IMPACT OF MEDICATION-RELATED HARM IN OLDER ADULTS FOLLOWING HOSPITAL DISCHARGE

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A thesis submitted in partial fulfilment of the requirements of the University of Brighton and the University of Sussex for the degree of Doctor of Philosophy

October 2018
DECLARATION

I, Nikesh Parekh, declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

Nikesh Parekh
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I dedicate my achievement to Ambaji Ma.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>A&amp;E</td>
<td>Accident and Emergency</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Drug Event</td>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reactions</td>
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<tr>
<td>AF</td>
<td>Atrial Fibrillation</td>
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<tr>
<td>AIC</td>
<td>Akaike’s Information Criterion</td>
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<tr>
<td>AMTS</td>
<td>Abbreviated Mental Test Score</td>
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<tr>
<td>AUROC</td>
<td>Area under the Receiver Operating Curve</td>
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<td>AUKBH</td>
<td>Age UK Brighton and Hove</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>CCF</td>
<td>Congestive Cardiac Failure</td>
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<tr>
<td>CHEERS</td>
<td>Consolidated Health Economic Evaluation Reporting Standards</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-Analyses</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CLD</td>
<td>Chronic Lung Disease</td>
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<tr>
<td>CPT</td>
<td>Clinical Pharmacology and Therapeutics</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>eGFR</td>
<td>estimated Glomerular Filtration Rate</td>
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<tr>
<td>EPC</td>
<td>End Point Committee</td>
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<tr>
<td>FCE</td>
<td>Finished Consultant Episode</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GMC</td>
<td>General Medical Council</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>GSTFT</td>
<td>Guy’s and St Thomas’ NHS Foundation Trust</td>
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<tr>
<td>HES</td>
<td>Hospital Episode Statistics</td>
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<tr>
<td>HRG</td>
<td>Healthcare Resource Group</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IHD</td>
<td>Ischaemic Heart Disease</td>
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<tr>
<td>IMD</td>
<td>Index of Multiple Deprivation</td>
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<tr>
<td>ISMN</td>
<td>Isosorbide Mononitrate</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter Quartile Range</td>
</tr>
<tr>
<td>MCA</td>
<td>Multicompartartment Compliance Aid</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines Health Regulatory Agency</td>
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<tr>
<td>MRH</td>
<td>Medication Related Harm</td>
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<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
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<tr>
<td>MICE</td>
<td>Multiple Imputation by Chained Equations</td>
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<tr>
<td>MSU</td>
<td>Mid Stream Urine</td>
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<tr>
<td>MUR</td>
<td>Medicines Use Review</td>
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<tr>
<td>MUST</td>
<td>Malnutrition Universal Screening Tool</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>NNT</td>
<td>Number Needed to Treat</td>
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<tr>
<td>NSAID</td>
<td>Non Steroidal Antiinflammatory Drug</td>
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<tr>
<td>OOH</td>
<td>Out Of Hours</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PIM</td>
<td>Potentially Inappropriate Medicine</td>
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<tr>
<td>PRIME</td>
<td>Prospective study to develop a model to stratify the Risk of Medication related harm in hospitalized Elderly patients</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral Vascular Disease</td>
</tr>
<tr>
<td>RfPB</td>
<td>Research for Patient Benefit</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UPIN</td>
<td>Unique Patient Identifier Number</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VIF</td>
<td>Variance Inflation Factor</td>
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ABSTRACT
Reducing medication-related harm (MRH) is a World Health Organisation patient safety campaign, with transitions of care a focus. Medication-related harm includes adverse drug reactions, and harm from poor adherence and medication errors. The aim of my research was to investigate the epidemiology of MRH in older adults (≥65 years) following hospital discharge, and examine if this harm can be predicted. The thesis consists of six data chapters based on three studies. The first was a systematic review of studies internationally that investigated the incidence of MRH in older patients following hospital discharge. No studies had been conducted in the UK, and methodological heterogeneity of the included studies limited the scope to draw conclusions on the burden of MRH post-discharge. The second study was qualitative, involving semi-structured interviews and focus groups with a purposive sample of independent and housebound older adults. This research explored the lived experience and impact of MRH on patients, and risk factors from the patient perspective. Four predominant themes around patient experience of the healthcare system, practicalities of using medicines, management of medication problems and personal beliefs were identified. The third study was a multicentre, prospective cohort study of 1280 older patients discharged from five hospitals in England. This cohort was followed up for eight weeks to identify MRH and associated health service utilisation, using three data sources; hospital readmissions, patient interviews and primary care records. Out of 1116 patients that completed follow-up, 37% experienced MRH and half the cases were potentially preventable. High-risk medicine groups were opiates, antibiotics, and benzodiazepines. The cost to the National Health Service of healthcare use due to MRH was estimated at £396 million annually. An investigation of whether discharging doctors in hospitals could predict the occurrence of MRH showed no association between the prediction and outcome, irrespective of clinical experience. Using data from the PRIME study, a risk prediction tool was developed through a multivariable stepwise regression using Akaike’s Information Criterion. The tool was internally validated using a bootstrap resampling method and has a discrimination C-statistic of 0.66 with good calibration. The tool now requires external validation prior to clinical implementation.
CHAPTER 1.
Introduction
1.1 Statement of intent

The work I have performed, which is described in this thesis, explores the impact of medication-related harm (MRH) to older adults. This work focuses on the transition period around hospital discharge with patients using the National Health System (NHS) in England. In the broadest sense, I sought to investigate the extent of this harm and whether it can be predicted to reduce its burden.

1.2 Iatrogenic illness

In 1974, the Austrian philosopher Ivan Illich published his infamously damning Lancet article ‘Medical Nemesis’, opening with the assertion ‘Within the last decade medical professional practice has become a major threat to health’\(^1\).

Illich argued that the major advancements seen in the 20\(^{\text{th}}\) century in longevity and improved population health were at best only slightly attributable to medicine, and at worst not at all. This was a position shared by other eminent academics at the time \(^2\). However, Illich took his argument further and in 1976 wrote ‘A vast amount of contemporary clinical care is incidental to the curing of disease, but the damage done by medicine to the health of individuals and populations is very significant. These facts are obvious, well documented, and well repressed.’\(^3\)

The term ‘iatrogenic’ originates from the Greek ‘iatros’ (healer) and ‘genesis’ (origin). Iatrogenic illness refers to illness that is brought forth by a health professional. Ivan Illich defined clinical iatrogenesis as comprising ‘all clinical conditions for which remedies, physicians, or hospitals are the pathogens’ \(^1\). One of the first major international examples of iatrogenic injury due medication was the teratogenesis discovered as a result of widespread thalidomide use in 1960s to alleviate nausea in preganant women \(^4\). Over 10,000 children were born with phocomelia (malformation of their limbs) due to this adverse drug reaction (ADR). Whilst this stimulated rapid tightening in regulatory approval processes for new drugs, it was
not until the 1990s that the extent of iatrogenic harm within healthcare systems received attention as a major patient safety priority. The Harvard Medical Practice Study, published in 1991 in the New England Journal of Medicine, reviewed the medical records of over 30000 patients across 51 randomly selected hospitals in New York State, US\(^5\). The study found that 3.7% of patients experienced injury due to medical care, and the incidence was highest in those aged 65 years and older (5.7%)\(^5\). The most common adverse events were drug-related, accounting for 19.4% of all events of which one in seven led to serious disability. Those 65 years and older were at three times the risk of an adverse drug-related event compared with those aged 16 to 44 years. This work was then followed up by another major US study of 28 hospitals in Utah and Colorado which demonstrated the large financial costs of iatrogenic injury, also finding that drug-related events were a primary contributor\(^6,7\).

A study in England, published in 2001, confirmed that this public health problem was not isolated to the US. In this study patient records were reviewed from two large hospitals in London, England, found that 11% patients experienced iatrogenic injury. This was then followed up by a major prospective study looking specifically at ADR in England, involving almost 19000 adult patients over six months in two hospitals, which found that 6.5% of hospital admissions were caused by ADR\(^8\). The average age of patients admitted due to ADR was 76 years old, and over 70% of events were considered preventable. By the turn of the century, unquestionable evidence had been shown in the Western world of iatrogenic harm, of which medication-related harm (MRH) was the most common type. I will now consider how the use of medicines has changed over recent decades to create a situation where the balance of risk to benefit of many medicines is unclear.
1.3 Changing patterns of disease and medicine use

The discovery of penicillin in 1928 by Alexander Fleming, professor of bacteriology at St. Mary’s hospital in London, was a defining moment in the history of medicine. A medicine had been discovered that was curative of ill health. This was a life-saving treatment that alleviated pain, suffering and high-risk of death. People were symptomatically unwell when they were diagnosed with a disease, and were subsequently cured by medicine where a bacterial infection was the cause. Numbers needed to treat were equal to one i.e. one person treated, one person expected to be cured of disease. In 2018, the two most commonly used medicines in England are antihypertensive and lipid-lowering medicines9. High blood pressure and hypercholesterolemia are not diseases defined by patients feeling unwell and seeking healthcare, they are diseases defined by the medical profession with the best of intentions. Hypertension and hypercholesterolemia are important risk factors in the development of cardiovascular disease, as opposed to diseases in and of themselves. Only in the most extreme of cases would a patient seek medical attention for symptoms caused by hypertension or hypercholesterolemia. The pharmaceutical industry has by no means been a silent bystander in this re-defining of disease and expansion of the ‘disease’ taxonomy. The industry has flagrantly influenced the perception of the public and healthcare professionals as to what constitutes disease and the threshold at which pharmacological intervention should take place 10–12. Thus, we have seen the medical profession shift its role from treating disease to treating risk factors for disease12. In theory, this can be a sensible approach from a public health perspective; prevention of disease is more cost-effective than management of disease 13. However this shift to a population-based approach in the use of medicines, whilst perhaps cost-effective to healthcare systems, may be harmful to a majority of patients. For instance, the Blood Pressure Lowering Treatment Triallists’ Collaboration found that the number needed to treat with antihypertensive medication for five years to prevent one cardiovascular event ranged from 26 in a high-risk population (>21% five-year cardiovascular disease risk) up to 71 in a lower risk population (<11% five-year risk of cardiovascular disease)14.
This means that in a group of individuals at high risk of a cardiovascular event, 25 out of 26 individuals would need to use the drug daily with its inherent risk of side-effects for five years to prevent one individual from suffering. Of course, it must be borne in mind that these numbers are based on randomised controlled trials, where the recruitment of patients is often poorly representative of the ‘real world’ target population\textsuperscript{15–17}. Furthermore, in the real world patients do not take their medicines in controlled environments. Between 30% and 50% of patients have been shown in studies to poorly adhere to their medicines, and therefore the ‘numbers needed to treat’ in the real-world are likely to be less favourable.\textsuperscript{18–20}

So approaching half a century on from Ivan Illich’s radical indictment, growth in expenditure on medicines by the National Health Service (NHS) in England averages five percent a year totalling £17.4 billion in 2016/17\textsuperscript{21}. This represents a consumption of 14% of the total NHS budget of £122.5 billion for that year\textsuperscript{22}. In primary care, where most medicines are prescribed, the number of prescriptions for medicine increased by almost 50% to 1.1 billion items in the decade leading to 2016\textsuperscript{21}. The older population (65 years and older) in England consumes the largest number of medicines of any age group; only 1 in 13 older adults do not take regular medicine and 1 in 2 use five or more regular medicines\textsuperscript{23}. Compared with data from 20 years ago, this is a steep increase in the use of medicines. Just 1 in 10 older people used five or more regular medicines 20 years ago\textsuperscript{23}. Over a similar time (1990-2013) in England, there has been a marginal decline in morbidity alongside a substantially larger decline in premature mortality\textsuperscript{24}. This essentially means that more people in England are living longer with poor health in comparison with two decades ago.

As the number of medicines that people take increases, their risk of MRH inevitably increases. For instance, the risk of bleeding from the use of non-steroidal anti-inflammatory drugs (NSAID) increases 12-fold alongside corticosteroid use, 11-fold with spironolactone and 7-fold with Selective Serotonin Reuptake Inhibitors (SSRI)\textsuperscript{25}. Guthrie \textit{et al} (2015) conducted a population-based cross-sectional study of prescribed medicines in 1995 and again in 2010 within one region of Scotland. The
study sought to identify the changing nature of polypharmacy and the frequency of potentially serious drug-drug interactions between 1995 and 2010. Over these 15 years, the number of older adults prescribed 10 or more medicines tripled from 4.9% to 17.2% of the population. Over the same time, the proportion of older adults with at least one serious drug-drug interaction increased from 15.2% to 34.1% (figure 1.1).

Figure 1.1 Change in proportion of Tayside (Scotland) population with serious drug-drug interactions between 1995 and 2010, by age group.
The number of hospital admissions in England due to ADR has also been rising. Between 2009 and 2015 the number of hospital admissions in England attributable to ADR rose by 50% from approximately 60,000 to 90,000, based on International Classification of Diseases (ICD) Coding 27.

Based on the prevalence and preventability of ADR-related hospital admissions in England observed in the study by the Pirmohamed et al (2004), the National Institute for Health and Care Excellence (NICE) estimated in 2015 that the cost of preventable hospital admissions due to ADR in England was £530 million per year 28. As multimorbidity and polypharmacy become increasingly prevalent in England with a rapidly ageing population, it is highly likely that this burden of harm to patients and the NHS will increase unless urgent action is taken.

In 2017, the WHO announced their third global patient safety campaign ‘Medication without harm’. The two previous global patient safety campaigns ‘clean care is safer care’ and ‘safe surgery saves lives’ generated widespread political commitment and galvanised action from healthcare leaders to reduce patient harm from unclean healthcare environments and surgical errors. The fact that the WHO has committed their third global patient safety campaign to reducing serous, avoidable MRH by 50% by 2022 firmly places MRH on the agenda of national Governments. Now there is an obligation on researchers in the area to produce robust and current evidence of the burden of the problem in England and offer evidence-based solutions. To this effect, I hope that the work I have performed and described in this thesis, provides a valuable contribution to this call.

1.4 Defining medication-related harm

Medication-related harm (MRH) includes adverse drug reactions, and harm from poor medication adherence or medication error. Intentional medication overdose is excluded. This is a simple, patient-centered term that is useful to discuss the overall burden of harm to patients that is related to medication. It is the term operated by
the WHO for its global patient safety campaign. A crucial difference between medication-related problems and MRH is that the latter are events where patients have actually come to experiencing harm, whilst the former includes events that could potentially lead to harm.

Most prior research in the field of MRH has been specifically of ADRs, defined as a noxious and unintended consequence of using medication at therapeutic dose. This term has originated from the pharmacovigilance and regulatory sectors. However, its exclusion of MRH caused by poor adherence and medication error does not reflect the reality of patient experience or clinical practice. The term ‘Adverse Drug Event’ (ADE) has also been commonly used, and derives from the patient safety community, however the term has become rather less useful because a wide spectrum of definitions has been used within existing literature to denote this term. Therefore, whilst some definitions of this term might indeed be similar or synonymous with the MRH definition stated above, in other places the term does not include the harm arising from ADR, poor adherence and medication error.

1.5 Older adults are a high-risk population

The research presented in this thesis focuses on older adults aged 65 years or above. The older population is at greatest risk of experiencing MRH for multiple reasons. First and foremost, they are the largest consumers of medication globally. The European Health Interview Survey conducted between 2006-2010 found that the proportion of people using prescribed medication increases with age and peaks in the oldest age groups. In the age group of 85 and older, between 72% and 95% of people take a prescribed medication. In England, just 1 in every 13 older adults do not have regular medication and half of older adults use five or more regular medicines.

A meta-analysis highlighted that the proportion of hospital admissions due to ADR was four times higher in older adults aged 65 years plus (16.6%) compared to those
younger than 65 years (4.1%)\textsuperscript{40}. This increased vulnerability of the older population is multifactorial, and beyond polypharmacy includes multimorbidity\textsuperscript{16,41,42}, poor adherence\textsuperscript{43,44}, and age-related changes in physiology, pharmacokinetics and pharmacodynamics\textsuperscript{45,46}. In addition to this, the evidence for safety of medicines is often limited due to the common exclusion of older people, particularly those with multimorbidity, from clinical trials\textsuperscript{47,48}. Table 1.1 and table 1.2 below highlight some key changes in pharmacokinetics and pharmacodynamics that increase the susceptibility of the older person to MRH.

Table 1.1 Selected examples of changes in pharmacokinetics with ageing\textsuperscript{46}

<table>
<thead>
<tr>
<th>Pharmacokinetics</th>
<th>Effect of ageing</th>
<th>Medication examples</th>
<th>Examples of adverse clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Absorption</td>
<td>slower gastric emptying and increased gastric pH</td>
<td>Vitamin B12, iron, calcium, levodopa</td>
<td>Anaemia, constipation</td>
</tr>
<tr>
<td>Drug Distribution</td>
<td>Relative increase in total body fat:total body water ratio. Decrease in serum albumin</td>
<td>Benzodiazepines, lithium, warfarin, gentamicin, digoxin</td>
<td>Drowsiness, cardiac arrhythmia, bleeding</td>
</tr>
<tr>
<td>Reducd hepatic metabolism</td>
<td>Reduced hepatic mass and blood flow. First-pass metabolism reduced</td>
<td>Morphine, paracetamol, amitriptyline propanol, perindopril, Glyceryl trinitrate</td>
<td>Drowsiness, confusion, constipation, blood pressure instability</td>
</tr>
<tr>
<td>Reduced renal excretion</td>
<td>Reduced glomerular filtration rate</td>
<td>Digoxin, morphine, gentamicin, NSAIDs, lithium, furosemide</td>
<td>Confusion, acute kidney injury, nausea and vomiting, gastritis</td>
</tr>
</tbody>
</table>
Table 1.2 Selected examples of age-related changes in pharmacodynamics of commonly used medicines

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on body</th>
<th>Age-related activity change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Sedation</td>
<td>Increased</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Blood pressure lowering</td>
<td>Increased</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Peak diuresis</td>
<td>Reduced</td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesia</td>
<td>Increased</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Anticoagulation</td>
<td>Increased</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Blood pressure lowering</td>
<td>Increased</td>
</tr>
</tbody>
</table>

1.6 Transitions of care are a high-risk time

Transitions between care settings was highlighted as a key cause of iatrogenic patient harm that warrants further research by the WHO safer primary care expert working group in 2013\textsuperscript{49}. In 2017, the WHO identified transitions of care as one of three priority areas in its global campaign to reduce MRH \textsuperscript{29} The most common transitions of care for patients are admission and discharge from the hospital setting. In the 2016/17 financial year, there were 16.5 million hospital admissions in NHS hospitals in England \textsuperscript{50}. The coordination of care to ensure safety and continuity is highly complex, and requires patient activation, standardising information communication between providers, through to commissioning responsibility within healthcare systems for the provision of transitional care \textsuperscript{51}. For patients, especially the older population, transitions of care represent a period of vulnerability where adverse incidents relating to information exchange, community support service provision and drug regimen are common \textsuperscript{52}.

There are patient and provider (healthcare system) factors that generate increased risk of adverse events in the transition back into the community following hospital discharge. At the point of discharge, many patients are still continuing their recovery from being acutely unwell, they may be malnourished, sleep deprived, and have sustained muscle loss and functional loss in a period of institutionalisation \textsuperscript{53}. Furthermore it is highly likely they will have had multiple medication changes\textsuperscript{54}, and
might have poor understanding of their post-discharge care and medication management\textsuperscript{54,55}. A retrospective review of a sample of general practice patient safety reports, associated with hospital discharge, and, submitted to the National Reporting and Learning System (NRLS) in the UK found that 16\% of reports were medication-related incidents. It was further noted that 87\% of these incidents caused harm to patients.

1.7 National policy landscape around medication-related harm

There is a policy drive in England and the rest of the United Kingdom to optimise medication use and reduce MRH. Guidance and reports within the last decade from NICE, the Royal Pharmaceutical Society and major think-tanks such as the King’s Fund have generated attention to a national medicines optimization agenda\textsuperscript{20,30,56–59}. In 2015, through NHS England, the Department for Health and Social Care in England launched a £30 million pilot project to integrate almost 500 clinical pharmacists into General Practice to optimize medicines use including cost-effectiveness and safety in the community\textsuperscript{60}. In 2017, following a successful pilot evaluation\textsuperscript{61,62}, the Government committed to a further £112 million to integrate an additional 2000 pharmacists into General Practice. This would enable a coverage of 40\% of GP surgeries in England. Four Regional Medicines Optimisation Committees were set up in NHS England in 2017 to integrate decision makers and clinicians from the local, regional and national level to provide expert, unified advice and make recommendations to Government for the optimal use of medicines for patients and the NHS. They will operate within an established framework of medicines optimization, which includes the patient experience, evidence base for medicines, safety of medicines use and routine implementation of medicines optimization into healthcare processes (figure 1.2).
Involving patients more closely in healthcare related decisions and supporting this process by improving population health literacy is recognized nationally\textsuperscript{63,64}. At a legislative level, the UK Government has enshrined a duty on healthcare providers in the NHS through the Health and Social Care Act 2012 to involve patients and the public in planning, managing and making decisions about healthcare \textsuperscript{65}. Most recently, in late 2017 the Department for Health and Social Care established a Short Life Working Group on reducing MRH which reported its findings in February 2018. This group was specifically established to act on the WHO’s launch of their ‘Medication without Harm’ global patient safety campaign. This group provided advice directly to Government of a programme of work that was required to improve medication safety. A brief extract from the executive summary of this report is copied below as it ideally frames the importance of the work that I will describe in this thesis\textsuperscript{66}.
“Technology will also play an important part in better shared decision-making, so that patients and carers are encouraged to ask questions about their medications. By improving the information available to patients, it will promote joint decision-making and healthy challenge between patients and health care professionals. With patients and carers playing a more active role in their medication management, we will move towards an environment in which they are their own safety advocate...

Cultural change within health care systems must also occur in order to deliver the best results for patients. Health care professionals should work closely together across all areas, in order to not only address the significant issue of over medication, which can lead to medication safety issues, but improve shared care with more comprehensive knowledge and support. Professional regulation in parallel to this will help adequate training in safe and effective medicines use be embedded in undergraduate training, as well as continuing professional development.”
Chapter 2: A systematic review of existing studies to identify what is already known of the epidemiology of MHI post-discharge in older adults.

Chapter 3: A qualitative study to explore the lived experience of older adults with MHI and their older persons' perspective on risk factors.

Chapter 4: Methods of the multicentre prospective cohort primary study to investigate post-discharge MHI. Data from this observational study informs the


Chapter 6: Analyses of health service utilisation as a result of MHI and the subsequent costs to the NHS. Costs are extrapolated to estimate the economic impact of MHI post-discharge in England. Risk factors for MHI are examined.

Chapter 7: This study investigates whether the clinical judgement of discharging hospital doctors is sufficient to predict MHI requiring healthcare use following hospital discharge. A quantitative analysis of the accuracy of the doctors' decision for discharge is important in influencing the risk of MHI.

Chapter 8: This chapter reports the development and external validation of a risk prediction tool to identify older patients at high risk of experiencing MHI that will require healthcare use post-discharge.

Figure 1.3: A flow chart to provide an overview of the data chapters of this thesis.
CHAPTER 2.
The epidemiology of medication-related harm in older adults following hospital discharge: A systematic review
Chapter Summary

This chapter systematically explores the existing literature body on medication-related harm experienced by older adults following discharge from hospital. A systematic review was conducted to assess the incidence, severity, preventability and risk factors for medication-related harm (MRH) in community-dwelling older adults following hospital discharge. The search included four major databases; MEDLINE, Embase, CINAHL, and the Cochrane Library. The search was undertaken without time restrictions to identify all published studies on this topic. Eligible studies included observational studies investigating adverse drug reactions (ADR) or adverse drug events (ADE) in older adults (average age ≥65 years) following hospital discharge within a defined follow-up period. The abstracts of 584 identified articles were initially screened to exclude obviously irrelevant articles. The remaining articles were read in full to determine their eligibility for inclusion. Eight studies met the inclusion criteria; five North American and three European. Data extraction included study characteristics, MRH incidence and risk factors. The Joanna Briggs Institute critical appraisal tool for prevalence studies was used to examine the quality of the included studies. Most of the included studies were of moderate quality. There was a wide range in MRH incidence, from 0.4% to 51.2% of patients, and 35% to 59% of MRH was preventable. The MRH incidence within 30 days post-discharge ranged from 167 to 500 events per 1000 patients discharged (17-51% of patients). Substantial methodological heterogeneity was found across multiple domains of the studies, including ADR and ADE definitions, characteristics of recruited populations, the follow-up duration post-discharge, and data collection. The study reported in this chapter found that medication-related harm is a common problem following hospital discharge in older adults. However, a clear understanding of the epidemiology is hampered by methodological inconsistencies between studies, the modest overall quality of the literature pool, and a paucity of data on risk factors.
2.1 Introduction

In Chapter 1 the importance of investigating the epidemiology of MRH during the time of transition from hospital to home was outlined. This period is one that has ample opportunity for the development of MRH due to biological and structural factors related to the health system. Biologically, during hospitalisation patients are often poorly nourished, have sleep deprivation and experience muscle wasting from inactivity. The practical tasks that patients encounter in the home-setting, for instance taking their medicine, preparing meals, and often washing, are managed for the patient by healthcare professionals. A process of institutionalization occurs.\(^{53}\) This deconditioning from hospital admission with an ongoing recovery from illness in the immediate post-discharge setting\(^{53}\) increases the vulnerability of patients to adverse post-discharge outcomes. The average length of hospital stay of older patients in the UK has been decreasing (12.9 days in 2010/11 to 11.9 days in 2014/15)\(^{67}\), which could reflect improved discharge efficiency. However, older patients and carers indicate that they are being discharged from hospital before they are fully recovered\(^{68,69}\). There are important structural factors that may lead to confusion and inaccuracies in medicines management at hospital discharge. Medication discrepancies affect up to one in two older patients around hospital discharge\(^ {70}\), and patients often encounter administrative difficulties receiving medicines and insufficient education of medicines use\(^ {71}\) (figure 2.1). Whilst patients may receive some information at the point of discharge regarding their medicines in the hospital setting, there are often competing concerns that patients are faced with at the point of discharge (e.g. support at home, transport, food shopping, personal belongings brought into hospital, finances etc.). These issues could reduce patients’ receptiveness to complex medicines-related information.
Problems with coordination following hospital discharge between secondary care, primary care, and patients and carers, are common. Based on four studies from the US and Australia, a systematic review showed that between 5% and 38% of discharge summaries are never received by primary care doctors. The quality of information communicated can additionally be a cause of confusion and medication reconciliation errors; the same systematic review found that 40% of discharge summaries failed to provide diagnostic test results, 75% provided no information on pending investigations, 22% lacked information on discharge medicines and in 58% there was no communication of follow-up plans.

Reducing MRH by 50% over the next five years is the World Health Organisation’s third global patient safety challenge, and transitions of care are highlighted as a priority area to address.
Medication-related harm is often described in terms of (1) adverse drug reactions (ADR), where patients experience a noxious and unintended reaction caused by a medicine at appropriate dosage, or, (2) adverse drug events (ADE) which includes an ADR or an injury related to medicine use at inappropriate dosage (e.g. a medical error)⁴⁵,⁴⁶,⁷³–⁷⁵. In this chapter, ADR and ADE are discussed as ‘medication-related harm’ (MRH), in accordance with recent World Health Organisation (WHO) terminology²⁹.

The last review of medication problems experienced by older adults around hospital discharge was conducted a decade ago⁷⁶. Fourteen studies of medication problems in community and care home settings, including medication discrepancies, education, non-adherence, drug interactions and MRH, were included. The authors of this review could not estimate the magnitude of MRH or medication-related problems more generally due to study heterogeneity. Over recent years, despite no systematic quantification of the problem, there have been numerous interventional studies to reduce MRH in the post-discharge period ⁷⁷,⁷⁸. One example is the UK Government’s multimillion pound investment in pharmacists working in primary care⁶⁰.

