121**	**100.00**	

The number of comorbidities can be illustrated in the following chart, *Chart R4*, and *Appendix R10* shows the distribution histogram from Stata.



High Risk Pre-admission Medicines (HRPAMs)

The 'tab HRPAM' command was used in Stata to tabulate the number of high risk pre-admission medicines (HRPAMs) taken by the 121 patients. The variable HRPAM was represented as a discrete variable, able to take on whole, positive values representing the number of HRPAMs taken as per Medication Reconciliation undertaken by the Clinical Pharmacist. The number of HRPAMs taken by individuals in the sample population ranged from 0 to 6, as tabulated in *Table R1*. The values for HRPAM showed a non-normal distribution for the sample (see *Appendix R11*) and so median values would be considered more appropriate to describe the average value of this variable compared to the mean. In the sample population (n=121), the median value for HRPAM was 1 with an IQR of 1 to 3.

Number of interventions on first Clinical Pharmacist review

The outcome chosen for this study is the number of Clinical Pharmacist Interventions (CPhIs) made at the first (Pharmacist) review and is a quantitative, discrete variable (as values have to be positive and whole numbers). The following table, *Table R7*, summarises the number of interventions made for patients on initial review by a Clinical Pharmacist, ranging from 0-12, with 246 interventions made overall.

Table R7: The number of interventions received for patients on initial review by a Clinical Pharmacist

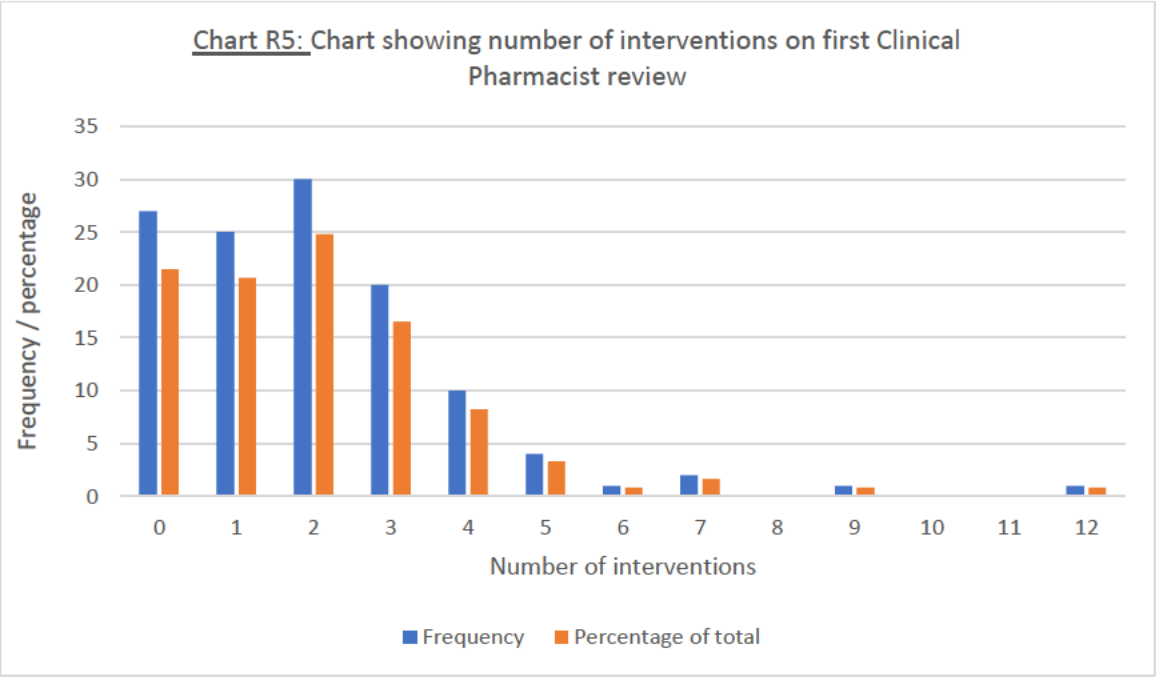
Number of interventions	**Frequency**	**Percentage of total (%)** (to 2 d.p)
0	27	22.31
1	25	20.66
2	30	24.79
3	20	16.53
4	10	8.26
5	4	3.30
6	1	0.83

7	2	1.65
8	0	0.00
9	1	0.83
10	0	0.00
11	0	0.00
12	1	0.83
TOTAL number of patients	**121**	
TOTAL number of interventions	**246**	
Mean (S.D.) = 2.03 (1.92)		
Median (IQR) = 2 (1-3)		

In the study population, 22.31% of the patients did not receive any interventions upon the first Clinical Pharmacist review whilst the remaining 77.69% of the study population received one or more intervention at this point.

The mean number of interventions (on first review) for a patient was 2.03 (S.D.=1.92) but the data do not appear to follow a normal distribution (see histogram in *Appendix R12*) so it may be more appropriate (and consistent with consensus opinion) to consider the median value of 2 with an IQR of 1-3, where IQR is the interquartile range.

The following chart, *Chart R5*, shows the frequency of the different number of interventions made on first Clinical Pharmacist review.



Consideration of the number of interventions (outcome) according to each of the independent variables measured.

- **Number of interventions and gender**

The following table, *Table R8*, shows how the number of interventions received by patients varied according to gender with patients receiving between 0 to 12 interventions on first Clinical Pharmacist review.

Table R8: Number of interventions according to gender

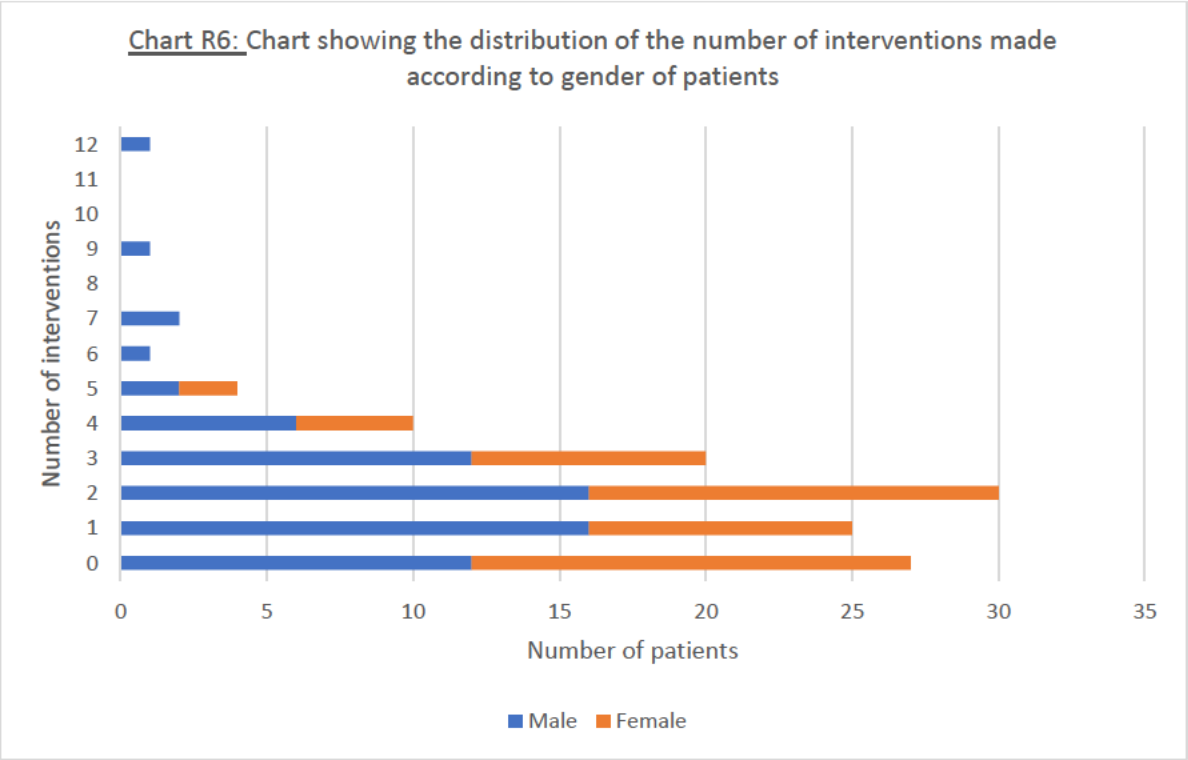
Number of interventions	GENDER		
	Male (total number of interventions)	Female (total number of interventions))	Total number of patients (male & female)
0	12 (0)	15 (0)	27
1	16 (16)	9 (9)	25
2	16 (32)	14 (28)	30
3	12 (36)	8 (24)	20

4	6 (24)	4 (16)	10
5	2 (10)	2 (10)	4
6	1 (6)	0 (0)	1
8	0 (0)	0 (0)	0
7	2 (14)	0 (0)	2
9	1 (9)	0 (0)	1
10	0 (0)	0 (0)	0
11	0 (0)	0 (0)	0
12	1 (12)	0 (0)	1
Total	**69 (159)**	**52 (87)**	**121**

Note : Male denoted as '0' in Stata and Female as '1' for ease of manipulation.

A total of 159 interventions were made to the male patients (n=69 male patients) which is equivalent to an average (mean) of 2.30 interventions per male patient (median = 2, IQR = 1-3). A total of 87 interventions were made to the female patients (n=52 female patients) which is equivalent to an average (mean) of 1.67 interventions per female patient (median = 2, IQR = 0-3). This suggests a possible gender difference with respect to the number of interventions received.

The following chart, *Chart R6*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to the gender of patients.



- **Number of interventions and age**

The full results for analysis of the distribution of the number of interventions according to age are included as *Appendix R13*. This is because of the number of fields involved, across an age range of 33 years (presented per year) and with a range of zero to 12 interventions. Therefore, to aid in the summarising of the results, the ages have been 'grouped together' into 6 groups (and as used earlier when describing the baseline characteristics of the participants, see *Table R3*), summarised in *Table R9*, with each group except group 6 accounting for 5 years (e.g. group 1, between 65-69 years old), and where group 6 represented those aged 90 or more years (and where the ages included ranged from 90 -97 years and *represented* just 7 participants overall).

Table R9: Summary of age groupings and frequency

Age Group	**Frequency**
1 (65-69 years)	12
2 (70-74 years)	19
3 (75 – 79 years)	29
4 (80-84 years)	27
5 (85-89 years)	27
6 (90/+ years)	7
Total	**121**

The following table, *Table R10*, shows the number of patients in the different age groups who received between 0 and 12 interventions on first Clinical Pharmacist review. See *Appendix R14* for details of Stata commands used to analyse and present data in this way.

Table R10: The number of patients receiving different numbers of interventions, presented according to patient age groups (1-6).

Number of Interventions	**Number of patients according to age groups 1-6**						
	Group 1 (65-69y)	**Group 2 (70-74y)**	**Group 3 (75-79y)**	**Group 4 (80-84y)**	**Group 5 (85-89y)**	**Group 6 (90/+y)**	**Total**
0	6	5	3	6	6	1	27
1	1	5	11	4	4	0	25
2	4	5	3	7	8	3	30
3	0	2	7	4	6	1	20
4	0	1	2	4	2	1	10
5	1	0	0	2	0	1	4
6	0	0	0	0	1	0	1
7	0	0	2	0	0	0	2
8	0	0	0	0	0	0	0
9	0	1	0	0	0	0	1
10	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0
12	0	0	1	0	0	0	1
Total	**12**	**19**	**29**	**27**	**27**	**7**	**121**

These results can then be analysed to calculate the average (mean) number of interventions per patient, according to age group (see *Appendix R14* for Stata commands) to illustrate the relationship between age and the number of interventions received, as summarised in *Table R11* below.

Table R11: The mean number of interventions received by patients according to their age groups (1-6), with standard deviation (S.D.), minimum and maximum values also included.

Age Groups (1-6)	Number of patients	Mean Number of Interventions	S.D.	Minimum	Maximum
1 (65-69yr)	12	1.167	1.528	0	5
2 (70-74yr)	19	1.789	2.097	0	9
3 (75-79yr)	29	2.483	2.544	0	12
4 (80-84yr)	27	2.074	1.591	0	5
5 (85-89yr)	27	1.926	1.492	0	6
6 (90/+ yr)	7	2.571	1.618	0	5
TOTAL	121	2.033	1.923	0	12

This suggests that those patients aged over 75 years of age, appear to have a higher mean number of interventions (per patient) than those aged 65-74 years old (i.e. in age groups 1 and 2), with individuals aged 90/+ years having the highest mean number of interventions (=2.571) and those aged 65-69 years old having the fewest (mean = 1.167). Those patients aged 75-79 years old received the second highest mean number of interventions.

In view of the non-normal distribution of the number of interventions (as illustrated in the histogram included as *Appendix R12*), the results are also presented in *Table R12* below as the median value, interquartile range (IQR) as well as the mean number of interventions for individuals in the different age groups. The median value of the number of interventions for patients in each of the age groups 3-6 is equal to 2 and is less for those in groups 1 and 2 (with median values of 0.5 and 1 respectively), again consistent with the interpretation of the mean values which showed that those individuals aged between 65-74 years of age received less interventions than those aged 75 years or older. The

commands used in Stata to present the data in this way are included in the *Appendices* (*Appendix R15*).

Table R12: The median number of interventions received by patients according to their age groups (1-6), with the interquartile range and mean number of interventions also shown.

Age Group	Median (p50) number of interventions	IQR (p25-p75) number of interventions	Mean number of interventions
1 (65-69yr)	0.5	0-2	1.167
2 (70-74 yr)	1	0-2	1.789
3 (75 – 79 yr)	2	1-3	2.483
4 (80-84 yr)	2	1-3	2.074
5 (85-89 yr)	2	1-3	1.926
6 (90/+)	2	2-4	2.571
Total	**2**	**1-3**	**2.033**

- **Number of interventions and number of pre-admission medications taken (PAMs)**

The full results for analysing the distribution of the number of interventions according to the number of pre-admission medications taken (PAMs) are included as *Appendix R16* due to the number of rows and columns making presentation of the data concisely difficult.

As when presenting the baseline characteristics for the study population, the number of PAMs taken can be considered as a number of distinct groups in an attempt to summarise the average number of interventions according to whether the patients were (regularly) taking less than five, between five and nine ('polypharmacy') or ten or more medications ('hyperpolypharmacy') prior to admission. These groups can be summarised as below in *Table R13.*

Table R13: Summary of the different PAMs group and their frequency in the study population

PAMs Group	Frequency
1 (PAMs=0-4)	9
2 (PAMs = 5-9)	26
3 (PAMs = 10/+)	86
Total	**121**

The mean average value for the number of interventions according to the number of PAMs groupings is shown in the following tables, along with standard deviation (S.D.), minimum and maximum values (*Table R14*) and showing mean, median and IQR (*Table R15*) (see *Appendix R17* for details of commands used in Stata to generate these values).

Table R14: The number of interventions (INTERVENT) according to PAMs group expressed as mean, and showing standard deviation (S.D.), minimum and maximum values.

PAMs Group	Number of patients	Mean Number of INTERVENT	S.D.	Minimum	Maximum
1 (PAMs=0-4)	9	0.222	0.667	0	2
2 (PAMs = 5-9)	26	1.538	1.104	0	4
3 (PAMs = 10/+)	86	2.372	2.069	0	12
Total	**121**	**2.033**	**1.923**	**0**	**12**

Table R15: The number of interventions according to PAMs grouping expressed as mean, median (p50) and IQR.

PAMs Group	Median (p50) number of interventions	IQR (p25-p75) number of interventions	Mean number of interventions
1 (PAMs=0-4)	0	0-0	0.222
2 (PAMs = 5-9)	1.5	1-2	1.538
3 (PAMs = 10/+)	2	1-3	2.372
Total	**2**	**1-3**	**2.033**

These findings show that the average number of interventions received was highest in those patients receiving hyperpolypharmacy (i.e. in PAMs group 3, receiving 10 or more medicines), with a mean value of interventions of 2.372 (to 3 decimal places, 3 d.p.) compared to 1.538 (to 3 d.p.) for those receiving between 5-9 medications pre-admission (regularly) (PAMS group 2) and 0.222 for those receiving between 0-4 medications pre-admission (PAMS group 1) and median values of interventions of 0, 1.5 and 2 respectively for PAMS group 1, 2 and 3.

- **Number of interventions and whether patients were taking systemic antimicrobial on/prior to (within 7 days) admission (treatment or prophylaxis)**

The following table (*Table R16*) shows how the number of interventions received by patients on first Clinical Pharmacist review varied according to whether patients were receiving systemic antimicrobial therapy on admission/within a week of admission.

Table R16: The number of interventions received by patients according to whether they were receiving systemic antimicrobial therapy at the time of admission or within a week prior to admission to SUH.

Number of interventions	**ANTIMICRO (Taking systemic antimicrobial therapy)**		
	No (%age)	**Yes (%age)**	**Total**
0	20 (74%)	7 (26%)	27
1	17 (68%)	8 (32%)	25
2	17 (57%)	13 (43%)	30
3	13 (65%)	7 (35%)	20
4	8 (80%)	2 (20%)	10
5	2 (50%)	2 (50%)	4
6	1 (100%)	0 (0%)	1
7	1 (50%)	1 (50%)	2
8	0 (0%)	0 (0%)	0
9	0 (0%)	1 (100%)	1
10	0 (0%)	0 (0%)	0
11	0 (0%)	0 (0%)	0
12	0 (0%)	1 (100%)	1
Total	**79 (65%)**	**42 (35%)**	**121**

(Note: Percentages calculated going across the table.

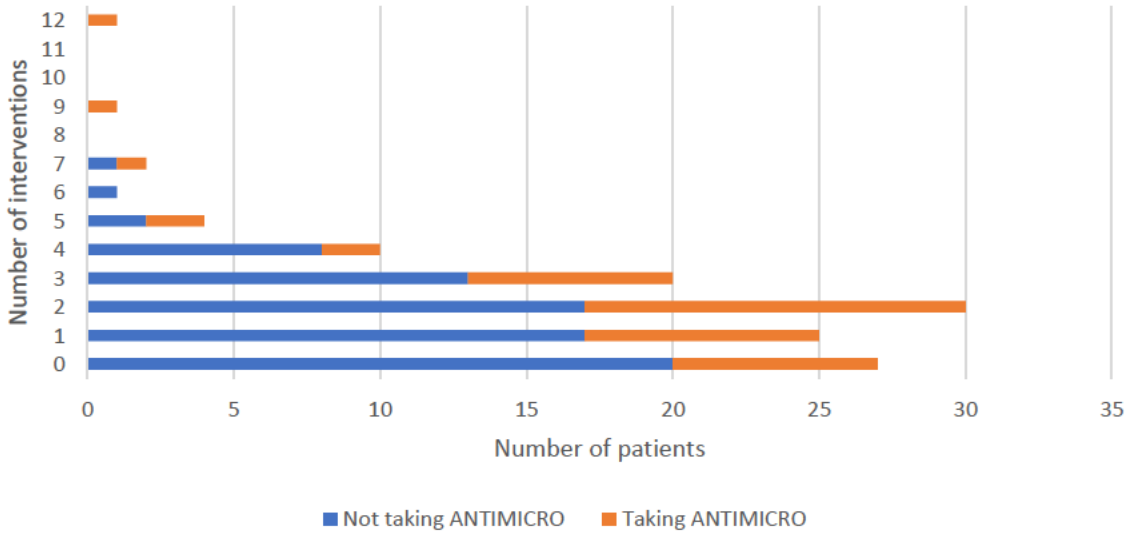
As the table shows and as per baseline characteristics table, 35% of patients overall were receiving systemic antimicrobial therapy at the time of, or within the week prior to, their admission to SUH. For the individuals who received the highest number of interventions, nine and 12 interventions each, on first Clinical Pharmacist review (one patient for each), they were both taking systemic antimicrobial

therapy on admission or within the week prior to admission accounting for 100% of the patients who received those numbers of interventions, and the patient who received six interventions on first review was not taking systemic antimicrobial agents either on admission or within the week prior to admission. For the other number of interventions, less patients were receiving antimicrobial therapy on/within the week preceding admission with the exception of the patients who received five and seven interventions on first Clinical Pharmacist review, with 50% of patients taking systemic antimicrobials and 50% not taking them, on admission or within the week preceding admission for both groups (for those who received five or seven interventions).

Looking at the tabulated results, there does not appear to be a clear directly proportional relationship between patients taking systemic antimicrobial at the time of admission (or within the previous week) and the number of interventions made, i.e. those individuals taking systemic antimicrobial therapy at/around the time of admission did not appear to receive significantly more interventions than those who had not been taking such medication.

The following chart, *Chart R7*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to whether patients were taking systemic antimicrobial therapy at the time of/within the week prior to admission.

Chart R7: Chart showing the distribution of the number of interventions made according to whether patients were taking systemic antimicrobial therapy at the time of/within week prior to admission



- **Number of interventions and whether patients had abnormal white cell count (ABWCC) and/or neutrophil count at the time of admission**

The following table, *Table R17*, shows how the number of interventions received by patients on first Clinical Pharmacist review varied according to whether patients had an abnormal white cell count (WCC) and/or neutrophil count (ABWCC) at the time of admission (based on first admission bloods as documented in notes or confirmed via laboratory results accessed via Lab73 system).

Table R17: The number of interventions received by patients according to whether they had ABWCC on their (first) admission blood test results.

Number of interventions	ABWCC		
	No (%age)	Yes (%age)	Total
0	16 (59%)	11 (41%)	27
1	9 (36%)	16 (64%)	25

2	18 (60%)	12 (40%)	30
3	8 (40%)	12 (60%)	20
4	7 (70%)	3 (30%)	10
5	1 (25%)	3 (75%)	4
6	0 (0%)	1 (100%)	1
7	1 (50%)	1 (50%)	2
8	0 (0%)	0 (0%)	0
9	0 (0%)	1 (100%)	1
10	0 (0%)	0 (0%)	0
11	0 (0%)	0 (0%)	0
12	0 (0%)	1 (100%)	1
Total	**60 (49.6%)**	**61 (50.4%)**	**121**

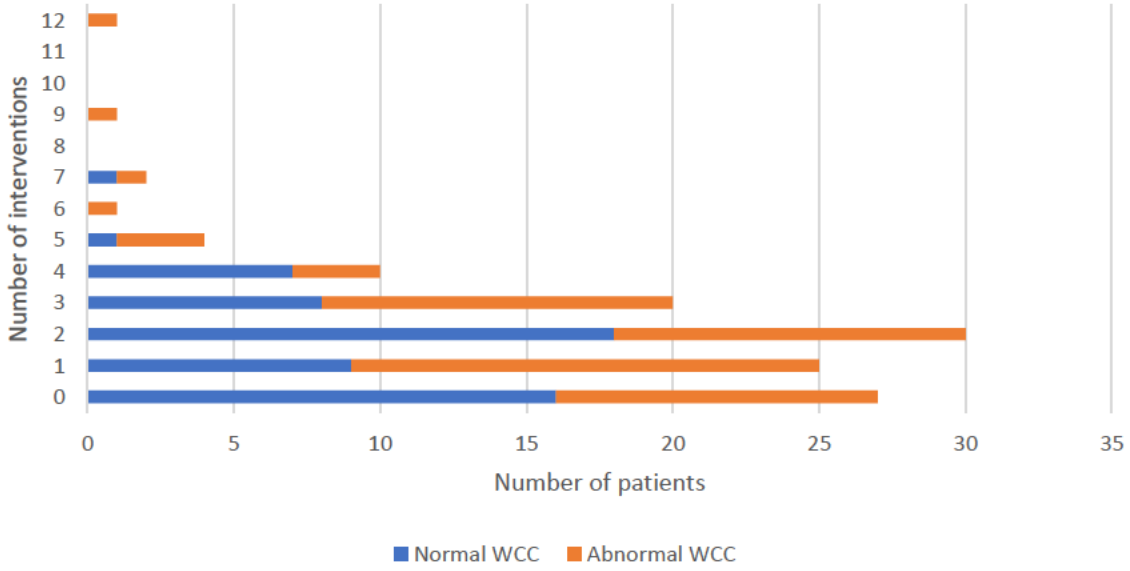
(Note: Percentages calculated as a percentage of total going across the table.)

The results show that, overall, approximately half of patients had abnormal WCC (ABWCC) and/or neutrophil count on their first admission blood test results as tabulated in baseline characteristics table (*see Table R1*). The above table, *Table R17*, also shows that, when considering the incidence of ABWCC as a function of the number of interventions received at first Clinical Pharmacist review, for the majority of the different number of interventions, the percentage of patients with ABWCC on admission was around the 50% level (+/- 15%) e.g. accounting for those patients who received 0, 1, 2, 3 and 7 interventions.

Looking at the tabulated results, there does not appear to be a clear directly proportional relationship between ABWCC on admission and the number of interventions made, i.e. those individuals with ABWCC did not appear to receive significantly more interventions than those who had normal WCC on admission.

The following chart, *Chart R8*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to whether WCC (total and/or neutrophil count) was abnormal at the time of admission.

Chart R8: Chart showing the distribution of the number of interventions made according to whether WCC (total and/or neutrophil count) was abnormal



- **Number of interventions and renal function (on admission)**

Similar to the consideration of the possible relationship between the number of interventions at first Clinical Pharmacist review and age, the full results tabulating the number of interventions according to renal function is included as an appendix due to the number of columns and rows making it difficult to summarise concisely (see *Appendix R18*). The baseline characteristics for the individuals included in the sample included renal function and these were presented according to recognised categories, G1 to G5 as summarised again here,

G1 represents an eGFR = 90/+ ml/min/1.73m^2

G2 = 60-89 ml/min/1.73m^2

G3a = 45-59 ml/min/1.73m^2

G3b = 30-44 ml/min/1.73m^2

G4 = 15-29 ml/min/1.73m^2

G5 <15 ml/min/1.73m^2.

For ease of review, the number of interventions received can be presented according to these categories of renal function, as shown in *Table R18*.

Table R18: The number of interventions received by patients according to renal function category G1 to G5 at admission.

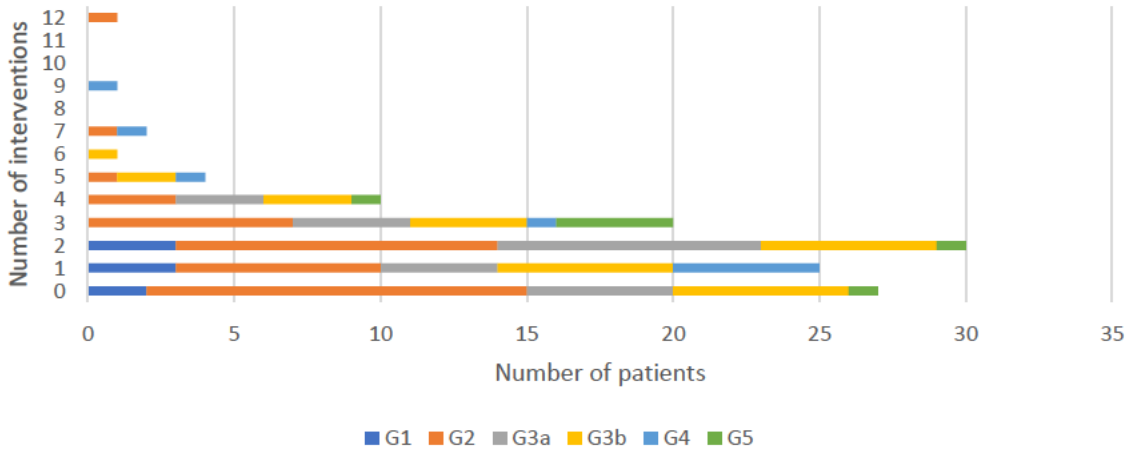
Number of interventions	**eGFR categories (number, (%age to 1 d.p.)**						
	G1	**G2**	**G3a**	**G3b**	**G4**	**G5**	**Total**
0	2 (7.4%)	13 (48.1%)	5 (18.5%)	6 (22.2%)	0 (0.0%)	1 (3.7%)	27 (100.0%)
1	3 (12.0%)	7 (28.0%)	4 (16.0%)	6 (24.0%)	5 (20.0%)	0 (0.0%)	25 (100.0%)
2	3 (10.0%)	11 (36.7%)	9 (30.0%)	6 (20.0%)	0 (0.0%)	1 (3.3%)	30 (100.0%)
3	0 (0.0%)	7 (35.0%)	4 (20.0%)	4 (20.0%)	1 (5.0%)	4 (20.0%)	20 (100.0%)
4	0 (0.0%)	3 (30.0%)	3 (30.0%)	3 (30.0%)	0 (0.0%)	1 (10.0%)	10 (100.0%)
5	0 (0.0%)	1 (25.0%)	0 (0.0%)	2 (50.0%)	1 (25.0%)	0 (0.0%)	4 (100.0%)
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)

7	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2 (50.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1 (100.0%)
10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
11	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
12	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Total	**8 (6.6%)**	**44 (36.4%)**	**25 (20.7%)**	**28 (23.1%)**	**9 (7.4%)**	**7 (5.8%)**	**121 (100.0%)**

(Note: Percentages calculated going across the table.)

The following chart, *Chart R9*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to the renal function category of the patients at admission (G1 to G5).

Chart R9: Chart showing the distribution of the number of interventions made according to renal function categories G1 to G5



From the results as presented in *Table R18* and *Chart R9*, it does not appear to be a simple directly proportional relationship between the number of interventions made and the renal function category at admission. Of those 16 patients with the worst renal function at admission, corresponding to categories G4 and G5, 12 (75%) received three or less interventions at first Clinical Pharmacist review. Of the 52 patients with the 'best' renal function, represented by categories G1 and G2, 46 (88.5%) received three interventions or less, at first Clinical Pharmacist review. The patient who received the most interventions at first Clinical Pharmacist review (12 interventions) had an estimated renal function within category G2.

- **Number of interventions and whether the patients had abnormal liver function on admission**

The following table, *Table R19*, shows how the number of interventions received by patients on first Clinical Pharmacist review varied according to whether patients had an abnormal liver function (ABLF) at the time of admission.

Table R19: Table showing the number of interventions received by patients according to whether they had ABLF (as per definition in *Methodology*).

Number of interventions	**Abnormal liver function (ABLF)**		
	No (Normal) (%age to 1 d.p)	**Yes (Abnormal) (%age to 1 d.p)**	**Total**
0	26 (96.3%)	1 (3.7%)	27
1	24 (96.0%)	1 (4.0%)	25
2	27 (90.0%)	3 (10.0%)	30
3	19 (95.0%)	1 (5.0%)	20
4	9 (90.0%)	1 (10.0%)	10
5	4 (100.0%)	0 (0.0%)	4
6	1 (100.0%)	0 (0.0%)	1
7	2 (100.0%)	0 (0.0%)	2
8	0 (0.0%)	0 (0.0%)	1
9	1 (100.0%)	0 (0.0%)	1
10	0 (0.0%)	0 (0.0%)	0
11	0 (0.0%)	0 (0.0%)	0
12	1 (100.0%)	0 (0.0%)	1
Total	**114 (94.2%)**	**7 (5.8%)**	**121**

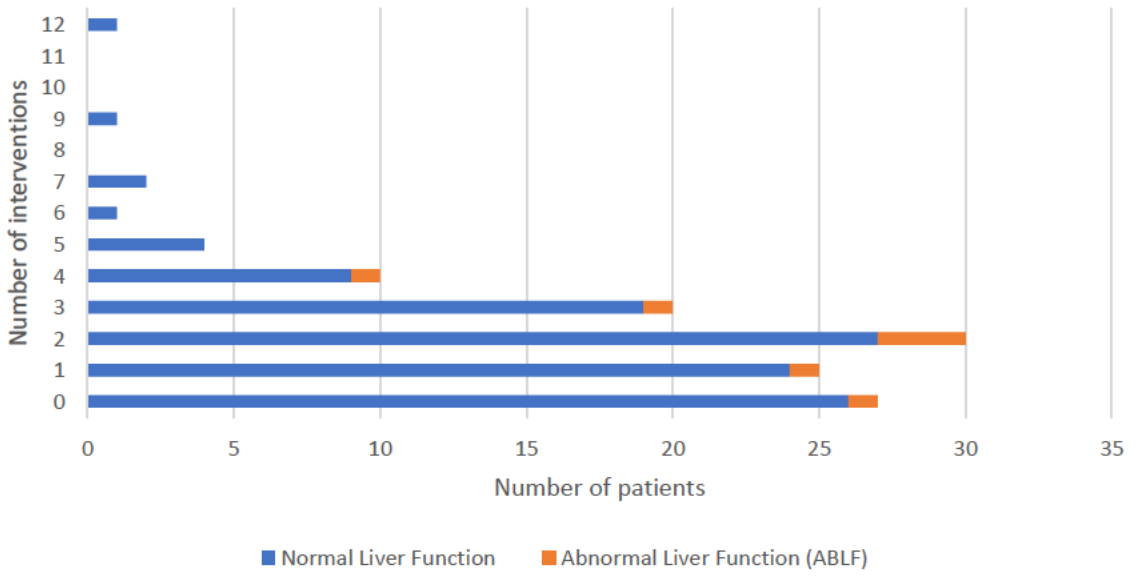
(Note: Percentages calculated going across the table.)

As shown in *Table R19*, only a small number of the included 121 patients were identified as having abnormal liver function (according to the criteria described in the methodology), just seven patients overall (accounting for 5.8% of the sample population) and those individuals received between 0 and 4 interventions on first Clinical Pharmacist review (3 individuals received 2 interventions each; note the category with the highest number of interventions, regardless of liver function status, was those

receiving 2 interventions accounting for 30 of the total of 121 patients). Therefore, there does not appear to be a clear directly proportional relationship between abnormal liver function and the number of interventions made, i.e. having abnormal liver function (as per methodology definition) does not appear to be directly (proportionally) related to receiving a higher number of interventions at first Clinical Pharmacist review.

The following chart, *Chart R10*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to whether the liver function of individual patients was normal or abnormal at the time of admission.

Chart R10: Chart showing the distribution of the number of interventions made according to whether liver function was abnormal



- **Number of interventions and falls**

The following table, *Table R20*, shows how the number of interventions received by patients on first Clinical Pharmacist review varied according to whether patients had a documented falls history or falls risk, or falls were part of their presenting complaint on this admission.

Table R20: The number of interventions received by patients according to falls risk/history/current presentation.

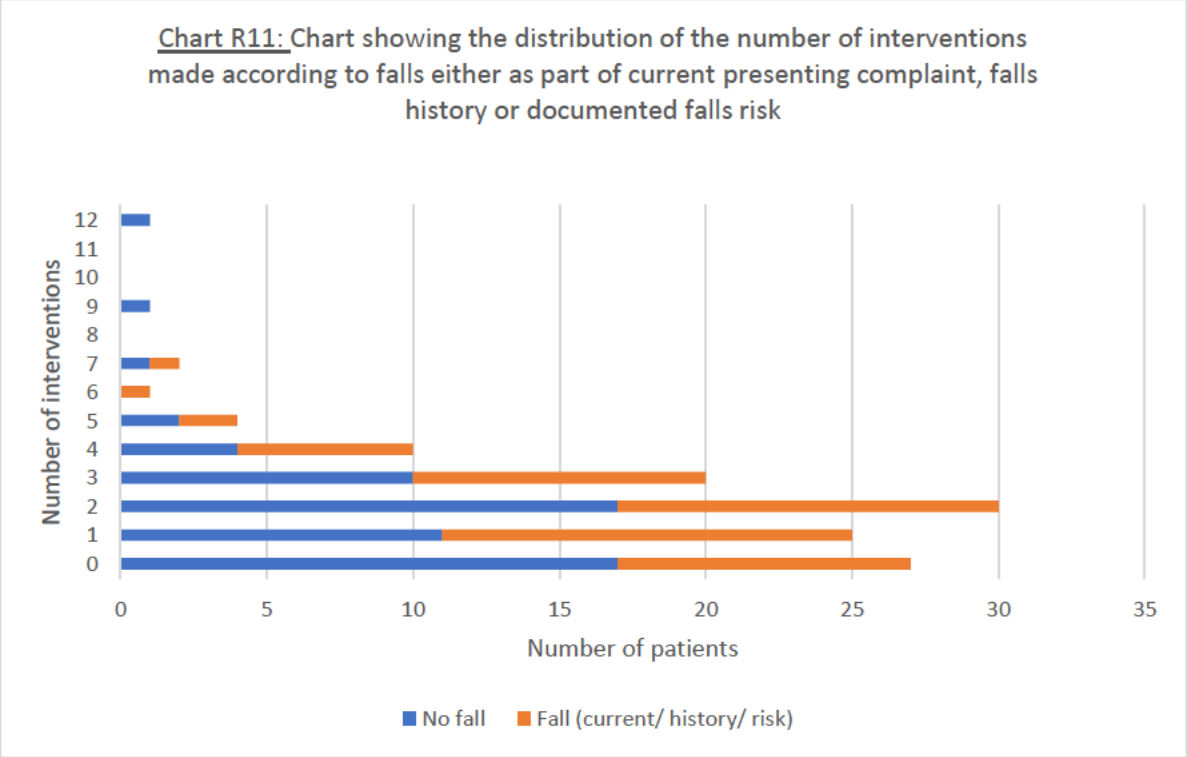
Number of interventions	FALL		
	No fall (%age)	**Fall (current/ history/ risk) (%age)**	**Total**
0	17 (63.0%)	10 (37.0%)	27
1	11 (44.0%)	14 (56.0%)	25
2	17 (56.7%)	13 (43.3%)	30
3	10 (50.0%)	10 (50.0%)	20
4	4 (40.0%)	6 (60.0%)	10
5	2 (50.0%)	2 (50.0%)	4
6	0 (0.0%)	1 (100.0%)	1
7	1 (50.0%)	1 (50.0%)	2
8	0 (0.0%)	0 (0.0%)	0
9	1 (100.0%)	0 (0.0%)	1
10	0 (0.0%)	0 (0.0%)	0
11	0 (0.0%)	0 (0.0%)	0
12	1 (100.0%)	0 (0.0%)	1
Total	**64 (52.9%)**	**57 (47.1%)**	**121**

(Note: Percentages calculated going across the table.)

As can been seen from the table, approximately half of the patients in the sample population had experienced a fall as part of their presenting complaint on current admission, had a documented falls history and/or had documented falls risk (47.1%). There does not appear to be a clear directly proportional relationship between falls and the number of interventions made, i.e. having had a

current fall/ history of falls/ documented falls risk (as per methodology definition) does not appear to be directly related (proportional) to receiving a higher number of interventions at first Clinical Pharmacist review; the two patients who received the highest number of interventions in the sample population (9 and 12 interventions) did not present with a fall as part of their current admission, did not have a documented (recent) fall history nor have a documented falls risk. Of the 57 patients with a current fall, falls history and/or documented falls risk, 53 (equivalent to 93.0%) received between 0 and 4 interventions on first Clinical Pharmacist review.

The following chart, *Chart R11*, illustrates the distribution of the number of interventions made at first Clinical Pharmacist review according to whether falls was part of the presenting complaint for current admission, whether the patient had a documented (recent) falls history and/or documented falls risk, or not.



- **Number of interventions and number of co-morbidities (COMORB)**

The number of documented co-morbidities for patients in the sample population ranged from 1 to 15.

The following table, *Table R21*, shows how the number of interventions received by patients on first Clinical Pharmacist review varied according to the number of documented co-morbidities on the current admission.

Table R21: The number of interventions (abbreviated to No. INT for this table) received by patients according to the number of documented co-morbidities.

No.	**Number of documented co-morbidities on current admission**															
INT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Total**
0	2	1	4	4	5	1	3	2	1	2	0	1	0	0	1	**27**
1	0	0	1	3	6	2	3	3	2	1	0	2	1	1	0	**25**
2	0	0	5	5	2	3	5	3	1	2	2	1	0	1	0	**30**
3	0	1	3	2	3	3	0	2	2	2	1	0	1	0	0	**20**
4	0	0	0	1	3	3	0	0	2	0	1	0	0	0	0	**10**
5	0	0	0	1	1	0	1	0	0	0	0	0	0	1	0	**4**
6	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	**1**
7	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	**2**
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
9	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	**1**
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
12	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	**1**
Total	**2**	**2**	**14**	**16**	**21**	**13**	**12**	**11**	**8**	**7**	**4**	**5**	**2**	**3**	**1**	**121**

(Note: No. INT in table heading used to indicate 'Number of interventions'.)

The table is quite cumbersome to interpret and identify trends, given the number of columns and rows. Therefore, to simplify the results so any possible pattern/relationship between number of co-

morbidities and number of interventions might be readily identified, creating groups for the number of co-morbidities may facilitate review.

The following groups were created in Stata retrospectively as follows in the table below, *Table R22* (see *Appendix R19* for Stata command details).

Table R22: Table showing the COMORB Groups created.

Number of co-morbidities	**COMORB Group**
0-5	1
6-10	2
11/+	3

The following table, *Table R23*, shows the number of interventions received by patients depending upon the groups for number of co-morbidities, Groups 1- 3.

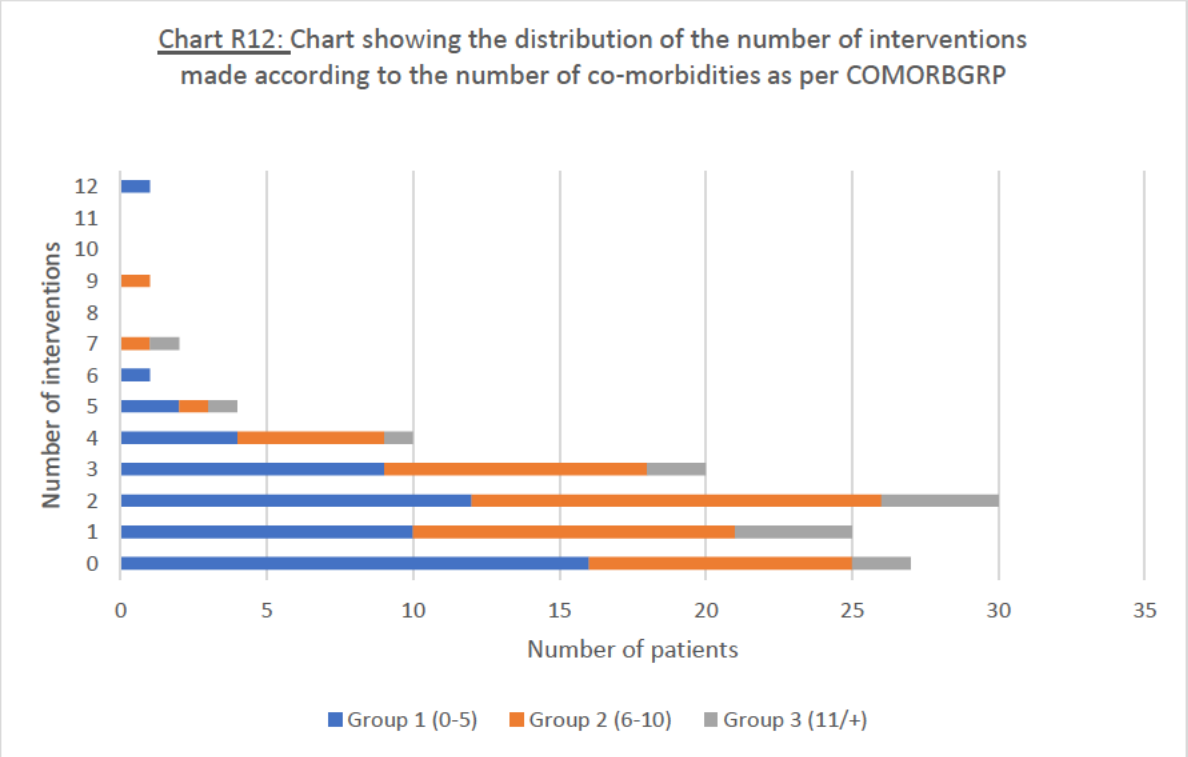
Table R23: The number of interventions received by patients according to the groupings for the number of documented co-morbidities, Groups 1 - 3.

Number of interventions	**RECODE of COMORB (COMORBGRP)**			
	Group 1 (0-5) (%age, to 1 d.p.)	**Group 2 (6-10) (%age, to 1 d.p.)**	**Group 3 (11/+) (%age, to 1 d.p.)**	**Total**
0	16 (59.3%)	9 (33.3%)	2 (7.4%)	**27**
1	10 (40.0%)	11 (44.0%)	4 (16.0%)	**25**
2	12 (40.0%)	14 (46.7%)	4 (13.3%)	**30**
3	9 (45.0%)	9 (45.0%)	2 (10.0%)	**20**
4	4 (40.0%)	5 (50.0%)	1 (10.0%)	**10**
5	2 (50.0%)	1 (25.0%)	1 (25.0%)	**4**

6	1 (100.0%)	0 (0.0%)	0 (0.0%)	**1**
7	0 (0.0%)	1 (50.0%)	1 (50.0%)	**2**
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
9	0 (0.0%)	1 (100.0%)	0 (0.0%)	**1**
10	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
11	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
12	1 (100.0%)	0 (0.0%)	0 (0.0%)	**1**
Total	**55**	**51**	**15**	**121**

(Note: Percentages calculated going across the table.)

The following chart, *Chart R12*, shows the distribution of the number of interventions made at first Clinical Pharmacist review according to the COMORBGRP groupings of the number of co-morbidities.



Of the 15 patients who had 11/+ documented co-morbidities (COMORBGRP group 3), the majority (12 of 15, 80%) received between 0 and 3 interventions on first Clinical Pharmacist review. This is similar

to the proportion of patients in COMORBGRP groups 1 and 2 who received between 0 and 3 interventions (47 out of 55, and 43 out of 51 patients respectively, equivalent to 85.5% and 84.3% of patients within those groups). Of the two patients receiving the most interventions at first Clinical Pharmacist review, namely 8 or more interventions, one had between 0–5 documented comorbidities (COMORBGRP group 1) and one had between 6–10 documented comorbidities (COMORBGP group 2), and none had 11/+ comorbidities. This suggests that there is not a clear (as in directly proportional) relationship between the number of comorbidities and the number of interventions at first Clinical Pharmacist review.

- **Number of interventions and high risk pre-admission medications (HRPAMs)**

The following table, *Table R24*, shows the number of interventions made at first Clinical Pharmacist review according to the number of high risk pre-admission medications (HRPAMs) taken by patients. The number of HRPAMs taken ranged from 0 to 6, inclusive.

Table R24: Table showing the number of interventions received by patients according to the number of HPRAMs taken

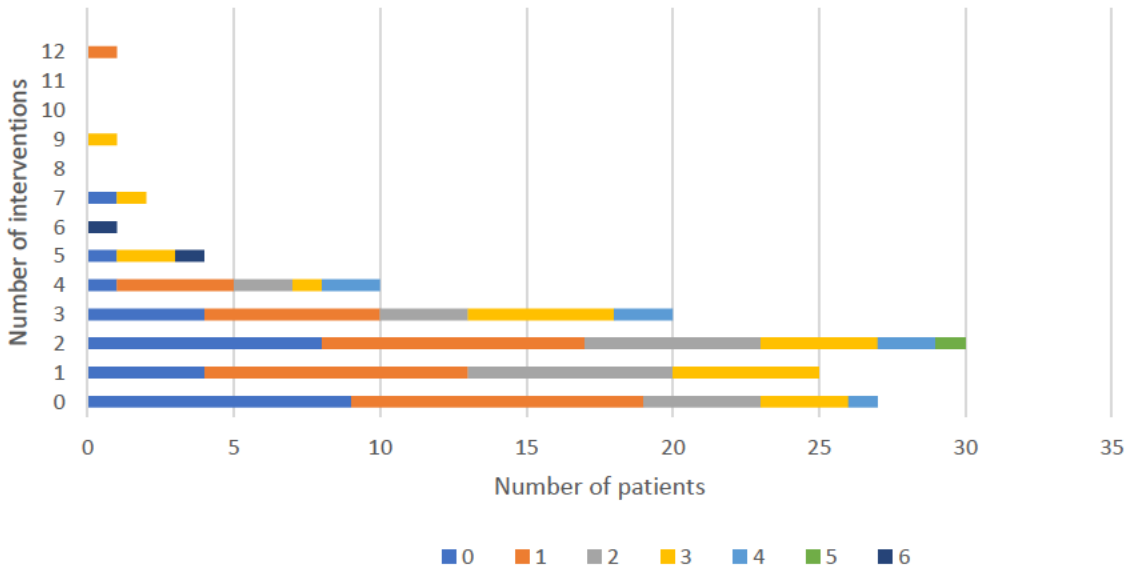
Number of interventions	**Number of HPRAMs (%age to 1 d.p.)**							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
0	9 (33.3%)	10 (37.3%)	4 (14.8%)	3 (11.1%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	**27**
1	4 (16.0%)	9 (36.0%)	7 (28.0%)	5 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**25**
2	8 (26.6%)	9 (30.0%)	6 (20.0%)	4 (13.3%)	2 (6.6%)	1 (3.3%)	0 (0.0%)	**30**
3	4 (20.0%)	6 (30.0%)	3 (15.0%)	5 (25.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	**20**

4	1 (10.0%)	4 (40.0%)	2 (20.0%)	1 (10.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	**10**
5	1 (25.0%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	**4**
6	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	**1**
7	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**2**
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1**
10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
11	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**0**
12	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**1**
Total	**28**	**39**	**22**	**22**	**7**	**1**	**2**	**121**

(Note: Percentages calculated going across the table.)

The following chart, *Chart R13*, shows the distribution of the number of interventions made at first Clinical Pharmacist review according to the number of HPRAMs taken.

Chart R13: Chart showing the distribution of the number of interventions made according to the number of HRPAMs taken (0-6)



From review of the table and chart (*Table R24* and *Chart R13*) it can be seen that, of the 10 patients who were taking four or more HRPAMs, six (60%) received between 0-3 interventions on first Clinical Pharmacist review. Of the two patients who received the most interventions, namely 8/+ interventions on first Clinical Pharmacist review, one was receiving just one HRPAM (and received 12 interventions) and the other patient (who received 9 interventions) was taking three HRPAMs. This suggests that there is no clear relationship (as in, not directly proportional) between the number of HRPAMs taken and the number of interventions at first Clinical Pharmacist review in the sample population.

Type of interventions made

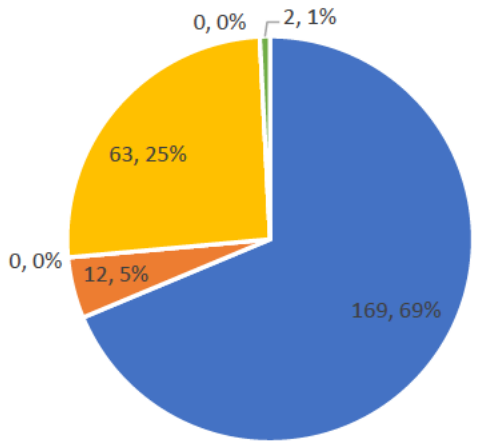
The data collection form categorised the type of interventions made by the Clinical Pharmacist at the time of the first review. The different categories and the number of interventions made belonging to these categories are summarised in the following table and chart *(Table R25 and Chart R14)*. It can be seen that approximately 69% of interventions made were related to Medication Reconciliation issues (n=169, 68.7%) and approximately 25% of interventions belonged to the category

advice/recommendation to prescriber (n=63, 25.6%). Two interventions, relating to allergy status and indication for prescribing a medication, fell into the 'Other' category for type of intervention, accounting for 0.8% of the total interventions.

Table R25: Table showing the type of interventions made

Type of intervention	Number of interventions	Percentage (of total number of interventions made)
Medication Reconciliation issues	169	68.7%
Prescribing error	12	4.9%
Medication administration issue	0	0.0%
Advice/recommendation	63	25.6%
Patient counselling	0	0.0%
Other	2	0.8%
Total	246	

Chart R14: Chart showing the different types of intervention made at first Clinical Pharmacist review (frequency and percentage)



Variable selection

Consistent with the approach described in detail in the *Methodology*, a backward selection Poisson regression was used to identify possible predictors of the outcome (the number of interventions), out of the 10 candidate variables studied. At each step, variables were removed based on p-values, and the value $p<0.157$ (generally regarded as a proxy for the AIC) was used. Univariable analysis of the individual independent variables was not conducted (rationale for this decision is discussed in *Methodology*). The detailed commands used in Stata to conduct this backward selection regression and the output generated are included in *Appendix R20.*

The Wald test was conducted and the following table, *Table R26*, shows which variables did not meet the level of statistical significance, $p<0.157$, and were removed from the model (began with full model and variables were removed using backward selection). *Table R27* shows which variables met the level of statistical significance chosen.