In this chapter, I report a systematic review I conducted to investigate the epidemiology of MRH, in contrast to all medication problems (which may or may not manifest in patient harm).

The aims of this chapter are to use my systematic review of existing literature to

1. Assess the incidence of MRH in community-dwelling older adults following hospital discharge.
2. Assess the severity and preventability of MRH in this context
3. Identify risk factors for MRH in this context
2.2 Methods

The methods for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance in conjunction with the Joanna Briggs Institute methodological guidance for systematic reviews of observational epidemiological studies79.

2.2.1 Search strategy

A literature search was conducted electronically using four mainstream healthcare databases; MEDLINE, Embase, CINAHL, and the Cochrane Library (Table 2.1). The search was initially conducted in June 2016 without time or language restrictions. The search was re-run in June 2017 to look for any new studies. The search strategy was designed in MEDLINE (using the Healthcare Databases Advanced Search from the National Institute of Health and Care Excellence) using a combination of key words and Medical Subject Headings (MeSH). The search strategy was subsequently adapted for Embase and CINAHL. Core concepts in the search strategy were ‘adverse drug reaction’, ‘elderly’ and ‘hospital discharge’. For each of these, synonyms, related terms and controlled vocabulary terms were selected and combined using Boolean and proximity operators, and truncation, to ensure alternative forms were retrieved. Furthermore, reference lists of relevant articles were scanned to identify any articles that may not have been identified by the electronic search. In addition, studies that were included in a review on medication-related problems post-discharge published in 201076 were read and forward citation searches were conducted on this prior review and on studies that we identified for inclusion. Finally, the authors of the included studies were contacted to ensure that all relevant studies had been located. Correspondence was successful with investigators of four included studies to ensure no important research was missed from this systematic review.
### Table 2.1 Search Strategy designed in MEDLINE and adapted to other databases

<table>
<thead>
<tr>
<th>#</th>
<th>Search term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>exp *DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS/ep</td>
</tr>
<tr>
<td>2</td>
<td>((drug* OR medication* OR medicine*) ADJ2 adverse) ADJ2 (effect* OR reaction* OR event* OR problem*).ti,ab</td>
</tr>
<tr>
<td>3</td>
<td>((drug* OR medication*) ADJ2 (toxicity OR cardiotoxicity OR hepatotoxicity)).ti,ab</td>
</tr>
<tr>
<td>4</td>
<td>(1 OR 2 OR 3)</td>
</tr>
<tr>
<td>5</td>
<td>exp AGED/</td>
</tr>
<tr>
<td>6</td>
<td>(elder* OR old OR older OR geriatr* OR gerontol* OR aging OR ageing OR senior* OR retiree* OR retired OR &quot;late* life&quot;).ti,ab</td>
</tr>
<tr>
<td>7</td>
<td>(5 OR 6)</td>
</tr>
<tr>
<td>8</td>
<td>*PATIENT DISCHARGE/</td>
</tr>
<tr>
<td>9</td>
<td>((patient* OR hospital* OR clinic* OR unit*) ADJ3 discharg*).ti,ab</td>
</tr>
<tr>
<td>10</td>
<td>(8 OR 9)</td>
</tr>
<tr>
<td>11</td>
<td>(4 AND 7 AND 10)</td>
</tr>
</tbody>
</table>

#### 2.2.2 Selection criteria

Studies were eligible for inclusion if they were:

1. published observational studies that evaluated MRH (specified as adverse drug reactions or adverse drug events)
2. the study population was community-dwelling older adults (average age of 65 years or older)
3. the study clearly defined a follow-up period after hospital discharge.
4. the incidence or prevalence of MRH was reported or could be calculated from the presented data.

Because the objective was to establish the extent of MRH in the general older population discharged from hospital, the following exclusion criteria were employed;

1. studies investigating only re-hospitalized patients,
2. studies only investigating patients with a specific disease, condition, or harms of one specific medication type,
3. studies recruiting solely institutionalized older adults e.g. patients admitted from care homes.

Studies investigating only re-hospitalised patients were excluded as this does not give an indication of the real burden of MRH in the community following discharge. Many patients will not seek healthcare, and many others will seek primary care only. Hospitalised patients represent the ‘tip of the iceberg’.

Studies that focussed on single diseases or medications were excluded. The challenges of applying single-disease frameworks to the complex, multimorbid older population with polypharmacy (especially those that have been hospitalised), are well-recognised. This systematic review’s interest was in establishing MRH in the general older population that clinicians discharge from hospital. The general older population has multimorbidity and polypharmacy; 80% of adults aged 80 years or above have multimorbidity. In addition, interventions to reduce MRH tend to be designed for the broad older population at risk rather than specifically targeting MRH in the context of one disease or drug.

Studies that only included patients that were admitted from an institutional setting were excluded. Community-dwelling older adults were chosen as the population of interest, because the objective of the review was to determine the incidence of medication harm post-discharge in the general older population. Data from the UK
Office for National Statistics\(^{83}\) and US Population Reference Bureau\(^{84}\) indicate that approximately 3% of adults over the age of 65 years live in care homes. The collation of data from institutionalised and non-institutionalised populations together would introduce excessive heterogeneity to the review. The average population characteristics, risk factors for, and support mechanisms against, adverse events in institutionalised and non-institutionalised populations are significantly different; care home residents are supervised with medicines supply and administration, they are frailer\(^{85}\), prescribed a higher total number of medicines\(^{26,86}\) and higher prevalence of inappropriate medicines\(^{87,88}\). For example, Boockvar et al (2004)\(^{89}\) investigated adverse events from medication changes post-discharge in a care home population, and found that 67% were totally dependent for ADLs and 52% has moderate or severe cognitive impairment.

### 2.2.3 Outcomes

The primary measure of interest was the incidence of MRH post-discharge. Secondary outcomes included the proportion of serious MRH events, preventable MRH events, and associated risk factors for MRH.

### 2.2.4 Study selection

The titles and abstracts of identified articles were screened by the primary researcher (myself) to exclude obviously irrelevant articles (n=338). The remaining papers (n=215) were independently screened by two researchers (myself and a research pharmacist, Dr Amy Page), excluding review articles, protocol papers, interventional studies, published conference abstracts, research letters and those articles not investigating the post-discharge period, or, those specifically about one medication type or condition. Two same two researchers independently reviewed full-text articles of potentially eligible titles and abstracts, and selected studies according to the inclusion criteria. These studies were then reviewed by a third researcher (Dr Khalid Ali, lead supervisor) to confirm their eligibility for inclusion. Any disagreement was resolved through discussion.
2.2.5 Data extraction

Data extraction was performed independently by two researchers (myself and Dr Amy Page) onto a standard data collection form (see appendix 1), and verified by a third reviewer (Dr Khalid Ali). We extracted the following data from included articles: study year and country, study design, discharge setting, duration of follow-up, methods used for data collection and causality assessment, ADE and ADR incidence or prevalence, severity, preventability, and, associated risk factors.

2.2.6 Quality assessment

Two researchers (myself and Dr Amy Page) independently assessed the quality of included studies using the Joanna Briggs Institute critical appraisal tool for prevalence studies 79. The nine domains in this tool address sampling bias (target population, sampling, sample size, description of participants and setting), coverage bias (coverage of identified sample), measurement bias (methods to identify outcome, reliability in outcome measurement, appropriate statistical analysis), and, non-response bias (response rate). Where any disagreements arose, these were resolved through discussion. A risk of bias figure was completed for included studies using RevMan Version 5.3.

2.2.7 Data synthesis

The incidence proportions of MRH stated in the included studies are reported. In studies where this was not clearly stated, the incidence proportion was calculated from the available data (number of persons that developed MRH / total population at risk). Where the number of events within the population was stated, the incidence of events per 1000 discharges was additionally calculated. Incidence rates (where follow-up time is incorporated into the denominator) are not reported as this could be misleading, given that the risk of MRH following hospital discharge is not constant over time. Data was extracted on the medicine classes commonly implicated in MRH. If this was reported in an alternative format e.g. mixture of
medicine classes and specific medicines themselves, we categorised the medicines using the WHO Anatomical Therapeutics Coding system\(^9\).

### 2.3 Results

#### 2.3.1 Study Selection

The systematic search strategy initially retrieved 794 results. Out of 794 results, 210 were excluded because they were duplicates. Of the remaining 584 results, 338 results were obviously irrelevant to the objectives of this systematic review based on their titles and abstract (e.g. five such articles were titled (1) ‘Sustained Hypotension Following Intravenous Metoclopramide’, (2) ‘Update on rheumatology: part 1.’, (3) ‘Is seizure prophylaxis really necessary in patients with traumatic brain injury?’, (4) ‘Mapping patients' experiences after stroke onto a patient-focused intervention framework’, (5) ‘Preferred propofol possibly problematic?’). The remaining titles and abstracts (n=246) were reviewed independently by two researchers (myself and Dr Amy Page), out of which 79 results were identified as review articles, interventional studies, conference abstracts, protocols, and research letters. A further 67 studies were excluded due to investigating a specific medication type or medical condition rather than MRH in the older general patients discharged from hospital, and 69 articles excluded as they were not investigating the post-discharge period e.g. inpatient studies etc. The remaining 31 articles were taken forward for full-text review. From these studies, following full-text review, 24 articles were excluded as they did not meet all the inclusion criteria. Therefore, seven studies were included that met our inclusion criteria directly from the systematic search and one additional study was identified for inclusion from the references of an included article (full PRISMA flow diagram can be seen in figure 2.2).
Figure 2.2 PRISMA flow diagram

Records identified through databases searching (n = 794)

Records screened after duplicates removed (n = 584)

Records excluded due to irrelevance of title and abstract (n = 338); review paper, interventional study, conference proceedings, research letters, protocol paper (n = 79); article related to specific medicine or condition (n = 67); study not investigating period post-hospital discharge (n = 69)

Full-text articles assessed for eligibility (n = 31)

Full-text articles excluded due to focus on medication issues other than MRH i.e. polypharmacy (n = 3), inappropriate prescribing (n = 3), medication discrepancies (n = 3), patient knowledge (n = 1), risk factors (n = 1); average participant age < 65 (n = 6); hospital-based study (n = 4); alternative analysis of included article (n = 1); not specific to post-discharge period (n = 2)

Additional records identified through other source (n = 1)

Studies included for systematic synthesis (n = 8)
2.3.2 Key study characteristics

The main characteristics of the eight included studies are outlined in table 2.2 and table 2.3. Out of the eight included papers, five studies were conducted in North America\(^{91-95}\), and three studies were conducted in Europe (Netherlands\(^{96}\), Croatia\(^{97}\), and France\(^{98}\)). The included studies were cohort studies (prospective, \(n=5^{91-93,96,97}\), retrospective, \(n=2^{94,95}\)), with the exception of one that was a prospective population-based study in France\(^{98}\). The total number of participants in the studies ranged from 209\(^{97}\) to 7540\(^{98}\), and the average age of participants from 67.7\(^{95}\) to 80.0 years old\(^{93}\).
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Country</th>
<th>Study design</th>
<th>Recruitment setting</th>
<th>Follow up duration (days)</th>
<th>Patients (number)</th>
<th>Average age (Mean, SD or Median, range)</th>
<th>Population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westberg (2017)</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>Three hospitals. Wards not reported</td>
<td>30</td>
<td>408</td>
<td>67.7 (SD 13.8)</td>
<td>Patients had been pre-selected based on risk profile as requiring medication review in the community. Key exclusions: palliative or neoplasm as primary diagnosis</td>
</tr>
<tr>
<td>Ahmad (2014)</td>
<td>Netherlands</td>
<td>Prospective cohort</td>
<td>Eight urban hospitals. All wards except psychiatry and oncology</td>
<td>14</td>
<td>340</td>
<td>76 (range 60-95)</td>
<td>Key exclusions: Patients using less than five long-term medicines; psychiatry or oncology patients; nursing home patients.</td>
</tr>
<tr>
<td>Marusic (2014)</td>
<td>Croatia</td>
<td>Prospective cohort</td>
<td>One hospital, one general medical ward</td>
<td>30</td>
<td>209</td>
<td>74 (range 65-89)</td>
<td>Key exclusions: impaired cognition, terminal illness, inability to be followed-up</td>
</tr>
<tr>
<td>Kanaan (2013)</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>One hospital. All wards, except psychiatry</td>
<td>45</td>
<td>1000</td>
<td>78.8 (SD 7.1)</td>
<td>Key exclusions: Psychiatric patients; discharged to care home</td>
</tr>
<tr>
<td>Hanlon (2006)</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>Eleven veterans-affairs hospitals. Medical or surgical wards.</td>
<td>365</td>
<td>808</td>
<td>Not reported. Age categories reported as 53.6% 65-74 years, 46.4% 75 years or over</td>
<td>Key exclusions: nursing home, previously had geriatric specialist input in community or hospital, disabling or terminal disease, severe dementia, unable to come to follow-up clinic visits.</td>
</tr>
<tr>
<td>Forster (2004)</td>
<td>Canada</td>
<td>Prospective cohort</td>
<td>One hospital. Medical wards.</td>
<td>30</td>
<td>328</td>
<td>71 (IQR 54-81)</td>
<td>Key exclusions: none reported</td>
</tr>
<tr>
<td>Letrilliart (2001)</td>
<td>France</td>
<td>Prospective national wide</td>
<td>All hospitals serving 305 general practices across France. All wards</td>
<td>30</td>
<td>7540</td>
<td>69 (range not reported)</td>
<td>Patients referred to hospital by participating general practices and then re-consulted within 30 days of hospital discharge. Key exclusions: none reported</td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>One hospital. Wards not reported.</td>
<td>30</td>
<td>312</td>
<td>80 (SD 7.3)</td>
<td>Patients receiving home nursing care. Key exclusions: terminally ill, recent MI or CVA, dementia without caregiver at home, non-ambulatory</td>
</tr>
</tbody>
</table>

Definitions: Medication-related harm (MRH), Adverse Drug Reaction (ADR), Adverse Drug Event (ADE), General Practitioner (GP), Standard Deviation (SD), Interquartile range (IQR). Note that MRH was a sub-category of adverse events in Forster (2004), and a sub-category of drug-related problems in Westberg (2017) and Ahmad (2014).
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Study aim</th>
<th>Definition of MRH</th>
<th>Causality assessment</th>
<th>Data collection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westberg (2017)</td>
<td>To describe the number, classification, and severity of drug therapy problems post-discharge</td>
<td>ADR comprised unsafe drug for patient, allergic reaction, contraindication, incorrect administration, clinically relevant drug interaction, undesirable effect</td>
<td>Not reported</td>
<td>Pharmacist initially documents drug-related problem during community medication review and then 3 clinician investigators evaluated the record to attribute clinical significance and likelihood of harm.</td>
</tr>
<tr>
<td>Ahmad (2014)</td>
<td>To investigate the occurrence of MRP in discharged patients</td>
<td>ADE. Definition not reported</td>
<td>Two clinical pharmacologists reviewed information from patient interviews, hospital discharge prescriptions and pharmacy information systems</td>
<td>Semi-structured patient interview by pharmacist technicians.</td>
</tr>
<tr>
<td>Marusic (2014)</td>
<td>To evaluate the incidence of ADRs in elderly patients following discharge from an internal medicine clinic</td>
<td>ADR is one that is noxious, unintended and occurs at a dose normally used in humans</td>
<td>Independent physician review using Naranjo Algorithm.</td>
<td>Follow-up interview and medical examination 30 days post-discharge where physician with clinical pharmacology expertise determined ADR.</td>
</tr>
<tr>
<td>Kanaan (2013)</td>
<td>Characterise ADR occurring during post hospitalisation period in older adults</td>
<td>ADE defined as an injury resulting from a drug, rather than an underlying disease. An ADE can be related to an error or an ADR without an error.</td>
<td>Physician-reviewers considered the sequential relation of drug exposure and event, and whether event was a known potential side-effect</td>
<td>Primary and secondary care medical record review by pharmacists</td>
</tr>
<tr>
<td>Hanlon (2006)</td>
<td>To examine the incidence of ADRs in frail elderly persons after hospital discharge</td>
<td>ADR is one that is noxious, unintended and occurs at a dose normally used in humans*</td>
<td>Blinded physician/pharmacist reviewer pairs evaluated the ADR narratives using the Naranjo algorithm.</td>
<td>Chart reviews by research nurse and telephone interview by research pharmacist for patient self-report of ADR.</td>
</tr>
<tr>
<td>Forster (2004)</td>
<td>To determine the risk, severity and type of adverse events after discharge</td>
<td>ADE are the subset of adverse events caused by medications - adverse events are adverse outcomes caused by medical care as opposed to the underlying disease process*</td>
<td>Two physicians reviewed each outcome and determined probability of causality by clinical judgement</td>
<td>Telephone interview with patient by nurse or physician and chart review if readmitted to same hospital</td>
</tr>
<tr>
<td>Letrilliart (2001)</td>
<td>To estimate the incidence of post-discharge ADR detected in primary care</td>
<td>ADR is noxious, unintended and occurs at a dose normally used in humans, but also includes harm occurring from discontinuation of a necessary drug during hospital stay</td>
<td>Combination of medical literature, physician expert judgement and published French algorithm</td>
<td>Teleinformatic data transfer from GP to central information centre based on a standardised protocol</td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>To describe the incidence of ADEs post-discharge in elderly patients receiving home health services</td>
<td>ADE. Definition not reported</td>
<td>Naranjo algorithm</td>
<td>Semi-structured patient interview by trained interviewers</td>
</tr>
</tbody>
</table>

*Definitions retrieved from contact with original investigators
2.3.3 Participant recruitment

The recruitment setting varied amongst the included studies, with most recruiting from general medical wards, whilst others included patients from surgical wards or specified all wards. Studies generally excluded patients admitted to psychiatric units, patients discharged to a nursing home, and patients with a terminal diagnosis. One study, however, exclusively recruited patients discharged to receive nursing care within the patient’s home setting. Patients with dementia were excluded from three studies; one study excluded all patients with dementia, one excluded only those patients with severe dementia and another study excluded patients with dementia and no home carer. The criteria used for the diagnosis and severity of dementia was not reported in any of the studies.

2.3.4 Participant follow-up

The follow-up period following hospital discharge was 30 days in five studies, whilst the shortest follow-up was two weeks and the longest one year. Four of the included studies recruited patients from more than one hospital. A nationwide study of post-discharge ADR from France recruited patients referred to hospital for all causes by their GP, and then followed up only the subset of patients that re-consulted their GP within 30 days of discharge.

2.3.5 Definition of MRH

The definitions of ADR and ADE varied considerably between studies. A definition proposed by the World Health Organisation for ADR was operated in two studies, and one study used a slight modification to additionally include MRH from therapy discontinuation. In another study a range of medication problems were classified as constituting an ADR including ‘unsafe drug for patient, allergic reaction, contraindication present, incorrect administration, clinically relevant drug interaction, undesirable effect’. Whilst two of the included studies reported ADEs based on a very similar definition, one of these studies included harm
experienced by patients from non-adherence to medicine. Two studies failed to report an explicit definition of MRH.

2.3.6 Data collection

Data collection on MRH took place most commonly through medical chart reviews and in six studies this was combined with patient interview; by telephone, in-person, and with one study the interview included a physical examination of patients.

Data collection was performed by a wide range of healthcare professionals between studies, including community-based pharmacy technicians, clinical pharmacists, GPs and physicians with expertise in clinical pharmacology.

2.3.7 Assessment of causality

Attributing causality to a medicine when a potential adverse event has taken place is important to distinguish between symptoms that may be due to underlying disease and those due to the use of a specific medicine (or combination of medicines). Half of the included studies reported use of a tool to attribute causality to a medicine. Three studies reported use of the validated Naranjo algorithm, and one study reported using an algorithm designed by French experts in pharmacovigilance.

2.3.8 Critical Appraisal

The critical appraisal of each included study is shown in table 2.4 below and an overall summary can be seen in figure 2.3. Overall, the literature base was of moderate quality. In five out of eight studies the sample frame (i.e. recruited cohorts to investigate the target population) was associated with a high risk of bias. Quality indices that were assessed as having a low risk of bias included the sample size, sampling method, and the methods used to identify MRH.
Table 2.4 Critical Appraisal of included studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate sample frame to address target population?</td>
<td>NO. High risk older adults selected for medicines review and eligibility changed during study and between recruitment sites</td>
<td>YES. All patients discharged over a 3 month period</td>
<td>NO. Participants recruited if on &gt;4 medications and half of participants discharged from cardiology unit.</td>
<td>YES. Consecutive discharges over 5 month period</td>
</tr>
<tr>
<td>Appropriate sampling of study participants</td>
<td>YES. random sample of records</td>
<td>YES. All patients discharged over a 3 month period</td>
<td>YES. All eligible patients were invited</td>
<td>YES. Consecutive discharges over 5 month period</td>
</tr>
<tr>
<td>Adequate sample size</td>
<td>YES. n=408</td>
<td>YES. n=209</td>
<td>YES. n=340</td>
<td>YES. n=1000</td>
</tr>
<tr>
<td>Study subjects and setting described in detail</td>
<td>YES. Full description in Appendix C of article</td>
<td>YES. Full description in Table 1 of article</td>
<td>YES. Full description in Table 2 and methods of article</td>
<td>NO. Insufficient detail of study participants</td>
</tr>
<tr>
<td>Data analysis conducted with sufficient coverage of the identified sample</td>
<td>YES. Retrospective</td>
<td>YES. No loss to follow up</td>
<td>UNCLEAR. Not enough detail about non-responders, only age and gender described</td>
<td>YES. Retrospective</td>
</tr>
<tr>
<td>Valid methods used for the identification of MRH</td>
<td>NO. Checklist not validated, and no causality assessment</td>
<td>YES. Naranjo algorithm</td>
<td>YES. Validated checklist used</td>
<td>YES. Three physician reviewers used structured review process described in prior studies</td>
</tr>
<tr>
<td>MRH measured in a standard, reliable way for all participants</td>
<td>YES. Training given to reviewers and consistent reviewers used</td>
<td>YES. One physician with clinical pharmacology training</td>
<td>NO. Sub-analysis of randomised trial where interventional pharmacists received additional training on medication review (detailed in study’s protocol paper)</td>
<td>YES. Inter-rater reliability for ADE assessment. kappa statistic = 0.63</td>
</tr>
<tr>
<td>Appropriate statistical analysis</td>
<td>NO. Number of people experiencing MRH not reported</td>
<td>YES. Clear information on MRH events and people in numerator and denominator</td>
<td>YES. Clear information on events and people in numerator and denominator</td>
<td>YES. Clear information on events and people in numerator and denominator</td>
</tr>
<tr>
<td>Response rate adequate</td>
<td>N/A. Retrospective</td>
<td>YES. No dropout</td>
<td>UNCLEAR. 69.5%</td>
<td>N/A. Retrospective</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Appropriate sample frame to address target population?</strong></td>
<td>NO. Discharge from veteran affairs hospital, 98% male</td>
<td>YES. Patients discharged home or to residential living</td>
<td>NO. Only included patients referred to hospital by GP</td>
<td>NO. Older people receiving home care. Patients with cerebrovascular or myocardial event in last two months excluded</td>
</tr>
<tr>
<td><strong>Appropriate sampling of study participants</strong></td>
<td>NO. Random sample of cohort recruited to a randomised trial of specialised geriatric care. Rate of adverse events is skewed by intervention</td>
<td>YES. Consecutive discharges</td>
<td>YES. GP referrals to hospital</td>
<td>YES. Tried to contact all eligible participants</td>
</tr>
<tr>
<td><strong>Adequate sample size</strong></td>
<td>YES. n=808</td>
<td>YES. n=328</td>
<td>YES. n=7540</td>
<td>YES. n=256</td>
</tr>
<tr>
<td><strong>Study subjects and setting described in detail</strong></td>
<td>YES. Full description in Table 1 of article</td>
<td>YES. Full description in Table 1 of article</td>
<td>NO. Insufficient details of study participants</td>
<td>YES. Full description in Table 3 of article</td>
</tr>
<tr>
<td><strong>Data analysis conducted with sufficient coverage of the identified sample</strong></td>
<td>YES. 808 out of 864 complete follow up</td>
<td>YES. 9% loss to follow up</td>
<td>UNCLEAR. Only patient data that GP submitted to centralised system , no information on non-reporting</td>
<td>YES. No significant differences in demographics between drop outs and non-drop outs</td>
</tr>
<tr>
<td><strong>Valid methods used for the identification of MRH</strong></td>
<td>YES. Patient self-report and chart review followed by naranjo algorithm for causality assessment</td>
<td>YES. Two independent physicians used a structured review process</td>
<td>YES. GP judgement and imputed algorithm</td>
<td>YES. Patient self-report followed by Naranjo algorithm for causality assessment</td>
</tr>
<tr>
<td><strong>MRH measured in a standard, reliable way for all participants</strong></td>
<td>YES. Trained clinical pharmacists followed by blinded paired assessments by geriatrician and geriatric specialist pharmacist</td>
<td>YES. Structured telephone interview by registered nurse and physician and then set criteria for defining adverse outcome.</td>
<td>NO. No consistent GP training to identify ADRs</td>
<td>UNCLEAR. Self-report using standard data collection form. Interviewers were trained. No interrater reliability assessment</td>
</tr>
<tr>
<td><strong>Appropriate statistical analysis</strong></td>
<td>YES. Clear information on MRH events and people in numerator and denominator</td>
<td>NO. Lack of information on total frequency of adverse events</td>
<td>YES. Clear information on events and people in numerator and denominator</td>
<td>YES. Clear information on events and people in numerator and denominator</td>
</tr>
<tr>
<td><strong>Response rate adequate</strong></td>
<td>YES. Good response</td>
<td>YES. Small dropout</td>
<td>UNCLEAR. No information provided</td>
<td>NO. Low response rate (51%)</td>
</tr>
</tbody>
</table>
Figure 2.3 Risk of bias assessment for included studies

A

B

<table>
<thead>
<tr>
<th>Study</th>
<th>Target population</th>
<th>Sampling</th>
<th>Sample size</th>
<th>Description of participants and setting</th>
<th>Coverage of identified sample</th>
<th>Methods to identify outcome</th>
<th>Reliability in outcome measurement</th>
<th>Appropriate statistical analysis</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad 2014</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>=</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Forster 2004</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gray 1999</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Hanlon 2006</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Kanaan 2013</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Letilliart 2001</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Marusic 2014</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Westberg 2017</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
2.3.9 Incidence of MRH

The incidence proportion of MRH ranged from 0.4% older adults within 30 days of discharge\textsuperscript{98}, in a study of ADR presenting to primary care in France post-discharge, to 51.2% in the Netherlands over a two-week post-discharge period\textsuperscript{96} in a study investigating medication ‘side-effects’ (Table 2.5). The actual incidence of MRH events ranged from 4 per 1000 patients over 30 days to 615 per 1000 patients over one year of follow-up\textsuperscript{92}. The follow-up period in the majority of studies was 30 days (n=5, 62.5%)\textsuperscript{91,93,95,97,98}. The MRH incidence within this 30 day follow-up period ranged from 167 to 500 events per 1000 patients (17-51% of discharged patients)\textsuperscript{91,93,95,97}, excluding the exceptionally small MRH incidence in the study that only followed up patients that consulted their GP post-discharge.\textsuperscript{98} The substantial heterogeneity in methods between studies precluded a reliable meta-analysis of the incidence of MRH\textsuperscript{79}. 
Table 2.5 Incidence, preventability, and, severity of MRH

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Incidence of MRH (events per 1000 patients discharged)</th>
<th>Incidence of MRH in study population, % (follow-up duration)</th>
<th>MRH Preventable, % (definition)</th>
<th>MRH Serious, % (definition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westberg (2017)</td>
<td>346</td>
<td>Not reported (30 days)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ahmad (2014)</td>
<td>500</td>
<td>51.2 (14 days)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Marusic (2014)</td>
<td>345</td>
<td>30.1 (30 days)</td>
<td>51.4 (errors that could have been avoided or severity reduced with different actions)</td>
<td>6.9 (fatal, life-threatening, hospitalisation or disability)</td>
</tr>
<tr>
<td>Kanaan (2013)</td>
<td>242</td>
<td>18.7 (45 days)</td>
<td>35 (due to error and preventable by any means possible)</td>
<td>24 (clinical judgement)</td>
</tr>
<tr>
<td>Hanlon (2006)</td>
<td>615</td>
<td>33 (365 days)</td>
<td>37.6 (prescribing, monitoring, dispensing or adhering errors)</td>
<td>26 (death, hospitalisation, permanent disability, need for intervention to prevent permanent impairment†)</td>
</tr>
<tr>
<td>Forster (2004)</td>
<td>167</td>
<td>16.8 (30 days)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Letrilliart (2001)</td>
<td>4.0</td>
<td>0.4 (30 days)</td>
<td>59 (French algorithm with six criteria*)</td>
<td>60 (fatal, life-threatening, hospitalisation or disability)</td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>250</td>
<td>20.3 (30 days)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*Imbs JL et al. Therapie 1998;53:365-70; † Data retrieved from contact with original investigator
2.3.10 Severity, preventability and risk factors

The severity of MRH events was determined in four out of the eight included studies\(^92,94,97,98\). Two studies used identical criteria to define serious MRH\(^97,98\); death, life-threatening, hospitalisation or disability. Within the four studies reporting severity, the proportion of MRH judged as ‘serious’ varied considerably from 6.9\(^%\)\(^97\) to 60\(^%\) \(^98\) (Table 2.5).