Table R26: Table showing the variables removed from modelling which began with full model and variables removed using backward selection; Wald test conducted; p<0.157

Variable	**P value (>/= 0.157)**
ABLF	0.7684
eGFR	0.5672
COMORB	0.4454
FALL	0.3814
ABWCC	0.2906
HRPAM	0.2549
AGE	0.2388
ANTIMICRO	0.1833

The following is copied from the Stata output when the command for backward elimination using Poisson regression was used, where p<0.157.

Poisson regression

Number of obs = 121

LR chi2(2) = 23.67

Prob > chi2 = 0.0000

Pseudo R2 = 0.0503

Log likelihood =-223.59564

Table R27: Table showing variables with p<0.157 when backward elimination using Poisson regression was performed (copied from Stata output)

INTERVENT	Coefficient	Standard error	Z	P>|z|	95% confidence interval	
1.GENDER	-.3325482	.1334672	-2.49	0.013	-.5941392	-.0709573
PAMS	.0488747	.0113218	4.32	0.000	.0266843	.0710651
_cons	.2277726	.1679583	1.36	0.175	-.1014196	.5569647

In layman's terms, in regression modelling, the P>|z| column represents the p -value that is associated with the value in the z value column. If the p-value is less than a certain significance level, in this case prespecified at (<) 0.157, it indicates that the predictor variable has a statistically significant relationship with the response variable in the model.

This means that the variables of patient gender (p=0.013) and the number of pre-admission medicines (PAMs) taken (p=0.000) were found to possibly be predictive of the outcome variable of the study, namely the number of interventions at first Clinical Pharmacist review and reached the prespecified level of statistical significance of p<0.157.

Calculating risk (or prediction) score/model

Equation for Poisson model regression:

Log(y) = a + b1x1 +b2x2 +…

Where y = count outcome (number of interventions in this case)

a = intercept, a = 0.2277726

b's = represent regression coefficients for each predictor in the model

x's = represent predictors

Using Stata outcome from backward Poisson regression corrected to 3 d.p.

a = 0.228

x1 = gender (male = 0, female = 1)

b1 = -0.333

x2 = PAMs

b2 = 0.049

Therefore, substituting values of a, x1, b1, x2 and b2 from Stata output into the equation:

Log (Number of Clinical Pharmacist Interventions) = 0.228 + (-0.333 *x1) + (0.049*PAMs)

Where * denotes multiply by

Number of Clinical Pharmacist Interventions = $e^{[0.228+(-0.333*x1)+(0.049*PAMs)]}$

Interpretation of the risk (or prediction) score/model

The above equation was developed from the modelling methods described (Poisson regression, backward elimination). The results of the regression modelling suggest that two variables, patient gender and the number of pre-admission medicines (PAMs) taken, were found to possibly be predictive of the number of interventions at first Clinical Pharmacist review, reaching the prespecified level of statistical significance. The values and equation derived show that the female gender appears to be associated with lower risk than the male gender. Meanwhile, the number of interventions received at first Clinical Pharmacist review appears to increase along with the (increasing) number of pre-admission medications taken.

Examples to illustrate the practical application of the developed equation/risk score

If there were two older patients, one male and one female, both taking the same number of pre-admission medicines, the male patient would be expected to be more likely to receive more interventions at first CPh review (by virtue of his gender), would have a higher score value (calculated using the developed equation), and could be prioritised for early CPh review (prioritised over the female patient).

If there were two older patients of the same gender, the patient taking the higher number of pre-admission medicines would be expected to receive the higher number of interventions at first CPh review, would have a higher score value (calculated using the developed score) and could be prioritised for early CPh review (prioritised over the patient with the lower number of PAMs).

Chapter summary

The *Results* chapter summarised the demographics of the study participants and studied the relationship between the primary outcome (number of Clinical Pharmacist Interventions) and the potential risk factors studied. The results of the statistical analyses conducted, and Poisson backward regression modelling were presented, along with the resultant formula for a risk/clinical prediction score. Overall, two variables (namely patient gender and the number of pre-admission medicines, PAMs, taken) were found to possibly be predictive of the number of interventions at first Clinical Pharmacist review and reached the prespecified level of statistical significance.

The next chapter (Chapter 5), *Discussion,* discusses the findings of this study and compares them with previous relevant research in this field.

Chapter 5: Discussion

Discussion

Chapter description

The *Discussion* chapter discusses the findings of this current study and compares them with previous relevant research. The study findings are compared with recently published literature (identified since the systematic review (SR) in *Chapter 2* was conducted), and the studies included in the SR.

Overview of research

The overall aim of this thesis was to identify variables that might highlight which older medically admitted patients at Sligo University Hospital (SUH) might benefit most from early Clinical Pharmacist Intervention (CPhI) and develop a prioritisation tool incorporating these variables.

A systematic review (SR) of the published literature was conducted to identify previous studies (primary research) looking at screening tools used by Clinical Pharmacists to identify older patients at risk of drug-related problems (DRPs) on hospital admission. Nineteen studies were identified that met the inclusion criteria and were included in the review. The variables/candidate predictors included in the screening tools described in these studies were considered and formed the basis for selection of the variables included in the primary research undertaken as part of this thesis. A data collection form was developed to collect data on patient demographics, potential variables (as identified from the SR) and interventions (number and type). Data collection was conducted in a sample size of 121 patient admissions, results were entered into Excel worksheets and statistical analysis performed to describe the results, using the statistics package Stata. Poisson regression and backward elimination were used in the modelling process to determine which variables were statistically significant and develop a final model.

Key findings

There were 121 patient admission episodes that met the inclusion criteria, for which data collection was successfully undertaken and that were included in this study. A total of 246 interventions were

made at the time of first Clinical Pharmacist review, equivalent to two (2) interventions per patient (mean = 2.03, median = 2).

Primary outcome measure of current study

The current study looked at the rate of Clinical Pharmacist Interventions (CPhIs) as the primary outcome measure.

In the 'Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration', Moons *et al.* stated that "The choice of outcome is a critical factor determining the clinical relevance of a model, and therefore the rationale for selecting a specific outcome should be given. Preferably, outcomes and duration of follow-up should be relevant to patients and clinical decision making"(139)(p.W11) .

A review looking at the clinical outcomes used in Clinical Pharmacy intervention studies in secondary care included 37 publications and identified 135 outcome measures showing the heterogeneity of outcome measures studied(143). The researchers found that "no apparent pattern was established among primary outcome measures"(143)(p.1) and commented that "choice of outcome measures is difficult"(143)(p.1). They also recognised that CPhIs are often "complex and non-specific"(143)(p.1).

The outcome measure of CPhIs was selected for this current study as it was felt by the Primary Researcher and Academic Supervisors (AB, ZJ and CEC) to be highly relevant, reflects usual clinical practice and was readily measurable, from the patients' medical notes and drug kardex(es). It was also recognised that Pharmacist-led interventions "have been shown to reduce the rate of DRPs, health care costs, and mortality and improve patients' quality of life"(144)(p.213) so there is evidence to support a relationship between CPhIs and reduced DRPs and specifically in older hospitalised patients(31, 144).

Rate of Clinical Pharmacist Interventions observed in this study

Of the 121 (older) patients included, 94 (77.69%) received at least one CPhI during the first review by a Clinical Pharmacist. The total overall (i.e. combined) number of interventions made by Clinical Pharmacists on these initial reviews was 246, ranging from zero interventions (for 27 patients, 22.31% of sample population) to 12 interventions. The vast majority of those who did receive interventions received between 1-4 interventions (accounting for 85 patients). The mean number of interventions received by patients in the study at first Clinical Pharmacist review was 2.03 and the median number was 2.

Type of Clinical Pharmacist Interventions made in this study

Of the 246 interventions made (at first review by a Clinical Pharmacist), the majority (68.7%) were medication reconciliation issues. This emphasises the importance of early Clinical Pharmacist review enabling early identification of unintentional prescribing discrepancies on admission and is consistent with the recommendations of the National Institute for Health and Care Excellence (NICE) in the UK recommending that medicines reconciliation is conducted within the first 24 hours post admission (to an acute setting) and the findings of Suggett who commented that medication reconciliation on admission "…makes the first 24 hours of admission crucial in terms of pharmacist intervention"(98)(p.107)(145, 146). Suggett concluded, from a review of the available literature, that there were "three key stages of a patient's stay at which they may be at risk of intervention, namely admission, discharge and during the two weeks post admission for long stay patients"(98)(p.162). According to NICE, "medicines-related patient safety incidents are more likely when medicines reconciliation happens more than 24 hours after a person is admitted to an acute setting"(146)(p.16). In this current research, 68.7% of interventions related to medication reconciliation issues. The next most common category of interventions made in the study was the 'Advice/recommendation' category, whereby the Clinical Pharmacist was offering prescribing advice/recommendations e.g. dosing guidance (accounting for 25.6% of interventions made) and the remaining interventions

belonged to the categories Prescribing Errors (not directly a medication reconciliation prescribing issue) and Other (accounting for 4.9% and 0.8% of all interventions made respectively).

Variables found to be predictive of Clinical Pharmacist Interventions from this current research

From the backward Poisson regression that was conducted, two of the variables studied were found to reach the pre-specified level for significance with respect to being predictive of older patients (at SUH) receiving Clinical Pharmacist Interventions (CPhIs), namely **gende**r (female gender being associated with reduced risk of receiving such interventions) and **the number of pre-admission medicines (PAMs)** taken. The other variables studied, that had been identified from the SR of previous research in this area, were not found to reach the level of statistical significance for predicting CPhIs and included abnormal liver function, renal function (eGFR), number of comorbidities, falls (recent/fall history/falls risk), abnormal white cell count (total WCC and/or neutrophil count), high risk pre-admission medicine(s), age and taking systemic antimicrobial therapy at the time of admission (or within previous week).

Previous research looking at drug related problems (DRPs) in older people and (hospital) pharmacist interventions

Whilst older people are known to be particularly vulnerable to drug related problems (DRPs), Walsh *et al.* commented that "There is little published literature specifically on pharmacists' interventions in older hospitalised patients"(147)(p.208). The outcome measure for the current study was the number of Clinical Pharmacist interventions (CPhIs) received by patients on first review by a Clinical Pharmacist. The average number of CPhIs made in the current study was 2 (mean=2.03, median=2), with the (pragmatic) assumption that interventions were made in response to DRPs (or potential problems).

There has been some research looking at DRPs/medication related problems (MRPs) and older patients and interventions to reduce these in the hospital setting, including some studies attempting

to quantify the incidence of such problems in older people. Another term used in some of the literature is Potential Inappropriate Prescribing (PIP) in older people. The following section considers some of the published literature considering these areas.

Walsh *et al.* conducted a systematic review (SR) and meta-analysis of (four) studies that used PIP validated tools with PIP reduction as the outcome measure(147). They found that three of the four studies reported statistically significant reductions in the Medication Appropriateness Index (MAI) score and other PIP tools used in the intervention groups(147). The impact of the interventions on other outcomes such as readmissions and mortality were more variable, and the studies may not have been sufficiently powered to assess these outcomes. The SR and meta-analysis were published in 2016 and so more recently published studies would not have been identified. The authors commented that (more) "user friendly PIP tools should be further developed to allow the effectiveness of interventions to be compared"(147)(p.207) highlighting some of the difficulties associated with using these tools, particularly as outcomes like MAI are subjective (rather than objective) and may be at risk of bias(147).

Primary research conducted in Ireland by Byrne *et al.* investigated the role of the Pharmacist in the multidisciplinary care of older adults in the intermediate care setting(148). This was a comparatively small study conducted over a twelve week period and included 91 patients, with a mean age of 82 years old (range: 67-93 years)(148). The mean number of clinically relevant DRPs identified was 5.4 (per patient), ranging from 0-19(148). There were 494 clinically relevant DRPs identified in 91 patients and 406 recommendations were made to the medical team, of which 89.2% were implemented(148).

Hailu *et al.* conducted research in geriatric[1] above patients (aged ≥60 years old) in a teaching and referral hospital in a developing country (Ethiopia)(31). Hailu *et al.* studied DRPs in admitted geriatric[1] patients and the impact of Clinical Pharmacist Interventions(31). The prospective interventional study included 200 patients with a mean age of 67.3 years old. The researchers found that approximately 82% of patients experienced at least one DRP with the average DRP per patient of 1.90. A total of 380

DRPs were identified, and 670 Clinical Pharmacist Interventions were provided. The prescriber acceptance rate for the Clinical Pharmacist Interventions was high at 91.7%(31).

Another relevant study was reported by Nachtigall *et al.*(149). The primary outcome for this study (conducted in Germany) was the percentage of geriatric in-patients having a DRP at the point of admission and at discharge(149). Assessment of medication was conducted for all patients both in the intervention and control groups at admission and discharge but recommendations were only made for patients in the intervention group. There were 411 patients included in the study with a median age of 82 years. The percentage of patients in the intervention group of patients with a DRP reduced from 86.6% at admission to 56.0% on discharge, compared with the control group where the percentage of patients with a DRP was 76.7% at admission and 76.2% at discharge(149). The acceptance and implementation rate of pharmacist recommendations was 80%. They reported that "overall multivariate regression model failed to prove a significant influence of the tested variables on the chance to have a DRP"(149)(p.6).

There has been interest in the use of technology and practice models to support Clinical Pharmacists, including in the prioritisation of patients. Research conducted in Ireland involved developing a computerised decision support system (CDSS) to support the structured pharmacist review of medications (SPRM) and testing this system in a prospective randomised controlled trial in a population of older people admitted to hospital with acute unselected illnesses(150, 151). The researchers prospectively studied 361 'intervention' patients, aged ≥65 years who were admitted to an Irish University Teaching Hospital over period of 13 months and included 376 patients in the control ('usual care') arm of the study. All intervention patients received the SPRM with pharmaceutical care interventions being generated in 296 (82.0%) of the patients. The SPRM/CDSS intervention generated 1000 recommendations, of which 42.3% related to medication reconciliation issues, and the overall prescriber acceptance rate of the interventions was 54.8%(150). The primary outcome for the study was the proportion of patients in either group (intervention or control groups) who experienced a

non-trivial adverse drug reaction (ADR) during their hospital stay and the researchers found that a SPRM, supported by appropriate software, significantly reduced ADRs in older acutely ill hospitalised patients. In the 361 intervention patients, 50 patients (13.9% of the intervention patients) experienced an ADR (total of 61 ADRs) compared to 78 of the 376 control patients (20.7%) experiencing an ADR (total of 91 ADRs)(150).

A major component of the aforementioned research was the development and utilisation of a (computerised) clinical decision support software (the E-Pharma-Assist system) which was developed by the primary researcher (O'Sullivan) and generated interventions. These computer generated interventions were then clinically "reviewed by the research pharmacist and a pharmaceutical care plan was generated, which outlined all of the clinically relevant interventions at the point of review"(150)(p.199). The CDSS software enabled standardisation of the data collection, medication review and ADR detection processes(150).

Comparison of number of Clinical Pharmacist Interventions (CPhIs) received by patients in the current study compared to previous related research

It is difficult to directly compare observed CPhIs in the current study with previous research due to methodological and definition differences as well as the use of different outcome measures by different researchers. However, the observed average number of CPhIs received in the current study at initial review (mean 2.03) is consistent with the average 1.90 DRPs per patient reported by Hailu *et al.* (based on the assumption that Clinical Pharmacist Interventions are related to/in response to actual or potential DRPs). The current study found that 77.69% of older patients included received at least one CPhI at first review whilst similar percentages of patients experienced DRPs in research by Hailu *et al.* (82%) and Nachtigall *et al.* (86.6%) and pharmaceutical care interventions were generated in 82.0% of the older patients included in the research by O'Sullivan *et al.*(31, 149, 151).

Comparison of current research findings in developing a prediction model with previous contemporary related research

A number of researchers have published research in the area of patient prioritisation by Clinical (hospital) Pharmacists in recent years that would not have been identified in the systematic review (SR) undertaken (and published) as part of this thesis (see *Chapter 2*). Such research may have been published outside of the date range selected in the searches conducted for the SR and/or may not have specifically mentioned older people as a search term or keyword. Additionally, in recent years there has been growing interest in patient prioritisation for hospital pharmacist review/services and defining pharmaceutical acuity. Therefore it seems appropriate to compare the current findings with contemporary research in this area, including academic theses(152).

However, there are some general limitations with comparing the current study with previous research. These limitations include methodological differences between the studies, differences in the study populations, varying definitions and differences in outcomes and measurement of outcomes.

- **Relevant academic theses**

Previous research submitted by Suggett as a thesis was entitled 'Risk assessment of patients in an Acute Trust as a means of directing a clinical pharmacy service'(98). This UK-conducted research found that CPhIs occurred in 34.9% of cases(98). This percentage is significantly lower than that observed in the current study (34.9% vs 77.69%). However, there were significant differences between the methodologies and patient demographics of these studies, making direct comparisons between the studies difficult.

Suggett's study was conducted in adult patients (with median age of 62 years and IQR=45-76 years)(98). Older patients are known to typically experience a higher number of drug related problems (DRPs) than younger patients and as such could be expected to require more CPhIs to identify, manage and resolve these DRPs(31, 98). Therefore, it is unsurprising that the proportion of the patients in

Suggett's study who received interventions (one or more intervention) from a Clinical Pharmacist was lower than observed in this current study as their sample population was not restricted to older patients (unlike the current research).

Outcome measurement varied in that Suggett looked at whether patients received one or more CPhIs during the (first) seven days of admission whilst the current study looked at number of interventions at first Clinical Pharmacist review. Suggett conducted two alternative approaches for data analysis of (1) binary outcome analysis and (2) time to event analysis and presented overall intervention rates at seven days using both of these analytical approaches (31.4% for the binary outcome approach and 36.4% for the time to event approach)(98). Suggett included a Kaplan-Meier curve to estimate the probability of an intervention occurring over the course of hospital stays of varying lengths, plotting cumulative intervention rate (as a percentage) against days from admission (over the first seven days).

Suggett conducted a backwards stepwise approach to select variables (from initial 23 variables) for inclusion in the developed model and a risk score was then produced based on the final model(98). The current study used a backwards selection approach for variable selection. The 'time to event' methodology was used by Suggett in the multivariable analysis and 19 risk factors (detailed in *Appendix D1*) were shown to be independently and significantly associated with the outcome, including age and female gender(98). This contrasts with the findings of the current study where number of PAMs and gender were found to be significant variables, although, unlike in Suggett's study, the female gender was negatively associated with the outcome.

The area under the receiver operating characteristic curve (ROC curve) for Suggett's developed risk score was 0.61(98). A good prediction model has strong discrimination, which is a model's ability to separate patients based on their estimated risk. The area under the receiver operating characteristic curve (AUC) is an overall measure of model discrimination"(153)(p.2). Models with AUC values of 0.6-0.7 have been described in the literature as being "poor"(153)(p.2). Whilst multiple factors were significantly and independently associated with an increased intervention rate, some (potential) risk

factors were unexpectedly found to be inversely related to the outcome(98). Suggett concluded that it "was not possible to generate a useful model for directing clinical pharmacy services"(98)(*Abstract*) and although the risk score "was found to be significantly predictive of the need for pharmacy intervention, the degree of predictive accuracy was low"(98)(p.174). Age was found to be the "dominant risk factor in the multivariable analysis"(98)(p.164) and, again, this provides support for the decision to focus the current study on older patients (aged 60/+ years old) who might be expected to most benefit from such input.

Whilst the patient dataset was large (58,918 patients), one limitation of the study by Suggett was its retrospective nature and, as Suggett commented, "it would be advisable to repeat this research in a prospective study"(98)(p.173). Another possible limitation to the methodology of Suggett's study is that validation of the risk score was carried out using a validation set of the data accounting for approximately 25% of the study population, with the remaining 75% of the sample used in the modelling set(98). Data splitting (at the moment of model development) should be avoided and "is unnecessary and not an improvement on using all the data for model development and reporting apparent performance when the sample size is large or using internal validation methods (e.g., bootstrapping, see below) when sample size is smaller"(154)(p.5). These observations about the limitations of splitting a dataset are "not new and has been stated in the methodological literature over 20 years ago"(154)(p.5).

Another relevant contemporary PhD thesis, submitted by Alshakrah, considered patient prioritisation for pharmaceutical care and led to the development of an Adult Complexity Tool for Pharmaceutical Care (ACTPC)(155). Alshakrah reported on research related to the development of a prioritisation tool including components/variables identified from a systematic review and interview data, and then developed from Delphi rounds and consensus into 33 items. The third part/study of the thesis was a feasibility study, testing if the ATPC was practical to use and to identify appropriate outcome measures.

A pre-post (implementation of the ACTPC) prospective study was conducted in the adult acute medical units of three NHS acute hospital trusts (October to December 2019). The outcome measures included prescribing errors (PEs) and pharmacist interventions, as well as data on length of stay and readmissions. The study involved 408 patients, 209 in the pre- and 199 in the post-implementation cohorts. The patient based prescribing error rate was 41% in the pre-implementation cohort and was reduced to 28% (statistically significant reduction) in the post-implementation cohort. There were 330 and 172 interventions made in the pre- and post-implementation cohorts respectively, equivalent to 1.6 and 0.9 interventions per patient for the respective cohorts(155).

However, although Alshakrah stated that they used an established definition of PEs (see *Appendix D2*) they opted to exclude the unintentional omission of regular medicines (which is part of the consensus definition of prescribing error (part of the transcription error subcategory, see *Appendix D3*) they referred to from their working definition of PEs(156). This omission would significantly impact the number of prescribing errors recorded using this methodology, making comparisons of prescribing error rates with other published research difficult (and potentially under-estimating the number of PEs) if other researchers classify the unintended omission of regular medicines on admission as a type of prescribing error, potentially limiting its usefulness.

It is also an interesting and perhaps surprising observation that in the post-implementation phase, with the use of the ACTPC tool to categorise and prioritise patients for pharmaceutical care, the number of interventions per patient actually decreased from 1.6 to 0.9 in the apparent absence of any other changes/interventions being made during the pre and post-implementation phases. Given that the definition for interventions used in the study included "identification and rectification of prescribing errors, optimisation (the enhancement of a patient's medication to improve efficacy of therapy) or a 'consult' (reactive provision of advice to a patient and/or a healthcare professional regarding a specific medication issue"(155)(p.90), it is somewhat difficult to understand how identification and prioritisation of the most high risk patients would actually result in a decrease in

(the number of) pharmacist interventions rather than more focussed interventions being made, particularly to the most high-risk of patients.

In addition to concerns about their working definition of PEs, another limitation of the research by Alshakrah is that they did not assess or test for the discrimination or sensitivity of the tool (unlike Suggett's research). Their study was conducted in a different patient population with respect to age than the current study and potentially included patients as young as 18 years of age and, due to incomplete data, 20 patients (of total 199) were excluded from analysis on assigned pharmaceutical complexity level in the post-implementation phase. There are some similarities between variables in the ACTPC tool and the variables found to be significant in the current study; Alshakrah included age over 70 years old as an amber criterion and polypharmacy although the definitions (or age cut-off) used varied compared to the current study.

Another contemporary tool that has been developed and described in the literature for the prioritisation of patients to target hospital pharmacist's input, is the Medicines Optimisation Assessment Tool (MOAT)(99). The development of the MOAT by prognostic modelling was described by Geeson in their PhD Thesis. Geeson conducted a prospective cohort study in adult medical wards at two UK hospitals. Geeson's research looked at medication related problems (MRPs) in patients aged 17-103 years old (median age of 75 years old) and found 59.5% experienced one or more MRP and 40.6% of the study admissions experienced the outcome event, namely one or more moderate or severe preventable medication related problems (MSP MRPs)(99). Of those admissions that experienced an outcome event (of one or more MSP MRP), they found that the number of MSP MRPs per admission ranged from one to ten, with a median of one (99). Data was retrospectively collected from the information departments at the study sites, laboratory reporting systems and patient medical records on potential risk factors, such as polypharmacy and the use of so-called 'high-risk' medications(99). "Multivariable logistic regression was used to determine the relationship between

potential risk factors and the study outcome, namely preventable MRPs that were at least moderate in severity"(99)(p.3) and a simplified electronic scoring system (the MOAT) was developed(99).

There are some notable similarities and differences between the research conducted by Geeson and the current research. Different outcome measures were used, with Geeson looking at the percentage of patients who experienced MRPs (outcome was one or more moderate or severe preventable MRP, MSP MRP) whilst the current research looked at the number and rate of Clinical Pharmacist Interventions received by (older) patients, and expressed these as interventions received per patient and the percentage of patients who received one or more intervention (almost 78% of the study population). As previously discussed, various terms and synonyms for DRPs are used, often interchangeably, including MRPs. Whilst different, the outcome measures are somewhat related as Geeson commented that their research looked at preventable MRPs to "ensure the MOAT identifies patients with MRPs that are amenable to pharmacist intervention"(99)(p.69). Geeson reported an average of 1.7 MRPs per admission. The average number of CPhIs made in the current study was 2 (mean=2.03, median=2) and the assumption is that interventions were made in response to DRPs (or potential problems) so there are similarities between these outcomes and indeed the observed values of the outcomes between the two studies.

The use of different outcome measures makes comparisons between the developed tools and the studies difficult. It is also of note that, as with Suggett's and Alshakrah's research, Geeson included a different demographic profile of patients and the incidence of DRPs/MRPs is known to be higher in older people who were the intended demographic of the current study whilst the study by Geeson included patients as young as 17 years old. It is "well known that drug-related problems (DRPs)…. are very common in older adults"(148)(p.2625) and the current research acknowledges this, focussing on this specific patient population, older people.

A strength of the study by Geeson is that it was the patient numbers were much larger, with 1503 eligible patient admissions of whom 610 experienced the study outcome, compared to the comparatively small number of patients included in the current study (n=121).

Geeson used a three-stage process to select candidate predictors. Identification and selection of predictors from the literature (following assessment of suitability), expert survey and final candidate predictor selection. The expert survey process involved the development of an electronic survey with target subjects comprising both healthcare professionals, specialist fora/networks as well as patient/public representatives and was somewhat similar to the Delphi questionnaire/process used by Alshakrah in developing the ACTPC tool in that it sought opinion and consensus. At the end of the process, 18 candidate predictors were pre-selected for use in the development of the MOAT and several of these were similar/consistent with the initial variables tested for in the development of the prediction/prognostic model in the current research, such as age, number of comorbidities, number of medicines prescribed, use of high-risk medicines, renal and liver function and white cell count, although there were some differences in the exact definitions and measurement.

In their methodology, Geeson described how MRPs were identified, individually validated by a MOAT expert panel to determine if it was a 'true MRP' and then validated MRPs considered to be preventable were assessed for severity by the expert panel. The expert panel included a hospital pharmacist, senior nurse and consultant physician as well as the primary investigator (Geeson) so this was a relatively time and resource intensive methodology and it was not feasible to adopt such a methodology in the current research due to workload, time and staffing constraints. Whilst Geeson used the expert panel to classify MRP severity, an objective outcome measure of the count of interventions made (as recorded by the Clinical Pharmacist who conducted the initial review) was utilised in the current study rather than subjectively reviewing the severity of the interventions (although a classification of different broad types of interventions was assigned by the Primary Researcher, AB).

Geeson used backwards elimination to reduce the set of candidate predictors during modelling, with the aim to include only the most significant predictors. This approach for variable selection was consistent with that used in the current study. In both the current research and that conducted by Geeson, a significance level of *p* greater than 0.157, comparable to the Akaike Information Criterion (AIC), was selected to exclude predictors. However, whilst Poisson regression was used in the current study as the outcome was count data, Geeson used backward logistic regression and also ran a multivariable fractional polynomial (MFP) model to check for non-linearity between the candidate predictors and the outcome and conducted adjustment for model optimisation.

Following the backward elimination modelling process and review of same (for practicality/sensibility reasons of inclusion), Geeson was left with 11 predictors in the final model (summarised in *Table D1*).

Table D1: Table summarising the 11 predictors in Geeson's final MOAT model(99)

Predictor/variable
Number of comorbidities
Number of medicines
Estimated glomerular filtration rate
White cell count
Previous allergy
Systemic aminoglycosides and glycopeptides
Other systemic antimicrobials
Epilepsy medicines
Primary diagnosis: nervous system and mental disorders
Primary diagnosis: respiratory system
Primary diagnosis: gastrointestinal system

One of the above variables, number of medicines, is very similar in definition to one of the two variables found to be significant in the current study, namely number of pre-admission medicines (PAMs). The definition used by Geeson differed from the definition of number of PAMs utilised in this work in that they used the number of medicines prescribed on the first full day (24 hours) of hospital admission which could include hospital-initiated medicines initiated, e.g. antibiotics.

Geeson reported on the predictive performance of the MOAT which was found to be fair (with a c-index of 0.66 after adjustment for optimism)(99). Decision curve analysis was undertaken and Geeson commented that this shows that "the MOAT has the potential to be clinically useful across a wide range of predicted risk probabilities (from approximately 15% to 70%)"(99)(p.3). The MOAT was "developed as a Microsoft Excel data entry sheet … that calculates individual patients' probability of an outcome event"(99)(p.247). Development of such a tool available for use by Clinical Pharmacists at SUH at 'the point of care/review' would be something for future work, following further statistical analysis of the results to assess the goodness of fit and clinical usefulness of the model which was not possible at this time.

- **Relevant recent studies (not included in the systematic review)**

A number of studies have been identified that were not included in the systematic review (SR) that may be relevant to the current research topic and contribute to the evidence base. Some of these studies may not have been published within the date limits used when conducting the SR, did not have the relevant MESH or keyword search terms or were not included in the selected (search) databases. However, having been identified from keeping up to date with the literature published in this field, those deemed to be highly relevant are considered here.

Recently published research by Clarke *et al.* looked at enhancing the Clinical Pharmacy service within a large urban academic teaching hospital in Ireland and developing a new clinical prioritisation tool (CPT^b)(152). As part of this, Clarke *et al.* conducted a survey among clinical pharmacists at the hospital "to evaluate how they prioritise patients and what criteria they use to support their clinical

prioritisation"(152)(p.2). The electronic questionnaire used was based upon one previously developed and published by Falconer *et al.* and locally adapted(45).

Previous research already considered in this *Discussion* and reported by Alshakrah, involved the development of the ACTPC tool which was presented as two forms, ACTPC-1 and ACTPC-2(155). Clarke *et al.*, with the necessary consent of the ACTPC-2 research team, used their survey results and peer review to modify and refine the ACTPC-2 form and develop their own prioritisation tool which was subsequently piloted and integrated into an existing electronic pharmacy care interface at the hospital(152). The developed tool categorised patients into three levels, Levels 1, 2 and 3 with Level 1 patients being the most complex and/or unstable. Clarke *et al.* conducted a pre- and post-intervention study, with data collection carried out for five days pre- and five days post-implementation of the tool (152). During the pre-intervention study pharmacists used their (previous) usual methods of clinical prioritisation, and for the post-intervention study the clinical prioritisation tool was available for clinical pharmacists to use (152).

Over the five-day pre-intervention period, clinical pharmacists reviewed 531 patients and conducted 168 medicines reconciliations compared with reviews of 516 patients and 159 medicines reconciliations in the post-intervention period(152). Clarke *et al.* reported a statistically significant difference in the numbers of Level 1 and Level 3 patients clinically reviewed post-intervention, with a statistically significant increase in the number of the most complex and/or unstable patients (Level 1 patients) being reviewed post-intervention (220 patients pre- vs. 238 patients post-intervention, $p < 0.05$) and a decrease in the number of stable patients reviewed (80 patients pre- vs. 44 patients post-intervention)(152). The authors concluded that their prioritisation tool may help Clinical Pharmacists to provide "a more targeted delivery of pharmaceutical care"(152)(p.5) and may offer additional benefits "in terms of potential time and resource savings arising from the de-prioritisation of low-risk patients"(152)(p.5).

The research by Clarke *et al.* and the current research were both conducted in hospitals in Ireland, albeit different locations and type (being located in the capital, Dublin and the West of Ireland, Sligo, respectively). One clear difference between the two hospitals is that the large teaching hospital setting for Clarke *et al.'s* research used electronic patient medication administration records (EPMAR) and has an electronic pharmacy care interface, whilst at Sligo University Hospital (SUH), no such interface exists and the general wards at SUH do not use EPMARs.

Clarke *et al.* utilised (and adapted for local use) tools and questionnaires previously developed by other researchers in conjunction with local consensus opinion. In contrast, the current research used the overall findings of the SR (see *Chapter 2*) to guide the selection of potential variables/predictors for the development of a novel prioritisation tool for use locally.

From their pharmacist survey, Clarke *et al.* identified the "top-rated criteria of age ≥ 65 years and high-risk medicines"(152)(p.5) and both of these variables are "known risk factors associated with medication-related harm and pharmaceutical interventions as reported in a systematic review by Suggett and Marriott"(152)(p.5)(157). Considering the current research, the patient population was entirely composed of older people (65/+ years old) and one of the potential variables (although not reaching statistical significance and so not included in the final model) was the prescribing of one or more high risk (pre-admission) medications (HRPAMs) showing similarities between the potential variables studied in the current research and Clarke *et al.'s* findings.

A key difference between the research by Clarke *et al.* and the current research relates to outcome measures. Clarke *et al.* reported on the number of patients classified at the different priority levels (Levels 1-3) who were reviewed before and after the implementation of the developed prioritisation tool whilst this current study looked at the number of CPhIs and intervention rate, and used statistical modelling methods to identify which, if any, of the potential variables were significant for determining the likelihood of needing early Clinical Pharmacist review and interventions.

Clarke *et al.* state that, in the post-implementation period, "priority levels were also retrospectively assigned by a member of the research team (RC) who applied the tool based on the reason for clinical prioritisation selected on the data collection form by the pharmacist"(152)(p.3) and, essentially, the sensitivity of the tool was based on analysis of the level of agreement between priority levels assigned by the researcher using the clinical prioritisation tool (CPT^b) and those assigned by pharmacists post-intervention. It may be more appropriate to consider this comparison as a measurement of the ease of use and/or reproducibility or reliability of using the tool as opposed to 'sensitivity' (see *Appendix D4* for definition of sensitivity of a clinical prediction model/tool). Additionally, the lack of any objective (rather than subjective, from consensus opinion) data to support the assigned Levels (1-3) (i.e. there is an assumption in the methodology that the priority level assigned by the researcher is correct) and the specified criteria for same may limit the usefulness of this research. The outcome measure of number of CPhIs chosen in this current research was objective (count data) to minimise subjective bias.

A strength of Clarke *et al.'s* research is that it attempted to assess the usefulness of the tool by the clinical pharmacists using it. Overall, "Pharmacists agreed that the clinical prioritisation tool helped them to prioritise on 29 of the 50 post-intervention days (58%)"(152)(p.4) with a higher percentage of basic grade pharmacists finding the tool useful compared to senior pharmacists (64% vs. 52%)(152). It would be useful in future work to look at a parameter such as user satisfaction following development of the prioritisation tool/score in this current research. Clarke *et al.'s* study population was also larger than in the current study (a methodological strength for Clarke *et al.*). Their study was conducted in general adult inpatient wards; the study writeup did not present the patient demographics such as age and therefore it is difficult to make comparisons with the findings of other research without knowing the basic demographic profile of the included study population or generalise the findings to other settings.

A major limitation of the research by Clarke *et al.* is that the observed increase in the number of Level 1 patients and the reduction in Level 3 patients reviewed in the post-implementation period (compared to the pre-implementation period) may be due to the "variety in the number and distribution of Level 1, 2, and 3 patients on any given week … irrespective of the prioritisation tool"(152)(p.7), i.e. the observed differences might not have been due to the tool at all.

Another study providing useful insight into the development of a prediction model and medication errors was reported by Nguyen *et al.*(158). They conducted a prospective cohort study involving 1,408 adult in-patients in the development of a model predicting in-hospital significant medication errors (PRISMOR)(158). Approximately 26% of patients experienced the outcome of one or more clinically significant medication errors (MEs). Univariate analyses were conducted and logistic regression performed to develop the multivariate model; multivariable fractional polynomials analysis was conducted to account for the non-linearity of continuous variables(158). Bootstrapping methods were used for internal validation of the model.

Eleven variables were used by Nguyen *et al.* to build a predictive model which demonstrated fair performance (c-statistic: 0.72), and major predictors were age and number of prescribed drugs. The researchers concluded that their model "enhanced the interception of potential adverse drug events by 17.5%, with a number needed to treat of 6 patients"(158)(p.1) compared to decisions based upon the criterion of age(158).

The study was not specifically conducted in older patients although the median age of included patients was 68 years. The outcome measure used by Nguyen *et al.* was the occurrence of at least one clinically significant ME during the in-hospital stay whereas the current study looked at the number of interventions at first Clinical Pharmacist review. Their study involved a larger number of patients which is a methodological strength of their study. The two major predictors in their model were age and number of prescribed drugs; the current study only included older patients and number

of pre-admission medications (PAMs) was found to be one of the significant predictive variables in the current study showing some similarities between the findings.

Further research not included in the SR was conducted by Parameswaran Nair *et al.* to develop and validate a score (the PADR-EC score) predicting ADR-related hospitalisations in elderly[1] community-dwelling patients (aged 65/+ years)(159). The study adopted a prospective, cross-sectional design, was conducted in two hospitals and included 768 patients in the derivation cohort. Approximately 15% of patients in the derivation cohort were admitted due to a definite or probable ADR; the ADRs were assessed for causality and preventability.

The variables found to be predictive of an ADR and incorporated in the score were the number of antihypertensives (found to be the strongest predictor of an ADR), presence of dementia, renal failure, drug changes in the preceding three months and use of anticholinergic medications(159). The Area Under the Receiver Operating Characteristics (AUROC) curve for the score in the derivation cohort was 0.70. The score was validated in a cohort of 240 patients (validation cohort) and yielded an AUROC of 0.67(159).

Parameswaran Nair *et al.'s* study involved a larger number of patients than the current research and provided validation of the developed score (using a validation cohort rather than bootstrapping methods). Their study was conducted in older patients similar to the current study (aged 65/+ years old in both studies) although the outcome measure (risk of hospitalisation versus number of CPhIs) varied; the predictive variables found to be significant in the developed models also varied between the studies.

Comparison of this research and its findings with those from studies included in the systematic review

The systematic review (SR) conducted and reported earlier (see *Chapter 2*) as part of this thesis identified 19 papers describing the development and/or validation of a number of screening tools for

identifying (older) patients at risk of DRPs on hospital admission. The studies were either exclusively conducted in older people or (from the demographic information provided) included older patients. One of the studies included in the SR has already been considered earlier in the *Discussion* in the section entitled *Relevant Academic Theses*, namely the research by Suggett which was a highly relevant, contemporary piece of research published as a PhD thesis, even though not exclusively conducted in older people(98). The tools or models discussed in the SR (excluding the research by Suggett) are summarised and considered in the context of the current research with regard to methodology, results and findings, in *Appendix D5* and were previously considered when conducting the SR.

The studies included in the SR are summarised in the below table, *Table D2*, along with an additional validation study which was conducted by Ferrández *et al*.(160) The study by Ferrández *et al.* was not included in the SR but provides external validation of the score developed by Urbina *et al.* and is described beneath the table *(Table D2)*(114, 160).

Table D2: Table summarising the 19 studies included in the SR and an additional validation study(160) of one of the scores

Author/researcher(s)	**Year of publication**	**Tool developed or validated**
Suggett(98)	2017	Risk score to identify patients who were at high risk of (hospital) pharmacist intervention (no specific name for risk score)
Tangiisuran B.(161) and Tangiisuran B. *et al.*(103)	2009 & 2014	Brighton Adverse Drug Reactions Risk (BADRI) model

Onder *et al.*(104)	2010	GerontoNet ADR score
O'Connor *et al.*(105)	2012	GerontoNet ADR score
Petrovic *et al.*(83)	2017	GerontoNet ADR score
Trivalle *et al*.(106)	2011	A geriatric risk score for ADEs
Alassaad *et al.*(118)	2015	The 80+ score
Hohl *et al.*(107)	2012	Clinical Decision Rules - The ADE Rule and the Adverse Drug Reaction Rule
Hohl *et al.*(108)	2017	Modified ADE Clinical Decision Rule
Saedder *et al.*(109)	2016	Medicine Risk Score, MERIS algorithm
Bonnerup *et al.*(110)	2016	Medicine Risk Score, MERIS algorithm
Kaufmann *et al.*(111)	2018	The Drug-Associated Risk Tool (DART)
Falconer *et al.*(112)	2014	The Assessment of Risk Tool (ART)
Falconer *et al.*(115)	2017s	The Assessment of Risk Tool (ART)
McAuliffe *et al.*(113)	2018	MEDCOINS score
McElnay *et al.*(81)	1997	Predictive model for adverse drug events (ADEs) in elderly[1] patients
Urbina *et al.*(114)	2014	A score to identify hospitalised patients at risk of drug-related problems
Ferrández *et al*.(160)	2018	DRP risk score developed by Urbina *et al.*

O'Mahony *et al.*(116)	2018	Predictive tool for assessing ADR Risk in Older People (acronym ADRROP)
Hickson *et al.*(117)	2017	Pharmaceutical assessment screening tool (PAST)

Note: [a] denotes a validation study of the score previously developed by Urbina *et al.* that was not identified or included in the SR but is included here as it adds additional (external) validation to the previously developed score.

Ferrández *et al.* conducted an extended validation study over a four-year period of the score developed by Urbina *et al.* to identify inpatients at risk of a DRP(114, 160). This validation study was not identified during the literature search undertaken as part of the SR but is being considered here as it provides external validation to the score developed by Urbina *et al.*(114). The study involved 52,987 admissions, with at least one DRP occurring in 14.9% of admissions(160). The AUROC of the score was 0.751, sensitivity 77.70% and specificity of 60.98% in this validation study. Ferrández *et al.* commented that their observed AUROC was higher than those reported in other studies validating risk score(160).

Similarities in variables found to be predictive of outcome in the current study and previous research

The current study was conducted entirely in older patients. Two variables were found to be statistically significant in predicting the primary outcome of (number of) CPhIs in the modelling process, namely number of pre-admission medicines (PAMs) and gender (with female gender being negatively associated with the outcome).

The following tables consider whether age (old age/increasing age), gender and/or number of pre-admission medicines were included in the final models developed, utilised or validated in previous research. The definitions of the variables included in the individual studies may vary from those used in the current study, including age ranges/cut-offs and number of medicines included in the definitions

of polypharmacy but the following tables are looking at broad similarities in variables incorporated in the final models. The data from the research is presented as two different tables, with *Table D3* relating to the research included in the systematic review and *Table D4* relating to the additional relevant research identified.

Table D3: Table summarising the inclusion of age, gender and number of pre-admission medicines (PAMs)/number of medicines taken for the studies identified in the systematic review (SR) (and including additional study by Ferrández *et al.* not included in SR but providing external validation to a score previously developed by Urbina *et al.*(114, 160))

Detail of score/tool			Variables in final model				
Author	**Year**	**Score**	**Age**	**Gender**	**Number PAMs/ Number medicines taken**	**Study restricted to older people**	**Modelling(M)/ consensus(C) used in variable selection**
Suggett(98)	2017	Risk score (predictive of requirement for pharmacy interventions)	Y	Y	Y	N	M
Tangiisuran B.(161) and Tangiisuran B. *et al.*(103)	2009 & 2014	Brighton Adverse Drug Reactions Risk (BADRI) model	N/A	N	Y	Y	M
Onder *et al*.(104)	2010	GerontoNet ADR score	N/A	N	Y	Y	M
O'Connor *et al.*(105)	2012	GerontoNet ADR score	N/A	N	Y	Y	M
Petrovic *et al*.(83)	2017	GerontoNet ADR score	N/A	N	Y	Y	N/A
Trivalle *et al.*(106)	2011	A geriatric risk score for ADEs	N/A	N	Y	Y	M

Alassaad *et al.*(118)	2015	The 80+ score	N/A	N	N	Y	M
Hohl *et al.*[$](107)	2012	Clinical Decision Rules - (a)The ADE Rule and (b) The Adverse Drug Reaction Rule	a) N	a) N	a) Y	a) N	a) M
			b) Y	b) N	b) N	b) N	b) M
Hohl *et al.*(108)	2017	Modified ADE Clinical Decision Rule	Y	N	N	N	N/A
Saedder *et al.*(109)	2016	Medicine Risk Score, MERIS algorithm	N	N	Y	N	C & M
Bonnerup *et al.*(110)	2016	Medicine Risk Score, MERIS algorithm	N	N	Y	N	N/A
Kaufmann *et al.*(111)	2018	The Drug-Associated Risk Tool (DART)	N	N	Y	N	N/A
Falconer *et al.*(112)	2014	The Assessment of Risk Tool (ART)	Y	N	Y	N	C
Falconer *et al.*(115)	2017	The Assessment of Risk Tool (ART)	Y[#]	N	Y	N	M[##]
McAuliffe *et al.*(113)	2018	MEDCOINS score	N	N	Y	N	M
McElnay *et al.*(81)	1997	Predictive model for adverse drug events (ADEs) in elderly[1] patients	N/A	N	N	Y	M
Urbina *et al.*(114)	2014	A score to identify hospitalised patients at risk of drug-related problems	Y[@]	N	Y[@@]	N	M
Ferrández *et al.*(160)[a]	2018	DRP risk score developed by Urbina *et al.*	Y	N	Y	N	N/A
O'Mahony *et al.*(116)	2018	Predictive tool for assessing ADR Risk in Older People (acronym ADRROP)	Y[£]	Y[££]	N[+]	Y	M

Hickson *et al.*(117)	2017	Pharmaceutical assessment screening tool (PAST)	N	N	N[%]	N	C

Note – explanation of symbols and abbreviations used in Table D3:

N/A - for "Age" indicates those studies whereby the study population only included older patients.

N/A – for "Consensus or modelling" refers to studies where the tool or model was utilised (rather than development of tool).

[$] - Hohl *et al.* identified 9 variables associated with ADEs and incorporated them into two CDRs.

[#] Age >75 years old showed a statistical trend towards the outcome (risk of unintentional medication discrepancies) in the study by Falconer *et al*.(115).

[##] Multivariable logistic regression was conducted by Falconer *et al.*(115) to identify combinations of flags significantly associated with risk of outcome.

[+] Whilst number of PAMs was not found to be an independent risk factor, the presence and number of STOPP criteria-defined potentially inappropriate medications was identified as an independent risk factor by O'Mahony *et al.*

[%] Taking and number of high risk medications were as risk factors in the model by Hickson *et al.*

[@] Urbina *et al.* found that age >60 years old was a risk factor associated with DRPs.

[@@] Urbina *et al.* found that number of drugs during hospitalisation >10 was associated with DRPs.

[£] The research by O'Mahony *et al.* was conducted in older people and multivariate analysis found age >70 years to be an independent predictive factor for ADRs.

[££] The female gender was identified as an independent risk factor for ADRs in the research by O'Mahony *et al.*

Table D4: Table summarising the inclusion of age, gender and number of pre-admission medicines (PAMs)/number of medicines taken for the additional relevant studies identified that were not included in the systematic review.

Detail of score/tool			Variables in final model				
Author	**Year**	**Score**	**Age**	**Gender**	**Number PAMs/ Number medicines taken**	**Study restricted to older people**	**Modelling/ consensus used in variable selection**
Alshakrah(155)	2021	ACTPC tool	Y (age >70)	N	Y	N	C
Geeson(99)	2018	Medicines Optimisation Assessment Tool (MOAT)	N	N	Y	N	M
Clarke *et al.*(152)	2023	Clinical prioritisation tool based on ACTPC-2 & locally adapted	Y	N	Y	N	C
Nguyen *et al.*(158)	2017	Model predicting in-hospital significant medication errors (PRISMOR)	Y (increasing age)	N	Y	N	M
Parameswaran Nair *et al.*(159)	2016	PADR-EC score to predict ADR-related hospitalisations in elderly[1] community-dwelling patients (aged 65/+ years)	N/A (conducted in pts aged 65/+)	N	N	Y	M

The previous tables (*Tables D3 & D4*)show that many of the other tools/models or scores identified and discussed included age (old age/increasing age) and the majority included (increasing) number of medicines taken (including various different definitions of polypharmacy) as variables in their final models. Only two of the studies included gender in their final models, with the female gender positively associated with the outcome measures, which is in contrast to the current findings where the female gender was negatively associated (i.e. less likely to occur) with the outcome (number of CPhIs)(98, 116). Nine of the overall studies[2] reported (including three relating to the development and validation of the GerontoNet ADR Score(83, 104, 105)) were wholly conducted in older people, although different studies used different age profiles(81, 83, 103, 104, 105, 106, 116, 118, 159, 161) . This suggests that the findings of the current study with respect to which variables might be predictive for the outcome of CPhIs are broadly consistent with previous related research findings with respect to age and PAMs (or similar variable such as polypharmacy and/or number of medications taken) being predictive of the (different but similar) outcomes related to DRPs/MRPs, adverse drug events, medication errors or similar/equivalent. Previous related research is less conclusive regarding the importance of gender as a variable and indeed if the female gender is positively or negatively associated with the outcomes of such studies (outcomes related to DRPs/MRPs, adverse drug events, medication errors or equivalent). However, differences between the methodologies, definitions used in different studies and outcome measures makes it difficult to compare the different models.

Strengths and limitations of the current study

There are a number of limitations and strengths associated with the current study. Some of these have already been considered when comparing the current study with other studies in this area. One

[22] Note that Tangiisuran B.161. Tangiisuran B. Predicting adverse drug reactions in the hospitalised elderly. Doctoral Thesis (PhD). University of Brighton, 2009.
. and Tangiisuran B. *et al.*103. Tangiisuran B, Scutt G, Stevenson J, Wright J, Onder G, Petrovic M, et al. Development and validation of a risk model for predicting adverse drug reactions in older people during hospital stay: Brighton Adverse Drug Reactions Risk (BADRI) model. PLoS One. 2014;9(10):e111254. refer to the same research and essentially counted as one piece of research (as opposed to two separate pieces of research)

significant limitation that will restrict the usefulness of the findings of the current study is the comparatively small sample size, mainly attributed to the impact of the COVID-19 pandemic and resultant restrictions, but also affected by staffing issues and procedural changes in the tracking of medical records at SUH. The sample size was expected to be in the region of several hundred patients over the selected time period of four months. A small sample size can be of concern as "The sample size of the development dataset must be large enough to develop a prediction model equation that is reliable when applied to new individuals in the target population"(162)(p.2). Therefore, a small sample size can result in (clinical prediction) model overfitting or inaccurate predictions. Another potential problem associated with small sample size is that the study may not be sufficiently powered to detect smaller effect sizes of some potentially important predictors which may have resulted in them being removed from the model.

It was not possible to conduct internal validation of the developed model using bootstrapping methods nor measure model performance at the time of analysing the results of the current study without access to more specialist statistical support. The use of Poisson regression in the model development process contributed to this, as the coding used in Stata for these purposes would differ from those used with models developed using more 'common' methods such as logistic regression or time-to-event modelling and included in the taught UoB course 'Statistical methods for risk prediction and prognostic models' that the Primary Researcher (AB) participated in. However, if these problems could have been overcome and internal validation and model performance conducted, it would have been useful to (hopefully) provide confidence in the developed model and enable comparison with other such models.

Recognising the implications and limitations of using a comparatively small sample size, it would be useful to repeat the study using a larger sample size with specialist statistical support to ensure that the sample size is appropriate and to facilitate carrying out bootstrapping for internal validation and performance measures.

Another limitation of the current study is that it was conducted in a single hospital, so any results and/or conclusions are applicable to that setting (and patient population) only and not generalisable. Additionally, direct comparisons with other research and prediction models may not be possible due to differences in the outcome measures used and terminology; this is not a problem unique to this current study(19, 163).

The current study did not assess acceptability of the developed model to Clinical Pharmacists. This could be addressed in a post-development study to assess ease of use of the developed model/score. Another possible limitation of the study is that there was no quantification of the severity or potential significance of any Clinical Pharmacist Interventions. Whilst this was intentional to simplify the methodology of the current study and to have an objective outcome measure, it might have been useful to consider the severity or potential significance of such interventions or the potential or actual drug-related problems (DRPs) that they related to, and this could have been presented as a separate outcome measure.

Despite these limitations, there are also a number of strengths associated with the current study. The current study looked to develop a local tool for use in one setting (Sligo University Hospital, SUH). The potential variables tested for modelling were identified from previous research as described in the SR, and then tested via regression modelling (Poisson regression) for statistical significance, making the process for inclusion of predictors objective rather than subjective.

The outcome measure selected for the current study, number of Clinical Pharmacist Interventions (CPhIs) at first review was practical, pragmatic, relevant and objective. CPhIs have been studied as an outcome measure by other Pharmacist researchers (31, 98, 149, 150, 151).