Data on the extent to which MRH was preventable was available in four studies with variable definitions, and ranging from 35\(^%\) to 59\(^%\) of total MRH\(^92,94,97,98\) (Table 2.5).

Four out of eight studies investigated risk factors associated with the incidence of MRH\(^92,93,97,98\). Three studies additionally performed multivariable analysis to identify independent predictors\(^92,93,97\) (Table 2.6). Polypharmacy\(^92,97\), new drugs at discharge\(^93\), furosemide\(^97\), warfarin\(^92,97\), female gender\(^93\) and impaired cognition \(^93\) were independent risk factors for MRH. Cardiovascular medications were the most frequently prescribed of all drug classes at hospital discharge.\(^93,97\) They were implicated most commonly in MRH events; 18.8\(^%\) to 55.7\(^%\) of events\(^92–95,97,98\). Anticoagulants were another very commonly implicated class of medication, associated with up to 20\(^%\) of MRH events.\(^98\).
Table 2.6 Risk factors and medicines commonly associated with MRH after hospital discharge

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Frequently implicated medicines in MRH (% of events)</th>
<th>Risk factors for MRH examined in study</th>
<th>Independent risk factors of MRH on multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westberg (2017)</td>
<td>Analgesics (28.4%), Psychotropics &amp; hypnotics (22.7%), Cardiovascular (20.6%)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ahmad (2014)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Marusic (2014)</td>
<td>Cardiovascular (40.3%), Anticoagulants (16.7%), Hypoglycaemic agents (13.9%)</td>
<td>Age, Gender, Number of discharge diagnoses, Individual diagnoses (Hypertension, Diabetes, Hyperlipidaemia, Ischaemic heart disease, Atrial fibrillation), Number of medicines*, Drug-drug interactions, Individual medicines/medicine class (ACE-I, Beta-blockers, Acetylsalicylic acid, Furosemide*, Statins, PPI, Potassium salts, Calcium-channel blockers, Warfarin*)</td>
<td>Number of medicines (≧4), Warfarin, Furosemide</td>
</tr>
<tr>
<td>Kanaan (2013)</td>
<td>Cardiovascular (55.7%), Opiates (9.5%)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hanlon (2006)</td>
<td>Cardiovascular (27.1%), Anticoagulants (8.6%)</td>
<td>Age, Dementia, Multiple prescriber*, Number of medicines*, Comorbidities, Renal disease, Previous ADR, Individual medicines/medicine class (Warfarin*, Theophylline, Anticholinergics, Opioids, Antipsychotics, Benzodiazepines*, NSAIDs*, Tricyclic Antidepressants*, Corticosteroids, Sedatives)</td>
<td>Warfarin, Number of medicines,</td>
</tr>
<tr>
<td>Forster (2004)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Letrilliart (2001)</td>
<td>Cardiovascular (26.7%), Anticoagulants (20%)</td>
<td>Age*, Gender, Type of admission (planned/unplanned), Type of hospital (public/private)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gray (1999)</td>
<td>Cardiovascular (18.8%), Antibiotics (17.2%), CNS (15.6%), Endocrine (15.6%)</td>
<td>Age, Gender (Female*), Living alone, Alcohol consumption, Depression, Self-rated health, Activities of daily living, Cognitive status (MMSE)<em>, Comorbidities, Number of medicines, Number of new discharge medicines</em>, Medicines increase</td>
<td>Female gender, Number of new discharge medicines, Lower MMSE score</td>
</tr>
</tbody>
</table>

Abbreviations: Central Nervous System (CNS), Ischaemic Heart Disease (IHD), Mini-Mental State Examination (MMSE). *Statistically significant P<0.05. In three studies 92,94,97, for consistency, medicines were combined to calculate the proportion due to cardiovascular agents, using the WHO-ATC system.
2.4 Discussion

This chapter presents my results from a systematic review to investigate what is known of the epidemiology of MRH in community-dwelling older adults following hospital discharge. This systematic review forms a strong basis for the further work required to more comprehensively understand the epidemiology of MRH in the UK. Indeed, the systematic search identified no relevant studies conducted in the UK. Eight studies from North America and other European countries were identified that met pre-specified inclusion criteria. A very wide range in the incidence of MRH was found, from 0.4% to 51.2% of discharged older patients. There was considerable heterogeneity in the methods used between studies, which precluded a meta-analysis. Important differences were found in the vulnerability of the population cohort recruited, MRH outcome definitions, the length of time over which post-discharge follow-up occurred, and data collection methods. The lack of consensus on conducting and reporting MRH research makes a meaningful interpretation of the problem challenging.

This review shows that MRH is an important public health and geriatric problem. The 30-day incidence ranged from 167 to 500 events per 1000 patients (17-51% of patients). This excludes one study that reported an anomalous MRH incidence (0.4% patients), where only patients consulting their GP were followed-up.\textsuperscript{98} This population-based study conducted in France excluded MRH that was self-managed at home or resulted in the use of the emergency department, and therefore it is highly likely that this study under reports the true magnitude of MRH. Conversely Ahmad et al.’s (2014) study in the Netherlands recorded an exceptionally high rate of MRH (half of recruited patients experienced MRH within the first two weeks post-discharge)\textsuperscript{96}. This most likely reflects the high-risk sample frame in this study i.e. older patients discharged with five or more medicines.

Studies identified a high proportion of MRH as preventable, ranging between 35% and 59%. This builds on evidence from a previous systematic review of all MRH in the community (not post-discharge and all age groups) which found between 11%
and 27.5% MRH preventable. It is not surprising that the proportion of MRH that is preventable in the post-discharge period is high. Medication discrepancies on discharge, deficiencies in information transfer to primary care, inadequate communication with patients of medication regimen changes and potential adverse effects, are all avoidable factors that contribute to increasing the risk of MRH in the transition of care.

2.4.1 Healthcare costs associated with MRH

None of the included studies considered the financial costs of MRH to healthcare systems. This is a crucial piece of information for policymakers that must prioritise intervention for public health problems by cost-effectiveness. Reducing preventable MRH post-discharge may be an important opportunity for financial savings within healthcare systems. Currently data on MRH costs are predominantly based on hospital inpatients. The last cost-analysis of MRH in a UK setting was from data collected in 2002; in an analysis of 18820 hospital admissions over six months to two hospitals in one UK city, 1225 (6.5%) were associated with MRH (specifically ADR) costing the NHS £466 million annually. Based on primary data from this study by Pirmohamed et al (2004), the National Institute for Health and Care Excellence (NICE) estimated an annual cost to the NHS in 2015 of £530 million from preventable hospital admissions caused by ADR.

2.4.2 Defining medication-related harm

This systematic review highlights the need for consensus in defining MRH, collecting MRH data, ascribing causality of harm to medication, and reporting findings. There are various definitions used for ADR and ADE, which can be contradictory. The WHO definition of ADR stipulates ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’ (excluding error), however the definition by Edwards and Aronson (2000) includes ADR related to alternative doses that might be due to error. Common exclusion of MRH arising from non-adherence and medical error in studies focusing on ADR poorly maps the reality of patient experience of MRH or indeed clinical practice. Future research
in this field should identify harm due to non-adherence and medical error alongside
ADRs, reporting them separately and collectively under a terminology of
‘medication-related harm’. This approach would align with the WHO’s global
medication safety initiative 29 and most crucially would align with real-world harm
that patients encounter from medicine use.

2.4.3 Data Collection

Collecting MRH data is more accurate if multiple sources can be used74,105. Studies
relying only on one source, e.g. medical chart review, are likely to underestimate
MRH 105; patient surveys and interviews are a crucial contribution to MRH data106,107
and this should be routinely captured to generate more robust evidence108.
Interestingly one study included a medical examination looking for physical signs of
MRH, conducted by a doctor with clinical pharmacology expertise.97 The proportion
of MRH that was identified with this approach, relative to chart reviews and patient
interview, was not reported. Several patients experiencing statin-induced myopathy
and corticosteroid-induced Cushing’s syndrome were identified that could have been
missed without a physical examination. The additional value of examination will
depend to a large extent upon the education and training of the physician
conducting it.

No gold standard exists for ascribing causality when assessing MRH109, although the
combination of an algorithmic approach, e.g. Naranjo algorithm110 alongside expert
opinion from a multidisciplinary team is comprehensive and might optimise the
accuracy of judgements about causality111.

A standard time-frame capturing the heightened risk of adverse events in the post-
discharge period is not available, and is problematic to dictate given the
biopsychosocial variation in older patients discharged from hospital. Most studies in
this systematic review followed participants for 30 days after discharge. Although
this is arbitrary, it is consonant with the period of heightened vulnerability described
as a ‘post-hospital syndrome’ of ongoing recovery, the effect of physiological stress
from hospitalisation, including poor nutrition, sleep deprivation, and overall deconditioning. Hanlon et al. (2006) conducted a one-year follow-up after hospital discharge and showed that MRH occurred predominantly in the first three months. However, some MRH manifests over an extended time-frame. For instance, immunosuppression-related sepsis or prednisolone induced osteoporotic fractures typically develop over many months.

2.4.4 Risk factors

Polypharmacy is a well-established risk factor for MRH in the inpatient setting and an increasing number of medicines at discharge is an independent predictor of post-discharge MRH. Prescribing warfarin at discharge was also shown in this review to be a significant risk-factor, however, the recent study by Westberg et al. (2017) did not find anticoagulants to be a particularly commonly implicated drug in causing MRH. It is feasible that this reflects changing prescribing patterns with warfarin losing favour to direct oral anticoagulants. There are indications that some direct oral anticoagulants have a better safety profile when compared with warfarin. Surprisingly, only one study explored the influence of psychosocial factors on the risk of MRH and found that reducing Mini-Mental State Examination scores (reducing cognition) was significant. The influence of other important variables such as frailty, health literacy, carer support, and socioeconomic status have not been investigated but could in future research increase our understanding of the pathways underlying MRH.

2.4.5 Limitations

Whilst a comprehensive literature search was performed, no attempt was made to identify unpublished studies other than direct contact that I made with the authors of included studies. Grey literature was not included, but may feature some important information that would contribute to a broader review. The primary outcome of interest for this review was the incidence of MRH, however the
heterogeneity between studies precluded a meta-analysis. Secondary outcomes of interest, such as the severity and preventability of MRH were reported in only a proportion of studies. Many studies excluded patients with dementia, however this group of patients should be represented in future work given their vulnerability to MRH from low cognition and frequent polypharmacy.

2.5 Conclusions

To conclude, this systematic review has identified a major gap in the patient safety literature. Despite the high risk for MRH around transitions of care, there has been a paucity of primary research to investigate the epidemiology of MRH following hospital discharge in older adults. Indeed, there has been no investigation of this in a UK setting.
CHAPTER 3.
Medication-related harm: A qualitative exploration of the older person’s lived experience
Chapter Summary

Medication-related problems (MRP) can lead to patient harm. The older person’s perspective on MRP has been seldom reported in published literature. This chapter describes a study that explored the lived experience of MRP in a sample of older adults with varying functional levels, focusing on the period around hospital discharge. A phenomenological framework was used to inform this qualitative study, conducted in Brighton and Hove, UK. A purposive sample of 20 older people with experience of MRP, involving carers, took part in focus groups and semi-structured interviews. Data were thematically analysed using a ‘framework’ approach. Four major themes associated with MRP were identified; (1) experience of the healthcare system, (2) practicalities of using medicines, (3) management of medication problems, and, (4) participant beliefs. Participants encountered problems in communication with healthcare professionals such as passive listening and paternalistic consultations. A conflict was acknowledged between participants’ implicit trust in the healthcare system and their negative experience of MRP. Participants felt vulnerable around hospital discharge, describing reduced capacity to comprehend information, pressured discharge circumstances, and lack of integrated care in the community. Drug formulations, packaging and information leaflets were felt to be poorly tailored to the needs of older people. The lived experience of older people with MRP is multifaceted and complex. Key areas for improvement that were identified by participants are communication around hospital discharge, and increased support with medicines offered in the community. Harm due to MRP could be lessened if the contributory factors, from the voices of patients with lived experience, can inform clinical and policy-level intervention.
3.1 Introduction

“The truth of art keeps science from becoming inhuman, and the truth of science keeps art from becoming ridiculous.”

— Raymond Chandler (1888-1959)

In Chapter 2 the paucity of epidemiological data on MRH in older adults following hospital discharge was established. It was nonetheless clear from the identified studies that MRH is a common problem for older adults in the post-discharge period. The foremost internationally recognised principle of good medical practice is to ‘first, do no harm’. The foundation of this ethical imperative is within the Hippocratic Oath, and in practice became legally visible on a global platform during the Nuremberg Trials of 1946 following the second world war. Given that all medicines have some inherent toxicity, the prescription of any medicine must be a balance of clinical judgement as to the likelihood of benefit against the likelihood of harm. This judgement can only be informed accurately with robust clinical trial evidence of health benefit from the use of medicines in the older age group. Whilst two-thirds of medicines prescribed in the community in England are to the older population, the clinical trial evidence supporting the use of a significant proportion of these is tenuous, especially in the frailer and multimorbid population. Older people are often excluded from medical research even where the majority of patients that the research is intended for are indeed the older age group. In trials that are conducted in the older age group, the very old (>85 years), multimorbid patients or patients with cognitive impairment are rarely included. Whilst the randomised-controlled trial has become the gold standard of evidence based medicine, the generalisability of this evidence to the real-world must be questioned in the older population. More than half of adults aged 65 years and older live with multimorbidity and this proportion increases to 80% of adults aged 80 years and above. Some academics have called into question the ‘evidence-based medicine’ movement that has engrained itself in healthcare over the last half-century. This is largely a consequence of the lack of ‘real-world’ applicability of the results of many
randomised-controlled trials\textsuperscript{17}. Whilst the RCT is justifiably the gold-standard for evidence of treatment efficacy, it is often misinterpreted as the gold-standard for evidence-based medicine (and treatment effectiveness). The crucial difference between evidence and evidence-based medicine is that the latter has real-world applicability which cannot just rely on quantitative data from a highly select group of people. Patients experiencing illness do not live within controlled environments and conditions, rather they may encounter a mix of a chaotic health system, poor health literacy, alternative priorities to their health, and biopsychosocial adversities that limit their engagement \textsuperscript{108}.

Given the uncertainties in the strength of evidence influencing prescribing decisions in everyday clinical practice, and the knowledge that a significant proportion of the older population experiences harm from medicine, it is both a moral and practical imperative that the academic debate includes the patient’s voice. However, medical research and practice have traditionally been situated within a positivist scientific paradigm which does not recognise patient’s lived experience as scientific evidence \textsuperscript{108,119}. Qualitative research is often criticised for its lack of generalisability, however as outlined earlier in the introduction, the generalisability of findings from the ‘gold-standard’ RCT to the real world is questionable. Six ‘biases’ within ‘evidence-based medicine’ leading to the systematic exclusion of the patient voice have been eloquently described by Greenhalgh \textit{et al} (2015) \textsuperscript{108}. These six biases are (1) minimal, and often tokenistic, input of patients and carers in the design and conduct of research; (2) the hierarchy of evidence within the pyramid of evidence-based medicine devalues individual patient/carer lived experience, (3) patient-centeredness is conflated with the use of shared-decision making tools, framing patient-centeredness through a medical lens, (4) power imbalance between the doctor and patient may inadvertently suppress the patient voice, (5) the clinical consultation is overemphasised in evidence-based medicine to the detriment of patient’s own coping strategies and support networks, (6) evidence-based medicine neglects those that do not seek or cannot access healthcare and the exclusion of this ‘hidden denominator’ may act to inflate the effectiveness of evidence-based medicine.
The lived experience of patients is a crucial element of evidence-based medicine if it is to be applicable to clinical settings\textsuperscript{17,108}. For instance, in the Canadian EMPOWER trial of patient education to support withdrawal of benzodiazepines in older users\textsuperscript{120}, the patient perspective was pivotal to understand the patient-provider context necessary for successful deprescribing\textsuperscript{121}.

There is a paucity of research of the lived experience of medication-related problems in older adults\textsuperscript{37}. A recent systematic review of qualitative studies on medication-related burden and patients lived experience with medicine identified 10 primary research studies set in the UK\textsuperscript{37}. None of the UK studies identified had a clear focus on medication-related problems in older adults. One study had a core focus on middle-aged patients’ experience of hospital admission due to adverse drug reactions\textsuperscript{122}, six were related to a specific medical diagnosis\textsuperscript{123–128}, one study was about patients experiences of obtaining medicine and integrated service provision\textsuperscript{129}, one study was focussed on patients attitudes around using medicines regularly in mid-life in the context of multimorbidity\textsuperscript{130}, and one study was about the impact of long-term medicines on everyday life\textsuperscript{131}.

This chapter describes a qualitative study that I designed and conducted of the lived experience of medication problems in a sample of older adults in England. The purpose for conducting such a study was to capture the patient voice and contribute to eliminating the bias against patient knowledge within evidence-based medicine. Given that my programme of research sought to investigate the impact of MRH in older adults, to not inform this work with the knowledge of those that have first-hand experience of MRH would seem negligent. The evidence captured from the lived experiences of patients with MRH was intended to complement the quantitative research reported in later chapters, and thus provide a comprehensive picture of the impact of MRH to patients and the NHS.

A phenomenological approach was adopted to explore two research questions to understand the impact of MRH on patients,

1. What is the older person’s lived experience of medication problems?
2. What are the contributing factors that lead to medication-related harm from the older person’s perspective?

3.2 Methods

This qualitative research uses a phenomenological approach to explore patients’ experience of medication problems and its associated harm. This approach considers subjective human experience as a valid basis of inquiry and knowledge. The Royal Pharmaceutical Society, in its guidance ‘Medicines Optimisation: Helping patients to make the most of medicines’, places an understanding of the patient’s experience as the first principle of medicines optimization. The origins of the word phenomenology come from the Greek word ‘phainemenon’ which means ‘appearance’. Taking a phenomenological approach requires the reader to consider how ‘disease’ and ‘illness’ are conceptualised differently according to the philosophical ‘lens’ applied; the former through a biomedical positivist lens and the latter through a sociological interpretivist lens.

3.2.1 Disease versus illness: the importance of lived experience

Disease and illness are often used synonymously as health-related terms, although they are conceptually different. Disease describes suffering through a pathological and objectively recognisable process occurring in the body, which is deviant from the biological norm, has the same pathogenesis in any societal context, and can be demonstrated to exist in ‘reality’ using experimental techniques. However, a rather more complex combination of a few models, including a sociological model, underpins the understanding of illness and it is this conceptualisation upon which patients often seek help from their doctors. Illness is understood through the lens of the patient’s world. Harvey Cushing (1869-1939), an eminent neurosurgeon, famously said “A Physician is obliged to consider more than a diseased organ, more even than the whole man – he must view the man in his world.” Patients can
suffer illness regardless of whether medical disease is present or not. If a doctor’s role is to help alleviate suffering then we cannot neglect the patient’s illness due to our inability to diagnose a disease. The illness does not cease to exist because an adverse pathological process in the body has not been seen in blood results, seen on radiological imaging, or seen in flesh. It is from this viewpoint, that it was of high importance in my PhD to explore the lived experience of MRH in older adults.

3.2.2 Setting and ethics

The study protocol was approved by the Brighton and Sussex Medical School Research Governance and Ethics Committee (RGEC 16/041/ALI). The work was funded through an award from the University of Brighton Community University Partnership Programme, following a successful application. The study was undertaken in Brighton and Hove, a city on the South coast of England with an estimated population of 275,800, of which 13% (36,684) are aged 65 years or older. The study is described in this chapter in accordance with the standards for reporting qualitative research published by O’Brien et al (2014)135. Patient and public involvement (PPI) informed the design and materials for the research study and is described later in this chapter.135

3.2.3 Conception and design

The initial idea for this study was proposed by myself in the autumn of 2015, and explored with Dr Beatrice Gahagan, Age UK Brighton and Hove (AUKBH), as a community partner and Dr Lizzie Ward, the School of Applied Social Science University of Brighton (SASS), as an academic partner. The importance of a community partner such as Age UK was to ensure the relevance of the research study, given the charity’s longstanding and trustful relationships with older people in the UK and more locally in Brighton & Hove. Age UK would also serve as an important partner in recruitment of potential participants to the study. The University of Brighton SASS has an established record of conducting reputable research into the lived experiences of older adults, and has previously conducted
such research into older people’s experience of well-being and in separate work their use of alcohol 136–138 in partnership with AUKBH. These projects have developed a participatory approach to researching older people’s experiences by developing a team of older ‘lay’ co-researchers who have been trained in all aspects of undertaking qualitative research and who acted as the PPI group for this study as detailed in the next section.

3.2.4 Patient and public involvement

Patient and public involvement (PPI) in research has been described as not only ‘doing the right thing, but doing the thing right’139. Five older adults (one male, four females; aged over 85 years) with previous experience of participatory research 136 acted as advisors and supported the conceptualisation and design of this study, and provided input to the protocol, consent forms, participant information sheets and topic guides (see appendices 2-4). A two-hour round-table meeting was held in June 2016, and then correspondence continued with the PPI group through telephone meetings, email and letters. The relevance of the study for patient benefit was explored and confirmed, and changes were made to the wording and length of the participant information sheet to improve readability and comprehension.

3.2.5 Definition

A pre-determined definition for medication-related problems was not adopted to ensure no restriction in the scope of participant discussion. Any definition would impose an academically driven boundary; the purpose of this study was to explore older person’s experience, and implicit within this is their own definition based on their experience of a medication-related problem.
3.2.6 Recruitment

A purposive sample of ambulatory older adults, and dependent, housebound older adults were invited to participate in this study. Participants were recruited via AUKBH, which organise activity groups, and, a ‘crisis’ service that gives social assistance and supports access to clinical help for older people following hospital discharge. The study was advertised by the organisation’s activity group leader using posters (see appendix 4), whilst participants recruited through the crisis service were invited to participate by the service manager. Participants were included if they met the following eligibility criteria; (1) age ≥65 years, (2) has personal experience of taking regular medicines or caring for someone taking regular medicines, (3) has personal experience of MRP or caring for someone that has experienced MRP, (4) has personal experience of hospital discharge or caring for someone that has experienced hospital discharge, (5) does not have severe cognitive impairment as assessed by the service managers. Participants self-defined themselves as having experienced MRP as the research team intentionally did not specify an MRP definition (see appendix 2). Written informed consent was taken from each participant.

Recruitment of participants continued until no new themes were being elicited and further recruitment would be highly unlikely to generate new insights into the research topic. Therefore recruitment continued to data saturation. The sample was not intended to be representative of the general older population because the purpose of the study was to explore the lived experiences of older people that have encountered medication problems.

3.2.7 Housebound participants

The AUKBH crisis service is specifically targeted at highly vulnerable individuals that have usually had a recent hospital admission and need immediate help following their discharge. AUKBH staff that provide this service screened users to determine their eligibility and suitability for the research study. If a service user was deemed both eligible and suitable then they were provided verbal and written information.
about the study in the form of the participant information sheet. The service user’s permission was then sought to be contacted. The AUKBH crisis manager then telephoned or emailed me to pass on the potential participants contact details, after which I followed this up with a telephone conversation and confirmed the service user’s interest, eligibility and suitability. This was an opportunity for potential participants to ask any questions or raise any concerns that they may have had. This opportunity was also used to emphasise that the discussions would be confidential, that there was no obligation to participate, and finally that if they did chose to participate then they could withdraw at any time without providing a reason.

Participants were visited at their home for an in-depth semi-structured interview between October 2016 and January 2017. Prior to the commencement of any interview, the participant was asked if they had any questions or any concerns arising from the participant information sheet. If they were satisfied and remained keen to participate, then their consent was sought to conduct the recorded interview. A topic guide was used to provide a general structure and direction to the interviews, however it emerged early in the interview process that stringently adhering to the topic guide would hinder the free-flow of the interview. Therefore, the topic guide was used less for directing the interview but more to ensure that the interview had covered all the main areas of interest to the research question.

3.2.8 Ambulatory participants

A recruitment advertisement flyer, alongside participant information sheets, were posted at two weekly activities held by AUKBH; A Tai-Chi Class and a coffee morning group. Interested attendees could register their details for a telephone call from me to further discuss the study with them and determine their interest in participating in a focus group. Three focus groups on different dates were held to best enable interested older adults to participate.
3.2.9 Data collection Approach

Both focus groups and semi-structured interviews were chosen for data collection. A focus group is a group interview, with a collection of people discussing specific topics, and the participants are selected because of their involvement or experience of something particular. This group participation was favoured to individual interviews where possible as I was interested in the interaction between participants as key themes emerged, and interested in exploring the rationalisation of individual views as ideas were shared within a group setting. Furthermore, focus groups offer less control to the researcher given the dynamic nature of a multi-group discussion, and this was favourable to support the surfacing of ideas that had not been pre-identified in the topic guide. Nonetheless, given the sensitive nature of talking about health-related issues, it was acknowledged that participants may have been less willing to share deeply personal experiences in a group setting. An effort was made to reduce the likelihood of this by keeping focus groups small, to a maximum of five participants. Additionally, participants for the focus groups were recruited from social activities organised by AUKBH, and therefore a majority of participants knew one another beforehand. These factors may have contributed to a more comfortable group setting for participants than otherwise might have been.

Semi-structured individual interviews were chosen as an optimal data collection method for housebound participants. Focus groups were not possible with this population due to their immobility and overall frailty. It was crucial to this research that this vulnerable population, that so rarely has its voice heard\textsuperscript{141}, was not excluded given that this is a high-risk group for medication related problems\textsuperscript{93}. It was further anticipated that individual interviews were also likely to be more appropriate for this population given they might have felt more vulnerable in an open setting, and possibly less willing to disclose their personal experiences amongst a group of unfamiliar people.
3.2.10 Thematic analysis

Interviews were recorded and transcribed verbatim. A framework approach to thematic analysis of the data was adopted due to its highly prescriptive methodology, which is suitable to multidisciplinary research teams that includes researchers with limited prior experience of analysis qualitative research\footnote{142}. The framework approach was originally developed at the UK National Centre for Social Research in the 1980s for application to social policy research\footnote{143}, and has recently been gaining popularity in applied health research\footnote{142}. The framework approach involves five key processes; familiarisation, coding, indexing, charting, interpretation\footnote{142}. These are not necessarily sequential steps, as familiarisation with the data is an ongoing process and coding and interpretation maybe iterative if a priori codes have not been assigned. Codes in this study were selected through a mixed deductive and inductive approach. The deductive codes were pre-selected in reference to the interview topic guides used and further themes were generated inductively through an open coding process. The benefit of this mixed approach is that the relevant data to explore pre-defined research questions can be identified and assigned within relevant themes, whilst still allowing for new and unexpected themes to emerge from the data. Initial codes were suggested by all four researchers individually based on individual familiarisation with two transcripts, and these were then discussed during a meeting and consensus was reached on the codes to be adopted. The remaining transcripts were coded based on this agreement, with new codes emerging inductively during the process of indexing the transcripts. New codes were discussed and their relevance explored between the researchers to decide upon whether it should be adopted.