The method of regression modelling used was Poisson regression and this was appropriate given the type of outcome data, count data. Backward elimination is one of the most commonly used methods for predictor selection in clinical prediction modelling and it's use in this current study was clearly defined and appropriate. Similarly, use of $p<0.157$, comparable to the Akaike Information Criterion

(AIC), for the measure of statistical significance in the modelling process was a pragmatic choice. Both the use of backward elimination for predictor selection and the use of $p<0.157$ were consistent with previous researchers in this field, including (in relevant) research by Geeson(99).

Unlike some other researchers who have adopted data splitting to essentially split the overall sample population into model development and testing samples, a methodology which is not recommended, the current study used all the available data for model development(162).

Other strengths in the methodology adopted in this current study included that data collection was conducted by a single researcher (AB) reducing potential variation in methodology or interpretation. Additionally, the methodology included clear definitions e.g. of Clinical Pharmacist Interventions and represented an objective measure (the count of the number of CPhIs at first review) which could be considered methodological strengths.

Chapter summary

The systematic review (SR) conducted as part of this research identified a number of tools/models/scores that could be used to help Clinical Pharmacists to identify older patients at risk of drug-related problems (DRPs) on hospital admission. The rationale behind this was that such high-risk patients could then be targeted for early Clinical Pharmacist review, mindful that Clinical Pharmacists are a limited resource(43). The outcome measures and definitions of the outcomes used in previous research varied making direct comparisons between the studies difficult. Some studies were not exclusively conducted in older patients, but included older patients within their sample population. Due to methodological limitations, including small sample sizes and/or lack of (external) validation, and poor performance of the tools the findings of the SR did not support the routine use of any of the tools/models in clinical practice.

Subsequent to the search dates for included papers in the SR, further research has been published in this and related fields, including a number of studies looking at the development of prioritisation tools

for use by Clinical Pharmacists. Some papers have been identified by broad internet searches into the area of (hospital) pharmacist prioritisation tools and/or comprehensive review of primary research included in other systematic reviews published in this area. A number of these tools have been developed solely via consensus/Delphi process and others by a combination of consensus, variables identified from published literature and/or statistical modelling methods such as univariate and multivariate logistic regression, and there are advantages and disadvantages associated with each of these approaches. The use of combinations of these methods may be advantageous, recognising the importance of expert opinion and ensuring that statistically significant results actually have clinical significance; incorporating consensus opinion offers a pragmatic approach and may encourage 'buy in' from those being asked to use such a prioritisation tool.

As with the studies included in the SR, many of these 'other' identified studies have been used in different sample populations and/or of different sizes, used different definitions, have different outcome measures and may have been measured at different times (e.g. at a single point, such as admission, or throughout a hospital stay/spell). Definitions used for the variables e.g. what constitutes liver impairment or impaired liver function tests were inconsistent between the studies. Many of the studies looked at outcomes that were complex and/or time consuming to determine and, in some cases, required expert panel determination of what constitutes an ADR/ADE which is a significant investment in terms of staffing/resources which may not be feasible in other settings, outside university hospitals. The outcomes might not be readily measurable and/or may be influenced by other factors; for example, the length of stay for a patient might not only be influenced by the intervention(s) being studied and could be influenced by other factors not measured e.g. pressures on early discharge due to overcrowding or even local outbreaks e.g. COVID-19 or Norovirus. The clinical relevance of the outcome in terms of targeting Clinical Pharmacists to those patients at highest risk of experiencing DRPs may also be debatable.

This current research aimed to address some of the problems identified with the existing research in this area of prioritising Clinical Pharmacists workload, specifically in older patients. The patient demographic was specifically defined as being aged 65/+ as this age group has previously been identified as being at increased risk of DRPs. The outcome measure was deliberately selected as number of Clinical Pharmacist Interventions to make it a relevant outcome for Clinical Pharmacists and readily measurable. The selected outcome measure was objective (number of interventions) and avoided the subjective assessment of severity/importance of interventions to simplify assessment and remove the need for review by expert panels which could prove time consuming and be resource intensive. The time period selected was felt to be appropriate, mindful of the practice of the Health Service Executive in Ireland routinely reporting quarterly figures for healthcare outcomes and in publications. Unfortunately, largely due to the impact of the COVID-19 pandemic, the chosen time period did not result in the expected number of patients being identified for the sample population. The research also was relevant for the current practice of Clinical Pharmacists locally at Sligo University Hospital (SUH) as it recognised the restrictions/limitations associated with the systems in use which remain predominantly paper-based and, even where electronic e.g. the laboratory results, these are not (fully) integrated. There are no computerised clinical support systems for Pharmacy at SUH currently as utilised in many of the studies included (that were conducted in university/university hospital settings) and, for example, ward census data does not contain flags for potential high risk patients from a Clinical Pharmacist perspective. Therefore, the study was designed to be relevant to the setting in which it was conducted (SUH), mindful of limitations in information technology at SUH, objective in its outcome measure and simple in terms of data collection with the aim that it would develop a tool that would be relevant, accurate and simple to apply at the point of use by the Clinical Pharmacist.

The next chapter (Chapter 6), *Conclusions,* will draw conclusions from the findings of the current study, discuss the potential impact of the findings on clinical practice and identify possible future research work.

Chapter 6: Conclusions, impact on clinical practice and future research

Conclusions, impact on clinical practice and future research

Chapter description

This chapter is looking at drawing conclusions from the findings of the current study and previous relevant research (including those studies included in the systematic review and more recently published literature). Additionally, the impact of these findings on clinical practice at Sligo University Hospital is considered as well as potential future research work, including consideration of the generalisability of the developed score.

Overall conclusions

This thesis has adopted a two-pronged approach in evaluating the existing research base and contributing further (via primary research) to it regarding screening tools and patient prioritisation by Clinical Pharmacists in the acute hospital setting, focussing on older patients.

The first approach, the systematic review (SR), identified previous primary research in the development, validation and/or utilisation of screening tools used by Clinical Pharmacists to identify older patients at risk of drug-related problems (DRPs) on hospital admission. A number of papers (19) and tools were identified, reviewed and evaluated; some of these tools were specific for the patient population of interest, namely older patients, whilst some of the tools were developed for adult patients in general but included older patients within their development/validation/utilisation studies. Whilst some of these tools showed promise, none of the tools were found to fully meet the four key stages required for the creation of a quality risk prediction model, namely development, validation, impact and implementation (164).

The second part of this thesis involved undertaking primary research to identify which, if any, variables (patient, disease or drug-related) could help Clinical Pharmacists at Sligo University Hospital (SUH) to identify and prioritise those older (medical) patients who might benefit most from early Clinical Pharmacist review and, where appropriate, intervention. This involved the identification of a sample

population, data collection, selection of an appropriate outcome measure and statistical analysis to summarise the findings and determine which variables were predictive of the outcome (Clinical Pharmacist Interventions, CPhIs). Whilst the sample size used was comparatively small (as a result of logistical issues with data collection during the COVID-19 pandemic and other challenges such as changes in the tracking processes of medical records within the hospital) the results suggested that two of the variables measured, gender and number of pre-admission medications (PAMs), showed statistical significance with respect to predicting the number of interventions received at first Clinical Pharmacist review. For the categorical variable gender, in this study and sample population defined as male and female (gender binary) as per medical note designation, the female gender was negatively associated with the outcome, i.e. being female was associated with a lower risk of receiving interventions (CPhIs) than being male. The number of CPhIs received increased with the increasing number of pre-admission medications taken. This enabled an equation and a potential risk score to be developed which could be utilised locally at SUH to prioritise older, medically admitted patients for early Clinical Pharmacist review. Unfortunately, given the specialist nature of statistical support needed for Clinical Prediction Tool development, it was not feasible to internally validate the developed model using bootstrapping methods (which would be desirable) nor determine the goodness of fit and calibration of the model developed via Poisson regression. However, the identification of the number of pre-admission medications as a possible predictor for (increased) Clinical Pharmacist Interventions is consistent with the findings of some of the previous studies and research in this area (98, 99, 104, 106, 109, 114). The female gender was associated with reduced risk of the outcome (CPhIs) in the current research, which conflicts with the findings of previous research in this area (98, 116, 165).

Impact of current research and potential future research work

This current research provided useful insight into the factors/variables that might help to prioritise older patients for early Clinical Pharmacist review and intervention at SUH. However, as already

recognised, the sample size was less than originally predicted and it was not possible to conduct bootstrapping nor determine the goodness of fit and calibration of the score at this stage. Future work could be carried out with the relevant, specialist statistical support required to conduct internal validation using bootstrapping methods and determine the goodness of fit and calibration of the score. In addition, work could be undertaken to refine and further validate the score in older patients at SUH. Subsequent to the systematic review that was undertaken as part of this thesis, further relevant research (in this field) has been published, as discussed in the *Discussion* section of this thesis. From reviewing these publications, any additional factors/variables identified by other researchers as being predictive of relevant outcomes such as drug related problems, medication related problems, adverse drug events and/or adverse drug reactions, could also be included as potential variables in any future work and then multivariate analysis used to develop a risk model/score.

It has been observed that, generally, the overall focus of studies involved in clinical prediction tools (or clinical prediction rules, CPRs) is the derivation phase with "only a minority progressing to validation and very few undergoing impact analysis"(166)(p.1). The members of the International Diagnostic and Prognosis Prediction (IDAPP) group concluded that "Impact analysis studies remain the most efficient way of assessing whether incorporating CPRs into a decision making process improves patient care"(166)(p.1) and that there needs to be a shift in emphasis from developing new CPRs to validating and implementing existing ones (166).

As previous researchers in this field have commented, once the risk score is refined and validated, further research will need to focus on how to use the score in practice and impact analysis (99). There are four proposed phases for impact analysis of CPRs namely the exploratory phase, preparation phase and experimental phase followed by the long-term implementation phase (166). Research on the use of the score in practice would require consideration of how to interpret and classify individual risk score values into different categories e.g. low, medium and high risk according to the likely number of Clinical Pharmacist Interventions. The assigning of these different categories, on the basis of score

value, would enable prioritisation of older patients medically admitted to SUH by Clinical Pharmacist according to risk category with those in the high risk category being seen first, followed by those in medium and low risk categories.

This current research has focused on the development of a tool/score for local use at SUH. However, it is recognised that prioritisation of patients by Clinical Pharmacists is an important issue with research in the development of such tools being conducted nationally, across Europe and worldwide. Therefore, following internal validation of the score (and following any refinement of the score), it would be appropriate to consider external validation of the score in different populations and settings to assess the accuracy and generalisability of the score as it may prove useful for Clinical Pharmacists in other hospitals.

Chapter summary

Overall, this thesis has identified and summarised some of the previous research in the field of patient prioritisation by Clinical Pharmacists in the acute hospital setting and added to the knowledge base in this area, focussing on older patients. Further research opportunities exist which may enable refinement of the score, assessment of goodness of fit and calibration of the score, validation (bootstrapping methods and external validation), impact analysis and implementation studies. Publication of the research involved in the development of the score (and any subsequent validation studies conducted) and presentation of same at relevant conferences will allow dissemination of the findings and share them with a wider audience, adding to the research base in this field and help to prioritise (older) patients for Clinical Pharmacist review according to need (evidence based) and Clinical Pharmacist workload.

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Appendices

Appendix M1

Pharmacist : _____	Ward: _____	Date of 1st Review (dd/mm/yy): _____day ____ /____ / 20

Addressograph (or equivalent details: name, PCN, DOB)	**Additional information**	**Addressograph (or equivalent details: name, PCN, DOB)**	**Additional information**

INCLUSION CRITERIA: ELDERLY PATIENTS (**AGED 65/+ YEARS**) ADMITTED BY MEDICAL TEAM TO MEDICAL WARDS (EXC. ICU); TO BE COMPLETED AT TIME OF FIRST PHARMACIST REVIEW FOR CURRENT PRESENTATION/ADMISSION
FOR PATIENTS TRANSFERRED FROM ANOTHER WARD: Do not complete if patient and Kardex have **already been reviewed** by another Pharmacist for this admission (&Kardex annotated accordingly). If uncertain, attach addressograph & annotate "Transfer" in "Additional information" column.
MEDICATION RECONCILATION ONLY CONDUCTED: Annotate "MR only" (in "Additional Information" column) if **MedRec only** conducted e.g. for patients seen in ED.

Appendix M2

SERVICE EVALUATION & IMPROVEMENT PROJECT PROPOSAL

Title:

The development of a screening tool to help hospital Clinical Pharmacists to identify elderly medical inpatients who are at increased risk of Drug Related Problems and/or most likely to benefit from Pharmacist review and interventions at Sligo University Hospital (SUH).

Abstract:

In recent years, a number of studies have been conducted looking at the development of tools to identify patients who are at increased risk of experiencing Drug Related Problems (DRPs) including elderly patients (but not specifically restricted to elderly patients in some tools) such as the ADRROP scale, BADRI score and GerontoNet risk score and this has also been the subject of a number of systematic reviews and postgraduate research[a-g]. There has also been interest in developing tools to prioritise patients for Clinical Pharmacist review, such as the "pharmaceutical assessment screening tool" (PAST) developed by Hickson et al. which was used "to assign all inpatients a patient acuity level (PAL) to then help teams of clinical pharmacists prioritise the frequency of, and the seniority of, pharmacists performing patient reviews"[h]. However, there is currently no validated screening tool widely used by hospital Clinical Pharmacists (hCPhs) to identify and prioritise those elderly (and possibly frail) patients most likely to experience DRPs and/or benefit from a medication review by a hCPh and appropriate interventions.

This service evaluation and improvement project will refer to previously published research in this area to identify potential (risk) factors for DRPs and needing hCPh intervention, and develop a screening tool to identify those elderly (medical in-) patients who are (1) at increased risk of DRPs and/or (2) most likely to need hCPh review and interventions.

Research Topic:

Elderly (or older) people, defined as those aged 65 years and older[i] with multiple co-morbidities receiving multiple medicines for management/treatment of long-term illness are prone to adverse drug reactions (ADRs) and are likely to be more susceptible to adverse drug events (ADEs)in general than the rest of the population[j]. The "oldest-old" are a subgroup of elderly people, defined by the WHO as those aged 80 years and older[k]

A DRP has been defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"[l]. DRPs include medication errors, adverse drug reactions (ADRs), and adverse drug events (ADEs)[m]. DRPs can cause serious harm, hospital admissions, increased healthcare costs and even death and are known to be prevalent in elderly patients both in community and in the hospital setting[j, n]. It is recognised that the elderly are at increased risk for DRPs and drug-related hospitalisations compared to the general population, due to altered pharmacodynamics and pharmacokinetics; increased incidence of multimorbidity and polypharmacy[o, p].

An ADR has been defined as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man"[q]. The reported percentages of ADRs for all hospitalised patients vary in different studies, populations and countries, with the percentage of hospital admissions due

to ADRs in some countries being in the region of (or exceeding) 10%[q] The incidence of ADRs is higher in older people and this may be because as they are prescribed significantly more drugs than younger individuals; older people are nearly seven-times more likely to be hospitalized due to an ADR when compared to younger people[r,s]. The average prevalence of ADRs in the elderly as reported in a systematic review was 11%[s] whilst a study conducted in a tertiary referral hospital in Ireland reported an ADR incidence of 26%[t].

Polypharmacy and increasing age have been identified as important risk factors for DRPs[u]. Polypharmacy has been defined by the World Health Organisation as "…the administration of many drugs at the same time or the administration of an excessive number of drugs"[v]. However, there are numerous working definitions of polypharmacy and no consensus definition of polypharmacy[w]. A systematic review, published in 2017, identified 138 definitions of polypharmacy and associated terms. The researchers found that "The most commonly reported definition of polypharmacy was the numerical definition of five or more medications daily"[w]. The term polypharmacy can subclassified according to appropriateness of prescribing, as appropriate or problematic polypharmacy[x]. Research suggests that "Up to 36% of Irish older patients receive a prescription that is potentially inappropriate"[y].

Review of previous research:

It is well-recognised both within Europe and internationally that there is a need for prioritising pharmaceutical care[h, z]. Within the National Health Service (NHS) in the United Kingdom, it is recognised that Clinical Pharmacists are a "limited resource" in NHS hospitals therefore there is a need to allocate this resource where it is most needed[h] whilst in America, a $0.5 million research grant was awarded by the American Society of Health-System Pharmacists to develop and validate a pharmaceutical complexity scoring tool[z]. Pharmacists need to prioritise and "identify those drug-related problems for which management or prevention would result in the greatest benefit for as many patients as possible"[aa]. Hickson et al. conducted research in a 900-bed teaching hospital in England which utilised a pharmaceutical assessment screening tool (PAST) to assign inpatients a patient acuity level, helping to prioritise hCPh workflow[h]. The NHS as a whole has acknowledged the need for "Targeted clinical pharmacy services" and that clinical prioritisation of patients "allows pharmacy services to focus on where the need is greatest and where it has the greatest impact on patient outcome"[bb].

The term "Medication review" is an umbrella term describing a number of interventions conducted by prescribers themselves or by other practitioners (usually a pharmacist)[cc]. A Comprehensive Medication Review conducted by a hCPh is "Distinct from the more routine review of drug charts that pharmacists make on ward visits"[cc]. Medication review interventions aim to identify ADEs and optimise medication use[dd].

In recent years, much work has looked at identifying and reducing inappropriate prescribing in elderly patients, both medications inappropriately prescribed (PIMs) and those medicines that should be prescribed but are not. A number of validated medication appropriateness checklists have been developed e.g. STOPP-START, Beers and MAI criteria to identify and reduce inappropriate prescribing[ee,ff] and are listed in *Appendix 1*. Some researchers have combined such a checklist with a pharmacist-led medication review of polypharmacy, to improve prescribing quality and clinical outcomes[gg].

Systematic review

A systematic review (SR) was conducted to identify any tools that have been developed to prioritise elderly (65/+ years old) medical inpatients for hCPh review.

Objectives of the SR:

The aims were to perform a systematic review of the literature to identify any previous research involving the methods used to prioritise elderly (aged ≥ 65 years old) patients for hCPh review.

Methods:

A systematic search of research articles published in peer-reviewed healthcare-related journals was performed using eight medical literature databases (from inception until April-May 2018) to identify all papers discussing the prioritisation of elderly patients for hCPh review in the acute hospital (inpatient) setting. Multiple databases were searched to try to ensure all relevant papers were identified and the choice of databases was consistent with those used by other hCPh researchers conducting systematic reviews[hh]. A number of search terms and combinations of search terms appropriate for the databases (for example, MeSH terms for PubMed searches) were used. Details of the databases used to perform the SR and the number of potential articles identified in each of them are included in *Appendix 2*.

The search terms included synonyms and various combinations of the following key words "elderly", "pharmacist", "hospital", "risk", "risk factor" and "risk assessment" with the combinations used reflecting the specific search capabilities of the different databases. For example, for those databases identifying a comparatively large number of articles from a search using the terms "elderly", "pharmacist" and "hospital", additional terms relating to risk were added to narrow the search to focus upon more relevant articles.

Results

Overall, 1030 records were identified through the search of the databases, including duplicates (*see Appendix 2*). The titles and (where titles were relevant) abstracts of papers identified from these searches were reviewed for relevance by the Principal Researcher. Following this review of titles and abstracts, full-text publications were accessed for all potentially relevant papers and evaluated through intensive reading by the Principal Researcher. Details of all sourced full-text articles were tabulated to allow validation of a final list of citations and for a final list of included papers to be drawn up. Details of any articles for which there were queries were also tabulated and were referred to two independent reviewers. Two reviewers considered the queries separately and then the three researchers discussed each individual query paper and reached agreement on whether it should be included in the SR. From the primary search of the eight databases, eight relevant papers were identified for inclusion in the SR.

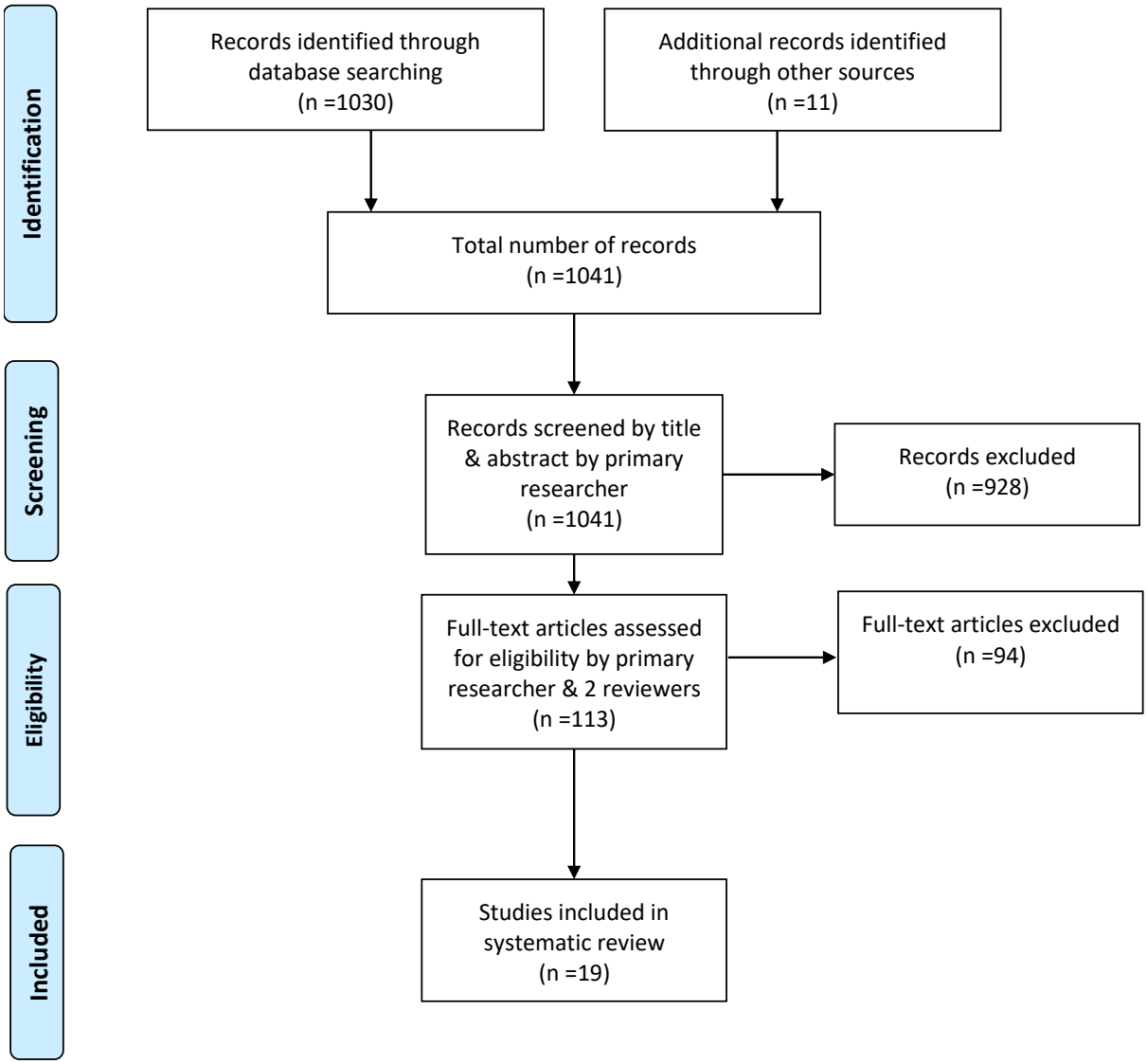
A number of additional papers (11 further papers) were identified for inclusion in this SR. An internet search using the search engine Google Scholar was used as part of a scoping exercise when the principal researcher was initially considering conducting research in this area, to gauge the amount of published research on this topic. The following combination of search terms was used: +risk tool +elderly +drug related problems. From this search, a relevant systematic review published in 2014 was identified assessing the use of risk prediction models to predict adverse drug reactions in older people[e]. The SR (which was not itself included in this SR, as it did not meet the inclusion criteria)

identified four relevant papers; these four papers were sourced and reviewed to determine if relevant for inclusion in this systematic review. An additional paper was also identified whilst trying to locate the full text article of one of the papers included in the aforementioned SR, namely a paper by Tangiisuran B. (PhD thesis published in 2009) which led to the identification of another paper by Tangiisuran et al. (published in 2014) reporting the same research, namely the BADRI risk prediction model; these two papers describe the same research and have been considered as a single piece of research in this SR[b,c]. Another two papers were also identified that described the same overall research and were therefore considered as a single piece of research in the SR[ii,jj].

Another four papers were identified having been referenced or mentioned in one of the 8 papers from the search of the medical databases or, in one case, a relevant paper (by the same lead author) was identified whilst trying to source a paper identified from the initial literature search. Three further papers were identified from keeping up to date with research publications and from review of relevant conference proceedings.

A total of 19 papers were identified and included in the SR through the systematic search of eight medical databases and other methods described as summarised in Figure 1 and listed in *Appendix 3.*

Figure 1: (Simplified) Prisma flow diagram



Discussion

The included studies varied significantly in design including in population demographics such as age, gender, sample size and ethnicity. The different studies examined the development/modelling, utilisation or validation of an assessment tool and combinations of these phases. The majority of the validation of the studies was internal whilst four provided external validation[b,c,d,t,kk], and one of these studies[b,c] included both internal and external validation. The majority of studies used separate populations to develop and subsequently validate their tools whilst two studies used the same populations and used bootstrapping techniques to test the developed tool[ii, jj, ll] and a third used internal cross validation methods[mm] . Nine studies involved the development and internal validation of the assessment tool. One study[nn] described the development only of an assessment tool which was subsequently utilised in a further study[mm]; another study described the development and subsequent utiliisation (rather than validation) of a tool[oo]. Four studies described the utilisation or internal

validation of a previously developed tool, and two studies provided external validation (only) of the previously developed GerontoNet risk score[,kk].

The primary outcomes for the studies varied quite significantly. Five studies looked at the incidence (or rate) of ADRs, and another three studies looked at the incidence (or rate) of ADEs. There were also subtle differences between studies with the same broad primary outcomes with respect to definitions/interpretations, for example one study looked at the incidence of "non-trivial ADRs" and another specified that their primary outcomes were ADEs that required a change in medical therapy, diagnostic testing, consultation, or hospital admission. The primary outcomes for the remaining studies were more specific/individual to each study and included incidence of Medication Errors per patient, time to rehospitalisation or death during the year following discharge, number of DRPs per admission, rate of potentially avoidable hospital readmission at 30 days and rate of pharmacist intervention. These variations in the primary outcomes (and even differences in the exact definitions included within these primary outcomes) made it very difficult to compare or collate the results and findings of the different studies as they were not measuring the same parameters.

The risk factors included in the various studies and tools/scores were identified via a number of methods; these included clinical judgement, from literature review (alone), patient characteristics/variables and by combinations of methods. The number of risk factors identified by and included in the risk scores/tools ranged from 3[ll,mm,oo,pp] (in the Geriatric score, MEDCOINS and MERIS tool) to 38[qq].

There were also differences in the statistical analyses undertaken in the different studies (reported in 17 of 19 studies), development of point scores, and in the testing of the score performance.

As a result of the numerous differences between the methodologies and outcome measures of the included studies is that it was not possible to combine the results of the individual studies as a meta-analysis. The area under the receiver operator characteristic curve (AUROC curves), which assesses the ability of the risk score to predict ADRs. Table 1 summarises the AUROC data reported for studies included in the SR.

Table 1: Table showing the reported AUROC data for studies included in the SR

Author	**Tool**	**AUROC**	**Comment**
Onder et al.[d]	GerontoNet ADR Risk Score	0.71 0.70 in valdiation study	
Trivalle et al.[ll]	Geriatric Score	0.70	
Suggett E.[rr]	Novel score: risk score for patients as potential recipients of pharmacist intervention.	main data, AUROC = 0.607 validation set, AUROC = 0.616.	
Falconer N. et al.[ss]	Assessment of Risk Tool (ART)	0.72	Tool shows moderate discrimination

Urbina O. et al[m]	DRP Risk Score	0.776 (95%CI [0.759, 0.792]) in the validation set cohort	
Saedder E. et al.[oo]	MERIS (Medicine risk score)	In the prospective population AUROC = 0.76. The final risk score was AUROC = 0.87 in a recent patient population, 0.74 in a population of internal medicine and 0.66 in an orthopaedic population.	Final risk score found to be quite robust
Petrovic M. et al.[kk]	GerontoNet ADR Risk Score	AUC =0.64 probably or definitely related to drug use and AUC=0.69 to detect type A ADRs	
O'Connor M.N. et al[t]	ADRROP score	derivation cohort = 0.623, validation cohort = 0.592	AUC of ADRROP and GerontoNet compared: GerontoNet ADR Risk Score yielded an AUC of 0.566 suggesting that neither tool predicted ADRs reliably

The discriminatory ability of the 80+ score was assessed by Alasaad et al. using C-statistics. C-statistics, which can range from 0.5 (no discrimination) to 1 (perfect discrimination), provides the probability of the model giving a higher predicted risk to the patient that will have an event than the one that will not. Comparing the C-statistics for the score compared to other tools were positive for the 80+ score developed by Alasaad et al.; the C-statistics were 0.71 (80+ score), 0.57 (Screening Tool of Older Person's Prescriptions, STOPP), 0.54 (Screening Tool to Alert doctors to Right Treatment START) and 0.63 (Medication Appropriateness Index, MAI)[ii,jj].

Some of the other included studies reported sensitivity and specificity for the developed tools, Hohl et al[nn] looked at two clinical decision rules; the more sensitive rule had a sensitivity of 96.7% (95% CI = 91.8% to 98.6%) and required 40.8% (95% CI = 37.7% to 42.9%) of patients to have medication review. The more specific rule had a sensitivity 90.8% (95% CI = 81.4% to 95.7%) and required 28.3% of patients to proceed to medication review.

The revised Drug-Associated Risk Tool (DART) developed by Kaufmann et al.[tt] reported an average specificity of 88% (range 27–100) and an average sensitivity of 67% (range 21–100).

Conclusions

None of the included studies met the four key stages involved in accurate risk prediction models, namely development, validation, impact and implementation suggesting that further research is needed in this area and that there is currently insufficient evidence to support the routine use of any of the currently developed tools in routine clinical practice[e].

Project question:

Can a tool be developed that will accurately predict which elderly medical inpatients are most likely to benefit from early hCPh review and intervention(s) at SUH where appropriate.

Project design:

This service evaluation and improvement project will use a cohort design to prospectively include elderly medical inpatients at SUH. Data on DRPs and hCPh interventions for the study patients will be recorded and collected by hCPhs as part of their routine assessment of patients upon admission to the relevant ward/clinical area, along with basic demographic details and medication history. The study will focus exclusively on DRPs and interventions made at the time of the first review by a hCPh during their admission/hospitalisation (not ongoing during their stay). This approach is consistent with the opinion of secondary care Chief Pharmacists in the UK[uu]. Data on a number of predefined potential risk factors for DRPs including renal impairment, recent/current use of systemic antimicrobials and the use of "high risk" medicines will be collected (either at the time of initial review or retrospectively from the patient medication records and laboratory reporting systems). Multivariable logistic regression modelling will be carried out to determine the relationship between the potential risk factors and the number of hCPh interventions and to formulate a model/tool. The developed model will then be validated using bootstrapping techniques or equivalent, as advised by statisiticians based at the University of Birmingham.

Population and eligibility criteria:

The study population will be elderly patients (aged 65/+ years) medically admitted to SUH who are assessed by a hCPh during their admission. The eligibility criteria are patients aged 65/+ years old (at the time of Pharmacist review), who are medically admitted. Exclusion criteria include patients who are aged <65years old, surgically admitted or admitted to a surgical/orthopaedic/CCU or ICU ward. Patients will be reviewed as part of the "normal" Clinical Pharmacy service which operates Monday to Friday (between the core hours of 8:30-4:30 or 5pm) and excludes Public Holidays; cover during staff leave may not be provided. The study sample size will be influenced by practical considerations, including time, staffing and impact of data collection of staff workload. To obtain a meaningful sample size to allow the tool to be assessed whilst mindful of the aforementioned practical constraints, data will be collected over a period of six months, to obtain a minimum sample size in the region of several hundred patients (minimum 300 patients) which is an estimate on what is feasible in the hospital.

Outcome measures:

Previous researchers and senior hospital Pharmacists have reported difficulties with measuring the value of hCPh interventions. Dodds commented that trying to develop "meaningful pharmacy performance indicators has challenged senior NHS pharmacists for many years"[vv] whilst in their review the type, frequency and result of clinical outcomes used in studies assessing the effect of Pharmacist interventions on inpatient care, Kjeldsen et al. noted that the "evaluation of clinical pharmacy services is challenging due to the interventions often being complex and non-specific, and the purpose is often

to optimise the use of medications, reduce medication-related risks and improve symptom control" and that the "choice of outcome measures is difficult"[ww].

The objective of this project is to identify those patients most likely to benefit from hCPh interventions and/or who experience DRPs. Many of the studies identified from the SR used outcomes such as ADR and ADE incidence and referred to detailed definitions of same e.g. the WHO definitions and the Naranjo ADR Probability Scale that can prove time consuming to utilise and which may limit the ability of hCPhs to conduct as part of their routine clinical practice.

Previous research looking at hospital interventions across (NHS) hospitals in Wales, provided evidence of pharmacy value both in promoting the safe use of medicines in patients and financially to the hospital (or the NHS as a whole)[xx].In a literature review of the economic effects of Clinical Pharmacy interventions, cost–benefit analyses suggested that these interventions are associated with cost savings although there were limitations in the methodological quality and the applicability of these analyses to current practice[yy]. Therefore, for the purposes of this research, the primary outcome being measured will be the number of hCPh interventions made, recognising that previous research has demonstrated the benefits of such interventions for the individual patients and in reducing healthcare costs (for the hospital and/or healthcare system).

Instruments:

This service evaluation will use a data collection form (DCF) developed by the Principal Researcher. The included potential risk factors for DRPs and/or hCPh intervention were identified as being associated with increased risk of outcomes (such as DRPs, ADEs and/or ADRs) in the published studies included in the SR. In recognition of the workload of hCPh at SUH, it was decided that the hCPh would be asked to record basic identifying details for patients meeting the inclusion criteria on a form (*Appendix 4)* and these patients would be followed up by the Principal Researcher (and/or other Clinical Pharmacist). The DCF is included as *Appendix 5* and will be completed retrospectively by the Principal Researcher (and/or by other Clinical Pharmacist) by referring to computerised laboratory results, patients' medical notes and copies of hCPh intervention notes.

Procedures:

Subjects who meet the inclusion criteria will be identified on the included wards at SUH by the relevant hCPh assigned to these areas as part of the normal day-to-day clinical practice. At the time of the first review of an individual patient by the hCPh during an admission, basic demographic details will be documented on the Patient Identification Form, *Appendix 4,* which will completed daily by hCPh on the relevant wards. The Principal Researcher (Researcher (and/or other Clinical Pharmacist) will then complete a DCF retrospectively using a combination of methods including review of the patient's medical records, laboratory results and hCPh intervention records. Details will be inputted into a password protected Excel worksheet on the Pharmacy department server, mindful of data protection legislation and patient confidentiality.

Ethics:

The Principal Researcher will submit this proposal (in this or amended format depending upon the requirements of the Research and Ethics Committee, REC, at SUH) and seek ethical approval to conduct this service evaluation and improvement project from the REC at SUH. The completed Patient Identification and Data Collection Forms will be stored in a locked, designated (filing) cabinet

until the research is completed and published after which it will be shred (as confidential material). Data will be saved on secure password protected databases in the Pharmacy department at SUH and anonymised where possible.

Impact:

It is anticipated that the results of this service evaluation and improvement project will facilitate elderly patients being appropriately prioritised for medication reconciliation and review by a hospital hCPh at SUH. The Principal Researcher intends to publish the results of this project, and if the developed tool is found to accurately prioritise elderly patients for hCPh review, it would be expected that its use may become incorporated as part of routine clinical practice to help prioritise elderly patients at SUH.

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APPENDIX 1

Frequently used tools for optimization of pharmacotherapy in older people[ee]

Explicit tools (drugs to avoid, drugs to avoid in certain diseases/syndromes, drugs to be used with caution)

Beers (1991, updates 1997, 2003, 2012)

McLeod (1997)

ACOVE: Assessing Care of Vulnerable Elders (2001)

IPET: Improved Prescribing in the Elderly Tool (2002)

Zhan criteria (2001) [46] Rancourt criteria (2004)

Laroche criteria (2007): French Consensus Panel List

Australian Prescribing Indicator Tool (2008)

Thailand criteria (2008) [51] STOPP: Screening Tool of Older Person's Potentially inappropriate prescriptions (2008, update 2015)

NORGEP: Norwegian General Practice Criteria (2009)

PRISCUS list (2010)

Implicit tools

MAI: Medication Appropriateness Index (1992)

- Indication, effectiveness, drug-disease interactions, dose, correct directions, correct directions practical for the patient, drug–drug interactions, duplication of therapy, duration, costs

STRIP: Systematic Tool to Reduce Inappropriate Prescribing

- Structured history-taking of medication use, structured pharmaceutical analysis, pharmaceutical care plan (pharmacist–physician), patient consultation, follow-up and monitoring

APPENDIX 2

Database	Number of papers identified
PubMed (2 searches conducted)	238
	17
EMBASE (2 searches conducted)	45
	365
OVID HMIC	18
Cochrane Library	47
PsychInfo	9
CINAHL PLUS	39
Web of Science	206
Proquest Dissertations & Theses Global (2 searches conducted)	40
	6
TOTAL	**1030**

APPENDIX 3

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APPENDIX 4

Pharmacist		**Ward**	**Date:**
Patient addressograph	No. Pre-Admission Medicines	No. of interventions	Intervention sheet no./reference

APPENDIX 5: DCF: Pharmacist Intervention Prioritisation Tool for Elderly Patients

Patient Addressograph/details	Patient identifier

Ward code		Patient identifier				
Pharmacist identifier						
Date of Pharmacist r/v		Date of admission				
No. of PAMs		No of PAM	<5	<8	8/+	
On systematic Antimicrobial On admission/Within 7 days	Y ☐ or N ☐	**Laboratory results (1st results on presentation or within 48hr)**				
Total number of interventions made during 1st r/v (V1)		WCC		Level normal range	Y	N
Breakdown of interventions made (indicate number of interventions) during initial pharmacist review (V1)		Cr level				
		eGFR		Category		
MedRec issue		LFT: AST &/or ALT level >x2 of ULN		Y	N	
Prescribing error		Documented fall as part of /cause of current admission		Y	N	
Medication administration issue		Documented fall within last 12 mths		Y	N	
Advice/recommendation to Rxr* ☐		No. of documented co-morbidities				
Patient counselling*		On 1/+ high-risk medication (PAM)		Y	N	
Other*		No of high-risk medications (PAM)				

Details for interventions denoted with *	**Type of high-risk medication prior to admission**	
	Anti-coagulants (oral)	
	Antidiabetics (oral/parenteral)	
	Antiepileptic	
	Antiparkinson's disease	
	Antipsychotic	
	Benzodiazepine &/or Z-drug or equivalent (regularly or taken twice or more weekly))	
	Opioid use (regularly or, taken twice or more weekly))	
	Therapeutic heparin (inc. LMWH)	
	TDM medicines (lithium, digoxin, theophylline, aminophylline, carbamazepine, valproate, aminoglycoside)	
	Details	

Appendix M3





Research Ethics Committee
Sligo University Hospital
Chairperson: Dr.Miriam O'Sullivan
Admin: Aileen Concannon

10 December, 2019

Re. Research Ethics Application No: 783

Dear Amanda,

The Research Ethics Committee (REC) at Sligo University Hospital has received your submission for ethical review of the study:

"The development of a screening tool to help hospital Clinical Pharmacists to identify elderly medical inpatients who are at increased risk of Drug Related Problems and/or most likely to benefit from Pharmacist review and interventions at Sligo University Hospital (SUH)."

The application underwent review and the REC Committee has given the opinion that this application does not currently fall under the description of healthcare related research and therefore does not require ethical approval.

Yours sincerely

[redacted]

Dr. Miriam O'Sullivan
REC Chairperson

PLEASE ENSURE THAT DATA PROCESSING COMPLIES WITH THE NEW GDPR REGULATION WHICH CAME INTO EFFECT ON 25th May 2018. *This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place. Your attention is drawn to new EU regulations concerning Data Protection, and provisions in Irish legislation for application of these regulations in Medical Research. Guidance is available from HRB on the following links:*
http://www.hrb.ie/funding/gdpr-guidance-for-researchers/health-research-regulations-2018-faq/
https://www.youtube.com/watch?v=icfSRpvxY5A
The REC at SUH cannot interpret GDPR or approve consent waivers.

Appendix R1

Baseline characteristics - Tabulation of AGE

AGE	Freq.	Percent	Cum.
65	1	0.83	0.83
66	1	0.83	1.65
67	1	0.83	2.48
68	6	4.96	7.44
69	3	2.48	9.92
70	1	0.83	10.74
71	2	1.65	12.40
72	4	3.31	15.70
73	7	5.79	21.49
74	5	4.13	25.62
75	3	2.48	28.10
76	9	7.44	35.54
77	6	4.96	40.50
78	2	1.65	42.15
79	9	7.44	49.59
80	7	5.79	55.37
81	2	1.65	57.02
82	7	5.79	62.81
83	6	4.96	67.77
84	5	4.13	71.90
85	5	4.13	76.03

86	3	2.48	78.51
87	4	3.31	81.82
88	5	4.13	85.95
89	6	4.96	90.91
90	4	3.31	94.21
91	1	0.83	95.04
92	2	1.65	96.69
93	2	1.65	98.35
96	1	0.83	99.17
97	1	0.83	100.00
Total	121	100.00	

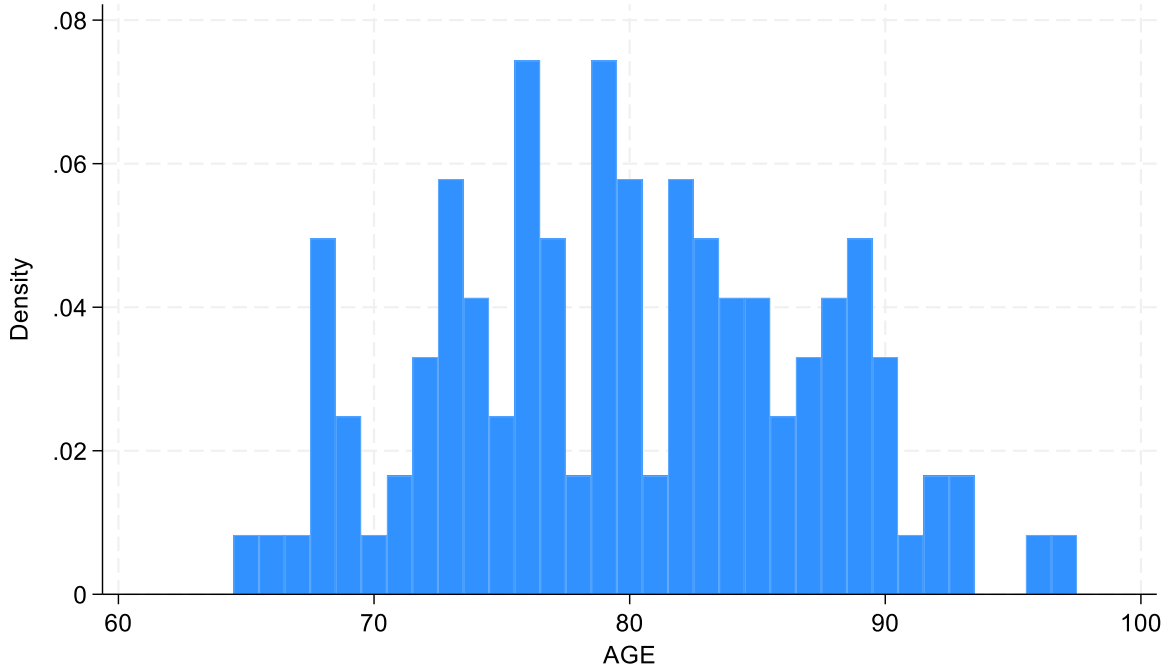
Appendix R2

Age categories were retrospectively created after running initial Stata analyses using the command 'recode'. The command typed in Stata was as follows, to create 6 groups to group the ages in a meaningful manner:

'recode AGE (65/69=1) (70/74=2) (75/79=3) (80/84=4) (85/90=5) (90/max=6), gen (AGEGRPv2)'

Appendix R3

Histogram from Stata plotting age as a discrete variable



Appendix R4

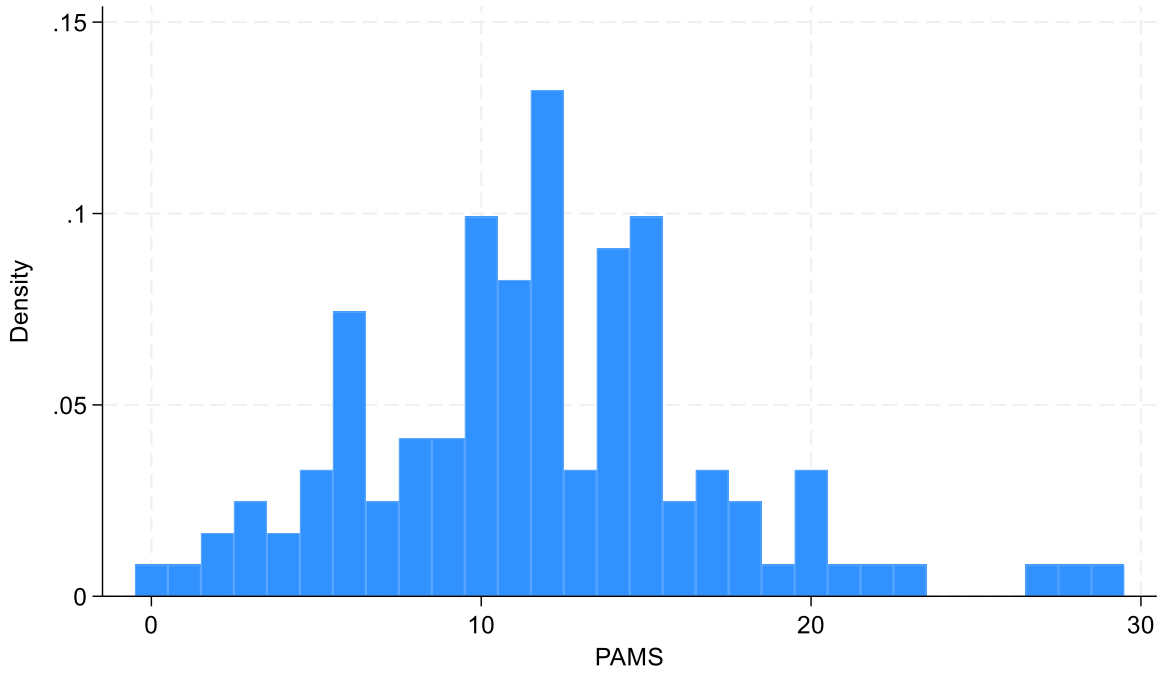
Baseline characteristics - Tabulation of PAMS

PAMS	Freq.	Percent	Cum.
0	1	0.83	0.83
1	1	0.83	1.65
2	2	1.65	3.31
3	3	2.48	5.79
4	2	1.65	7.44
5	4	3.31	10.74
6	9	7.44	18.18
7	3	2.48	20.66
8	5	4.13	24.79
9	5	4.13	28.93
10	12	9.92	38.84
11	10	8.26	47.11
12	16	13.22	60.33
13	4	3.31	63.64
14	11	9.09	72.73
15	12	9.92	82.64
16	3	2.48	85.12
17	4	3.31	88.43
18	3	2.48	90.91
19	1	0.83	91.74
20	4	3.31	95.04

21	1	0.83	95.87
22	1	0.83	96.69
23	1	0.83	97.52
27	1	0.83	98.35
28	1	0.83	99.17
29	1	0.83	100.00
Total	121	100.00	

Appendix R5

Histogram from Stata plotting number of PAMs as a discrete variable



Appendix R6

Categories for the number of PAMS were retrospectively created after running initial Stata analyses.

This was conducted using the recode command in Stata to create 3 categories/groups as follows:

'recode PAMS (0/4=1) (5/9=2) (10/max=3), gen (PAMSGRPS)'

and the resultant table exported to Word using asdoc command

'asdoc tab PAMSGRPS'.

Appendix R7

Baseline characteristics: Tabulation of eGFR

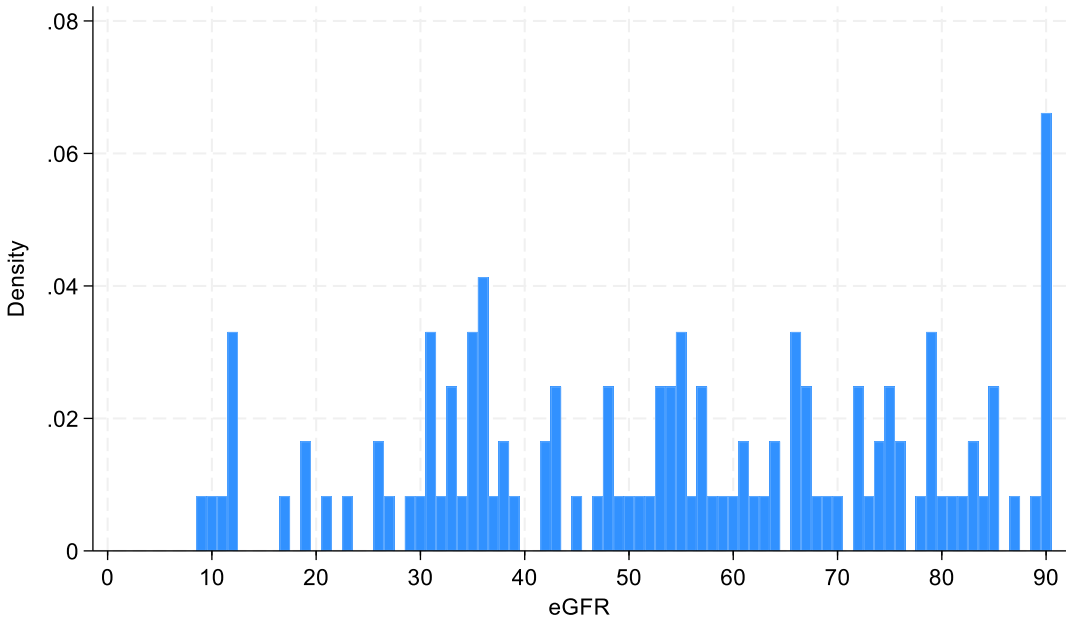
eGFR	Freq.	Percent	Cum.
9	1	0.83	0.83
10	1	0.83	1.65
11	1	0.83	2.48
12	4	3.31	5.79
17	1	0.83	6.61
19	2	1.65	8.26
21	1	0.83	9.09
23	1	0.83	9.92
26	2	1.65	11.57
27	1	0.83	12.40
29	1	0.83	13.22
30	1	0.83	14.05
31	4	3.31	17.36
32	1	0.83	18.18
33	3	2.48	20.66
34	1	0.83	21.49
35	4	3.31	24.79
36	5	4.13	28.93
37	1	0.83	29.75
38	2	1.65	31.40
39	1	0.83	32.23

42	2	1.65	33.88
43	3	2.48	36.36
45	1	0.83	37.19
47	1	0.83	38.02
48	3	2.48	40.50
49	1	0.83	41.32
50	1	0.83	42.15
51	1	0.83	42.98
52	1	0.83	43.80
53	3	2.48	46.28
54	3	2.48	48.76
55	4	3.31	52.07
56	1	0.83	52.89
57	3	2.48	55.37
58	1	0.83	56.20
59	1	0.83	57.02
60	1	0.83	57.85
61	2	1.65	59.50
62	1	0.83	60.33
63	1	0.83	61.16
64	2	1.65	62.81
66	4	3.31	66.12
67	3	2.48	68.60
68	1	0.83	69.42
69	1	0.83	70.25

70	1	0.83	71.07
72	3	2.48	73.55
73	1	0.83	74.38
74	2	1.65	76.03
75	3	2.48	78.51
76	2	1.65	80.17
78	1	0.83	80.99
79	4	3.31	84.30
80	1	0.83	85.12
81	1	0.83	85.95
82	1	0.83	86.78
83	2	1.65	88.43
84	1	0.83	89.26
85	3	2.48	91.74
87	1	0.83	92.56
89	1	0.83	93.39
90	8	6.61	100.00
Total	121	100.00	

Appendix R8:

Histogram from Stata plotting eGFR (as a measure of renal function) as a discrete variable



Appendix R9

Categories for the renal function (as per eGFR) of patients were retrospectively created after running initial Stata analyses. This was conducted using the recode command in Stata to create 6 categories/groups as follows (including 3a and 3b, represented by 3.1 and 3.2 in above coding):

'recode eGFR (90/max=1) (60/89=2) (45/59=3.1) (30/44=3.2) (15/29=4) (min/14=5), gen (eGFRGRPSv2)'

and the resultant table exported to Word using asdoc command

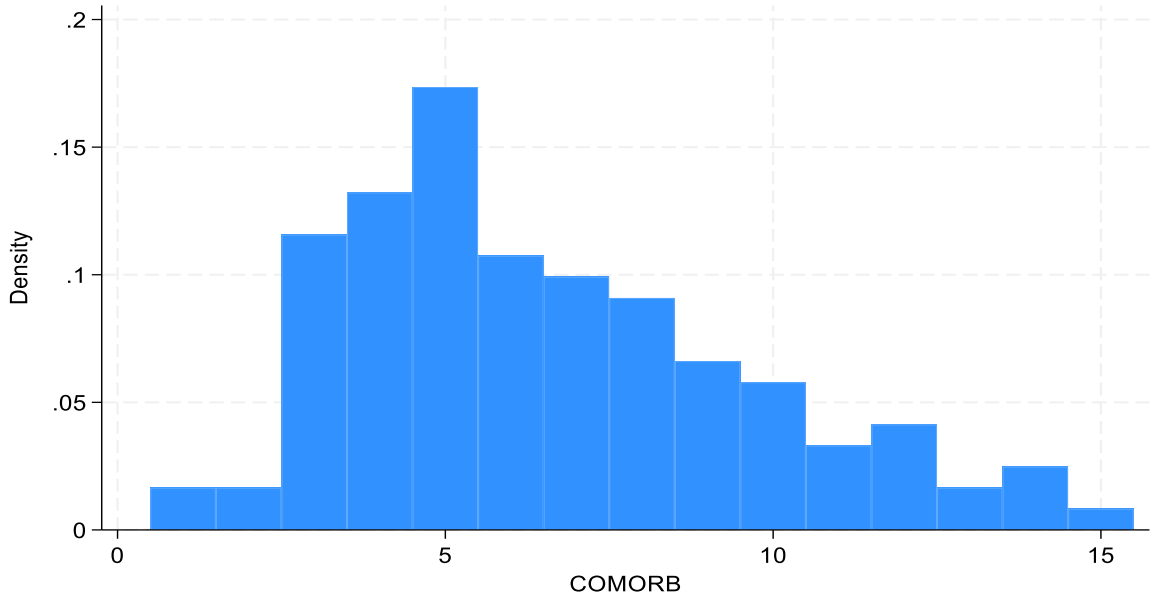
'asdoc tab eGFRGRPSv2'.