Codes were categorised into four meta-constructs of themes in relation to MRP, (1) experience of the healthcare system, (2) practicalities of using medicines, (3) managing MRP (4) participant beliefs. Themes were then extracted from interrogating the data within the context of these categories and codes, after charting the data by participants and codes in a spreadsheet. This matrix was then analysed by comparison within and between cases under columns of codes, in
conjunction with brief field notes made immediately post-interviews, to extract meaning and data interpretation.

3.2.11 Reflexivity

In qualitative research where one is trying to draw learning of the ‘how?’ and ‘why?’ in the real world, it is accepted that the researcher cannot entirely separate their own experiences, values and perspectives from the conduct of the research \(^{140}\). Rather than deny the impact of the subjective experiences qualitative researchers address this issue through the practice of reflexivity, that is a process of building awareness of the researcher’s subjectivity and making its impact visible within the research. It was my intention to adopt as neutral a position as possible through a transparent process of written reflection by debrief discussions with my lead supervisor (Dr Khalid Ali). As a medical doctor by training, the benefit that medicines can provide to preventing, managing and curing ailment was well known to me. Therefore, I was aware that I was approaching interviews and focus groups with a medical ‘lens’. This meant that it was impossible to entirely distance oneself from the clinical rationale for the prescription of certain problematic medicines. This might have limited my ability to fully engage in the experiences described by the participant(s) given my capacity to speculate on the clinical decision making that could have taken place around the participant. Nevertheless, a diary was kept following each interview and focus group so that I could reflect on these preconceptions, engage with this prior knowledge and consider how it might have impacted on my verbal and non-verbal body language during interviews. This process, alongside regular debrief discussions with my lead supervisor, enabled me to partially compartmentalise my medical background during the process of interpreting the transcripts. Further efforts to limit subjectivity were made by designing semi-structured interviews and focus-groups and a multidisciplinary approach to interpretation of the data. The key categories and coding framework was initially drawn from two interview transcripts by the four partners in this research study; one junior clinical academic (myself) and one senior clinical academic, both for whom MRP is a prior area of research interest, one social
scientist for whom this was a new area of study and a health programmes manager at Age-UK Brighton and Hove also for whom this was a new area of research exploration. This broad range of backgrounds to collaborate on this exploration of the lived experiences of older people limited the bias arising from the preconceptions and prior experiences of any one researcher.

3.3 Results

Twenty participants were recruited and consented to participation. The average age of participants was 78 years (range 65 to 98 years), and all were of Caucasian background (Table 3.1). Eleven participants lived alone whilst the other nine participants lived with partners. The average number of regularly prescribed medicines in the total sample was five, however amongst the housebound participants the average number was 8 and amongst the ambulatory participants the average number was 3. Two participants in focus groups were not presently taking any medicines themselves. One of these participants was a carer for her mother who was experiencing medication related problems. The other participant was taking regular medicines but had stopped taking all regular medicines because of experiencing adverse effects. Ten participants had experienced a hospital admission in the past year.
Table 3.1 Baseline participant characteristics

<table>
<thead>
<tr>
<th>Participant number*</th>
<th>Gender</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Last hospital admission</th>
<th>Regular medicines (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Female</td>
<td>79</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>3</td>
</tr>
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<td>P2</td>
<td>Female</td>
<td>68</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>0</td>
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<td>White British</td>
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<td>1</td>
</tr>
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<td>P4</td>
<td>Female</td>
<td>69</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>0</td>
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<tr>
<td>P5</td>
<td>Female</td>
<td>65</td>
<td>White British</td>
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<td>N/A</td>
</tr>
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<td>P6</td>
<td>Female</td>
<td>72</td>
<td>White British</td>
<td>last 5-8 months</td>
<td>3</td>
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<tr>
<td>P7</td>
<td>Female</td>
<td>72</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>3</td>
</tr>
<tr>
<td>P8</td>
<td>Female</td>
<td>74</td>
<td>White British</td>
<td>unknown</td>
<td>7</td>
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<td>P9</td>
<td>Female</td>
<td>85</td>
<td>White British</td>
<td>last 9-12 months</td>
<td>6</td>
</tr>
<tr>
<td>P10</td>
<td>Male</td>
<td>74</td>
<td>White British</td>
<td>in last month</td>
<td>5</td>
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<tr>
<td>P11</td>
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<td>74</td>
<td>White British</td>
<td>last 9-12 months</td>
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<td>White British</td>
<td>&gt; 12 months ago</td>
<td>3</td>
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<tr>
<td>P13</td>
<td>Female</td>
<td>79</td>
<td>White Irish</td>
<td>in last month</td>
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<td>P14</td>
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<td>White British</td>
<td>in last month</td>
<td>3</td>
</tr>
<tr>
<td>P15</td>
<td>Female</td>
<td>79</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>8</td>
</tr>
<tr>
<td>P16</td>
<td>Male</td>
<td>85</td>
<td>White British</td>
<td>in last month</td>
<td>9</td>
</tr>
<tr>
<td>P17</td>
<td>Male</td>
<td>75</td>
<td>White British</td>
<td>&gt; 12 months ago</td>
<td>7</td>
</tr>
<tr>
<td>P18</td>
<td>Male</td>
<td>98</td>
<td>White British</td>
<td>last 9-12 months</td>
<td>4</td>
</tr>
<tr>
<td>P19</td>
<td>Female</td>
<td>86</td>
<td>White British</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>P20</td>
<td>Female</td>
<td>84</td>
<td>White British</td>
<td>last 1-4 months</td>
<td>12</td>
</tr>
</tbody>
</table>

*P1 to P12 participated in focus groups. P13 to P20 were interviewed in their homes; P5 and P19 were interviewed as informal carers of older people with medication-related problems; P15 was interviewed in a dual role as an informal carer and individual that met eligibility for participation.

A summary figure is presented below which highlights the key issues that older adults in the study attributed to causing medication problems and harm (figure 3.1).

This is then followed with detailed results with excerpts from the focus groups and semi-structured home interviews, under the four meta-constructs of themes identified during the coding process; (1) experience of the healthcare system, (2) practicalities of using medicines, (3) managing MRP (4) participant beliefs.
3.3.1 Experiences of the healthcare system

The transition from hospital to home was considered a particularly vulnerable time due to ongoing recovery from illness and related to this, a reduced capacity to retain information provided at the point of discharge, and a lack of community follow-up. Changes made to regular medicines whilst in hospital contributed to participant’s confusion when back in their own homes. This situation led to poor adherence of medicines. It was often suggested that additional help was needed around hospital discharge to avoid MRP, through shared-decision making in hospital, standardised input from hospital pharmacists to guide patients through their discharge medicines, and more accessible community support for medication-related concerns. Pharmacists were mentioned as a valuable support in the community, offering...
greater time compared to GPs for addressing participant concerns regarding medicines, and highlighting prescribing errors which could lead to harm.

3.3.1.1 Communication

Almost all the participants raised the issue of experiencing some form of poor communication either between themselves and health professionals, or recognising this between healthcare professionals, as a contributor to medication-related problems.

One participant remarked:
‘there was contradiction between the hospital prescriptions and the doctor’s prescriptions. The communication obviously between the hospital doctor and the GP wasn’t good’ [P3]

Communication with General Practitioners (GP) often took place over the telephone due to a lack of available face-to-face appointments, and some felt that this limited the quality of communication and capacity of GPs to seriously address MRPs. This experience was in some cases felt to be passive listening and a lack of attention to patient-reported adverse outcomes which subsequently resulted in greater patient harm.

For instance, P20, an 84 years old housebound lady taking 12 medicines, said:
‘I kept telling her (GP) I was getting more and more suicidal, I told her, and then all she said was “oh well, you’ve had these depressive states before”, which was nothing at all to do with these tablets (steroids), this was something different’ [P20]

Another housebound lady, 79 years old, described her experience of conflict with her doctor over the source of her back pain:
‘I asked the doctor for something to relax my back and he said, you’re not having any Diazepam and that’s the only thing that would touch it... he says you’ve got depression and I said, I’m not depressed, I said, I’m low I said from the pain I’ve got all the time’ [P13]
Some participants described the choice of language used by doctors to be inconsiderate to their own lived experience of adverse effects from their medicine, ‘some of the doctors would really argue with you and I was told that I was dreaming and I was, there’s no such thing as side-effects or “you’re reading the leaflet and making it up”’ [P4]

“‘There’s nothing wrong with you,” they just dismiss you’ [P14]

And participants described how they could feel patronised when communicating with their doctor,

‘You’re not supposed to be intelligent yourself’ [P3]

" No, I’ll tell you when it hurts.” [P5]

One participant, during a focus group, described their experience of a difference in consultation style between older and younger GPs:

‘The younger ones now I think are better. I’d rather see a younger one because they’re much more open to discussion and to listen to your worries and fears’ [P4]

Others pointed out instances where important medicines-related information was not communicated leading to confusion and unnecessary anxiety:

‘for some reason they stopped it (perindopril), but they didn’t say why they stopped it’ [P16]

‘and no-one, (nor the) GP could tell me when I was going to stop taking these medicines, in the end he said, “Look, they’re not making you better, they’re keeping you alive,” which is fine, but I’d like to have known that slightly earlier.’ [P10]

‘all doctors explain to you, I’ll give you so-and-so and you take 2 a day and see what relief you get, basically it’s that and don’t forget to read the instructions’ [P15]
Participants described the lack of consistency in the communication received regarding their medicines in the period around hospital discharge both in community and secondary care settings.

One participant described her confusion:
‘my son said it was 3 a day because I can’t see, when the doctor writes how many he prescribes... the chemist said 1 a day, the girl that was here from the chemist said 2 a day, so you get all different things, you know, I said to her, 1, 2 or 3’ [P13]

None of the participants described feeling involved in decisions made about their medicines, for instance when changes were made to their regular medicines during a hospital admission. Nevertheless, in response to adverse events, some reported changes in their own behaviour (e.g. asking a standard set of questions about any new medicine), to ensure they were given opportunity to participate in and understand the rationale for medication-related decisions:
‘They (doctors) just say, you know, “We’re changing your medicines, you’re not taking that anymore” or something like that and most people just go along with it, they don’t question it’ [P16]

‘when you’re in hospital and you get prescribed these pills they don’t ever tell you what they are and what they’re for... they discuss things themselves and the patient is not involved, which is wrong...it’s like a secret society’ [P17]

Highlighting the importance of good communication, a 75 years old housebound man living on his own commented:
‘“Communication, communication, communication’...It goes a long way, if you’re informed in these things you can do something about it. If you’re not informed you’re stuck’ [P17]
3.3.1.2 Inappropriate prescribing

There were several instances of participants describing their experiences of potentially inappropriate prescribing of medicines, particularly in the context of an interruption in the continuity of their care with locum staff.

A 69 years old lady who stopped taking her regular medicines because of her concerns around their adverse effects said in a focus group:

‘I think what some patients do though, they’ll go back to the doctor and maybe see someone different and then say “oh I’ve got this wrong with me” and they might be given another drug but it’s not looked at that it might be the first drug that’s causing that problem. And this is what I find’ [P4]

In another instance, a participant described being alerted to a potentially harmful drug-drug interaction by their community pharmacist:

‘I was being given, up until last week, two tablets together, Escitalopram and Quinine Sulphate, which I only found out by accident, from a pharmacist, that I should not be taking together, it somehow affects the heart’ [P20]

3.3.1.3 Hospital discharge

The period around the transition of care for an older patient from hospital to home was felt by participants to be a particularly vulnerable time for the older person, and a time at which additional help was needed to avoid medication problems.

‘if you’ve just come out of hospital and you’ve had the kind of experience I had, no you’re not with it and you do need some help’ [P7]

‘for under-fives you’ve got the health visitor who pops in, maybe for vulnerable people coming home, of whatever age, you actually need somebody like the health visitor turning up to say let’s go through this, let’s look at how you’re doing this.’ [P8]
Experiences of the medicines-related information received prior to hospital discharge was mixed, for example one participant described his wife’s recent hospital discharge as a “good story”:

‘the pharmacist came around and talked to her about it and explained it and everything, she was going to change one of the medicines, so she had a good story before she came out of hospital’ [P10]

However, others reported serious difficulties with regards to their medicines during the transition between hospital and home, and this resulted in them not adhering to their discharge medication:

‘I come out and they give me a pile of medicine to take which I didn’t know what to do with and I had to get somebody, don’t know what it was, come around and sort out medicine for me… that was that, and that’s for afternoon and two of them, you know, ‘cos I didn’t know’ [P14]

Several participants mentioned the changes that were made to their medicines whilst in hospital leading to confusion and error due to a lack of information and follow-up. An 85 year old man, interviewed at home having just been discharged from hospital in the preceding week, remarked:

‘while I was there (in hospital) they changed my medicines a bit, stopped my Perindopril but had a proviso temporarily until something is sorted out but then that’s ended and that got transpired that it was stopped for good... nobody has then followed on to see that it was only stopped temporarily.’ [P16]

Another participant in the study, a carer for her husband and struggling with the complexity of managing both her and her husband’s medication regimens, said:

‘When he came out of hospital, the medication had changed...one of the doctors changed it completely and he wasn’t so well after that...and that was a bit of a problem ’cos we weren’t sure, you know, if he wasn’t very well, was it the medication’ [P19]
3.3.2 Practicalities of using medicines

Many participants experienced difficulties with medicine formulation, packaging and/or instructions. They felt that medicines themselves were not tailored to meet the needs of an older person, with tablets such as aspirin being too small to handle and other medicines such as calcium/vitamin D combinations too large to swallow. These problems were especially noted in the context of impairments in vision or dexterity e.g. arthritis.

Medication compliance aids (MCA), for example, blister packs and dosette boxes, were broadly felt to be helpful; however, some noted difficulties with removing tablets from the packs and requiring sharp instruments to cut into each pocket. A major source of concern were the inconsistencies in the colour and shape of medicines placed in the MCAs. Other inconsistencies mentioned that led to MRP for participants were foreign language packaging and differences in the drug interactions listed for the same drug but from different manufacturers. Participants associated the time between taking a medicine and experiencing a side-effect as the key factor in attributing harm to a medicine rather than to an underlying illness or an alternative explanation.

3.3.2.1 Formulation, Packaging and instructions

There was a clear feeling across the sample of older adults recruited in this study that the manufacturing of medicines and their packaging were not conducive to safety or ease of use to support adherence. One person drew a comparison with the treatment of children and remarked:

‘somе pills they аrе hуguе...imаginе giving а bіg pill lіkе thаt tо а kіd’ [P17]

Participants described MCAs as helpful in principle but challenging in practice. They often experienced difficulties with pushing tablets out and some resorted to sharp implements to assist them. A major source of concern described by several participants were inconsistencies in the colour and shape of medicines placed in the MCAs between weeks. One lady described the pros and cons for her of having a blister pack during a focus group:
‘it is easier in the (blister) pack because that they’re altogether and, you know, otherwise you get a month’s supply, I get a weekly supply which is a little bit more helpful...sometimes the colour changes or the shape, and that does concern me because you know, I think have they made a mistake. It’s written on the side but it’s very difficult to work out, especially when your eyes are getting bad’ [P9]

Two participants reported confusion having received their medicines in foreign language packaging. One described their medicines in Spanish packaging, and another said during a focus group:

‘I find I can get a different packet from a different company one month and out so if you have an expectation that the packet that you collect from the chemist is going to look the same as the last ones, there’s no particular reason as far as I can see that it will like the fact when my Rivaroxaban is all in Polish’ [P6]

Participants reported paying mixed attention to the information leaflets within medicine packets, with some finding them valuable and others choosing not to read them as they felt the information was excessive and anxiety-provoking. One participant described herself and her husband’s concern over taking the same blood pressure pills but from different manufacturers, because the information leaflets gave conflicting information,

‘my husband and I were both taking the same blood pressure pills but they were from different, the same name but from different manufacturers. And my instructions said “not suitable for epileptics taking Phenobarbitone”, he is an epileptic taking Phenobarbitone but that didn’t say it in his instructions but it did in mine’ [P4]

A 65 years old carer looking after her unwell husband described her husband’s concern at the information provided on a medication leaflet:

‘The last one that he was prescribed that he’s flatly refused to take and I do not blame him because the minute you look on this advisory leaflet, one of the first things it says is “this is not recommended for elderly people”’ [P5]
3.3.2.2 Side-Effects

Many of the interview participants described their experiences of adverse reactions to prescribed medicines. A selection is shown in table 3.2. Timing was the key characteristic mentioned by participants to support their attribution of adverse reactions to a specific medicine.

Table 3.2. Adverse drug reactions experienced by participants

<table>
<thead>
<tr>
<th>Medicine as mentioned by participant</th>
<th>Experience of adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>made my head fuzzy</td>
</tr>
<tr>
<td></td>
<td>I feel myself talking</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>they give me constipation</td>
</tr>
<tr>
<td>Alzheimer’s tablet</td>
<td>rather loose to the toilet</td>
</tr>
<tr>
<td>codeine</td>
<td>upsets my stomach</td>
</tr>
<tr>
<td>doxycycline</td>
<td>lethargic</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>they made me very, very depressed</td>
</tr>
<tr>
<td>Tegretol</td>
<td>tiredness and the awful slothfulness</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>they paralysed me, I couldn’t move my arms more than that in about two weeks</td>
</tr>
<tr>
<td>Micardis combination pill (Telmisartan-Hydrochlorothiazide)</td>
<td>gout</td>
</tr>
<tr>
<td>Statin</td>
<td>pain in my thigh and numbness of the digits</td>
</tr>
<tr>
<td>Statin</td>
<td>pains in my calves and my leg muscles</td>
</tr>
</tbody>
</table>

3.3.3 Management of medication problems

Participants managed their MRP in very different ways. Whilst some sought medical attention, primarily from their GP or alternatively a community pharmacist, many did not seek help due to perceived lack of time of the GP.

Self-management of MRP was attempted using various information sources, including medical books, the online British National Formulary, newspapers articles, and the advice of friends or family. ‘Trial and error’ adjustment of medicines to overcome adverse effects, without consulting any healthcare professional, was a common approach.
3.3.3.1 Information and Support

Participants did not usually feel that their GP was an available support for them when experiencing a medication-related problem. This feeling appeared to originate from two different viewpoints however, of which one related to the GPs demonstrated lack of time and patience when approached and the other being the participant’s fear of being a nuisance preventing them from using their GP for information and support.

An 86 years old carer of her housebound husband said:

‘I suppose you could go to your doctor if you were worried (about medicines) to ask a few questions, but we’re the sort of people that, you know, ‘oh I’m afraid to go to the doctor’, you know, ‘he’s too busy to mess about just answering silly questions like that’’ [P19]

Two participants described using medical literature as a source for information. One said, when interviewed at home:

‘got books here, ones on drugs. And the other one, the other one, medical dictionary’ [P17]

And another participant commented during a focus group:

‘first of all it comes from the little leaflets and then you read about it further, and you can get the BNF online’ [P8]

3.3.3.2 Non-Adherence

Some participants spoke of non-adherence to medicine as a potential contributing factor to medication-related problems usually through simple forgetfulness, or cognitive impairment described by two carers:

‘He was different with the Alzheimer’s with regards his tablets. He was forgetting to take them and he’d go to bed’ [P15]

However, participants equally described intentional non-adherence (or self-management) as a direct consequence of experiencing side-effects or a lack of
information on how to use the prescribed medicines. One older man was experiencing severe pain during toileting, and commented on how he changed his use of a three-times a day prescription of codeine phosphate:

‘They said three a day but see they give me constipation, I know that much, they give me constipation, I take one at maximum a day’ [P14]

3.3.4 Participant beliefs

A prominent sub-theme that emerged was risk to benefit analysis where participants weighed up the benefits of medicine, such as additional life years, against the trade-off from any problems encountered irrespective of the impact on quality of life. There was also a tension between the participant’s expectations of medical treatment, based on implicit trust in their doctors, and their adverse lived experiences with some medicines.

3.3.4.1 Risk to Benefit analysis

There was a belief amongst several participants that medicines were keeping them alive in their older age, and this justified and associated discomfort as it was a trade-off. One lady described her dilemma in a focus group:

‘it’s a major problem because I’m now awake at night, it’s not life and death but it would be nice not to wake up itching all the time... I know I’ve got to take the tablets, because I’d like to be around for a little bit longer’ [P7]

3.3.4.2 Conflict between expectation and experience

There was a dichotomy between participant expectations, based on implicit trust in the medical profession, and their adverse lived experiences. This trust contributed to some of the participants continuing to use medicines despite their adverse effects.

One housebound lady described how she was suffering back pain but was prescribed an antidepressant from which she felt very unwell and yet continued to take it. She remarked:
‘they must help if the doctor gives them to you…but they’re not (helping), not in my body’ [P13]

Another participant, during a home interview, commented on his polypharmacy with nine daily medicines:
‘I often wonder if you take too much, is one lot having an effect on another lot, you know, but somebody should presumably, people monitor that but do they?’ [P16]

Regarding patient expectations around information provision, one older man said:
‘Well I trust my doctor to tell me but that’s a big mistake because they don’t, I will give you these for that and see how you get on, that’s all the information you get.’ [P17]

3.4 Discussion

This chapter describes the first community-based study in England exploring the lived experience of older people with MRH. Several key challenges are highlighted that are of concern to older patients; poor communication with prescribers, vulnerability during the transition of care at hospital discharge, inconsistency in medicines information and packaging, the onset of side-effects and difficulties in obtaining medical advice when encountering problems.

The importance of listening to patients’ narrative was highlighted in an article ‘Shared decision-making – The pinnacle of patient-centered care’ in the New England Journal of Medicine; ‘If we can view the health care experience through the patient’s eyes, we will become more responsive to patients’ needs and, thereby, better clinicians’.144

3.4.1 Communication and information support

Inadequate communication with healthcare professionals was a key theme in this study including passive listening, paternalism, insufficient information provision and inconsistent healthcare advice. Some participants reflected that had their concerns
been actively listened to, then subsequent medication harm might have been avoided. A study in the Netherlands compared the subjective reporting of medicine side effects by older patients with an objective measure of adverse drug reactions, and found that patient reports were accurate in nearly 80% of cases. Thus, a passive approach to patient concerns regarding adverse medication effects is poor clinical practice. Furthermore, a recent systematic review of patient perspectives found that patients recognise poor communication not only as a key risk factor for adverse events, but as an important adverse event in and of itself. The authors of this review concluded that efficient communication can therefore prevent the occurrence of physiological and psychological patient harm, and reduce the risk of litigation if harm does occur.

The sample of older adults in this study strongly felt that the medication related information provided was insufficient to meet their needs. Adequate information provision is crucial to obtaining informed consent to any treatment. However, clinicians are often in an inherently difficult position of balancing the benefits of providing detailed medicines information and the risks of doing so through the ‘nocebo’ phenomenon. In general, participants did not desire detailed information on the side-effects profile of medicines, but wanted clear and contextualised information on why they were prescribed a medicine and a discussion of the anticipated risks and benefits for them as individuals. A large questionnaire survey of ambulatory patients in the US found that an overwhelming majority of participants wanted information on potential side-effects of medication. Without the provision of information, patients are less able to participate in shared decision making despite often having a desire to do so. The WHO recognises this issue as key, describing in its 2017 report ‘medication without harm’ that ‘patients and the public are not always medication-wise. They are too often made to be passive recipients of medicines and not informed and empowered to play their part in making the process of medication safer’. The theme of inadequate information provision was closely related to a perceived lack of time for doctors to talk with patients. This is similar to findings in a qualitative study involving twelve frail older people in Sweden, where short
consultations and lack of physician support for adverse events was a source of insecurity.\textsuperscript{151}

One participant in this study described the lack of information provision and transparency by health practitioners as analogous to a ‘secret society’. This feeling that clinicians act as the ‘sole guardians of medical knowledge’ might be interpreted as a conscious or sub-conscious effort by the medical profession to reinforce the asymmetrical power balance inherent in the doctor-patient relationship. These observations are reminiscent of the ‘clinical gaze’ described by Michel Foucault in the mid-twentieth century, which suggested that modern medicine systematically elevated medical knowledge over the patient’s views and experience of illness.\textsuperscript{152}

3.4.2 Hospital discharge

The transition to home following a hospital admission was noted by participants to be anxiety-provoking and an important risk factor for MRP. The increased physiological vulnerability of older patients in this transition period has been referred to as a ‘post-hospital syndrome’.\textsuperscript{53} Participants highlighted that changes made to their medicines in hospital were not optimally communicated between secondary and primary care resulting in fragmented care and less vigilant monitoring in the post-discharge period. Information transfer to primary care at the time of hospital discharge is commonly delayed, often lacking in sufficient detail of post-discharge medications, and, in almost one in ten cases the discharge summary is never received in primary care.\textsuperscript{153} A previous study in the UK explored the hospital discharge experience of twelve carers and seven older people, in relation to their medicines management and organisation.\textsuperscript{55} The participants in the study by Knight \textit{et al} (2013) were not selected for their personal experience of MRP. Nonetheless, our findings resonate with this work in that participants in both studies identified delayed communication with insufficient information to primary care as a key concern.
3.4.3 Practical medication issues

Notenboom et al (2014) highlighted key practical problems that older people experience with medication use in the Netherlands, including issues of reading and comprehending information leaflets, handling medicines, the formulation and taking the medicine. These were all issues that were frequently mentioned by participants in this UK study; those issues were particularly prominent in older adults with sensory impairments. Additional issues such as the dispensing of medicines in foreign language packaging and inconsistent medicines usage information between drug manufacturers are risk factors for MRH that came up from this study. To overcome drug-specific risk factors will require the concerted efforts of the UK Medicines and Healthcare products Regulatory Agency (MHRA), the Royal Pharmaceutical Society and the Association of the British Pharmaceutical Industry.

3.4.4 Impact of adverse experience with medicine

The impact of adverse experience with medicines extended wider than the immediate physical manifestations of medicines side effects; for instance, participants described the erosion of their implicit trust in the healthcare system and practitioners, and their increased anxiety about using medicines more generally. This lasting impact of a negative experience can increase the likelihood of future adverse experiences through patients’ poor healthcare expectations and the ‘nocebo’ phenomenon.

Several factors play an important role in the complex relationship between the experience of ADRs and adherence to medicine, including the type of side-effect, patient education, comorbidity, anxiety and depression, stress, the provider-patient relationship amongst others. A complex relationship exists between side-effects and adherence to medicines from the older person’s perspective, and some participants believed that stopping their prescribed medicine following adverse effects was the correct approach, whilst others spoke of their body getting used to the medicines and others spoke of a trade-off required to obtain the medicine benefits.
A lack of patient knowledge and understanding of medication use is associated with non-adherence, and the data in this chapter support this. An anxiety and fear was reported by some participants that were prescribed medicines but with inadequate information for usage; their response was to avoid the medicines altogether rather than taking the medicine erroneously.

3.4.5 Limitations

This qualitative study was based on the experience of a small number of participants in one UK city, and therefore the results may not be applicable to other healthcare settings. A purposive sample of older people with experience of MRP were recruited, and this must be taken into consideration when interpreting the data. Almost all the older adults interviewed were ‘White British’ ethnicity, and therefore the findings may be poorly representative of the MRH experiences of older adults from other ethnic backgrounds.

3.5 Conclusions

This chapter has shown that the older person’s lived experience of medication problems is multidimensional and complex. This study has shown the qualitative impact of MRH on a sample of older adults that includes both highly independent and housebound people. Older people perceive that MRH in the post-discharge period results from several underlying factors, including lack of communication, uncoordinated processes around the transition of care, inappropriate prescribing, and poor drug formulation and packaging. Listening to the older person’s voice on the topic of medication problems provided a valuable insight to understanding the breadth and depth of the patient burden. The lived experience of patients is a crucial contribution to evidence-based medicine and should be used to inform the design of interventions to reduce the incidence of MRH. Within the programme of research reported in this thesis, the qualitative work underpins the importance of the quantitative work that follows. Neglecting the impact of MRH, as described through patient lived experience, would have missed the day to day impact on the
quality of life of older people. The richness of the feelings expressed by older people including confusion, anxiety, mistrust, confusion, disenchantedment and helplessness are a firm call to action for the healthcare profession.
CHAPTER 4.
The PRIME study: methods for a multicentre prospective cohort study to investigate medication-related harm following hospital discharge
Chapter Summary

This chapter describes the methods used for a multicentre prospective cohort study, the PRIME study, which informs the analyses in chapters 5 to 8. This observational study was designed to collect robust data on the epidemiology of MRH in older adults following hospital discharge in the South of England. The definition of medication-related harm included adverse drug reactions, harm experienced from poor adherence, and harm from medication error. The period of study observation within the community was 8-weeks. Participants were recruited by trained research nurses on medical wards of five teaching hospitals located in the South of England. Patients were recruited as near to planned hospital discharge as possible. Whilst all discharged older adults were eligible for recruitment, the recruitment strategy was based on available resources for follow up by senior pharmacists. Baseline data collection by nurses included patient demographics, clinical, psychological and social data. Trained, research pharmacists initially determined whether patients experienced MRH during follow-up using three sources (1) GP records, (2) patient/carer telephone interview, (3) clinical reviews of patients readmitted to hospital in conjunction with the medical consultant. Using these same data sources, any healthcare use associated with MRH was identified. The validated Naranjo algorithm was used to attribute causality of symptoms to adverse drug reactions. A modified Morisky medication adherence scale was used to identify poor adherence to medicines. An endpoint committee of senior pharmacists and geriatricians, independent from data collection, scrutinised and reviewed all cases of suspected MRH for final verification.
4.1 Introduction

Patient groups, Government and academic institutions all acknowledge the high risk of adverse health outcomes that older people experience in the immediate post-discharge period. The previous chapter (chapter 3) in this thesis explored the qualitative impact of MRH on older patients during the transition of care from hospital to home. It considered how medication problems arise from the views and experiences of patients themselves, and how these result in MRH. Chapter 2 showed the paucity of research internationally to investigate MRH in the vulnerable post-discharge period and identified the need for good data from a large multicentre, prospective study. Only eight studies were identified in a systematic search, with no UK study identified. The overall quality of these studies was moderate. Several methodological issues hindered a comprehensive understanding of the epidemiology of MRH in the post-discharge period. The selection of specific patient groups that were not necessarily representative of the average patient discharged from hospital, variation in MRH definitions and MRH assessment made it a challenge to collate the available literature. Exploration of MRH risk factors was limited in scope (i.e. did not investigate a range of biopsychosocial predictors) and depth (i.e. few multivariable analyses to identify independent predictors). Nevertheless, data from the systematic review strongly indicate that MRH is an important public health problem.

4.2 Using a public health approach to reduce MRH

This Chapter describes the methods for a multicentre, prospective cohort study in the South of England. Addressing a health problem such as MRH should be guided by core public health principles, including (1) data collection/surveillance to understand the nature and extent of a problem, (2) identifying risk factors associated with the problem and (3) using this information to develop an intervention that is evaluated and (4) subsequently scaled-up (see figure 4.1). Surveillance allows data to be captured, and this might occur through a national surveillance system like the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card ADR reporting scheme or through an observational research study. In the UK, the Yellow
Card scheme was introduced in 1964 in response to the deformities of infants born to mothers given thalidomide during pregnancy. The system collects patient and health professional reports of adverse drug reactions under certain circumstances, however the system is exceptionally under-utilised thus limiting its overall value. Best estimates from public survey have shown that only 8.5% of the public are aware of the reporting scheme,\textsuperscript{158,159} although this data was captured in 2009. Therefore, a prospective observational study involving a large cohort of older adults from multiple settings is an ideal study design to generate reliable data on the extent and nature of MRH in England. The PRIME study was designed to address this need. In this chapter, the methods for the PRIME study are reported. Data from the PRIME study are then used to inform the studies reported in the subsequent chapters in my thesis.

Figure 4.1 A public health approach to reduce MRH
Important data to be collected to understand the epidemiology of MRH can be conceptualised under a traditional disease causation multimodal approach\textsuperscript{160}. This classifies potential risk factors within a context of the agent, host and environment. Translating the model to MRH, the host is the older patient at risk, the agent is the medicine itself and the environment relates to the surroundings of the older person that influences their risk of medication problems. This conceptualisation supports an understanding of the variables chosen to investigate the problem of MRH. Medicine-specific variables, such as type, dose, frequency, previous adverse drug reaction, provides ‘agent’ specific and medication regimen complexity information which impact on MRH risk\textsuperscript{161}. Data regarding the patients themselves, including multimorbidity, cognitive function, psychological issues, substance misuse and sensory impairment are all pertinent to the susceptibility of the ‘host’ in the disease causation model. The risk for MRH that is generated by the ‘environment’ considers social support for the older adult, including packages of care, living arrangements (ie. with or without family members), inappropriate prescriptions, and inadequate information provision.

### 4.3 My involvement in the PRIME Study

My involvement in the PRIME study begun at the point of data collection once recruitment into the study had commenced. I was involved in collecting data from primary care, which was one of the key follow-up data sources for participants in the PRIME study. Thereon in, I was the primary researcher for all stages of the research as shown in the flow chart below.
4.4 Aims

The aim of the PRIME study was to collect the most robust UK data on the epidemiology of MRH and associated healthcare utilisation by older adults following hospital discharge. This data could subsequently be used to develop and validate a risk prediction tool for the identification of high-risk patients who would benefit from additional medication-related support.

4.5 Objectives

- To determine the incidence, severity and preventability of MRH
- To identify common MRH events and risk attributable to drug groups
- To evaluate NHS resources used secondary to MRH
- To identify risk factors for healthcare use secondary to MRH
- To develop and internally validate a risk prediction tool to identify older patients at high risk of MRH requiring healthcare use
• To compare the prognostic ability of the risk prediction tool with routine clinical judgement of discharging doctors

4.6 Design and recruitment sites

The PRIME study was an observational, prospective cohort study conducted at five NHS teaching hospitals in the South of England over a 2-year period (September 2013-November 2015). This study was led by the Academic Department of Geriatrics (Brighton & Sussex University Hospitals NHS Trust) in collaboration with the Department of Ageing and Health (Guy’s & St Thomas’ NHS Foundation Trust). The five hospitals participating in the study were (1) Royal Sussex County Hospital, Brighton, (2) St Thomas’ Hospital, London, (3) The Princess Royal Hospital, Haywards Heath, (4) The Queen Alexandra Hospital, Portsmouth, (4) Worthing Hospital, Worthing.

The Royal Sussex County Hospital is an acute teaching hospital, located in the city of Brighton and Hove, since 1828. It is administered by Brighton and Sussex University Hospitals NHS Trust. The hospital predominantly serves the population of Brighton and Hove, and much of East Sussex. The hospital is a tertiary centre for various specialties on the south coast of England, including trauma, cancer and HIV. Sussex itself, comprising East Sussex, West Sussex and Brighton and Hove, has a population of 1.6 million. The Princess Royal Hospital in the town of Haywards Heath is an acute teaching hospital founded in 1991, and, also administered by Brighton and Sussex University Hospitals NHS Trust. This is the main hospital for the Mid-Sussex area, serving a predominantly rural population.

St. Thomas’ Hospital is a large teaching hospital in central London, administrated by Guy’s and St Thomas’ NHS Foundation Trust (GSTFT). The capacity of GSTFT is 1200 hospital beds, with residents of the London borough of Lambeth and Southwark comprising the highest proportion of patients. However, St Thomas’ Hospital is a tertiary centre for many specialties such as paediatrics and rheumatology, and therefore also serves a wider population across London and farther afield.
Worthing hospital is a medium sized district general hospital founded in 1828 with approximately 500 beds. It provides a full range of acute services, from emergency to intensive care, maternity and general medicine and surgery. It is administered by Western Sussex Hospital NHS Foundation Trust. Worthing is a seaside town on the south-coast of England with a population estimated in the last census of 107,000. The Queen Alexandra Hospital in Portsmouth is administered by Portsmouth Hospitals NHS Trust and is a 1200 bed hospital. The hospital has 132,000 unplanned attendances per year. The hospital serves the population of the city of Portsmouth, Gosport and surrounding areas with an approximate population of 205,100 based on the 2011 census.

4.7 Patient recruitment

4.7.1 Inclusion and exclusion criteria

Hospitalised patients were eligible for recruitment providing they were aged 65 years or older, had a registered GP so that primary care follow-up information could be obtained. Eligible patients were included providing they could consent to their participation, or if they lacked capacity but a consultee could provide assent. Patients were not eligible for recruitment if they did not match these inclusion criteria or were terminally ill and unlikely to survive the 8-week follow-up period. Patients were additionally not eligible if they were transferring to another acute inpatient healthcare unit e.g. psychiatric unit, as this was not a discharge to the community.

Table 4.1 Criteria for patient recruitment into study

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 65 years or above</td>
<td>Patient lacks capacity and has no consultee</td>
</tr>
<tr>
<td>Registered with a General Practitioner</td>
<td>Patient transferring to another healthcare unit (excluding step-down facilities i.e. rehabilitation unit)</td>
</tr>
<tr>
<td>Consent (or assent) obtained</td>
<td>Patient has terminal illness with anticipated life expectancy of less than 8 weeks</td>
</tr>
</tbody>
</table>
4.7.2 Recruitment process

Recruitment of patients to the study occurred from elderly care and other general medical wards across the five hospitals over a 26 month-period, between September 2013 and November 2015. Patients were invited by Good Clinical Practice (GCP) trained research nurses to participate in this study once they had been deemed medically fit for discharge by the hospital ward team. Patients were recruited in strict accordance with the Declaration of Helsinki ‘Ethical Principles for Medical Research involving Human Subjects’, adopted by the World Health Assembly in 1964\textsuperscript{162}. Patients were provided verbal information to inform them of the purpose and process of participation in the study and were also provided with a patient information sheet with written details about the study and what participation would entail. Patients were given a minimum of 24 hours to decide if they wanted to take part in the study and if so, verbal and written consent was obtained as near to discharge as possible. Where a patient lacked capacity to consent, their next of kin was asked to act as a personal consultee and to support their relative taking part in the study. It was important to include those who lack capacity in this study, as we did not wish to exclude those older adults who are at particularly high risk of MRH\textsuperscript{93}. Capacity was assessed by the recruiting research nurses, who had undertaken capacity training in accordance with the Mental Capacity Act 2005. If a potential participant lacked capacity and the next of kin was not available, they were not eligible for study inclusion. Patients who consented were allocated a Unique Patient Identifier Number (UPIN), and all data collection was anonymised.
Figure 4.3 Process for recruitment and follow-up

Population
- Medically fit for discharge from older persons or general medicine ward, ≥65 years old

Recruitment - Inpatient ward
- Verify inclusion/exclusion criteria
- Written informed consent/assent
- Demographic data (e.g. age, gender, ethnicity)
- Clinical (e.g. past medical history, routine biochemistry)
- Social (e.g. living arrangements, care package)
- Medication (e.g. prescribed medication, use of compliance aid, regular community pharmacy)
- Nutritional status (MUST)
- Physical function (e.g. Barthel Index, Hand Grip)
- Cognitive function (AMTS)
- Depression and anxiety assessment (PHQ2, GAD2)
- Medical team prediction of MRH

Follow up (6 week period)

<table>
<thead>
<tr>
<th>Re-admission review (prospective)</th>
<th>Patient interview (retrospective)</th>
<th>GP records review (retrospective)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ADR causality assessment (Naranjo)</td>
<td>• ADR causality assessment (Naranjo)</td>
<td>• ADR causality assessment (Naranjo)</td>
</tr>
<tr>
<td>• Adherence (modified Morisky)</td>
<td>• Adherence (modified Morisky)</td>
<td>• Adherence (review of medication ordering)</td>
</tr>
<tr>
<td>• Healthcare utilisation (primary and secondary care services)</td>
<td>• Healthcare utilisation (primary and secondary care services)</td>
<td>• Healthcare utilisation (primary and secondary care services)</td>
</tr>
</tbody>
</table>

Final outcome
- Triangulation of follow up data
- Overall assessment of MRH
4.8 Baseline patient data collection

Baseline data was collected on a standardised Case Report Form (CRF) by the research nurses at all recruitment sites. This information was obtained from a combination of patients and/or carers, medical records, laboratory results and the medical team directly involved in the care of the patient. Using multiple sources enabled data collection that was as accurate and complete as possible. Baseline data to be collected was determined during face-to-face expert panel meetings, including senior academic and clinical geriatricians and pharmacists, and in consultation with existing literature in the area\textsuperscript{112}. Alongside standard patient demographic information (e.g. age, gender, ethnicity) and admission related information (e.g. admission and discharge diagnosis, length of stay, admission and discharge medicines, place of discharge), other variables were considered within a range of biopsychosocial domains to investigate new and existing MRH risk factors. Where possible, validated indices and instruments were used to measure variables.

4.8.1 Biological variables

*Disease Status*

Data pertaining to comorbidities was collected based on the validated Charlson Index\textsuperscript{163}, along with some other conditions that are not included in the index but are important comorbidities in older adults. Key conditions for which data was collected that is not in the Charlson Index are atrial fibrillation, Parkinson’s disease, anaemia, hypertension, osteoporosis, thyroid dysfunction, glaucoma, benign prostatic hypertrophy, peripheral neuropathy and hyperlipidaemia.

*Haematological and biochemical variables*

A range of laboratory data were collected pertaining to overall health status, inflammation and chronic disease in patients. These included some parameters that have previously been found to predict MRH, such as white cell count, glomerular filtration rate, albumin and, liver transaminases\textsuperscript{41,164–166}. Other parameters that have not previously been described in the literature such as sodium, potassium, and haemoglobin levels were explored in the PRIME study given their relevance to kidney
function, chronic disease, and drug-disease interactions which could impact on the risk of MRH. For instance, thiazide diuretic use in a mild and asymptomatic hyponatraemic patient could push them into a symptomatic and life-threatening hyponatraemia\textsuperscript{167,168}.

\textit{Frailty}

Frailty had not been explored using a validated indicator in relation to MRH. Hand Grip strength is a validated indicator of frailty status\textsuperscript{169}, and was measured in patients by trained nurses using the JAMAR Hydraulic Hand Dynamometer as detailed in the Southampton Protocol for Adult Grip strength Measurement\textsuperscript{170}. Functional deficits impacting on activities of daily living are also related to frailty, and the validated Barthel Index was used to measure functional dependence\textsuperscript{171,172}. The Barthel Index for activities of daily living assesses the functional dependence of older adults across a range of domains, including washing, grooming, eating, toileting, and mobility. The collection of a wide range of variables associated with impairment in older age and crossing multiple domains (i.e. biological, psychological and social), can be considered cumulatively in a ‘deficits’ model of frailty\textsuperscript{173,174}. The deficits model characterises frailty as an accumulation of deficits across a range of health domains. A frailty index can therefore be generated from different lists of variables, providing there are a sufficient number of potential health-related impairments (usually more than 30 advised) and they cross biological, psychological and social health-related domains\textsuperscript{173,175}.

\textit{Nutritional status}

Nutritional status was measured using the validated Malnutrition Universal Screening Tool\textsuperscript{176} (MUST) score, which is routinely captured on elderly care wards. It is a five-step screening tool to identify adults, who are malnourished or undernourished. The tool considers the individual’s body mass index, degree of unintentional weight loss over 3-6 months, and the effect that any acute disease might have on nutrition over the ensuing week.

4.8.2 Social Variables
Data was collected on the living arrangements for all patients, such as whether they are living alone or with relatives or friends, and their discharge destination. Social information relevant to medicines support for patients such as a care package, the use of a multicomartment compliance aid (MCA) e.g. a blister pack, or, a regular community pharmacist was collected. These impact upon a seamless supply and administration of medicine and can thus lead to harm. Other social data included smoking status, alcohol consumption and residential postcode for classifying socioeconomic status using deprivation quintiles on the Index of Multiple Deprivation (IMD) for England\textsuperscript{177}.

4.8.3 Psychological variables

Data was collected using validated tools for cognitive function, anxiety and depression. Cognitive function was assessed using the Abbreviated Mental Test Score (AMTS)\textsuperscript{178}, which is a routinely collected score in older patients that are hospitalised. It consists of ten short questions that can be rapidly administered and provide a valid screen for memory impairment. The AMTS has high sensitivity and specificity (>80\%) at a cut-off of 8. A rapid screening tool was used to assess patient’s for current depression, Patient Health Questionnaire-2\textsuperscript{179}. This is a validated two-item questionnaire that enquires about anhedonia and low mood. Similarly, a two-item screener was used to test for symptoms of anxiety. The Generalised Anxiety Disorder Scale-2\textsuperscript{180} enquires on how often patients experience uncontrollable worrying and feelings of nervousness.

4.8.4 Medicines information

Information on patient’s medicines, prescribed and over-the-counter, was recorded at hospital admission following medicines reconciliation by a hospital pharmacist. At discharge the information was taken from the patient discharge summary once approved by the ward pharmacist. Information of names, doses and frequencies of discharge medicines was recorded. If the patient was to be discharged with an MCA e.g. a blister pack, then this was recorded. Following data collection, all recorded
medicines were coded in accordance with the World Health Organisation Anatomical Therapeutic Classification (WHO-ATC). This is an international standard for the taxonomy of medicines into drug groups, enabling comparison of medicines-related data across international studies.

Table 4.2 WHO-ATC codes used to attribute commonly used drugs to specific medicine groups

<table>
<thead>
<tr>
<th>Selected Medicine Groups</th>
<th>WHO-ATC codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>J01</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>N04A, R03BB, S01FA</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>B01AA, B01AB, B01AE, B01AF, B01AX</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>N06A</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>N03A</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>C02, C03A, C03B, C07, C08, C09</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>B01AC</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>N05BA, N05CD, N03AE01, N05CF02</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>H02, A07EA01</td>
</tr>
<tr>
<td>Diuretics</td>
<td>C03</td>
</tr>
<tr>
<td>Hypoglycaemics</td>
<td>A10A, A10B</td>
</tr>
<tr>
<td>Laxatives</td>
<td>A06A</td>
</tr>
<tr>
<td>Opioids</td>
<td>N02A, R05DA04</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>N05A, N05B, N05C</td>
</tr>
</tbody>
</table>

4.9 Defining Medication-Related Harm

As described in chapter 1 and chapter 2, various phraseology has been used to describe harm that patients encounter in relation to their medicines. Terms include adverse drug reactions, adverse drug events, adverse drug effects, drug-related problems. There is no accepted definition internationally, and definitions of the same terms can vary, and even be contradictory. For example, the WHO definition of ADR stipulates ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’.
error), whereas the definition by Edwards and Aronson (2000) includes ADR related to alternative doses that might have arisen by error\textsuperscript{73}. The common exclusion of MRH due to non-adherence and medical error in ADR studies does not reflect the reality of patient experience\textsuperscript{37} or clinical practice\textsuperscript{38}. Indeed, non-adherence is a very common medication-related problem\textsuperscript{20,38} and is associated with serious adverse health outcomes\textsuperscript{181}. Other studies that have used the broader term of adverse drug events have also been inconsistent in their use of definitions, making comparisons in the literature very challenging. For instance, a population-based retrospective study of medical records of all patients in a region of Sweden included intentional drug overdoses in their definition of ADE\textsuperscript{182}, which contrasts with the major multicentre ‘HARM’ study across the Netherlands which excluded intentional drug overdoses\textsuperscript{183}. Whilst a seminal paper of terms to describe harm from medicines indicates that a failure to use medicines is not an adverse drug event on the grounds that complete non-adherence is not a use of medicine, many studies do include harm from non-adherence as a ADE\textsuperscript{35,92,183,184}.

The PRIME study used the term ‘Medication-Related Harm’ (MRH), as outlined in the introduction to this thesis. This term included ADR or harm arising from a failure to receive medication due to non-adherence. Harm arising from medication error was included where reported. Intentional overdose was excluded. Adverse drug reactions were defined as a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’.\textsuperscript{75} This definition is guided by the definition of a drug-related problem by Strand et al (1990) ‘an event or circumstance involving drug treatment that actually or potentially interferes with the patient’s experiencing an optimum outcome of medical care’.\textsuperscript{185} The PRIME study did not seek to identify potential harm, in contrast to the Strand et al (1990) definition. A medicine was defined by its inclusion in the World Health Organisation-Anatomical Therapeutics Coding (WHO-ATC) system.\textsuperscript{90} This definition was agreed by a multidisciplinary expert panel including two Professors of geriatric medicine, UK and Netherlands; two consultant geriatricians, UK; one Professor of clinical pharmacy and therapeutics, UK; two clinical pharmacists specialising in geriatrics, UK. The terminology ‘medication-related harm’ is consistent with the WHO’s global safety challenge (2017), which sets a target for nations to reduce severe avoidable
MRH by 50% over 5 years\textsuperscript{29}. This key report targeted at policymakers globally shifts the focus of medication safety from the pharmacovigilance terminology of ADRs to the more patient-centered concept of MRH, which includes both appropriate and inappropriate medicines use.

4.10 Causality of MRH

There is no gold standard approach to attributing causality of symptoms that may be MRH to a medicine rather than to an alternative agent or the symptoms of underlying disease itself\textsuperscript{109}. There is invariably a strong degree of clinical judgement involved given the non-specific nature of many symptoms of MRH e.g. nausea, dizziness, pruritus, fatigue. Highly specific symptoms such as tardive dyskinesia with an antidopaminergic drug e.g. metoclopramide, or gynaecomastia with antiandrogenic drug e.g. finasteride, are easier to attribute causally to a particular medicine but are rarer than the non-specific symptoms. Therefore the PRIME study combined expert, multidisciplinary opinion with the use of the validated Naranjo algorithm\textsuperscript{110}, British National Formulary (BNF) and Summary of Product Characteristics (SPC) by senior pharmacists to maximise the likelihood of accuracy in attributing causality\textsuperscript{111}. Two senior study pharmacists provided case-based training to research pharmacists involved in data collection at all participating sites to optimise the reliability of MRH assessments. Additionally, cross-site case discussions were regularly held between the research pharmacists to ensure standardisation of MRH assessments. The Naranjo Algorithm was originally devised to assess causality of inpatient ADR and maximise interrater reliability. Although many methods exist, the Naranjo algorithm is the most widely used method internationally to assess ADR causality\textsuperscript{109}. The algorithm assesses causality based on 10 questions with a weighted answer of ‘yes’, ‘no’ or ‘don’t know’ relevant to the reaction and associated medicine use (Table 4.3). The scores are summed and probability of an ADR classified as doubtful (0), possible (1-4), probable (5-8), definite (>8). It was acknowledged that two assessment questions are not applicable to the PRIME study as it would be unethical to readminister a medicine believed to cause harm or trial a placebo to determine if the reaction reappeared. Therefore, using the Naranjo algorithm on its own skews causality assessments away from attributing causation of symptoms to a
drug. To mitigate this, pharmacists used the Naranjo algorithm in conjunction with established resources including the BNF and SPC in order to make an initial informed judgement of causality. This was then adjudicated further by an End Point Committee (EPC) independent of data collection. The EPC consisted of three senior geriatricians and a senior academic in clinical pharmacy, who were provided structured case summaries of MRH cases by the research pharmacists. The role of the committee was to review, scrutinise and finally confirm or reject these cases by consensus. This process provided an additional level of standardisation of MRH assessment.

Table 4.3 Adverse drug reaction causality assessment based on the Naranjo Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>Weighting of answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous reports on this reaction?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
<tr>
<td>Did the adverse event appear after the suspected drug was administered?</td>
<td>Yes (2), No (-1), Don’t Know (0)</td>
</tr>
<tr>
<td>Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
<tr>
<td>Did the adverse reaction reappear when the drug was readministered?</td>
<td>Yes (2), No (-1), Don’t Know (0)</td>
</tr>
<tr>
<td>Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>Yes (-1), No (2), Don’t Know (0)</td>
</tr>
<tr>
<td>Did the reaction reappear when a placebo was given?</td>
<td>Yes (-1), No (1), Don’t Know (0)</td>
</tr>
<tr>
<td>Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
<tr>
<td>Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
<tr>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>Yes (1), No (0), Don’t Know (0)</td>
</tr>
</tbody>
</table>

It is prudent to remember the true words of epidemiologist, Sir Austin Bradford Hill, to whom the so-called Bradford-Hill Criteria for causality are attributed. Indeed, Sir Austin Bradford Hill actually wrote in his famed 1965 paper ‘The Environment and disease: Association or causation?’, “what I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect.” This is especially important in
the context of MRH where evidence shows that the nocebo phenomenon exists. This describes MRH which is psychosomatically grounded, rather than a direct effect of the pharmacological properties of a drug. Whilst the cause may not itself be the pharmacology of the drug, the impact of taking the medicine on the patient’s quality of life and well-being and use of healthcare services for symptoms has widespread implications. This should not be discounted given that clinical trials of medicines have shown that up to one in four patients taking placebo may drop out due experiencing adverse symptoms i.e. perceived MRH.

4.11 Medication non-adherence

Non-adherence to medicine was evaluated in the PRIME study using multiple methods. There is no gold standard approach for measuring adherence. Nine questions were asked to participants during a follow-up semi-structured telephone interview based on the validated 4-item Morisky Medication Adherence Scale, and this was used in conjunction with primary care records showing the dates of issue and re-ordering of medication for patients. The questions that were asked by pharmacists to make a clinical judgement on patient adherence are shown in Table 4.4.

Table 4.4 Evaluation of patient adherence to medications

<table>
<thead>
<tr>
<th>Questions to elicit medication non-adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you forget to refill your prescription on time?</td>
</tr>
<tr>
<td>2. Are you careless at times about taking your medicines?</td>
</tr>
<tr>
<td>3. When you feel better do you sometimes stop taking your medicines?</td>
</tr>
<tr>
<td>4. Sometimes if you feel worse when you take your medicines do you stop taking it?</td>
</tr>
<tr>
<td>5. Do you ever forget to take your medicine?</td>
</tr>
<tr>
<td>6. Do you know the long-term benefits of taking your medicine as told to by your doctor?</td>
</tr>
<tr>
<td>7. Do you find it difficult to get the GP, hospital pharmacy to obtain supply?</td>
</tr>
<tr>
<td>8. Do you find it difficult to get the medication out of the packet or use the device e.g. inhaler?</td>
</tr>
<tr>
<td>9. When you left hospital did you stop taking any of your medication because you were unsure if you had to keep taking them?</td>
</tr>
</tbody>
</table>
4.12 Severity of MRH

Classification of MRH severity was based on the guidance of Morimoto et al (2004). The severity of MRH is an important consideration because all drugs have inherent toxicity but the severity of the incident might dictate the risk to benefit analysis of continuing use of the medicine. Nonetheless, severity can be determined from various perspectives; the prescriber, the patient or the healthcare system. The classification by Morimoto et al (2004) is based on the judgement of expert health professionals, but does partly include the healthcare system perspective by incorporating ‘additional healthcare visit’ into the severity grading. There are no MRH severity classifications that have been published to classify MRH severity from a patient perspective as opposed to a clinical perspective. Whilst one hopes that the two perspectives commonly overlap, the findings of chapter 3 showed that constipation or pruritus deeply impact on a patient’s quality of life but might not receive urgent clinical attention. In contrast an acute kidney injury would demand an urgent clinical review although it is most likely the patient’s asymptomatic. This is not to disparage the significance of a kidney injury as it can of course be life-threatening, but just to exemplify the validity of Greenhalgh et al’s argument that ‘evidence-based medicine’ is in some ways biased against patients.