Cateogry G3a was (re)coded as 3.1 in Stata due to formatting requirements

Category G3b was (re)coded as 3.2 in Stata due to formatting requirements

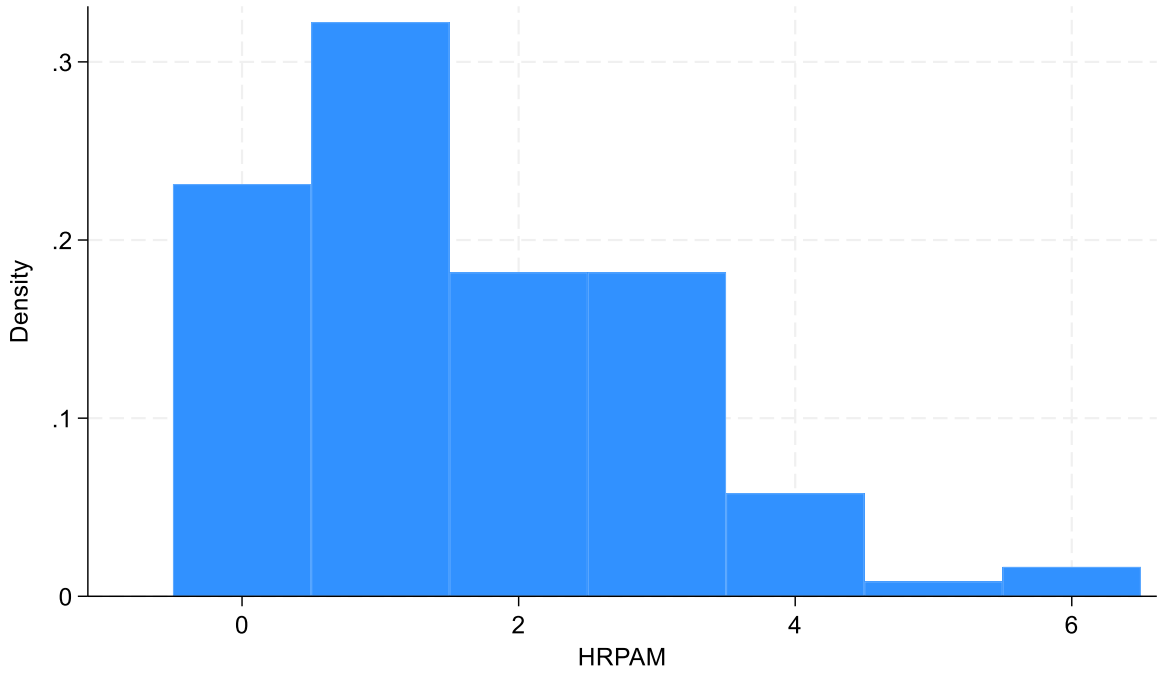
Appendix R10

Histogram from Stata plotting COMORB as a discrete variable



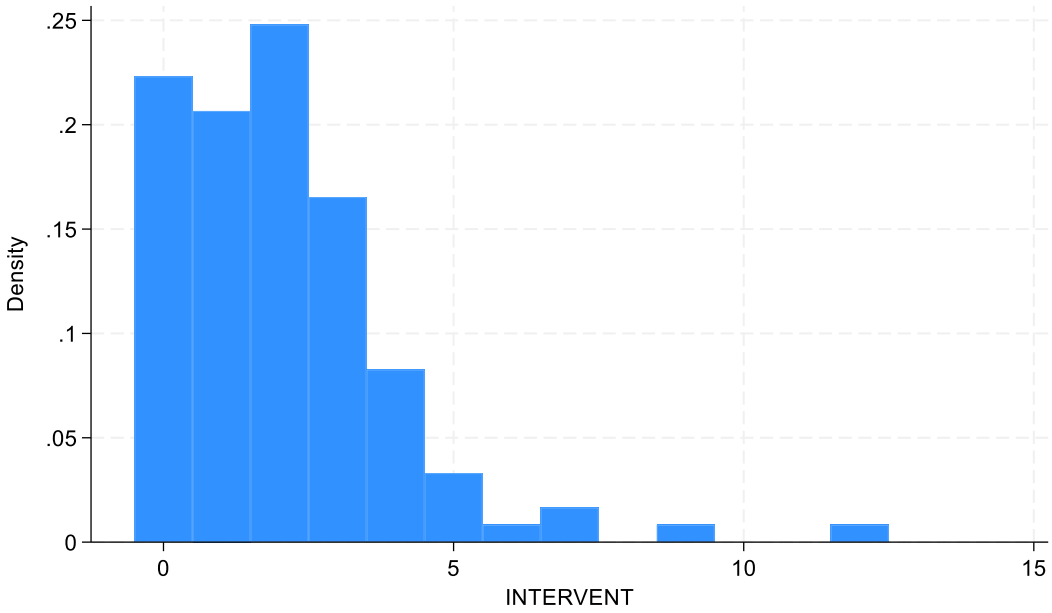
Appendix R11

Histogram from Stata plotting HRPAM as a discrete variable



Appendix R12

Histogram from Stata plotting number of interventions (outcome) as a discrete variable



Appendix R13: Table showing the distribution of the number of interventions (INTERVENT) made for patients according to their age

AGE (years)	INTERVENT											
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**12**	**Total**
65	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
66	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
67	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
68	3	1	1	0	0	1	0	0	0	0	0	6
	50.00	16.67	16.67	0.00	0.00	16.67	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	4.00	3.33	0.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	4.96
69	2	0	1	0	0	0	0	0	0	0	0	3
	66.67	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48

70	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
71	1	0	0	1	0	0	0	0	0	0	0	2
	50.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.di00	100.00
	3.70	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
72	0	0	2	1	1	0	0	0	0	0	0	4
	0.00	0.00	50.00	25.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	6.67	5.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
73	1	3	2	0	0	0	0	0	1	0	0	7
	14.29	42.86	28.57	0.00	0.00	0.00	0.00	0.00	14.29	0.00	0.00	100.00
	3.70	12.00	6.67	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	5.79
74	3	1	1	0	0	0	0	0	0	0	0	5
	60.00	20.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	4.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
75	0	2	0	1	0	0	0	0	0	0	0	3
	0.00	66.67	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	8.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48

76	1	2	1	3	1	0	0	1	0	0	0	9
	11.11	22.22	11.11	33.33	11.11	0.00	0.00	11.11	0.00	0.00	0.00	100.00
	3.70	8.00	3.33	15.00	10.00	0.00	0.00	50.00	0.00	0.00	0.00	7.44
77	1	2	0	2	1	0	0	0	0	0	0	6
	16.67	33.33	0.00	33.33	16.67	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	8.00	0.00	10.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	4.96
78	0	2	0	0	0	0	0	0	0	0	0	2
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	8.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
79	1	3	2	1	0	0	0	1	0	0	1	9
	11.11	33.33	22.22	11.11	0.00	0.00	0.00	11.11	0.00	0.00	11.11	100.00
	3.70	12.00	6.67	5.00	0.00	0.00	0.00	50.00	0.00	0.00	100.00	7.44
80	1	2	1	0	2	1	0	0	0	0	0	7
	14.29	28.57	14.29	0.00	28.57	14.29	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	8.00	3.33	0.00	20.00	25.00	0.00	0.00	0.00	0.00	0.00	5.79
81	0	0	0	2	0	0	0	0	0	0	0	2
	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65

82	2	0	2	1	1	1	0	0	0	0	0	7
	28.57	0.00	28.57	14.29	14.29	14.29	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	0.00	6.67	5.00	10.00	25.00	0.00	0.00	0.00	0.00	0.00	5.79
83	1	1	3	1	0	0	0	0	0	0	0	6
	16.67	16.67	50.00	16.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	4.00	10.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.96
84	2	1	1	0	1	0	0	0	0	0	0	5
	40.00	20.00	20.00	0.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	3.33	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
85	0	1	1	2	1	0	0	0	0	0	0	5
	0.00	20.00	20.00	40.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	3.33	10.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
86	0	1	0	2	0	0	0	0	0	0	0	3
	0.00	33.33	0.00	66.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
87	1	0	3	0	0	0	0	0	0	0	0	4
	25.00	0.00	75.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
88	2	0	1	1	1	0	0	0	0	0	0	5

	40.00	0.00	20.00	20.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	0.00	3.33	5.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
89	2	1	2	1	0	0	0	0	0	0	0	6
	33.33	16.67	33.33	16.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	6.67	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.96
90	1	1	1	0	0	0	1	0	0	0	0	4
	25.00	25.00	25.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00	100.00
	3.70	4.00	3.33	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	3.31
91	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
92	0	0	1	0	1	0	0	0	0	0	0	2
	0.00	0.00	50.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
93	1	0	0	1	0	0	0	0	0	0	0	2
	50.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
96	0	0	1	0	0	0	0	0	0	0	0	1

	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
97	0	0	0	0	0	1	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	0.83
Total	27	25	30	20	10	4	1	2	1	0	1	121
	22.31	20.66	24.79	16.53	8.26	3.31	0.83	1.65	0.83	0.00	0.83	100.00
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	0.00	100.00	100.00

First row has *frequencies*; second row has *row percentages* and third row has *column percentages*

Appendix R14:

Stata commands used when analysing the number of interventions made as a function of the patients' age group.

Note the variable AGEGRPv2 had previously been created (see *Appendix R2*).

The Stata commands used to present the data were:

'asdoc tab INTERVENT AGEGRPv2'

'asdoc bysort AGEGRPv2: summarize INTERVENT'

Appendix R15:

The commands used in Stata to present the data analysing the number of interventions as a function of the age groups as mean values, medians and IQR are:

'tabstat INTERVENT, by (AGEGRPv2) stat (p50 p25 p75 mean)'

Appendix R16:

Table showing the distribution of the number of interventions (INTERVENT) made for patients according to the number of Pre-Admission Medications PAMS)

PAMS	**INTERVENT**											
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**12**	**Total**
0	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
1	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
2	2	0	0	0	0	0	0	0	0	0	0	2
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
3	3	0	0	0	0	0	0	0	0	0	0	3
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
4	2	0	0	0	0	0	0	0	0	0	0	2
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65

5	2	2	0	0	0	0	0	0	0	0	0	4
	50.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	8.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
6	3	2	2	2	0	0	0	0	0	0	0	9
	33.33	22.22	22.22	22.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	8.00	6.67	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	7.44
7	0	1	1	0	1	0	0	0	0	0	0	3
	0.00	33.33	33.33	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	3.33	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
8	0	3	1	1	0	0	0	0	0	0	0	5
	0.00	60.00	20.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	12.00	3.33	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
9	0	0	4	1	0	0	0	0	0	0	0	5
	0.00	0.00	80.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	13.33	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
10	2	2	3	3	0	1	0	1	0	0	0	12
	16.67	16.67	25.00	25.00	0.00	8.33	0.00	8.33	0.00	0.00	0.00	100.00
	7.41	8.00	10.00	15.00	0.00	25.00	0.00	50.00	0.00	0.00	0.00	9.92
11	2	1	2	4	1	0	0	0	0	0	0	10

	20.00	10.00	20.00	40.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	6.67	20.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	8.26
12	3	4	6	0	3	0	0	0	0	0	0	16
	18.75	25.00	37.50	0.00	18.75	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	16.00	20.00	0.00	30.00	0.00	0.00	0.00	0.00	0.00	0.00	13.22
13	1	0	1	1	0	0	0	0	0	0	1	4
	25.00	0.00	25.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	25.00	100.00
	3.70	0.00	3.33	5.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	3.31
14	1	4	2	2	1	1	0	0	0	0	0	11
	9.09	36.36	18.18	18.18	9.09	9.09	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	16.00	6.67	10.00	10.00	25.00	0.00	0.00	0.00	0.00	0.00	9.09
15	2	4	2	2	2	0	0	0	0	0	0	12
	16.67	33.33	16.67	16.67	16.67	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	16.00	6.67	10.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	9.92
16	1	0	0	0	0	1	0	1	0	0	0	3
	33.33	0.00	0.00	0.00	0.00	33.33	0.00	33.33	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	25.00	0.00	50.00	0.00	0.00	0.00	2.48
17	0	0	2	0	1	0	0	0	1	0	0	4

	0.00	0.00	50.00	0.00	25.00	0.00	0.00	0.00	25.00	0.00	0.00	100.00
	0.00	0.00	6.67	0.00	10.00	0.00	0.00	0.00	100.00	0.00	0.00	3.31
18	0	1	0	1	0	1	0	0	0	0	0	3
	0.00	33.33	0.00	33.33	0.00	33.33	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	5.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	2.48
19	0	0	0	0	1	0	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
20	1	0	1	2	0	0	0	0	0	0	0	4
	25.00	0.00	25.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	3.33	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
21	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
22	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
23	0	0	0	1	0	0	0	0	0	0	0	1

	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
27	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
28	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
29	0	0	0	0	0	0	1	0	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.83
Total	27	25	30	20	10	4	1	2	1	0	1	121
	22.31	20.66	24.79	16.53	8.26	3.31	0.83	1.65	0.83	0.00	0.83	100.00
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	0.000	100.00	100.00

First row has *frequencies*; second row has *row percentages* and third row has *column percentages*

Appendix R17:

The following commands were used in Stata to summarise the results for the average number of interventions according to PAMS groups, 1-3, presented as mean values, median (p50) and interquartile range (IQR) in table R15:

'tabstat INTERVENT, by (PAMSGRPS) stat (p50 p25 p75 mean)'

Appendix R18:

Table showing the distribution of the number of interventions (INTERVENT) made for patients according to patient's renal function as estimated by eGFR

eGFR	INTERVENT											
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**12**	**Total**
9	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
10	0	0	0	1	0	0	0	0	0	0	0	1
	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
11	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
12	0	0	0	3	1	0	0	0	0	0	0	4
	0.00	0.00	0.00	75.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	15.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
17	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83

19	0	1	0	0	0	0	0	1	0	0	0	2
	0.00	50.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	1.65
21	0	0	0	0	0	1	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	0.83
23	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
26	0	1	0	1	0	0	0	0	0	0	0	2
	0.00	50.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
27	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
29	0	0	0	0	0	0	0	0	1	0	0	1
	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.83

30	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
31	0	1	1	1	1	0	0	0	0	0	0	4
	0.00	25.00	25.00	25.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	3.33	5.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
32	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
33	0	0	2	0	1	0	0	0	0	0	0	3
	0.00	0.00	66.67	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	6.67	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
34	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
35	2	1	0	1	0	0	0	0	0	0	0	4
	50.00	25.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
36	2	1	1	0	1	0	0	0	0	0	0	5

	40.00	20.00	20.00	0.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	3.33	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	4.13
37	0	0	0	0	0	0	1	0	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.83
38	0	1	0	0	0	1	0	0	0	0	0	2
	0.00	50.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	1.65
39	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
42	0	1	0	1	0	0	0	0	0	0	0	2
	0.00	50.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
43	0	0	1	1	0	1	0	0	0	0	0	3
	0.00	0.00	33.33	33.33	0.00	33.33	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	5.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	2.48
45	1	0	0	0	0	0	0	0	0	0	0	1

	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
47	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
48	0	1	0	0	2	0	0	0	0	0	0	3
	0.00	33.33	0.00	0.00	66.67	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	20.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
49	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
50	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
51	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
52	1	0	0	0	0	0	0	0	0	0	0	1
	100.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.0

	0											0
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
53	1	0	1	0	1	0	0	0	0	0	0	3
	33.33	0.00	33.33	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	3.33	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
54	0	0	3	0	0	0	0	0	0	0	0	3
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
55	0	1	0	3	0	0	0	0	0	0	0	4
	0.00	25.00	0.00	75.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	15.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
56	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
57	0	1	1	1	0	0	0	0	0	0	0	3
	0.00	33.33	33.33	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	3.33	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
58	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00

	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
59	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
60	0	1	0	0	0	0	0	0	0	0	0	1
	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
61	1	0	0	1	0	0	0	0	0	0	0	2
	50.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
62	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
63	0	0	0	1	0	0	0	0	0	0	0	1
	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
64	0	0	2	0	0	0	0	0	0	0	0	2
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	6.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65

66	2	1	1	0	0	0	0	0	0	0	0	4
	50.00	25.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	4.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
67	1	1	1	0	0	0	0	0	0	0	0	3
	33.33	33.33	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	4.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
68	0	0	0	1	0	0	0	0	0	0	0	1
	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
69	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
70	0	0	0	0	1	0	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
72	1	1	1	0	0	0	0	0	0	0	0	3
	33.33	33.33	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	4.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
73	0	0	1	0	0	0	0	0	0	0	0	1

	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
74	0	0	0	0	1	0	0	0	0	0	1	2
	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	0.00	50.00	100.00
	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	100.00	1.65
75	1	1	0	0	0	1	0	0	0	0	0	3
	33.33	33.33	0.00	0.00	0.00	33.33	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	4.00	0.00	0.00	0.00	25.00	0.00	0.00	0.00	0.00	0.00	2.48
76	0	1	1	0	0	0	0	0	0	0	0	2
	0.00	50.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	4.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
78	0	0	1	0	0	0	0	0	0	0	0	1
	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
79	3	1	0	0	0	0	0	0	0	0	0	4
	75.00	25.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	11.11	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.31
80	0	0	0	1	0	0	0	0	0	0	0	1

	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
81	0	0	0	0	1	0	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
82	0	0	0	0	0	0	0	1	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.83
83	0	0	1	1	0	0	0	0	0	0	0	2
	0.00	0.00	50.00	50.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	3.33	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.65
84	1	0	0	0	0	0	0	0	0	0	0	1
	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
85	2	0	0	1	0	0	0	0	0	0	0	3
	66.67	0.00	0.00	33.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	3.85	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.48
87	1	0	0	0	0	0	0	0	0	0	0	1
	100.0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.0

	0											0
	3.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
89	0	0	0	1	0	0	0	0	0	0	0	1
	0.00	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	0.00	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.83
90	2	3	3	0	0	0	0	0	0	0	0	8
	25.00	37.50	37.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00
	7.41	12.00	10.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	6.61
Total	27	25	30	20	10	4	1	2	1	0	1	121
	22.31	20.66	24.79	16.53	8.26	3.31	0.83	1.65	0.83	0.83	0.83	100.00
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

First row has *frequencies*; second row has *row percentages* and third row has *column percentages*

Appendix R19:

The coding used in Stata to create groups for the number of co-morbidities is as follows:

'recode COMORB (0/5=1) (6/10=2) (11/max=3), gen (COMORBGRP)'

and then the Stata run repeated using the COMORBGRP groupings

'asdoc tab INTERVENT COMORBGRP'

Appendix R20:

Stata commands for multivariate analysis conducted

The command 'stepwise, pr' performs selection with pr indicating that the **selection is backward**. The number in brackets (after the command pr, pr(#)) indicates the level of p at which/exceeding which terms are removed. Typing:

Stepwise, pr(#): *command*

Performs backward-selection estimation using the Poisson estimation command (where poisson is used for *command*).

Command	**Description**
stepwise, pr	Backward selection
Poisson	Poisson regression
pr(#)	Significance level for removal from the model

Note: Despite the command being "stepwise, pr' this command is used for backward selection whilst a command incorporating 'pr' and 'pe' is used with 'stepwise' to run a stepwise selection.

To remove terms with p>/+0.157, pr (0.157) is used.

The Stata commands used to conduct the multivariate Poisson analysis using backward selection modelling and a significance level p<0157 (where p<0.157 is chosen as it is generally regarded as a proxy for the Akaike Information Criterion (AIC)) and where the outcome measure was the number of interventions (INTERVENT), were:

```
stepwise, pr (0.157): poisson INTERVENT AGE PAMS eGFR COMORB HRPAM i.GENDER i.ANTIMICRO
i.ABWCC i.FALL i.ABLF
```

The prefixes 'i' were used to denote variables that were categorical in nature, namely patient gender, whether patients were taking systemic antimicrobials, whether the white cell count (total &/or

neutrophil count) were abnormal, fall on current admission/recent fall history/ documented fall risk and abnormal liver function tests/documented current or history of hepatic dysfunction (GENDER, ANTIMICRO, ABWCC, FALL and ABLF respectively).

Wald test, begin with full model:

p = 0.7684 >= 0.1570, removing 1.ABLF

p = 0.5672 >= 0.1570, removing eGFR

p = 0.4454 >= 0.1570, removing COMORB

p = 0.3814 >= 0.1570, removing 1.FALL

p = 0.2906 >= 0.1570, removing 1.ABWCC

p = 0.2549 >= 0.1570, removing HRPAM

p = 0.2388 >= 0.1570, removing AGE

p = 0.1833 >= 0.1570, removing 1.ANTIMICRO

Poisson regression:

Number of obs = 121

LR chi2(2) = 23.67

Prob > chi2 = 0.0000

Pseudo R2 = 0.0503

Log likelihood = -223.59564

INTERVENT	Coefficient	Std. err.	Z	P>|z|	95% confidence interval	
1.GENDER	-.3325482	.1334672	-2.49	0.013	-.5941392	-.0709573
PAMS	.0488747	.0113218	4.32	0.000	.0266843	.0710651
_cons	.2277726	.1679583	1.36	0.175	-.1014196	.5569647

Appendix D1:

Variables found to be independently and significantly associated with the outcome from research by Suggett(98).

Variable
Age
Female gender
Number of allergies
Number of comorbidities
Presence of liver dysfunction
Presence of renal impairment
Record of an INR
Requirement for a blister pack
Number of regular prescriptions
Refusal of medicines by a patient
Drug out of stock
Prescription of warfarin
Number of anti-epileptics
Number of thrombolytics/anticoagulants prescribed
Number of CNS agents prescribed
Number of opiates prescribed
Number of diuretics prescribed
Number of chemotherapy / immunosuppressants prescribed
Number of intravenous antimicrobials prescribed

Appendix D2: Working definition of prescribing error used by (and taken from thesis by) Alshakrah(155) and itself taken from Dean *et al.*(156).

"One which occurs when, as a result of a prescribing decision or prescription-writing process, there is an unintended, significant reduction in the probability of treatment being timely and effective, or an increase in the risk of harm when compared with generally accepted practice"(155)(p.89).

Appendix D3: Definition of prescribing errors

The reference that Alshakrah(155) referred to for the definition of a prescribing errors classified the following transcription errors as prescribing errors by consensus, namely:

Transcription errors

"On admission to hospital, unintentionally not prescribing a drug that the patient was taking prior to their admission".

"Continuing a GP's prescribing error when writing a patient's drug chart on admission to hospital".

"On admission to hospital, writing a medication order that unintentionally deviates from the patient's pre-admission prescription"(156)(p.234).

Appendix D4: Definition of sensitivity of a clinical prediction model

A "reliable predictive factor or model would combine both a high sensitivity with a high specificity. In other words, it would correctly identify as high a proportion as possible of the patients fated to have the outcome in question (sensitivity) while excluding those who will not have the outcome (specificity). In the table sensitivity can be defined as A÷(A+C) and specificity as D÷(B+D)"(167)(p.1).

Tabular representation of predicted versus actual outcomes of a predictive model (included as, and taken from, Table 1 from the reference(167)(p.5))

Predicted outcome	Actual outcome	
	Positive	Negative
Positive	A (true positive)	B (false positive)
Negative	C (false negative)	D (true negative)

Appendix D5: Review of the studies included in the systematic review (see *Table D2*), (excluding research by Suggett(98) which is discussed in the main *Discussion* in the section entitled *Relevant Academic Theses*) along with an additional validation study by and Ferrández *et al.*(160) and comparison with the current research undertaken.

- BADRI model

The Brighton Adverse Drug Reactions Risk (BADRI) model was developed in a prospective study involving 690 older patients (aged 65/+ years) in a UK hospital's NHS Trust(103, 161). There were 95 confirmed reports of the study outcome, adverse drug reactions (ADRs). A combination of univariate analysis followed by multivariate analysis using binary logistic regression analysis was used to in the statistical analysis and identified five clinical risk factors for developing an ADR in this population of patients, from a framework of potential variables. Backward stepwise elimination was used in the modelling process and "the process was then repeated with the forward selection procedure before final confirmation of the model"(103)(p.3). The researchers reported that internal validation produced an AUROC of 0.74, a sensitivity of 80%, and specificity of 55%; external validation was conducted on patient data (for 483 patients) gathered from four European centres and yielded the following results "AUROC was 0.73, with sensitivity and specificity values of 84% and 43% respectively"(103)(p.1). The five clinical risk factors included in the BADRI model are 8/+ drugs, hyperlipidaemia, raised white cell count, use of anti-diabetic agents, length of hospital stay 12/+ days(103).

There are similarities between the BADRI model and the current research with both involving older inpatient populations. The outcome measures differed between the studies. There were some similarities in the prediction tool modelling processes although the BADRI model used backward stepwise elimination and the current research utilised backward elimination, and the BADRI model was both internally and externally validated. Both developed models included a variable relating to number of medicines taken/polypharmacy.

- GerontoNet ADR Risk Score

Onder *et al.* developed the GerontoNet ADR score to identify elderly[1] patients (aged 65/+ years) at risk of adverse drug reactions (ADRs)(104). Their score was developed using a sample of 5936 patients from the Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA) database. The outcome studied was ADR(/s). In brief, univariate analysis followed by stepwise logistic regression was used for variable selection. The developed score was then validated externally in 483 older patients in hospital wards in four countries (Italy, Belgium, England and the Netherlands). The six variables included in the final model were:

Presence of ≥4 co-morbid conditions,

Heart failure,

Liver disease,

Number of drugs (≤5, 5-7, ≥8),

Previous ADR,

Renal failure,

with point scores assigned to the variables (weighted) and the final score ranging from 0 to 10(104). The GerontoNet score had an AUROC of 0.71 in the development population with a sensitivity and specificity of 68% and 65% respectively; in the external validation population, an AUROC of 0.7 was reported(104). The authors concluded the score to be a "practical and simple method of identifying patients who are at increased risk for an ADR"(104)(p.1142).

O'Connor *et al.* essentially conducted an external validation study of the GerontoNet score(105). They prospectively studied 513 older patients (aged ≥65 years), the outcome was ADR and the GerontoNet score was calculated for all patients. ROC curves were constructed to "test the ability of the GerontoNet score to predict ADRs"(105)(p.771). They found the AUROC was 0.62 (less than reported by Onder *et al.* in both development and validation populations) and logistic regression found that renal failure, increasing number of medicines, inappropriate medicines and age ≥75 years were

variables that increased the ADR risk(104, 105). The authors commented that the score incorrectly classified 38% of patients as low risk highlighting limitations in the usefulness of the score.

A further external validation study of the GerontoNet score was conducted and reported by Petrovic *et al.* "Data from the prospective CRIteria to assess appropriate Medication use among Elderly[1] complex patients (CRIME) cohort were used"(83)(p.135) with a sample size of 1075 patients of mean age 81.4 years old(83). They also aimed to assess the validity of the GerontoNet risk score in specific subpopulations of older inpatients. The researchers reported an AUC of 0.64 for predicting ADRs probably or definitely related to drug use, and an AUC of 0.69 to predict ADRs of type A(83). They concluded that the score might be useful "identifying specific subpopulations of older inpatients at increased risk of an ADR with a fair to good diagnostic accuracy"(83)(p.141) as summarised below *(Figure D1)*.

Validation of the GerontoNet ADR Risk Score in the CRIME Cohort

Table 3 Diagnostic accuracy of the GerontoNet ADR risk score to predict both ADRs probably or definitely related to drug use and type A ADRs in subpopulations of older inpatients with specific diseases or clinical characteristics

Fair diagnostic accuracy; AUC = [0.70; 0.79]
Age ≥80 years
Heart failure
Diabetes
History of any previous ADR
Good diagnostic accuracy; AUC = [0.80; 0.89]
Low BMI (>18.5 kg/m^2)
MMSE score of >24/30 points
Osteoarthritis

ADR adverse drug reaction, *AUC* area under the curve, *BMI* body mass index, *MMSE* Mini-Mental State Examination

Figure D1: Table 3 from Petrovic *et al.* reference showing the AUC for GerontoNet risk score in specific subpopulations of older inpatients(83)(p.141).

Like the model/score developed in the current study, the GerontoNet score was developed for use in older patients. The outcome measures used in the studies varied and whilst the current study used

Poisson regression and backward elimination for model development, the GerontoNet score was developed using stepwise logistic regression. The GerontoNet score has been validated whilst validation of the developed score was not feasible in the current study. Similar to the BADRI model, the GerontoNet score included a variable looking at the number of drugs taken in its final model which also featured in the model developed in the current study.

- A geriatric risk score for ADEs developed by Trivalle *et al.*

Trivalle *et al.* developed and validated a "simple and practical score to detect the risk of ADEs in elderly[1] hospitalized patients"(106)(p.284). The study, conducted in 526 elderly[1] inpatients (in geriatric rehabilitation centres in France) identified those who experienced adverse drug events (ADEs). Stepwise logistic regression was used to develop multivariable models, with highly correlated variables being analysed in separate models. Potential variables were retained in the model if they were found to have p-values of 0.05 or less and items were weighted in proportion to their regression coefficients in the score(106). ROC curves were constructed to evaluate the predictive value of the score and AUCs were calculated and bootstrapped for internal validation purposes(106). The risk factors included in the final score were:

Number of medications (if ≥7),

The presence of antipsychotic treatment,

Recent anticoagulation(106).

The final score was between zero and 34 and the AUROC of the developed geriatric score was 0.70. The researchers also "proposed a classification of risk of the drugs most frequently associated with ADEs"(106)(p.284).

There are a number of similarities between this and the current research. Both were conducted in older patients, although the demographics varied in location (country) and type of hospital. Trivalle *et al.* used stepwise regression in the model development process whilst the current study used

Poisson regression and backward elimination. Unlike the current study, the predictive value of the score developed by Trivalle *et al.* was evaluated and bootstrapping conducted for validation, with the AUROC=0.70. Both models/scores included a variable relating to the number of medications taken/polypharmacy.

- The 80+ score

Alassaad *et al.* developed and internally validated "a risk score, the '80+ score', for revisits to hospital and mortality for older patients, incorporating aspects of pharmacotherapy"(118)(p.1). Data was analysed for 368 hospitalised inpatients aged 80/+ years old from a randomised controlled trial conducted in a Swedish hospital investigating the effects of a comprehensive clinical pharmacist intervention. The primary outcome for the study was time to rehospitalisation or death during the year after discharge from hospital(118). A number of potential clinical, drug-disease and drug variables were identified and (after testing and adjusting for collinearity) backward stepwise Cox regression likelihood-ratio elimination was conducted and the resultant set of statistically significant variables (seven) extracted became the components of the 80+ score. The seven variables included in the score were:

eGFR (mL/min/1.73 m^2),

Social support (living in nursing home vs living alone or with spouse),

Pulmonary disease (asthma or chronic obstructive pulmonary disease, COPD, vs not),

Malignant disease (current or past diagnosis, vs not),

Prescription of drug for peptic ulcer and GERD (vs not),

Prescription of opioid drug (vs not),

Prescription of non-tricyclic antidepressant drug (vs not).

The researchers followed the Framingham Heart Study methodology in developing a point score system for the 80+ score(118).

The 80+ score was internally validated (bootstrapping methods described by the researchers) and the discriminatory ability of the score compared with that of three validated tools for measuring inappropriate prescribing: Screening Tool of Older Person's Prescriptions (STOPP), Screening Tool to Alert doctors to Right Treatment (START) and Medication Appropriateness Index (MAI) using C-statistics(118). They found that the "C-statistics were 0.71 (80+), 0.57 (STOPP), 0.54 (START) and 0.63 (MAI)"(118)(p.1) and concluded that their "score outperforms scores for inappropriate medication use in risk-prediction ability"(118)(p.7).

The research by Alassaad *et al.* differed from the current study in that, whilst both were conducted in older populations, the age profile of the included patients varied with Alassaad *et al.* focussing on those aged 80/+ years old. Their methodology had a number of strengths over the current study in respect to internal validation and assessment of the discriminatory ability of the score, although further research could focus on these areas for the score/model developed in this current study.

- Clinical Decision Rules - The ADE Rule and the Adverse Drug Reaction Rule

Hohl *et al.* conducted a prospective observational cohort study (reported in 2012) in two Canadian tertiary care hospitals looking at adverse drug events (ADEs) in adult patients who presented to the Emergency Department and who had ingested at least one prescribed or over-the-counter medication within the previous two weeks(107). Patients were assessed by a Pharmacist for ADEs and the primary outcome of the study was an ADE requiring a change in medical therapy, diagnostic testing, consultation or hospital admission; the secondary outcome was an adverse drug reaction (ADR). Data on potential predictor variables was collected by nurses and physicians (Pharmacist assessing for ADEs was blinded from variable data) and inter-rater agreement was measured using described statistical methods. The strength of association between the potential predictor variables and the outcomes were measured (again individual statistical tests/methods used for different types of variables, e.g.

continuous and categorical were described) and recursive partitioning analysis was used to derive the clinical decision rules (CDRs). Of the 1591 included patients, 131 experienced the primary outcome (experiencing 134 moderate or severe ADEs) and 65 patients experienced the secondary outcome (one or more moderate or severe ADR).

They found the following variables were associated with ADEs: "1) presence of comorbid conditions, 2) antibiotic use within 7 days, 3) medication changes within 28 days, 4) age ≥80 years, 5) arrival by ambulance, 6) triage acuity, 7) recent hospital admission, 8) renal failure, and 9) use of three or more prescription medications"(107)(p.640). These associations were used these to develop two CDRs, one for each outcome measure. Both CDRs used the same low-risk criteria to screen patients first (which then determined whether further assessment/workup was needed). The ADE Rule (derived for primary outcome measure) had a sensitivity of 96.7% and would have required 40.8% of the patients included in the study to have a medication review; the Adverse Drug Reaction Rule (derived for the secondary outcome measure and "designed for use in EDs with more limited pharmacist resources"(107)(p.644)) had a sensitivity of 90.8% and would have required 28.3% to have a medication review(107).

The patient population for this study were adults with a mean age of 51.4 years and the median number of prescribed medications was 2, so the patients were significantly younger and taking less prescribed medications than in the current study and the outcome measures used by Hohl *et al.* differed (ADEs and ADRs versus Clinical Pharmacist Interventions) making comparisons between the studies difficult.

Hohl *et al.* carried out and evaluated a quality improvement project in three Canadian hospitals incorporating a modified ADE clinical decision rule into the Emergency Department triage pathways, allowing nurses to identify patients at high-risk for adverse drug events(108). They used quasi-random patient allocation methods and propensity score modelling(108). High-risk patients either received standard care or the intervention, of medication review. The primary outcome was the number of

days spent in-hospital over 30 days, as ascertained using administrative data. Overall, the median number of hospital days was reduced by 0.48 days in the medication review group compared to usual care, and, in patients under 80 years of age, this reduction was greater (with the median number of hospital days reduced by 0.60 days) whilst medication review had no effect on the median number of (in-patient) hospital days in those patients aged over 80 years(108). There was no significant effect on Emergency Department revisits, admissions, readmissions, or mortality(108).

Their project was conducted over a 12 month period in the three hospitals and included a large number of patients (10,807 high-risk patients, of whom 6,416 received early pharmacist-led medication review and 4,391 received usual care)(108). Patients aged 19 years and over were included so the geographical location and demographic profile differed from that of the current study, the CDR used was developed to identify patients at high risk of ADEs and the outcome measure(s) used differed from the current study being described in this thesis.

- <u>The MERIS score</u>

Saedder *et al.* reported on the development and validation of a Medicine Risk Score, MERIS, designed to identify patients at increased risk of medication errors (MEs)(109). They conducted a literature search to identify potential drug-related and patient-related risk factors, Delphi process, construction of algorithm, calibration of algorithm and prospective pilot study to develop the algorithm and used the number of MEs as their outcome measure. They used a combination of two historic patient populations (from clinical trials), a recent patient population and a prospective patient population (in Denmark) for modelling; there were differences in the demographic profiles and inclusion criteria of the patients in these different populations (for example, the recent patient population included patients aged 18 years and older, compared to aged 65/+ and 70/+ years in the historic populations as well as differences in the type of admission (orthopaedic vs internal medicine department).

The developed algorithm was used to assign risk scores to patients, based on information from their electronic medical records. After discharge, the records and laboratory results were reviewed to

determine whether a ME had occurred (reviewers blind to the risk scores) and "the resulting list of MEs was used as the gold standard for the evaluation of the sensitivity and specificity of the algorithm"(109)(p.145). The predictive variables were assigned theoretical weightings dependent upon type, e.g. if they were drugs causing harm, drugs causing interaction or patient-related risk factors, and different models developed first in the historic populations and then those with the highest sensitivity and specificity were carried into the recent patient population to find the risk score with the highest precision(109). This study showed the practical usefulness of the algorithm. The variables included in the final risk score were "reduced renal function, the total number of drugs and the risk of individual drugs to cause harm and drug-drug interactions"(109)(p.143). The final risk score was validated in the prospective pilot study and had a sensitivity of 0.64, specificity of 0.75 and the area under the ROC curve was 0.76(109).

Saeddar *et al.* concluded that they had "developed a simple and robust score, MERIS, with the ability to detect patients and divide them according to low and high risk of MEs in a general population admitted at acute admissions unit. The accuracy of the risk score was at least as good as other models reported using multiple regression analysis"(109)(p.143).

Of note, the outcome measure used in this score differed from that used in the current research (number of MEs versus number of Clinical Pharmacist Interventions), the score was developed using a number of different patient populations (some of which differed from the demographic profile of those included in the current study) and whilst the researchers reported promising results regarding the accuracy of the risk score compared to tools developed by others with respect to sensitivity and specificity, it is limited by the fact that it was developed and validated in a comparatively small number of patients overall (302 patients in all four populations). Both the MERIS score and the results from this current research found that the number of medicines taken by patients was predictive of the outcome (although other predictive variables differed between them).

Bonnerup *et al.* used the MERIS algorithm to assess acute admission unit patients at a University hospital in Denmark(110). Patients classified as high-risk according to the algorithm were offered a

medication review, the clinical relevance of which was assessed retrospectively. Of the 103 patients included in this interventional pilot study, 38 were stratified as high-risk and 65 as low-risk patients. A total of 848 drugs were prescribed for these 103 patients, with 155 DRPs, including 88 prescribing errors (10.4%) identified, 62 of which were in high-risk patients(110). Half (50%) of the recommendations made as part of the medication review were implemented. This study showed the practical usefulness of the algorithm and the authors concluded that the MERIS was "applicable in a clinical setting and stratified most patients with prescribing errors into the high-risk group"(110)(p.143).

- The Drug-Associated Risk Tool (DART)

The DART is a "patient self-assessment risk screening tool"(111)(p.1) based upon 27 risk factors for drug related problems, previously identified from a literature search and expert opinion using the Delphi technique. Kaufmann *et al.* conducted a prospective validation study of the DART. The DART was completed by 164 adult patients before an initial validation was conducted. Statements found to have a low sensitivity were identified and reworded before testing the revised DART (v2.0) in a further 31 patients. The answers provided by patients in the DART were compared by the researchers with objective patient data from medical records and laboratory data. The researchers concluded that the DART "showed a satisfying feasibility and reliability"(111)(p.1) and the specificity of the included statements was mostly high but the sensitivity was variable.

The study population criteria included adults aged 18/+ years so differed from the current study population in that it included younger patients whilst excluding vulnerable patients unable to communicate meaningfully such as those with advanced dementia, and so the utilisation of a self-assessment tool might not be as suitable for some older patients or those with communication barriers, and compared to some other studies, the population size was quite small (195 patients overall with 164 patients completing the DART v1.0 and 31 completing the revised DART v2.0).

- The Assessment of Risk Tool (ART)

Falconer *et al.* developed an electronic patient prioritisation tool (ART) for clinical pharmacist interventions in New Zealand(112). The ART incorporates 38 prespecified clinical 'flags' for high-risk medication use and other adverse drug event (ADE) risk factors, with each flag assigned a weighted score. The total ART score is calculated (from the sum of the item scores) indicating low, medium or high ADE risk and patients are prioritised by the ART score for pharmacist interventions, e.g. clinical review(112). They reported increases in the average number of patients receiving medication reconciliation per month following implementation of the ART among other outcomes.

Falconer *et al.* conducted a prospective observational study (247 patients) to validate the ART and to determine which of the selected 25 flags (from initial 38 flags, 13 flags associated with laboratory results were excluded) were "significantly associated with risk of unintentional medication discrepancies and prescribing errors"(115)(p.320). Pharmacist interventions were recorded electronically and retrospectively analysed "to determine the association between a patient's ART score and number of unintentional medication discrepancies…and other prescribing errors"(115)(p.321). The researchers found that there were significant differences between the numbers of unintentional medication discrepancies in the ART risk groups (highest in those in the high-risk ART group) but no significant differences in prescribing errors between the different ART risk groups. The flags found to be significantly associated with increased risk (of unintentional medication discrepancies) included more than eight admission medications and readmission within 30 days, with an AUROC of 0.72 indicating moderate discrimination(115).

The ART was an electronic patient prioritisation tool with information for the flags extracted from the hospital electronic systems; currently, limitations on the implementation of information technology at SUH means the extraction of such information electronically is not possible and instead is dependent on manual extraction and recording of such data which is time and labour consuming. The

patient population for the validation study included a wider age range of patients than in the current study being described in this thesis and there were differences in the outcome measures used.

- MEDCOINS score

McAuliffe *et al.* conducted a retrospective cohort study "to identify predictors of potentially avoidable 30-day readmissions"(113)(p.111) using transitions-of-care pharmacy notes and electronic medical record data. Univariate and multivariable logistic regression analyses of "factors associated with unplanned readmissions in the study cohort"(113)(p.111) were performed and a risk prediction MEDCOINS tool was developed. Three variables were found to be predictive of readmission within the cohort, namely medication count, comorbidity count and health insurance status at discharge. The MEDCOINS tool had fair discriminatory performance (C-statistic = 0.65) with good calibration (Hosmer-Lemeshow goodness of fit test p =0.99)(113). Their study was conducted in a larger sample size (study cohort n=690) than the current study and over a more prolonged period (of 22 months); the outcome measures of the studies vary but both found that the medications taken (recorded as medication count by McAuliffe *et al.* and number of pre-admission medications in the current study) to be predictive (although other predictive variables differed between them) of the outcomes.

- Predictive model for adverse drug events (ADEs) in elderly[1] patients by McElnay *et al.*

McElnay *et al.* developed a predictive model for ADEs in elderly[1] patients (aged 65/+ years)(81). Demographic, medical and social data were obtained from chart review, computerised information and patient interview. Phase 1 of the study included 929 elderly[1] patients admitted to a hospital in Northern Ireland for unscheduled care of whom approximately 16% experienced a possible ADE. An ADE score was "assigned to each patient using a modified Naranjo algorithm scoring system"(81)(p.47) with scores ranging from 0 to 8. Scores of 4 or more were regarded as constituting "a high risk of an ADE"(81)(p.47) for the purposes of developing the risk model. Univariate analysis was conducted and identified a number of variables for which data was collected in the study and which were found to significantly influence the ADE score. Multivariate analysis was then conducted to develop a risk

model, using stepwise backward elimination and a risk model composed of seven variables was produced. These variables were:

Prescribed antidepressants,

Prescribed digoxin,

Gastrointestinal problems,

Abnormal potassium level (<3.6 or >5.2mmol/L),

(Patient) Thinks drugs were responsible for hospitalisation,

Experiences angina,

Experiences COAD.

Validation of the model was conducted in Phase 2, involving 204 elderly[1] patients, and found that the model had a specificity of 69%, sensitivity of 41% and overall accuracy of 63%(81). The researchers concluded that the model was not "a satisfactory predictor of ADEs"(81)(p.54).

The study by McElnay *et al.* was conducted in a population belonging to the same overall age demographic as the current study (i.e. older patients, aged 65/+ years) and in similar (geographical) settings (Northern Ireland versus Sligo, Ireland) but had a larger sample size for the development of the model and a separate validation sample and additionally the healthcare systems within the two locations vary. Despite some similarities, the studies differed in their outcome measures and there was no crossover between the variables found to be predictive (of the outcome) for the two studies.

- A score to identify hospitalised patients at risk of drug-related problems by Urbina *et al.*

Urbina *et al.* developed a score to identify hospitalised patients at risk of drug-related problems (DRPs) in a tertiary university hospital between January and August 2009(114). There were 8713 patients included in the training set, used to develop the score. DRPs were detected through a pharmacy warning system, which was integrated into the computerised medical history(114). Bivariate analysis

of the data was used to determine whether each of the potential variables were associated with (at least one) DRP. They "modeled the risk of the occurrence of at least one DRP with a binary multivariate logistic regression analysis"(114)(p.926). The researchers found that approximately 28% of admissions in the training/development set experienced at least one DRP, with the mean number of DRPs being 1.89 (per admission).

The variables associated with risk of DRP were "prescription of a higher number of drugs, higher comorbidity, advanced age, certain groups of the Anatomical Therapeutic Chemical classification system, and some major diagnostic categories"(114)(p.923) and "were used to compute the DRP risk score"(114)(p.923).

The AUROC for the development set was 0.778(114). The developed score was then validated in a further 4058 admissions, and the AUROC was 0.776(114). The researchers commented that the cohorts of patients used in the development and validation of the score were much larger than those used in some other studies, which is a methodological strength. The study was conducted in adult patients with a mean age of 58.9 years (in development/testing set) in a tertiary university hospital in Spain so the demographic profile of the patients varied in Urbina *et al.*'s study compared with those in the current study which was limited to older patients. In addition, the outcome measure differed, and the methodology used by *Urbina et al.* involved detection of DRPs using a computerised pharmacy warning system which is outside information technology capabilities currently at SUH and the scope of practice.

- Predictive tool for assessing ADR Risk in Older People (acronym ADRROP)

O'Mahony *et al.* used four databases to identify independent risk factors for adverse drug reactions (ADRs) from 1687 older patients (who made up the derivation cohort) and used these to develop the ADRROP score(116). Univariate logistic regression was used and eight independent ADR risk factors were identified: "female gender, age >70 years, estimated GFR <30ml/min/1.73m^2, assistance required for ≥1 daily activity, ≥4 co-morbidities, liver disease, presence and number of STOPP criteria-

defined potentially inappropriate medications, and ≥1 fall in the previous year"(116)(p.193). Backwards likelihood ratio stepwise regression was used to develop the multivariate model with forced retention of some variables of "scientific relevance"(116)(p.194). The outcome of the study was ADRs.

The AUC value of the ADRROP score was 0.623 in the derivation cohort(114). The score was prospectively validated in a further 530 patients (validation cohort used rather than bootstrapping methods) yielding an AUC of 0.592(114). The researchers compared the results to that of the GerontoNet ADR risk score (for the combined derivation and validation cohorts) and the AUC for the GerontoNet ADR risk score was 0.566(114). Whilst the score was developed in a comparatively large sample size and in older patients, as in the current study, the outcome measures differ with O'Mahony *et al.* studying ADRs whilst the current study looked at pharmacist interventions. In addition, despite the size of the study the observed AUC values for both derivation and validation cohorts were disappointing and the researchers concluded that neither the ADRROP nor the GerontoNet ADR risk score predicted ADRs "to a high level in hospitalized older people with multi-morbidity"(116)(p.191).

- <u>Pharmaceutical assessment screening tool (PAST)</u>

Hickson *et al.* developed and evaluated a pharmaceutical assessment screening tool (PAST) "to measure patient acuity and prioritise pharmaceutical care in a UK hospital"(117)(p.74). The tool was developed by local consensus methodology and assigned inpatients a patient acuity level (PAL), with those deemed to be at the greatest risk of adverse drug events assigned a PAL score of 3 while those at lowest risk received a PAL of 1. The criteria for the different levels of PAL assigned, as developed by consensus, are shown in *Figure D2.* Patients with the higher PAL levels were expected to then be cared for by the most experienced clinical pharmacists available, enabling prioritisation of the most experienced pharmacists' time. The assigned PAL was recorded on the ward's electronic patient summary board and this could be viewed remotely in the Pharmacy department, so information technology supported the in-practice use of the PAST(117).

Level 3 Patients

- Patient is severely unwell with more than one acutely decompensated organ (kidney, liver, heart, lung, bone marrow, brain)
- Patient is on a high-risk medicine (HRM)* or a medicine requiring Therapeutic drug monitoring (TDM) plus one acutely decompensated organ
- Patient stepped down from ICU or under review by ICU outreach team
- An acute admission managed (or jointly managed) by an infectious diseases (ID) consultant
- Cystic fibrosis, organ transplant or patients with HIV
- Being considered for home IVs / out-of-hospital respiratory service
- Patient with Parkinson's disease on apomorphine pump
- Patient taking or being considered for a high-cost medicine (eg, posaconazole) that requires alternative funding stream (e.g. Payment by Results (PbR))
- **Patient's condition or drug therapy regimen outside of the competency of a junior pharmacist**

Level 2 Patients

- Patient is on a high-risk medicine (HRM)*
- Patient is on a medicine requiring Therapeutic Drug Monitoring (TDM)
- Patient has one acutely decompensated organ

Level 1 Patients

- Low-risk medicines only
- Limited comorbidities
- Medicine regimen stable
- Clinically stable
- Medically fit and awaiting care packages for discharge

***High-Risk Medicines (HRM)**

- Anticoagulants warfarin and novel oral anticoagulants (excluding enoxaparin ≤ 40 mg daily)
- Insulin
- Regular strong opiates (excluding codeine/ dihydrocodeine, tramadol)
- Drugs with a Narrow Therapeutic Index
- Chemotherapy
- Antiretrovirals
- Clozapine

Figure D2: Figure showing the criteria for assisting pharmacists to assign a PAL using the PAST (copied from Hickson *et al.*(117)(Figure 1, p.75))

A small-scale "quasi-experimental service evaluation study was conducted 6 months after implementation of the tool to quantify agreement between pharmacist-documented and expected per-guidance PALs"(117)(p.74) with 35 patients on the relevant wards selected by random clusters; 57% of the patients had a pharmacist-documented PAL that agreed with the expected per-guidance

PAL. There are few similarities between the methodology adopted in the development of the PAST and the current study, with the PAST being developed by local consensus rather than using regression modelling as in the current study. Whilst the service evaluation study showed relatively low adherence to the patient acuity tool, the PAST may be considered a pragmatic approach to the problem of prioritising the limited resource of Clinical Pharmacy resources.