Table 4.5 Morimoto et al (2004) classification of MRH severity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>Patient died due to the incident</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Patient transferred to the intensive care unit. Patient has an anaphylaxis. The MRH results in mental status change.</td>
</tr>
<tr>
<td>Serious</td>
<td>Additional healthcare visit for treatment or additional medications. Gastrointestinal bleed, altered cognition, kidney injury, postural hypotension and light-headedness, allergic reaction.</td>
</tr>
<tr>
<td>Significant</td>
<td>Any significant event that is identified by the patient but not requiring a change in therapy.</td>
</tr>
</tbody>
</table>

4.13 Preventability of MRH

The large variation in MRH rates post-discharge, shown in Chapter 2, indicates that MRH is preventable in some cases. One well established set of criteria are those
published by Hallas et al (1990). Identifying the incidence of preventable MRH events is an important indicator for the scope of potential harm reduction.

Table 4.6 Hallas et al (1990) classification of MRH preventability

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely preventable</td>
<td>Treatment inconsistent with current knowledge of good medical practice or was unrealistic taking circumstances into account.</td>
</tr>
<tr>
<td>Possibly preventable</td>
<td>Event could have been avoided by an effort exceeding obligatory demands.</td>
</tr>
<tr>
<td>Not preventable</td>
<td>Could not have been avoided by any reasonable means.</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>Could not be classified as insufficient information to make judgement.</td>
</tr>
</tbody>
</table>

4.14 Follow-up

Consented patients were followed up in the community for an eight-week period after hospital discharge. Three data sources were used; patient (or carer) self-report by semi-structured telephone interview, GP records and hospital readmissions. Hospital readmissions prospectively captured MRH, whilst the GP records and patient interview were conducted at 8 weeks and therefore were retrospective sources of MRH data. Cases of MRH were categorised based on the likelihood that harm had occurred into doubtful, possible, probable and definite. This is consistent with other studies in this research area.

4.14.1 Telephone Interview

Eight-weeks following hospital discharge, the research pharmacist at each site conducted a retrospective telephone interview with the patient and/or carer using a standard questionnaire to identify potential MRH. The patient was asked whether they had encountered any unwanted reactions or effects from their medications. The patient’s adherence to their medications was determined using a modified version on the 4-item Morisky scale. Patients were also asked about their health service utilization over the preceding 8 weeks (including GP visits, out of hours visits,
outpatient specialist appointments, hospital attendance/re-admissions). Patients were specifically asked about the date and reason for their consultations to establish which of the consultations were associated with MRH. Patient self-reported MRH has been shown to provide important and reliable additional data190,191.

4.14.2 Primary care records

Access to patient primary care information from GP surgeries for the 8-week follow-up period was facilitated by the UK Primary Care Research Network. At the 8-week point a letter was sent to the patient’s GP surgery requesting a copy of the patient records for the 8-week observation period. The records were then reviewed thoroughly to elicit whether a consultation took place associated with MRH. In addition to this, medication orders were reviewed to indicate the level of patient adherence to their prescribed medicines.

4.14.3 Hospital readmissions

Participants readmitted to hospital within 8 weeks of discharge were all prospectively reviewed to elicit whether MRH was a cause of the readmission. This assessment was made by the pharmacist in conjunction with the medical consultant in charge of overseeing the patient’s hospital admission. Information was gathered to build a case history for readmitted patients, including the presenting clinical history, their current medications and any recent changes, the ADR profile of the prescribed medicines, an assessment of patient adherence, relevant comorbidities to identify disease-drug interactions, and any relevant clinical observations and investigations.

4.15 Data triangulation

For each participant, a final stage of data convergence took place with the benefit of all data sources (i.e. patient interview, GP data and hospital readmission data where applicable). This stage was conducted by myself in conjunction with Dr Khalid Ali (Chief Investigator and Geriatrician) and Professor Graham Davies (Chief study doctor).
pharmacist). Based on the three data sources, the data convergence process generated the final overall output for each participant for the following outcomes:

1. Has the patient suffered MRH? (Definite; Probable; Possible; Doubtful)
2. Was the MRP preventable? (Definite; Possible; Not preventable)
3. What was the severity? (Fatal; Life threatening; Serious; Significant)
4. What was the main cause? (ADR; Non-adherence; Error, combination)
5. What was the MRH event?
6. What were the implicated drug(s)?

Consistent with other studies, participants that experienced ‘possible’, ‘probable’ or ‘definite’ MRH events were classified as MRH cases and those participants with a ‘doubtful’ outcome were the participants with no MRH. In the case of different sources attributing different medications to a single event, then the readmission data and the primary care records took precedence over the participant’s self-report. The rationale behind this decision was the independent clinical judgement that accompanied the primary care data (ie. the GP) and hospital readmissions (ie. the admitting medical consultant). Additionally, readmission data and the recording of GP notes was prospective, whilst participant interviews were retrospective and therefore recall bias was a limitation.

4.16 Withdrawal arrangements

Any patient that asked to be withdrawn from the study following recruitment was offered the opportunity do so at any point without need to provide explanation.

4.17 Loss to follow up

Every effort was made by the research pharmacists to trace participants to prevent loss during the follow up period. This entailed up to a total of twenty telephone attempts on different days following the 8-week period, and efforts made to contact GPs with up to two reminder letters for the sharing of their records on the participant
for the preceding 8 weeks. Due to resource limitations, participants that were readmitted to and discharged from hospital within one weekend would not be prospectively reviewed and recorded. However, this information would either be sought through the primary care records or participant interview at the 8-week follow up.

4.18 Reporting of adverse events

Medication-related harm was discussed by the local investigators and the end-point committee as required, and the participant’s admitting physician or GP was notified if indicated.

4.19 Sample size

A sample size calculation was performed assuming a sensitivity of 80% with a 95% confidence interval width of 5% around the best estimate (i.e. sensitivity 0.80, 95% CI 0.75-0.85), and based on an MRH prevalence rate of 30%\textsuperscript{193,194}. The nomogram designed by Carley et al (2005)\textsuperscript{195}, based on the work of Buderer et al (1996)\textsuperscript{196}, was used to determine a sample size of 1500 patients. This calculation was based on the anticipated development of a risk prediction tool from the data collected in the PRIME study (detailed in chapter 8). The preliminary methods for the development of a risk prediction tool required a split-sample validation method, where the recruited population would be split to form a ‘derivation cohort’ for developing a risk prediction model and the other 50% cohort would be the validation sample. More recently ‘bootstrap’ resampling methods have demonstrated less bias during out-of-sample validation of risk prediction tools in comparison with a split-sample approach\textsuperscript{197}. The bootstrap method removes the need to split the sample. On this basis, the sample size required to estimate population parameters in the PRIME study e.g. incidence of MRH, with a precision of 80% sensitivity and width of the 95% confidence interval no greater than 5% is approximately half of the original calculation (n=820)\textsuperscript{196}. 

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4.20 Data protection

All patients were given a unique participant identifying number to preserve confidentiality. This number was entered into a password protected database using Microsoft Excel, and only traceable to an individual participant by accessing the CRF for the patient from a secure location at the Research and Development department at each study centre. The CRF was generated using Formic Solutions version 5.51 build 005 computer software. This software enabled data to be scanned directly from the CRFs into an electronic database that could be exported into Microsoft Excel. Data cleaning with validation checks took place in Microsoft Excel, after which data was exported to statistical software packages (SPSS and Stata) for various analyses. All electronic data was password protected and only core members of the research team had access to the full set of electronic data generated within the study.

4.21 Ethical Approval

The PRIME study protocol was approved by the National Research Ethics Service, East of England (Norfolk; REC Reference 13/EE/0075), and was funded by the National Institute of Health Research (NIHR)- Research for Patient Benefit (RfPB) (PB-PG-0711-25094) The study was adopted as a Clinical Research Network Portfolio study (Ageing and Primary Care). The sponsor was Brighton and Sussex University Hospitals NHS Trust. The funder and sponsor had no role in the PRIME study design; data collection, analysis, or interpretation; in the writing or the decision to submit work arising from the study for publication.
CHAPTER 5.
PRIME study results: demographics, incidence, severity and preventability of medication-related harm
Chapter Summary

This chapter presents the descriptive results of the PRIME study, the methods for which were detailed in Chapter 4. One thousand two hundred and eighty (1280) adults aged 65 years and above were recruited at hospital discharge to the study, of which 1116 (87%) completed follow-up. There were no clinically significant differences between the patients that completed follow-up and those that did not. The median age of those followed up was 82 years, and 58% were female. Over half of the patients (52%) had two or more comorbidities defined by the Charlson Index, and the median number of medicines that patients were discharged with was 9 (IQR 7-12). There were 556 events of medication-related harm (MRH) per 1000 patients discharged. These events were experienced amongst 413 patients, 37% of those followed-up. Out of 413 patients that experienced MRH, 81% of cases were serious and 52% potentially preventable. Four patients experienced MRH that was fatal for them. The most common MRH events were gastrointestinal (n=158, 25%) and neurological (n=111, 18%). Medicine classes associated with the highest risk of MRH were opiates (399 events per 1000 prescriptions), antibiotics (189 events per 1000 prescriptions), and benzodiazepines (185 events per 1000 prescriptions). Potentially inappropriate medications (PIMs) were determined using the Beers 2015 criteria for medicines to avoid in older adults. Two hundred and seventy-six patients (22%) were prescribed one or more PIMs at hospital discharge. The main PIM classes prescribed at hospital discharge were benzodiazepines and related drugs (30%) and antidepressants (27%). In 51 cases (12%), MRH was attributable to a PIM.
5.1 Introduction

As demonstrated by the systematic review in chapter 2, there is no published literature on the epidemiology of medication-related harm in older adults following hospital discharge in England. This was surprising given the fact that the transition period from hospital to home is a high-risk period for medication-related problems. Nonetheless, there have been studies in England that have looked at MRH identified within the hospital setting. Tangiisuran et al (2012) studied four elderly care medical wards in one hospital. They prospectively followed 560 older adults (aged 80 years or above), and observed an incidence of adverse drug reactions of 13.2%. Pirmohamed et al (2004) investigated the proportion of hospital admissions caused by ADR amongst all aged adults in two English hospitals, and reported that 6.5% of hospital admissions were caused by ADR (median age of those with ADR was 76 years and those without was 66 years). The lack of studies in the community setting to explore the post-discharge high-risk period is likely in part to reflect the increased challenge and resource required to follow up older adults in the community. The PRIME study was designed and conducted to address this gap in the literature.

My aims for the study described in this chapter were to use the PRIME study data to:

1. determine the incidence, severity and preventability of MRH post-discharge in older adults,
2. describe the main MRH events and implicated medications,
3. report on potentially inappropriate prescribing at hospital discharge.

All the work undertaken in this chapter from collecting patient data and data validation to designing and conducting analysis and interpretation is my own.
5.2 Patient Recruitment

The study recruitment period started in September 2013 and ended in November 2015. During this time, 2990 patients were screened near to their hospital discharge from 25 wards of 5 hospitals in the South of England (Table 5.1). Patients were approached for study participation if they met the study inclusion criteria. All patients aged 65 years or above were eligible for recruitment, except those that were terminally ill and not expected to survive the follow-up period, those that had no capacity and no consultee, and those that were to be transferred to another acute health unit e.g. psychiatric unit. The study design was complex, involving considerable resource related to the follow-up of patients by senior pharmacists to determine MRH, including hospital readmission. The sampling strategy was based on the resource available to conduct both the recruitment (in hospital) and comprehensive patient follow up in the community (patient/carer interview, examination of primary care records, prospective review of all readmissions). Although it was not possible within available resources to screen every older patient admitted to the recruiting wards of the five hospitals, the sampling strategy enabled a very high completion rate (68%) compared to prior research in this field (55%)\textsuperscript{198}. 
Table 5.1. Patient recruitment at five hospitals in the South of England

<table>
<thead>
<tr>
<th></th>
<th>Royal Sussex County Hospital</th>
<th>Queen Alexandra Hospital</th>
<th>Princess Royal Hospital</th>
<th>St Thomas' Hospital</th>
<th>Worthing hospital</th>
<th>Total/Average (5 hospitals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wards</td>
<td>5 elderly care; 2 general medicine; 1 respiratory,</td>
<td>3 elderly care; 1 cardiac; 1 respiratory; 2 general medicine; 2 surgical</td>
<td>2 general medicine; 1 respiratory</td>
<td>3 elderly care</td>
<td>1 elderly care; 1 cardiac</td>
<td>25 hospital wards</td>
</tr>
<tr>
<td>Screened</td>
<td>468</td>
<td>555</td>
<td>411</td>
<td>1122</td>
<td>436</td>
<td>2990</td>
</tr>
<tr>
<td>Consented</td>
<td>199 (16)</td>
<td>227 (18)</td>
<td>219 (17)</td>
<td>397 (31)</td>
<td>238 (19)</td>
<td>1280</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>80</td>
<td>78</td>
<td>80</td>
<td>83</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Gender (female, %)</td>
<td>59%</td>
<td>49%</td>
<td>56%</td>
<td>65%</td>
<td>58%</td>
<td>58%</td>
</tr>
<tr>
<td>Not consented</td>
<td>269</td>
<td>328</td>
<td>192</td>
<td>725</td>
<td>198</td>
<td>1710</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>N/A</td>
<td>80</td>
<td>83</td>
<td>83</td>
<td>N/A</td>
<td>82</td>
</tr>
<tr>
<td>Gender (female, %)</td>
<td>59%</td>
<td>56%</td>
<td>50%</td>
<td>60%</td>
<td>N/A</td>
<td>58%</td>
</tr>
</tbody>
</table>

There were no major differences in age and gender of those patients screened and those recruited; there were 1280 patients recruited out of 2990 screened, with average age of those consented 81 (vs 82 of those not consented), and 58% of both groups were female gender.

5.3 Patient follow-up

From the 1280 recruited patients, 17 (1.3%) died without follow-up, and 147 patients (11.5%) were lost to follow-up because they were not readmitted, their GP records were unavailable, and they could not be contacted. Research pharmacists completed a telephone interview with 873 patients (68.2%) and retrieved GP records of 922 patients (72.0%). Therefore, our final cohort included 1116 (87.2%) patients (Figure 5.1).
Figure 5.1 Flow chart of screening to final cohort for data analysis

- Patients screened (n=2990)
- Patients meeting inclusion criteria and giving informed consent (n=1280)
- Cohort for data analysis (n=1116, 87.2%)
- Lost to follow up, total n=164, 12.8% (Death with no follow-up, n=17, 1.3%; no patient interview, GP records or hospital readmission (n=147, 11.5%)

### 5.4 Statistical Analysis

The distributions of variables were examined using histograms and were described by their medians and interquartile ranges (IQR) due to evident skewness. For categorical variables, frequencies and percentages were used to describe the data. The characteristics of the cohort included in the final analysis with those lost to follow-up in Table x were compared using the Mann-Whitney U-test. Fisher’s Exact Test was used to compare categorical variables.

Incidence of MRH is reported as (1) an incidence proportion (number of patients experiencing MRH/total sample), and, (2) incidence of events per 1000 discharged patients (number of events x 1000/total sample). Other descriptive statistics are based on frequency calculations. Incidence proportions are presented with accompanying 95% confidence intervals. Data were analysed using IBM SPSS Statistics, version 22, IBM corporation, Armonk, NY.
5.5 Baseline patient characteristics

There were no significant differences in the baseline demographic, clinical or social characteristics of included and excluded patients, with the exception that included patients were marginally more functionally dependent (Barthel Index 17 versus 18 out of 20, \(P=0.04\)) (Table 5.2). The median age of the patients that completed follow-up was 82 years (IQR 76-87) and 58% were female. The median length of hospital stay of the patients was one week, and more than half had two or more serious comorbidities. The primary discharge diagnosis of the final cohort was most frequently a respiratory, musculoskeletal or cardiovascular illness (Figure 5.2). Approximately five percent of the cohort had a diagnosis of dementia, and 50% lived alone following discharge. The median number of medicines that patients were prescribed at discharge was 9 (IQR 7-12).
Table 5.2 Baseline patient characteristics of included and excluded patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included patients† (n=1116)</th>
<th>Excluded patients (n=164)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>81.9 (75.5-86.9)</td>
<td>80.5 (74.7-86.2)</td>
<td>0.123</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>652 (58.4)</td>
<td>93 (56.7)</td>
<td>0.673</td>
</tr>
<tr>
<td>Men</td>
<td>464 (41.6)</td>
<td>71 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, median (IQR), days</td>
<td>7 (3-14)</td>
<td>7 (3-13)</td>
<td>0.595</td>
</tr>
<tr>
<td>Number of Charlson Index comorbidities (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>541 (48.5)</td>
<td>88 (53.7)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>575 (51.5)</td>
<td>76 (46.3)</td>
<td></td>
</tr>
<tr>
<td>Selected comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>611 (54.7)</td>
<td>86 (52.4)</td>
<td>0.615</td>
</tr>
<tr>
<td>CLD</td>
<td>326 (29.2)</td>
<td>56 (34.1)</td>
<td>0.202</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>279 (25.0)</td>
<td>43 (26.2)</td>
<td>0.773</td>
</tr>
<tr>
<td>Diabetes</td>
<td>269 (24.1)</td>
<td>31 (18.9)</td>
<td>0.167</td>
</tr>
<tr>
<td>IHD</td>
<td>224 (20.1)</td>
<td>38 (23.2)</td>
<td>0.352</td>
</tr>
<tr>
<td>CKD</td>
<td>150 (13.4)</td>
<td>20 (12.2)</td>
<td>0.713</td>
</tr>
<tr>
<td>CCF</td>
<td>150 (13.4)</td>
<td>20 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>51 (4.6)</td>
<td>6 (3.7)</td>
<td>0.839</td>
</tr>
<tr>
<td>Dementia</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td>0.087</td>
</tr>
<tr>
<td>Charlson index, median (IQR)</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td></td>
</tr>
<tr>
<td>Barthel Score, median (IQR)</td>
<td>17 (13-20)</td>
<td>18 (14-20)</td>
<td>0.035</td>
</tr>
<tr>
<td>Hand grip strength*, median (IQR)</td>
<td>18 (12-24)</td>
<td>18 (12-26)</td>
<td>0.345</td>
</tr>
<tr>
<td>Falls* (2 or more in last year), n (%)</td>
<td>401 (36.4)</td>
<td>57 (35.2)</td>
<td>0.794</td>
</tr>
<tr>
<td>Number of discharge medicines, median (IQR)</td>
<td>9 (7-12)</td>
<td>9 (6-12)</td>
<td>0.393</td>
</tr>
<tr>
<td>Multicompartment compliance aid, n (%)</td>
<td>371 (33.2)</td>
<td>43 (26.2)</td>
<td>0.074</td>
</tr>
<tr>
<td>Discharge to care home, n (%)</td>
<td>30 (2.7)</td>
<td>8 (4.9)</td>
<td>0.136</td>
</tr>
<tr>
<td>Living alone after discharge, n (%)</td>
<td>551 (49.4)</td>
<td>80 (48.8)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

IQR, interquartile range; CLD, chronic lung disease; IHD, Ischaemic Heart Disease; CKD, Chronic Kidney Disease; CCF, Congestive Cardiac Failure. †Ten patients were included following readmission which was not associated with MRH, for whom GP records were not available and were uncontactable at 8-weeks (median follow-up 29 days after recruitment). *Mann-Whitney U test for continuous variables and Fisher’s Exact test for categorical variables. *Missing data for hand grip strength, n=164, falls, n=15.
5.6 Incidence of MRH

Four hundred and thirteen patients (37%) experienced MRH over the 8-week follow-up period. Consistent with other studies, patients that experienced ‘possible’, ‘probable’ or ‘definite’ MRH events were classified as MRH cases and those patients with a ‘doubtful’ outcome were the patients with no MRH. A total of 856 medicines were implicated in 621 events. The incidence of MRH was 556 events per 1000 discharged older adults within 8-weeks.

As outlined in the methods (chapter 4), patient follow-up over the 8-week timeframe included semi-structured telephone interviews, review of GP records and reviewing hospital readmissions. Out of the 413 patients that experienced MRH, 64% of patients were identified through one data source and 36% from two or more concordant sources (Table 5.3).
Table 5.3 Sources of data for patients experiencing MRH

<table>
<thead>
<tr>
<th>Number of sources (Telephone interview, GP records, Hospital readmission)</th>
<th>Patients n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>266 (64.4)</td>
</tr>
<tr>
<td></td>
<td>Telephone Interview (n=129)</td>
</tr>
<tr>
<td></td>
<td>GP records (n=123)</td>
</tr>
<tr>
<td></td>
<td>Hospital readmission (n=14)</td>
</tr>
<tr>
<td>2</td>
<td>127 (30.8)</td>
</tr>
<tr>
<td>3</td>
<td>20 (4.8)</td>
</tr>
</tbody>
</table>

Four hundred and sixty MRH events (74%) were attributable to medicines prescribed at hospital discharge, with the remainder prescribed in the community during the 8-week observation period.

Of the 413 patients classified as experiencing MRH, 246 (60%) experienced at least one MRH event considered ‘probable’ (n=110) or ‘definite’ (n=136). The remaining cases were ‘possible’ (n=167) (table 5.4).

Adverse drug reactions were solely responsible for MRH in 301 out of the 413 patients that experienced MRH (72.9%), non-adherence in 45 patients (10.9%), and a medication error in 14 patients (3.4%) (see Table 5 for case examples). In five cases (1.2%) the patient experienced harm from both an ADR and a medication error. The underlying medication error was at the stage of prescribing in 11 cases, dispensing in four cases, administration by carer in three cases and patient error in the use of a medicine administration device in one case. In 48 patients (11.6%) harm was due to both an ADR and non-adherence. For instance, a patient experienced a gastric bleed associated with antiplatelet therapy but was also non-adherent to their proton-pump inhibitor. Indeed, at the point of follow-up 325 out of 1112 patients (29.2%) with complete adherence data were non-adherent to at least some of their medicines.

A quarter of adverse drug reactions occurred in the first week following hospital discharge, and 68% occurred within 30 days post-discharge.
5.7 Severity of MRH

The classification of MRH severity was based on the guidance of Morimoto et al. (2004), as detailed in chapter 4. Four patients (1%) experienced a fatal event associated with the MRH; one died following a fall and fractured neck of femur associated with lorazepam use, one from a major gastrointestinal bleed associated with use of Apixaban, one from a stroke associated with non-adherence to warfarin and one death from a lower respiratory tract infection associated with prednisolone-induced immunosuppression. Nine patients (2.2%) had a life-threatening event, and MRH was serious in a further 323 patients (78.2%). Use of healthcare for MRH is an objective measure of the severity of an event, with the caveat of variation in health-seeking behavior amongst people. In Morimoto et al.’s (2004) criteria, an ‘additional healthcare visit for treatment or additional medications’ is a key escalation step in distinguishing serious MRH from significant MRH. The use of healthcare attributable to MRH is described in the next chapter (chapter 6). Of the 413 patients with MRH, 85 (20.6%), who experienced 105 MRH events, managed their adverse event(s) without seeking healthcare input. These 85 patients experienced 105 MRH events. The most common events were diarrhoea (n=13, 12.4%), constipation (n=11, 10.5%), dizziness (n=8, 7.6%) and peripheral oedema (n=8, 7.6%).

5.8 Preventability of MRH

The preventability of MRH was determined using the established Hallas et al. (1990) criteria. These criteria are detailed fully in chapter 4. In summary however, the Hallas criteria classify MRH arising through poor clinical practice as ‘definitely’ preventable, and events where MRH might have been prevented by efforts exceeding basic clinical obligation as ‘possibly’ preventable. On this basis, amongst the study cohort 44 out of 413 MRH cases (10.7%) were determined to be ‘definitely’ preventable and 170 MRH cases ‘possibly’ preventable (41.2%). Thus, in total more than half of the MRH events were potentially preventable.
<table>
<thead>
<tr>
<th></th>
<th>21 (52.9%)</th>
<th>29 (70.3%)</th>
<th>31 (75.6%)</th>
<th>28 (68.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite (n=136, 32.9%)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Probable (n=160, 38.6%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Possible (n=157, 40.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>21 (52.9%)</th>
<th>29 (70.3%)</th>
<th>31 (75.6%)</th>
<th>28 (68.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite (n=136, 32.9%)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Probable (n=160, 38.6%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Possible (n=157, 40.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5.4 All MRH cases (n=413) by certainty, severity and preventability.
Table 5.5 Case examples of classifying medication-related harm

<table>
<thead>
<tr>
<th>Case 1: ADR</th>
<th>Likelihood MRH: definite, Severity: serious, Preventable: definitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history of MI, severe aortic stenosis, angina, COPD, diabetes. Patient sitting in chair and began to shake and with central chest pain and shortness of breath. Felt dizzy with pain, and thought she was going to collapse. Readmitted 15 days post-discharge with negative troponin. Patient experienced a similar pre-syncopal episode after morning medicines as inpatient, with BP dropping to 76/35mmHg. Impression: patient suffered a hypotensive episode secondary to combination of medicines which lower blood-pressure; losartan ISMN, nicorandil and diltiazem.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 2: Medication error</th>
<th>Likelihood MRH: definite, Severity: serious, Preventable: definitely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history of heart failure, COPD and dementia. Patient experienced increased shortness of breath and bilateral leg swelling. Discharged seven days previously with increased bumetanide dose. At home, carer administered medicines from old dosette box containing lower dose of bumetanide. Symptoms responded well to increased diuretics. Impression: exacerbation of heart failure due to administration of incorrect bumetanide dose.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case 3: ADR and non-adherence</th>
<th>Likelihood MRH: definite, Severity: serious, Preventable: possibly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past history of AF, diabetes, PVD, reduced mobility, grade 3 pressure sore. Daughter requested GP visit for patient six days post-discharge. Patient experienced nausea and constipation. No urinary symptoms, negative MSU. Had been prescribed buprenorphine patch and dihydrocodeine from hospital following fractured neck of femur. Has laxido but does not take it. Impression: constipation secondary to opioids and non-adherence to laxatives.</td>
<td></td>
</tr>
</tbody>
</table>

ISMN: isosorbide mononitrate; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; MSU: midstream urine; PVD: peripheral vascular disease; MI: myocardial infarction
5.9 Types of MRH and implicated medicines

The main body systems affected by MRH were gastrointestinal (25.4%) and neurological (17.9%), with the most common gastrointestinal symptoms being diarrhoea and constipation and dizziness, confusion and fatigue the most frequent neurological symptoms. The most common MRH events overall that were observed within the study cohort were diarrhoea (n=55, 8.9%), constipation (n=52, 8.4%), falls (n=35, 5.6%) and bleeding (n=31, 5.0%) (table 5.6).
Table 5.6 Type of MRH by affected body system and implicated medicine

<table>
<thead>
<tr>
<th>Body system</th>
<th>Total events (n=621), n (%)</th>
<th>Medication-related harm (n)</th>
<th>Commonly implicated medicines† (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>158 (25.4)</td>
<td>diarrhoea, 54, constipation, 52, nausea, 21, vomiting, 13, acid reflux, 12, abdominal pain, 5, acute liver injury, 1</td>
<td>opiates, 49, senna, 16, iron, 10, macrogol, 9, alendronate, 8, clopidogrel, 8</td>
</tr>
<tr>
<td>Neurological</td>
<td>111 (17.9)</td>
<td>dizziness, 25, confusion, 19, fatigue, 19, drowsiness, 14, headache, 14, sleep disturbance, 11, involuntary movements, 4, paraesthesia, 4, seizure, 1</td>
<td>opiates, 23, amlodipine, 10, bisoprolol, 9, ramipril, 6, amitriptyline, 5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>68 (11.0)</td>
<td>peripheral oedema, 26, postural hypotension, 17, syncope, 9, exacerbation of cardiac failure, 7, arrhythmia, 5, thrombotic event, 4</td>
<td>amlodipine, 15, furosemide, 10, bisoprolol, 8, bumetanide, 7, ramipril, 6</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>65 (10.5)</td>
<td>fall, 35, musculoskeletal pain, 27, gout, 2, fracture, 1</td>
<td>opiates, 18, bisoprolol, 10, furosemide, 8, ramipril, 7, simvastatin, 5</td>
</tr>
<tr>
<td>Dermatology</td>
<td>47 (7.6)</td>
<td>rashes and skin lesions, 20, pruritus, 13, candidiasis, 9, alopecia, 3, facial swelling, 1, unresolving infection, 1</td>
<td>clarithromycin, 4, amoxicillin, 3, flucloxacillin, 3, rivaroxaban, 3, furosemide, 3</td>
</tr>
<tr>
<td>Haematology</td>
<td>45 (7.2)</td>
<td>bleeding, 31, bruising, 9, anaemia, 4, immunosuppression, 1</td>
<td>clopidogrel, 12, rivaroxaban, 10, warfarin, 8, aspirin, 8, dalteparin, 4</td>
</tr>
<tr>
<td>Respiratory</td>
<td>31 (5.0)</td>
<td>dyspnoea, 19, cough, 11, unresolving infection, 1</td>
<td>ramipril, 9, salbutamol, 7, tiotropium, 7, seretide, 5, symbicort, 3</td>
</tr>
<tr>
<td>Renal</td>
<td>26 (4.2)</td>
<td>acute kidney injury, 15, electrolyte disturbance, 11</td>
<td>furosemide, 11, spironolactone, 6, ramipril, 6, bumetanide, 5, omeprazole, 2</td>
</tr>
<tr>
<td>Endocrine</td>
<td>25 (4.0)</td>
<td>hypoglycaemia, 12, hyperglycaemia, 11, gynaecomastia, 1, hot flushes, 1</td>
<td>insulin, 15, gliclazide, 6, metformin, 3, prednisolone, 3, liraglutide, 2</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>16 (2.6)</td>
<td>mood or behavioural disturbance, 16</td>
<td>opiates, 6, prednisolone, 3, zopiclone, 2, gabapentin, 2</td>
</tr>
<tr>
<td>Ear nose &amp; throat</td>
<td>14 (2.3)</td>
<td>dry mouth, 8, taste disturbance, 4, hoarseness, 1, oral ulceration, 1</td>
<td>omeprazole, 2, tiotropium, 2</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>9 (1.4)</td>
<td>incontinence, 4, urinary retention, 4, urine discoloration, 1</td>
<td>furosemide, 3</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>6 (1.0)</td>
<td>dry or sore eyes, 3, visual disturbance, 3</td>
<td>prednisolone, 2</td>
</tr>
</tbody>
</table>

†Top 5 medicines listed, except when the number of events caused by a medicine was <2; Given multiple formulations of codeine and morphine-related medicines, these are grouped into opiates
5.10 Risk of harm by medication type

Antihypertensives and opiates were implicated in the highest proportion of MRH events, 22.4% and 17.2% respectively. However, for antihypertensives, this is at least in part a reflection of the vast quantity of prescriptions for antihypertensives i.e. 1163 amongst the 1116 study cohort, which is 89% greater than the number of the second most prescribed medication class (laxatives, 616 prescriptions). The MRH risk, expressed as an incidence ratio, was highest for opiates (399 MRH events per 1000 prescriptions), followed by antibiotics (189 MRH events per 1000 prescriptions). The risk of MRH by medication class is shown in table 5.7.

Table 5.7 Risk of MRH by type of medication

<table>
<thead>
<tr>
<th>Medication type†</th>
<th>Prescriptions (n)</th>
<th>MRH events (n)</th>
<th>Proportion of MRH by medication type (%)</th>
<th>Risk of MRH by medication type (events per 1000 prescriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiates</td>
<td>268</td>
<td>107</td>
<td>17.2</td>
<td>399.3</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>344</td>
<td>65</td>
<td>10.5</td>
<td>189.0</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>81</td>
<td>15</td>
<td>2.4</td>
<td>185.2</td>
</tr>
<tr>
<td>Diuretics</td>
<td>496</td>
<td>76</td>
<td>12.2</td>
<td>153.2</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>147</td>
<td>21</td>
<td>3.4</td>
<td>142.9</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>158</td>
<td>21</td>
<td>3.4</td>
<td>132.9</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>311</td>
<td>41</td>
<td>6.6</td>
<td>131.8</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>269</td>
<td>34</td>
<td>5.5</td>
<td>126.4</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>1163</td>
<td>139</td>
<td>22.4</td>
<td>119.5</td>
</tr>
<tr>
<td>Hypoglycaemins</td>
<td>314</td>
<td>34</td>
<td>5.5</td>
<td>108.3</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>173</td>
<td>12</td>
<td>1.9</td>
<td>69.4</td>
</tr>
<tr>
<td>Laxatives</td>
<td>616</td>
<td>41</td>
<td>6.6</td>
<td>66.6</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>582</td>
<td>38</td>
<td>6.1</td>
<td>65.3</td>
</tr>
</tbody>
</table>

†Benzodiazepines include benzodiazepine-related drugs; WHO-ATC codes C03A and C03B are under both antihypertensives and diuretics
5.11 Potentially inappropriate medicines

Inappropriate prescribing is an avoidable risk factor for MRH in older adults and can be defined as medicines with a higher probability of causing harm than benefit to the individual\textsuperscript{199}. A systematic review found 46 different published tools to identify potentially inappropriate prescriptions. A substantial number of these assessment tools are explicit lists of medicines that should be avoided or used with caution in the older population\textsuperscript{200,201}. Widely recognized examples of these lists include the Beers criteria\textsuperscript{202}, the STOPP criteria\textsuperscript{203}, the EU-Potentially Inappropriate Medicines (EU-PIM) list\textsuperscript{204}, and the PRISCUS list\textsuperscript{205}. They have generally been developed through Delphi consensus methodology by expert geriatricians and clinical pharmacologists. The Beers Criteria were the first published guidance of potentially inappropriate medicines (PIMs) to avoid in older adults, developed in the USA in 1991 for use with nursing home residents\textsuperscript{202}. They have been updated four times since 1991, and are arguably the most established of the available lists. Indeed, many other lists are derived from the Beers Criteria\textsuperscript{200}. Crucially they are the only criteria where the strength of evidence for recommendations is reported \textsuperscript{206}. The applicability of the Beers Criteria across care settings and in Europe has increased with recent updates\textsuperscript{207}. In the UK, a cross-sectional analysis of almost 14000 primary care patients in 2012 found that 38\% were prescribed at least one Beers Criteria inappropriate medicine\textsuperscript{208}.

To provide an indication of medicines overuse in the older adults recruited into the PRIME study, the most recent Beers Criteria (2015) \textsuperscript{202} were used to examine potentially inappropriate prescribing of medicines at hospital discharge. The criteria were used to identify prescribed medicines that should be avoided in older adults, with at least a moderate grade of evidence.

Out of the 1280 patients recruited in the PRIME study, 276 (21.6\%) were prescribed at least one PIM at hospital discharge. There was a total of 315 prescriptions for 36 different PIMs (Table 5.8). The main PIMs prescribed at hospital discharge were benzodiazepines and benzodiazepine-related drugs (n=94, 30\%) and antidepressants (n=85, 27\%).
Out of the 413 study patients that experienced MRH, 51 patients (12.3%) experienced MRH due to PIMs. There were 57 MRH events specifically attributable to PIMs. The PIMs that most commonly caused MRH were benzodiazepines and benzodiazepine-related drugs (n=15, 26%), and antidepressants (n=14, 25%).

Table 5.8 Potentially inappropriate medicines prescribed at hospital discharge

<table>
<thead>
<tr>
<th>Medicine Class</th>
<th>Medicines</th>
<th>Total Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepenes and related drugs</strong></td>
<td>Zopiclone (24), Temazepam (19), Diazepam (17), Lorazepam (14), Nitrazepam (7), Zolpidem (6), Clonazepam (5), Lormetazepam (1), Oxazepam (1)</td>
<td>94 (29.8)</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>Amitriptyline (68), Paroxetine (7), Nortriptyline (3), Trimipramine (3), Clomipramine (2), Imipramine (2)</td>
<td>85 (27.0)</td>
</tr>
<tr>
<td><strong>Alpha-1-blocker</strong></td>
<td>Doxazosin (46)</td>
<td>46 (14.6)</td>
</tr>
<tr>
<td><strong>Propulsives</strong></td>
<td>Metoclopramide (22)</td>
<td>22 (7.0)</td>
</tr>
<tr>
<td><strong>Antihistamines</strong></td>
<td>Chlorphenamine (12), Promethazine (4), Hydroxyzine (2)</td>
<td>18 (5.7)</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>Prochlorperazine (12), Haloperidol (2), Risperidone (2)</td>
<td>16 (5.1)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Digoxin (9), Amiodarone (5), Nifedipine Immediate Release (5), Insulin sliding scale (3), Dipyridamole (2), Phenobarbital (2), Primidone (2), Ibuprofen (2), Naproxen (1), Dicyclomine (1), Oral Estrogen (1), Megestrol (1)</td>
<td>34 (10.8)</td>
</tr>
</tbody>
</table>
5.12 Discussion

This chapter describes the results of the first study in the UK to investigate medication harm in older adults following hospital discharge. The key findings are that MRH was experienced by one in three discharged older adults within 8 weeks and 80% of cases were serious. Half of the MRH cases were potentially preventable, and one in ten judged to be ‘definitely’ preventable.

Adverse drug reactions are the primary type of MRH experienced by older adults, and 25% manifest within one week of hospital discharge. A very high proportion of older adults are non-adherent to their medicines in the post-discharge period (29%), and this results in harm; non-adherence was implicated in 23% of MRH cases, including one death. Whilst the PRIME study did not seek to identify medication errors, harm attributable to a medication error was recorded and represented a very small proportion of the overall MRH burden (<5%). In most of these cases, the medication error was made at the prescribing stage. It was a notable finding that 1 in 5 older patients were prescribed a ‘medication to avoid’, as defined by the 2015 Beers Criteria, upon discharge from hospital. However, a relatively small proportion of total MRH observed in the study cohort was attributable to these medications.

5.12.1 Comparison with prior literature

Incidence

The proportion of patients experiencing MRH (37%) in the PRIME study is higher than previously reported in studies outside of the UK (see chapter 2).76 This is probably due to methodological differences as opposed to any peculiarities in the PRIME population or the healthcare system in England. A retrospective analysis of 1000 older patients in the United States found that 18.7% experienced MRH over a 45-day period following hospital discharge.94 This US study identified events through review of medical notes, contrasting with the PRIME study, which used prospective methods along with patient interviews. Retrospective studies and studies excluding patient interviews tend to report a lower incidence of MRH.99,209 A prospective European study of 209 patients (average age 74 years) found that 30% of their
cohort experienced an ADR over a 30 day post-discharge period. This finding is comparable to the PRIME study, and the slightly higher incidence of 37% probably reflects the inclusion of MRH from non-adherence.

**Non-adherence**

It has been widely reported that at least 30% people in the UK do not take their medicines as intended, and in the PRIME study this proportion was found to be 29%. There are clear adverse outcomes for patients and the health system because of this; non-adherence was partly or otherwise completely implicated in 27% of patients that suffered MRH. One fatality from a stroke that was associated with non-adherence to warfarin in the 8-weeks post-discharge was observed. Although multicompartmental compliance aids (MCA’s) e.g. a dosette box, may be expected to support adherence and reduce the risk of MRH, this may not be the case in general and for some may even be harmful.

**Preventability**

Whilst 11% of patients experienced MRH considered ‘definitely’ preventable, the true proportion is likely to be higher as 41% of MRH cases were possibly preventable. A systematic review published in 2011 by Taché et al reported 16.5% of MRH events in the community as preventable based on all age groups. The high proportion of preventable events in the PRIME study reflects the particularly challenging time-period investigated in an older population, and the inclusion of harm from non-adherence to medicines.

**High risk medicines**

The aforementioned systematic review by Taché et al (2011) found cardiovascular medicines to be most implicated in MRH in the community setting, reflecting the high prevalence of their use. In the PRIME study 22% of MRH was associated with antihypertensive medicines. However, the highest risk of MRH was associated with opiates. Concerns have been raised of the potential harm related to overuse of opiates in non-cancer patients in the UK, and the PRIME data demonstrate the actual harm associated with opiate use in older adults.
Medicines overuse

Only a small proportion of MRH was attributable to medications recommended to be avoided in older adults. A ‘hard and fast’ rules based approach, as is the case with explicit PIM lists, doesn’t account for the interplay of biological, psychological and social complexities which place patients at high risk of MRH\textsuperscript{215,216}. A personalised approach that combines knowledge of both PIMs and patient-specific complexities is needed to prescribe appropriately. In the BELFRAIL cohort of older Belgian community-dwelling patients PIMs use was common, however in 30% of these patients the medicines were in fact not considered inappropriate by an expert panel (including a Geriatrician, General Practitioner and Clinical Pharmacist) having considered the patient’s full clinical picture \textsuperscript{215}. A study of older outpatients of one large medical centre in the US similarly demonstrated the discordance between individualised medicine reviews by experts (physician/pharmacist pair) and medicines identified as inappropriate using two different explicit lists (Beers Criteria and Zhan Criteria).\textsuperscript{216} In this study, 61% of medicines identified as inappropriate by the Beers Criteria were not judged to be problematic based on individualised expert assessment (and 49% of medicines identified by the Zhan Criteria).

5.12.2 Implications for clinicians and policymakers

Given the high proportion of preventable MRH identified in the PRIME study, there is clearly considerable scope for patient safety improvements. The lack of prescriber knowledge of harms is a key driver of medicines overuse,\textsuperscript{217} and, clinicians are more likely to overestimate the benefits of treatment and underestimate the harms.\textsuperscript{218} This study highlights the extent of MRH during a critical juncture of healthcare provision, and can support increased pharmacovigilance amongst clinicians in secondary and primary care. Whilst most MRH in the post-discharge period was attributable to medicines prescribed in the hospital setting, one-quarter of implicated medicines were prescribed in the community. The reconciliation of medicines received by patients during discharge from hospital, with those already listed on the repeat prescription from the GP, and any additional medicines which the patient takes at home is paramount. Prescribers in the community must be wary
of the heightened vulnerability of patients to harm in the immediate post-discharge period, as physiological systems remain impaired during recovery from acute illness and the stressors associated with hospitalization (e.g. poor nourishment, deconditioning, sleep disturbance, delirium)

5.12.3 Limitations

There are several limitations to the results presented in this chapter which must be considered when interpreting the data. Patients’ involvement in this study could have heightened their awareness of potential adverse effects of medicines. They might have therefore been more attentive to medicines-related information and usage instructions, or more likely to seek healthcare where MRH was suspected. However, this increased knowledge might also have enabled patients to attribute and report MRH more accurately.

Retrospective patient interviews may have resulted in underreporting of MRH due to poor recall, and GPs may not have recorded all MRH encountered due to time pressures or perceived lack of severity. Harm arising from medication errors may be underestimated as there was no active searching for post-discharge medication reconciliation errors and assessment of impact. It is possible therefore that some MRH was misclassified as an ADR, rather than a harm due to medication error, as the reconciliation error would not have been elicited. Nonetheless, a very small proportion of medication errors actually lead to patient harm.

In line with other studies, the application of the 2015 Beers Criteria was limited to the drugs to avoid in all older adults (excluding criteria for drug-disease combinations). One Beers Criterion (avoid use of proton-pump inhibitors (PPI) for more than 8 weeks unless for high-risk patients) was not applied due to incomplete information on duration of PPI use. The PRIME study follow-up period for MRH was limited to 8 weeks to focus on the immediate post-discharge period, however MRH could have occurred after this observation period. Lastly, the results presented are based on prescribing practices in hospitals in the South England and may not be generalisable to other settings.
5.13 Conclusions

In conclusion, I have shown in this chapter that medication harm is a common problem for older people in the community in the immediate weeks following hospital discharge. Adverse drug reactions account for most of this harm, with most events occurring within the first month after discharge. Although non-adherence contributes to a small proportion of harm relative to ADR, this is usually preventable. Vigilance to high-risk prescribing, and supporting appropriate use of medicines in the community might reduce this problem. In the next chapter part two of my results from the PRIME study are presented. The focus of chapter 6 is on the healthcare utilisation caused by MRH in the post-discharge period and the costs of this to the NHS in England.
CHAPTER 6.
PRIME study results: Health service utilisation and cost of medication-related harm
Chapter Summary

The National Health Service has faced the greatest demand and financial pressure in its history over the last 5 years. The proportion of hospital admissions due to adverse drug reactions is increasing, and with an ageing population and an increasing prevalence of multimorbidity and polypharmacy, it is likely that the use of the NHS due to MRH will increase. This chapter reports an analysis of the health service utilisation due to MRH in the PRIME study, and a cost evaluation of this. The costs of MRH in older adults in the post-discharge period are estimated to the national level. This chapter also reports a multivariable analysis to determine what factors independently predict the use of health services by patients in response to MRH. Health service utilisation data for the 8 weeks follow-up after hospital discharge was obtained from three sources; a) patient and/or carer report during a semi-structured telephone interview at 8-weeks follow up, (b) hospital readmissions prospectively captured during the 8-week period, and (c) GP records for the 8-week post-discharge period. The Department of Health’s Payment by Results NHS tariff, as recommended by NICE for cost impact assessments in England, was used to cost health service use due to MRH in the PRIME study. The preventability of MRH (and therefore health service utilisation) was assessed using established criteria. In total, 328 patients out of 413 (79%) that experienced MRH used the health service as consequence of MRH, with an overall 441 episodes of healthcare. General Practitioner consultations (n=316, 71.7%) and hospital readmissions (n=96, 21.8%) accounted for over 90% of healthcare use. The overall incidence of hospital readmissions due to MRH from the PRIME study cohort was 8%. Half of hospital readmissions (52%), and 43% of GP consultations were potentially preventable. The cumulative cost of NHS use attributable to MRH was £225,747 over the 8-week study period. Extrapolating from this, the annual cost to the NHS in England of post-discharge MRH in older people is £395.5 million. Approximately £240 million of this cost is potentially avoidable. Comparing patients that accessed healthcare due to MRH (n=328, 79%) and those that experienced MRH but did not access healthcare (n=85, 21%), showed that frailty, impairment in activities of daily living, having a regular community pharmacist, and living in London were independent predictors of NHS use due to MRH.
6.1 Introduction

Medication-related harm (MRH) will inevitably lead to health service utilisation for some older adults. Medical attention may be sought at different levels of acuity due to MRH, including the GP, directly at urgent care clinics or hospital emergency departments, or, hospital admission. The findings described in chapter 5 showed that approximately 80% (n=328 out of 413) of patients that experienced MRH used NHS services in relation to this.

The NHS is experiencing unprecedented service demand for a wide range of reasons\(^\text{224–226}\). A key reason for this increased demand is an ageing population, where more people are living with multimorbidity than are not. It has been estimated that 80% of 80 year olds live with multimorbidity (defined as two or more long-term conditions)\(^\text{16}\). Between 2003 and 2015, the number of people aged 85 years or older grew by 40%\(^\text{225}\). As the costs of providing healthcare increase in conjunction with the increased demand, the NHS faces the most significant funding pressures in its 70 year history\(^\text{227}\).

Healthcare is a scarce resource, and there are opportunity costs associated with avoidable utilisation due to MRH. Opportunity costs are central to health economic evaluation and can be defined as those costs that could be better spent elsewhere in the NHS\(^\text{228}\). Evaluating the financial cost of MRH is necessary for policy-makers to rationalize investment (and limits of investment) to reduce the problem. Given the resource-limitations and increasing healthcare demand generating extreme pressures on the NHS\(^\text{224}\), the importance of cost-analysis has increased over time to ensure resources are used wisely. However, the health system is skewed towards evaluating the benefits of pharmacological therapy rather than the clinical, humanistic and economic costs \(^\text{114,218,229,230}\). The use of health services to treat MRH reduces the overall cost-effectiveness of using pharmacological treatment for a disease, although this is seldom factored into cost evaluations of treatment efficacy. Pharmacological treatment is approved on the basis of its efficacy i.e. effects under clinical trial conditions, rather than on the basis of effectiveness i.e. effects in real-
life situations. In real-life there are various reasons why the efficacy of a medicine, upon which it receives regulatory approval, does not translate into effectiveness. Crucially, adverse effects are not a primary outcome measured in clinical trials and can be measured and reported poorly. Additionally, patient self-report of MRH is not routinely collected in RCTs and therefore the reporting of harm is biased to the study team’s perspective. Outside of the controlled conditions in trials, it is difficult for a prescriber to know if a patient is going to adhere to their medicine, if they start using over-the-counter medicines that interact with the prescribed treatment, or if a carer is likely to make errors in medicine administration. Thus, in real-life many cases of MRH are entirely preventable, examples including harm related to non-adherence, medication error, suboptimal choice of pharmacological treatment etc. In these circumstance, a complete wastage of NHS resource has occurred. This resource might include the costs of medical consultation time, the cost of the prescription that has provided no benefit, the cost of prescription required to overcome harm (if anything more than medicine discontinuation), the diagnostics required to rule out alternative causes of illness, loss of productivity in employed individuals, and the time of carers where necessary. The costs of MRH can be considered as ‘direct’ or ‘indirect’. Direct costs are more straightforward to measure and include those of medical consultation time, diagnostics and treatment costs, and hospital stays. Indirect costs are less tangible but may be more substantial, and include those of out-of-work (loss of productivity) costs, additional care costs (formal or informal), and wasted medicines from non-adherence or conferring no therapeutic benefit.

In the UK, there have been few cost evaluations of NHS utilisation attributable to medication-related harm and none specifically in the population aged 65 years and over. In 2014, Frontier Economics produced a report for the Department of Health estimating the costs of unsafe care and adverse events in the NHS. It was estimated that the cost of all-cause preventable adverse events is at a minimum of £1 billion per year, but it could be up to £2.5 billion. Pirmohamed et al (2004) specifically evaluated the cost of hospital admissions caused by ADR in two large hospitals in one region in England. This prospective analysis included 18820
patients (aged 18 years or over, median 76 years old) admitted between 2001 and 2002. The estimated annual cost of hospital admission related to medication harm was £466 million. Within this, 72% was avoidable based upon established criteria to assess the preventability of MRH8,35. A systematic review published in 2012 evaluating the costs of MRH found that the vast majority of studies focused on hospital costs from inpatient episodes104. The authors concluded that studies were needed that evaluated MRH costs outside of the hospital setting. A paucity of recent data on MRH cost is likely to reduce the prioritization of prevention initiatives, and hold back NHS strategy development and health service planning in relation to MRH. Hence, there is a strong case for cost evaluation of MRH in a ‘real-world’ setting in the UK. This chapter investigates what healthcare resources were used in response to MRH by patients in the PRIME study, and what the costs of this were from the perspective of the NHS.

This chapter also investigates what factors predict the use of health services by patients in response to MRH. The factors that predict healthcare access in older adults when they experience MRH has not previously been explored. Healthcare access goes beyond solely the availability of health services, but pertains to the use of health services when there is need238. Need will inevitably be perceived differently between people, and a contrast may be present between need as defined by the provider and that perceived by the patient. The factors that influence healthcare access in older adults are numerous and complex, broadly including person-specific, organisational, geographical, social and cultural influences239. At a global level, healthcare access is heavily influenced by the healthcare system of the country240, including the type of health coverage and payment (state-provided universal coverage, insurance-coverage) 104, the strength of the primary care system (primary care consultation costs substantially less than hospitalization)241, the costs of healthcare resources (e.g. drugs, human resources etc)242. Whilst there have been studies to investigate the risk factors for hospitalization due to MRH, this informs us on factors associated with the incidence of MRH31,38, but not of the reasons why some patients with MRH will use healthcare and others not. One would inevitably expect the severity of MRH to be a key contributor to healthcare access, and indeed
receiving healthcare for MRH is an objective criteria defining ‘serious’ MRH from that defined as ‘significant’. Nonetheless, there are likely to be many other important factors that influence healthcare utilisation. Ford et al (2016) mapped a standard patient pathway to healthcare access involving six steps from problem identification through to a primary care interaction, involving the decision to seek help, actively seeking the help, obtaining an appointment, and getting to the appointment. Reaching each of these junctures involves a range of supporting capabilities. For instance, deciding whether to seek help may be influenced by prior experience of healthcare encounters, experience of symptoms, carer responsibilities, transport availability and self-esteem amongst others. Exploring the factors associated with healthcare utilisation is important to identify potentially modifiable drivers in patients with MRH. These factors may be targets for additional support in patients at high risk of MRH to reduce health resource use given the pressures on it.

The objectives of my work, as described in this chapter, were to:

1. describe the NHS utilisation attributable to MRH in the PRIME cohort,
2. cost this health service utilisation,
3. extrapolate the findings to the NHS in England,
4. determine the factors that influence healthcare use in patients with MRH

6.2 Methods

Based on the objectives outlined above for this chapter there are four methodological sections to report; (1) identifying health care utilisation attributable to MRH, (2) costing this healthcare resource use, (3) extrapolating this cost to the national context in England, (4) identifying the factors that are associated with healthcare utilisation in patients experiencing MRH. Each is discussed below, followed by the findings in the PRIME patient cohort.
6.2.1 Identifying health service utilisation

Health service utilisation data in the 8 weeks following discharge was obtained from three sources by trained research pharmacists; a) patient and/or carer report during a semi-structured telephone interview at 8-weeks follow up, (b) hospital readmissions prospectively captured during the 8-week period, and (c) GP records for the 8-week post-discharge period.

During telephone interviews patients (or carers where appropriate) were asked about any healthcare access in the 8 week follow up period, the reason and date for the consultation. This included GP consultations, out-of-hours consults, outpatient appointments, emergency department attendance and hospital readmissions.

Subsequently data were extracted pertaining to healthcare consultations that were specifically attributable to patient MRH. This data extraction was conducted by the research fellow in Geriatric medicine and each case was verified this with a Professor of Clinical Pharmacology and Therapeutics. This verification involved a review of the description given by patients of the healthcare episode, the reason for it and the date to ensure a temporal association with the MRH.

Hospital readmissions were prospectively captured, and MRH was determined to be the primary reason for readmission by both the research pharmacist and the medical consultant overseeing the patient’s care. General Practice consultations associated with MRH were identified using each patient’s 8-week primary care medical records. Where discrepancy existed between patient self-report and information from the other two sources (i.e. hospital readmission or GP records), then the patient self-report was recorded as a valid health service utilisation. Patient reported MRH is valid data to supplement medical records\textsuperscript{190}. It is well established that MRH is under-reported by health care professionals in medical records and national surveillance\textsuperscript{219,243,244}. Patient reports were also an important data source when GP records were unavailable, or readmission data was not captured e.g. patients readmitted to a different hospital than the site of their index admission.

Although it is acknowledged that community pharmacists are a valued source of healthcare advice in the UK, this was not measured as this is not a commissioned ‘activity’ and cannot be quantified or costed. Government funding for pharmacy is...
based on item dispensing rather than provision of patient healthcare. Advanced services, such as medication use reviews (MURs), are reimbursed however these are for selected patients and are not a responsive health service to MRH\textsuperscript{245}.

### 6.2.2 Cost of health service utilisation

An economic evaluation is a comparative analysis of costs following an intervention, defined by Drummond \textit{et al} (2005) as ‘the comparative analysis of alternative courses of action in terms of both their costs and consequences’ \textsuperscript{246}. Where there is no comparative assessment, but an analysis of cost can be described as a partial economic evaluation or cost evaluation. The PRIME study was an observational study, with no intervention or comparator. This cost evaluation is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)\textsuperscript{246}.

The estimated costs of MRH are highly affected by the choice of methods used in identifying MRH, attributing healthcare utilisation to MRH, and costing resources. For example, some studies have costed MRH using an average cost of a hospital bed-day\textsuperscript{8}, whilst others have costed resources used based on national or regional tariffs\textsuperscript{247,248}. There is no methodological consensus in this area\textsuperscript{249}, however NICE recommend using the NHS national tariff for cost impact assessments in England\textsuperscript{250}. Wherever possible the Department of Health’s 2013/14 Payment by Results NHS tariff was used to cost health service use\textsuperscript{251} (Table 6.1). Therefore the perspective of our economic evaluation was that of NHS resources and the ‘payer’ i.e. Department of Health, rather than provider i.e. hospital cost, or patient or other expenditure\textsuperscript{104}. The NHS tariff provides unit costs, under Healthcare Resource Groups (HRGs) for healthcare utilisation in secondary care. An HRG is a clinical grouping of patient activity during an inpatient episode, and is effectively the unit cost upon which commissioning of secondary care is standardized\textsuperscript{252}. Costing based on HRGs reflects the Payment by Results system that the NHS operates to reimburse secondary care providers for healthcare. Secondary care in the NHS has moved from a payment system of block budgets for providers prior to 2002, to reimbursement
through recorded activity, known as Payment by Results\textsuperscript{253}. Hospital admissions are reimbursed based on the main diagnosis (and procedures) considered alongside patient age and secondary diagnoses (as a proxy for the complexity of the Finished Consultant Episode (FCE)). This patient episode is reimbursed by assigning it to a HRG. NHS England publishes a national tariff for these ‘units’ (HRGs) annually\textsuperscript{251}. Accident and Emergency (A&E) department attendance and hospital appointments with specialists were also costed based on the Department of Health’s 2013/14 NHS tariff. A cautious approach was used to cost A&E consultations i.e. attendance with no investigations and no treatment, rather than as more complicated and costly consultations. This was unlikely to be the case for most patients, however, this approach avoids making incorrect assumptions about the extent of investigation and treatment that patients encountered given that this information was not available. Although primary care has some reimbursement that is activity based, known as the Quality and Outcomes Framework, primary care contracts are primarily based on ‘capitation payments’ i.e. payment based on the patient list size. Following standard practice, primary care consultations were costed using unit costs from the Personal Social Services Research Unit, University of Kent, for standard consultations of 11.7 minutes\textsuperscript{241}. This data source is recommended by NICE in its recommendation on cost impact assessments\textsuperscript{250}. Again, this is a conservative estimate made in the lack of data on duration of consultations, some of which may be longer. Out Of Hours (OOH) medical visits associated with MRH were costed using unit costs from the national audit office\textsuperscript{254}, which reports that 50% of cases of OOH care cost £53.60 to £86.30. The lower limit of £53.60 was multiplied with the number of consultations reported to obtain an estimate of costs from OOH care. Once again, a conservative estimate was used to avoid assumptions regarding the complexity of healthcare provided.

The average cost of health service utilisation per discharged patient and per health service user was calculated. The cost per patient is of higher interest to NHS commissioners as commissioning is based on patient populations, whereas cost per service user may be of greater interest to the service provider. Given the 2013/14 NHS tariff is consistent with the time of data collection, no pricing conversions or cost adjustments were required.
Table 6.1: Selected examples of MRH with cost relating to health service utilisation

<table>
<thead>
<tr>
<th>Case Examples</th>
<th>Source of cost data</th>
<th>Type of Cost</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Practice</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81 years old, male.</td>
<td>Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2014.</td>
<td>Unit cost</td>
<td>£38 (per 11.7 minute consultation)</td>
</tr>
<tr>
<td><strong>MRH:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR - postural hypotension with fall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implicated drug(s): doxazosin and hydralazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Features of causality:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Event following medicines administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Recognised ADR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Symptom improvement on discontinuation of medicines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accident &amp; Emergency</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Patient:</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>71 years old, female.</td>
<td>Department of Health. Payment by Results: NHS Tariff 2013/14</td>
<td>Cost by Healthcare Resource Group</td>
<td>£58 (HRG code VB11Z, no investigation with no significant treatment)</td>
</tr>
<tr>
<td><strong>MRH:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR - diarrhoea with fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implicated drug(s): lansoprazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Features of causality:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Event follows medicines administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Recognised ADR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) No clear alternative cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Out of hours visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MRH:</strong></td>
<td></td>
<td></td>
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<tr>
<td>ADR – bleeding gums</td>
<td></td>
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<tr>
<td>Implicated drug(s): warfarin</td>
<td></td>
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<tr>
<td><strong>Features of causality:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Event follows medicines administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Recognised ADR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(c) Previous similar ADR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Severity dose-dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cont’d Table 6.1: Selected examples of MRH with cost relating to health service utilisation

<table>
<thead>
<tr>
<th>Case Examples</th>
<th>Source of cost data</th>
<th>Type of Cost</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital readmission</td>
<td>Department of Health. Payment by Results: NHS Tariff 2013/14</td>
<td>Cost by Healthcare Resource Group (HRG) assigned to discharge diagnosis</td>
<td>£2321 (HRG code EB03I, Heart failure or shock without complication and comorbidity)</td>
</tr>
<tr>
<td>Patient: 66 years old, female.</td>
<td></td>
<td></td>
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<tr>
<td>MRH:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-adherence and ADR - decompensated heart failure with fast atrial fibrillation after stopping medicines. Medicines stopped due to dry mouth following medicines use <strong>Implicated drug(s):</strong> spironolactone bisoprolol rivaroxaban</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Features of causality:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a)Non-adherence as assessed by Morisky scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b)Dry mouth recognised ADR with rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c)ADR following medicines use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) ADR improved with discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e) ADR reappeared on re-administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient specialist visit</td>
<td>Department of Health. Payment by Results: NHS Tariff 2013/14</td>
<td>Unit cost by specialty (Breast consultant)</td>
<td>£150 (Breast consultant)</td>
</tr>
<tr>
<td>Patient: 82 years old, female.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRH:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR - breast discharge with hot flushes <strong>Implicated drug(s):</strong> gabapentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Features of causality:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a)Recognised ADR (b)No clear alternative cause (b)Severity dose-dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2.3 Extrapolating cost to the national context

A national annual estimate of NHS cost attributable to post-discharge MRH in older adults was calculated based on an extrapolation of the types and cost of MRH in the PRIME patient cohort. This was limited to the level of English NHS unplanned hospital admissions from the 2013/14 Health and Social Care Information Centre’s Hospital Episode Statistics (HES) 255. HES data is stratified by age for all admissions, but not specifically for unplanned admissions. It was therefore necessary to calculate the number of unplanned admissions in older adults. This figure was obtained by first calculating the proportion of older people admissions (planned/unplanned); dividing the number of admissions in older adults (n=5,582,544 for age ≥65 years) by the number of admissions in all ages (n=15,462,057). This proportion could then be used to estimate the number of unplanned admissions in older adults by multiplying it with the total number of unplanned admissions for all age groups. This resulting figure for the number of unplanned admissions of older people in 2013/14 in England was multiplied by the average healthcare cost associated with MRH per PRIME study patient.

Finally MRH costs were stratified by preventability. The preventability of MRH was assessed using Hallas et al’s (1990) established criteria;8,35 ‘definitely preventable’ (treatment inconsistent with best practice or unrealistic), ‘possibly preventable’ (preventable with efforts exceeding obligatory clinical demands), ‘not preventable’, or ‘not able to evaluate’. Reporting the preventable costs is essential to inform policy-makers of the opportunity costs, that is the avoidable NHS expenditure which might be better spent elsewhere.

6.2.4 Identifying factors associated with healthcare access in patients with MRH

To compare the characteristics of the two groups of older adults that accessed healthcare following MRH and those that did not, clinical, sociodemographic and socioeconomic variables were analysed descriptively. The distribution of the variables were examined for normality by plotting histograms and used in conjunction with the Kolmogorov-Smirnov test. Based on this analysis, a decision
was made on whether to use parametric or non-parametric methods to examine the relationship between variables of interest and healthcare access. For continuous variables the median and interquartile range (IQR) were calculated. Categorical variables are described by frequencies and percentages. The characteristics between the healthcare seeking and self-managing groups were compared using the Mann-Whitney U-test for continuous variables. To compare categorical variables Fisher’s Exact Test was used. A P-value of <0.05 was taken as statistically significant. Using logistic regression models, characteristics that were significantly different, at the 5% level, between the groups were further examined for their relationship with healthcare access and their independent predictive value. Univariable logistic regression models were used to calculate unadjusted odds ratios for the relationship between a range of variables and healthcare access. Multivariable models were used to calculate the adjusted odds ratios and identify independent predictors of healthcare access. Existing literature informed the choice of variables that were considered potential confounders and entered into multivariable regression models. 240,256–259 These included age, gender, comorbidities, functional impairment, polypharmacy, socioeconomic status, formal care provision and urban living.

6.3 Results

6.3.1 Healthcare access attributable to MRH

There were 328 patients that accessed healthcare associated with their MRH, out of the 413 that experienced MRH in the study (79.4%, 95% CI 75.2% to 83.2%). Overall, 284 out of 1116 patients (25.4%) were readmitted to hospital within 8 weeks of discharge, and, 87 of these patients were readmitted due to MRH (30.6%). Therefore the overall proportion of hospital readmissions due to MRH in our study was 7.8% (95% CI 6.3% to 9.5%). There were 295 patients that sought healthcare for MRH from their GP, and 23 patients used other NHS services (A&E, OOH, outpatient services) (figure 6.1). There were 441 medical consultation episodes, on average 1.1
consultations per patient that experienced MRH in the study. General Practitioner consultations (n=316, 71.7%) and hospital readmissions (n=96, 21.8%) accounted for over 90% of healthcare utilisation episodes.

The MRH resulting in health service use was ‘possibly’ or ‘definitely’ preventable in 198 out of the 441 total episodes (45%), based on the Hallas et al (1990) classification system\textsuperscript{35}. Just over half of the hospital readmissions (n=50, 52%), and 43% of GP consultations (n=135) were potentially preventable.

Figure 6.1. Flow chart of patient recruitment to MRH associated healthcare access
6.3.2 Comparison of baseline characteristics by patient access to healthcare

A comparison of characteristics of patients in the study that accessed medical care for MRH and those that did not are shown in table 6.2. There were 328 patients that accessed healthcare, whilst 85 did not. Patients that accessed healthcare were significantly (1) older in age, (2) had longer hospital admission and more discharge medicines, (3) had a higher disease burden, (4) more likely to live alone, (5) frailer with more functional impairment, (6) more socioeconomically deprived, (7) more likely to live in London, (8) more likely to have a regular community pharmacist, (9) more likely to have had a musculoskeletal MRH event e.g. fall. The severity of MRH experienced by patients was strongly associated with healthcare access. This finding is a function of the grading system, based on Morimoto et al’s (2004) standard approach, that was used to classify MRH severity;\textsuperscript{74} fatal, life-threatening, serious (requires therapy change and/or treatment by health professional) and significant. Hence, patients that were medically consulted for their MRH by this definition had experienced serious MRH.
Table 6.2. Characteristics of patients accessing healthcare compared with self-managing patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MRH patients using healthcare (n=328)</th>
<th>MRH patients self-managing (n=85)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR), years</strong></td>
<td>83.2 (76.3-86.7)</td>
<td>81.0 (73.5-86.0)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Gender, female (%)</strong>, 219 (66.8)</td>
<td>49 (57.6)</td>
<td></td>
<td>0.127</td>
</tr>
<tr>
<td><strong>Hospital stay, median (IQR), days</strong></td>
<td>8 (4-15)</td>
<td>6 (3-10.5)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Number of comorbidities (%)</strong></td>
<td>0-1</td>
<td>151 (46.0)</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Charlson Index, median (IQR)</strong></td>
<td>2 (1-3)</td>
<td>2 (1-2.5)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Barthel Index, median (IQR)</strong></td>
<td>17 (12-18)</td>
<td>18 (16-20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Grip strength, kg, (IQR)</strong></td>
<td>16 (11-22)</td>
<td>18.5 (12-30)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Number of discharge medicines, median (IQR)</strong></td>
<td>10 (7-13)</td>
<td>9 (6-11)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Multicompartion compliance aid, n (%)</strong></td>
<td>119 (36.3)</td>
<td>27 (31.8)</td>
<td>0.525</td>
</tr>
<tr>
<td><strong>Living alone after discharge, n (%)</strong></td>
<td>190 (58.1)</td>
<td>38 (45.2)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Care package, n (%)</strong>, 133 (40.7)</td>
<td>28 (33.3)</td>
<td></td>
<td>0.260</td>
</tr>
<tr>
<td><strong>Regular community pharmacist n, (%)</strong></td>
<td>317 (98.1)</td>
<td>75 (88.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Socioeconomic status (IMD decile, IQR, 1=most deprived)</strong></td>
<td>4 (2-7)</td>
<td>6 (3-8)</td>
<td>0.020</td>
</tr>
<tr>
<td><strong>Living in London, n (%)</strong></td>
<td>157 (47.9)</td>
<td>22 (25.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Depression, n (%)</strong>, 81 (24.7)</td>
<td>17 (20.0)</td>
<td></td>
<td>0.394</td>
</tr>
<tr>
<td><strong>Anxiety n, (%)</strong>, 101 (30.8)</td>
<td>27 (31.8)</td>
<td></td>
<td>0.896</td>
</tr>
<tr>
<td><strong>AMTS, median (IQR)</strong></td>
<td>9 (8-10)</td>
<td>10 (9-10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Previous ADR, n (%)</strong>, 113 (34.8)</td>
<td>32 (37.6)</td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td><strong>Falls (2 or more in 12 months), n (%)</strong></td>
<td>136 (42.1)</td>
<td>22 (25.9)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Type of MRH, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>56 (17.1)</td>
<td>8 (9.4)</td>
<td>0.093</td>
</tr>
<tr>
<td>Neurological</td>
<td>78 (23.8)</td>
<td>25 (29.4)</td>
<td>0.325</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>107 (32.6)</td>
<td>30 (35.3)</td>
<td>0.698</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>58 (17.7)</td>
<td>5 (5.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Renal</td>
<td>22 (6.7)</td>
<td>1 (1.2)</td>
<td>0.060</td>
</tr>
<tr>
<td>Respiratory</td>
<td>22 (6.7)</td>
<td>8 (9.4)</td>
<td>0.359</td>
</tr>
<tr>
<td><em><em>Severity of MRH</em>, n (%)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant</td>
<td>0 (0)</td>
<td>77 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>315 (96.0)</td>
<td>8 (9.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>9</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>4</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney U test for continuous variables and Fisher’s Exact test for categorical variables. IQR, interquartile range; AMTS, Abbreviated Mental Test Score; IMD, Index of Multiple Deprivation (England). **Healthcare access for MRH was a component of determining severity classification as indicated by Morimoto et al (2004) guidance.6*
6.3.3 Independent predictors of healthcare access

Multivariable analysis was performed to identify independent predictors of healthcare access due to MRH, as shown in table 6.3. A lower Barthel score (indicating greater functional impairment in activities of daily living), a lower hand grip strength (a measure strongly related to frailty and sarcopenia\textsuperscript{169,260}), having a regular community pharmacist and living in London were significant predictors of accessing healthcare on multivariable analysis. A one point increase in functional ability based on Barthel score was associated with a 10% lower odds of accessing healthcare due to MRH. A one kilogram increase in hand grip strength was associated with a 4% reduction in the odds of accessing healthcare. Patients that experienced MRH and lived in London had 2.5 fold increased odds of accessing healthcare and those with a regular community pharmacist had 4 times increased odds of accessing healthcare.
Table 6.3. Predictors of health care access in older people with MRH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.04 (1.00-1.07)</td>
<td>1.01 (0.98-1.04)</td>
<td>Charlson index, number of drugs, Barthel index, living alone</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>1.03 (1.00-1.06)</td>
<td>1.01 (0.97-1.04)</td>
<td>Age, Charlson index, number of drugs, Barthel index</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.24 (1.06-1.44)</td>
<td>1.13 (0.97-1.31)</td>
<td>Age, number of drugs, Barthel index</td>
</tr>
<tr>
<td>Grip strength (Kg)</td>
<td>0.95 (0.92-0.98)</td>
<td>0.96 (0.93-0.99)*</td>
<td>Gender, age, Charlson index, number of drugs, formal care</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>0.87 (0.81-0.94)</td>
<td>0.90 (0.83-0.98)*</td>
<td>Age, Charlson index, number of drugs, formal care</td>
</tr>
<tr>
<td>AMTS (higher score)</td>
<td>0.58 (0.44-0.77)</td>
<td>0.61 (0.46-0.82)*</td>
<td>Age, Charlson index, number of drugs, formal care</td>
</tr>
<tr>
<td>Falls (2 or more in 12 months)</td>
<td>2.08 (1.22-3.55)</td>
<td>1.83 (1.05-3.18)*</td>
<td>Age, Charlson index, number of drugs, formal care</td>
</tr>
<tr>
<td>Number of discharge medicines</td>
<td>1.09 (1.02-1.16)</td>
<td>1.05 (0.98-1.12)</td>
<td>Charlson index, age, Barthel index</td>
</tr>
<tr>
<td>Living alone</td>
<td>1.68 (1.04-2.72)</td>
<td>1.30 (0.77-2.21)</td>
<td>Age, gender, Charlson index, number of drugs, Barthel index, formal care</td>
</tr>
<tr>
<td>Socioeconomic deprivation (higher IMD decile)</td>
<td>0.91 (0.83-0.99)</td>
<td>1.06 (0.94-1.20)</td>
<td>Age, gender, number of drugs, Charlson index, living alone, living in London</td>
</tr>
<tr>
<td>Living in London (yes vs no)</td>
<td>2.63 (1.55-4.47)</td>
<td>2.56 (1.23-5.35)*</td>
<td>Age, gender, number of drugs, Charlson index, living alone, socioeconomic status</td>
</tr>
<tr>
<td>Regular pharmacist (yes vs no)</td>
<td>7.04 (2.48-20.0)</td>
<td>4.23 (1.41-12.70)*</td>
<td>Age, number of drugs, dossette box, Charlson index, living in London</td>
</tr>
</tbody>
</table>

6.3.4 Costs to the NHS of healthcare access attributable to MRH

The cumulative cost of 441 health service utilisations attributable to MRH for the PRIME study cohort in the eight weeks post-discharge was £225,747 (Table 6.4). The total cost of the 198 preventable medical consultations was £109,476. This cost is based on MRH in 328 patients that accessed NHS healthcare, out of 1116 patients that were followed up post-discharge. This represents an average cost of £202.28 (95% CI, £157.79 to £246.77) per discharged patient (£98.10 preventable), and per patient with MRH of £546.60 (£265.08 preventable). This cost largely constitutes the cost of hospital readmissions, totalling £210,096 (93%) (Figure 6.2), of which £102,508 was preventable. Disaggregating the MRH costs by adverse drug reactions
and non-adherence shows that almost 60% of health service utilisation costs arose from adverse drug reactions alone, and approximately 20% from non-adherence alone (Table 6.5). The remaining cost was MRH due to a combination of ADR and non-adherence.

The costs of NHS use based on the PRIME study cohort, were extrapolated to the NHS in England to estimate the cost burden of post-discharge MRH nationally, and the potential savings if preventable MRH were eliminated at a national scale. The annual cost to the English NHS of post-discharge MRH in older people was £395.5 million based on Department of Health data on hospital admissions in the financial year 2013/14\textsuperscript{255} (Table 6.6). Considering only costs associated with potentially preventable MRH, this estimate is reduced to a lower limit of £51.6 million per year (MRH ‘definitely preventable’) and upper limit of £243.4 million per year (MRH ‘definitely’ or ‘possibly’ preventable).

Table 6.4. Episodes and costs of healthcare attendance associated with MRH, by preventability

<table>
<thead>
<tr>
<th>Healthcare attendance</th>
<th>Data collection</th>
<th>Number of consultations (preventable episodes)</th>
<th>Total cost, £ (%)</th>
<th>Total cost, potentially preventable episodes, £ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Practice</td>
<td>Retrospective GP records review by pharmacist or GP trainee</td>
<td>316 (135)</td>
<td>12,008 (5.3)</td>
<td>5130 (4.7)</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>Prospective patient medical records review, including laboratory results. Patient interviewed if stable. Consultation between pharmacist and admitting medical consultant</td>
<td>96 (50)</td>
<td>210,096 (93.1)</td>
<td>102,508 (93.6)</td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>Retrospective patient/carer interview by pharmacist</td>
<td>12 (6)</td>
<td>2693 (1.2)</td>
<td>1441 (1.3)</td>
</tr>
<tr>
<td>Accident &amp; Emergency</td>
<td>Retrospective patient/carer interview by pharmacist</td>
<td>9 (5)</td>
<td>522 (0.2)</td>
<td>290 (0.3)</td>
</tr>
<tr>
<td>Out-of-hours visit</td>
<td>Retrospective patient/carer interview by pharmacist</td>
<td>8 (2)</td>
<td>428 (0.2)</td>
<td>107 (0.1)</td>
</tr>
</tbody>
</table>

Total | 441 (198) | 225,747 | 109,476 |
Figure 6.2. Proportion of total cost of medication-related harm by healthcare utilisation

Table 6.5. Healthcare cost associated with MRH disaggregated by type of MRH

<table>
<thead>
<tr>
<th>Type of MRH</th>
<th>Cost (£)</th>
<th>Proportion of total cost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>132,088</td>
<td>58.5</td>
</tr>
<tr>
<td>Non-adherence</td>
<td>31,847</td>
<td>14.1</td>
</tr>
<tr>
<td>Medication Error</td>
<td>8598</td>
<td>3.8</td>
</tr>
<tr>
<td>Combination</td>
<td>53,214</td>
<td>23.6</td>
</tr>
</tbody>
</table>

Table 6.6. Estimated NHS cost by classifications of MRH causality and preventability

<table>
<thead>
<tr>
<th>MRH classification</th>
<th>Total cost in PRIME cohort during 8-week follow-up</th>
<th>Average cost per patient in PRIME cohort (n=1116)</th>
<th>Estimated annual NHS cost (based on 1,955,241 admissions of older adults in England 2013/14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MRH cases (causality: definite, probable, possible) (preventability: possibly, definitely)</td>
<td>£225,747</td>
<td>£202.28</td>
<td>£395,510,565</td>
</tr>
<tr>
<td>MRH cases: Definite causality</td>
<td>£56,288</td>
<td>£50.44</td>
<td>£98,617,030</td>
</tr>
<tr>
<td>MRH cases: Definitely preventable</td>
<td>£29,465</td>
<td>£26.40</td>
<td>£51,622,918</td>
</tr>
<tr>
<td>MRH cases: Definite causality AND Definitely preventable</td>
<td>£21,373</td>
<td>£19.15</td>
<td>£37,445,668</td>
</tr>
</tbody>
</table>
6.4 Discussion

6.4.1 Summary of main findings

The main findings reported in this chapter are that approximately 80% of patients that experienced MRH accessed healthcare, and more than one in five with MRH were readmitted to hospital within 8 weeks post-discharge. Independent clinical predictors of healthcare access were frailty, regular falls, poorer cognition and functional dependency. Independent social predictors were living in London, and having a regular community pharmacist. Whilst nearly three-quarters of medical consultations were in General Practice, these were inexpensive compared to the 96 hospital admissions. Extrapolating costs of MRH post-discharge to England indicates a cost burden to the NHS of almost £400 million, out of which up to £240 million is potentially preventable.

6.4.2 Comparison with prior literature

The fact that four out of five patients experiencing MRH are found to access healthcare is an important indication of the severity of MRH events, and is indeed reflected in Morimoto et al’s classification system of MRH severity. The proportion of patients that accessed healthcare for MRH was very similar to that reported by Gray et al (1999) in their US study of MRH in older adults over a 30-day post-discharge follow-up (83% of patients experiencing MRH). A comparative study in the UK, involving 955 patients with average age of 62 years, found that 40% of patients were readmitted to hospital within one year of discharge, of which 20% were associated with MRH. In the PRIME study, with an average patient age of 82 years, one in four were readmitted to hospital and 30% of these were due to MRH. Age is a key risk factor for hospital readmission and MRH, and is likely to be an important reason for the higher incidence of MRH seen in this study. In both the UK study by Davies et al (2010) and the PRIME study, approximately half of the readmissions due to MRH were potentially preventable (57% vs 52%).
Access to medical care is a complex phenomenon, and pertains to the use of health services as opposed to solely to its availability. Aday & Andersen (1974) proposed a framework that has become an established conceptual model of healthcare access. This model includes the influences of national health policy, characteristics of the health delivery system, characteristics of the individuals or population at risk, the actual utilisation of services and patient satisfaction.

A comparison of the characteristics of community-dwelling older adults that have accessed healthcare following MRH, and those that have not, has not previously been studied. The PRIME study has found some important differences between these groups of patients. Overall, those patients that accessed healthcare were frailer, with a higher burden of disease and medicines, and more likely to live alone and live in socioeconomically deprived circumstances. Following confounder adjustment, including age, gender, comorbidities, polypharmacy and formal care, a lower Barthel index (indicating greater functional dependency), reduced grip strength (indicating lower muscle strength and frailty), regular falls, and poorer cognition on the AMTS independently predicted healthcare access. Therefore, older adults that might be considered most vulnerable with least capacity to self-manage injury, were indeed those that accessed healthcare. There are several possible explanations for these findings, and it is likely these synergistically increase the opportunity for frailer and more functionally dependent older adults to receive medical care for MRH. Regular falls, poorer cognition and reduced muscle strength are all common features of the frailer, more dependent older adult. Frailty is characterised by decreased reserve and diminished resistance to stressors. There is a bidirectional relationship between frailty and functional dependence. As a result, these individuals are likely to be familiar with utilising health services and to be closely monitored by GPs. General Practitioners may have facilitated healthcare access due to increased vigilance towards MRH in this high-risk population. For instance, in early 2014 NHS England commissioned the ‘avoiding unplanned admissions enhanced service’, which supported GP practices to case find and proactively manage patients with complex needs at high risk of admission. Strong evidence from observational studies has previously shown that
frailty independently predicts unplanned hospital utilisation in large studies\textsuperscript{175,268–270}. This is unsurprising given that frailty arises from the accumulation of vulnerability and poor health across multiple domains, which compound each other leaving the individual incapable of mounting an adequate response to overcome even a relatively small physiological insult\textsuperscript{173}. Therefore, MRH which might under other circumstances be self-managed, is likely to afflict a frailer individual to a greater degree and prompt efforts to access healthcare acutely\textsuperscript{271}.

Two unexpected findings are that living in London, and, having a regular pharmacist were both predictors of healthcare access. Seventy percent of health service utilisation for MRH was in General Practice and approximately 25% hospital readmission or emergency department attendance. The availability of GPs, considering the ratio of GPs to patients, is very similar when contrasting London with the South-East of England more broadly (7.7 vs 7.9 GPs per 10,000 patients respectively)\textsuperscript{272}. However, the ease of transportability to GP and hospital settings could offer some explanation for living in London as a predictor of healthcare access. In England, only 1% of people in urban areas live more than 2 kilometres from a GP surgery, in contrast to 37% in rural areas\textsuperscript{273}. Whilst the sites involved in the PRIME study are not rural themselves, except for Princess Royal Hospital in Haywards Heath, the sites outside of London serve a vast geographical catchment including many rural areas. Therefore, the patients recruited from sites outside of London would on average need to travel greater distances from their home, with reduced availability of public transport, to access healthcare. A recent systematic review to investigate the impact of travel time and distance on health outcomes of adults in developed countries found some evidence to suggest that greater distance from healthcare facilities is detrimental to healthcare access and health outcomes\textsuperscript{274}. Therefore, the ease of transport and reduced travelling time to healthcare facilities in patients recruited in London, compared with other areas, might explain their increased healthcare access when experiencing MRH.

The second unexpected finding is that having a regular community pharmacist was an independent predictor of accessing healthcare. In 2013, patients discharged from
hospital with a medication change in the prior 8 weeks became a national target group for Medicines Use Reviews (MUR) as part of an extended service by community pharmacies\textsuperscript{245}. Medicines use reviews, initially introduced in England in 2005, are defined as ‘a patient-pharmacist consultation to discuss the patient’s use of medicines and improve their knowledge about their purpose’\textsuperscript{275}. The purpose of these targeted reviews has been to support optimal usage of medicines, including the identification of problems such as MRH\textsuperscript{276} and thereon a potential referral to the patient’s GP. However clinical outcomes post-MUR have been poorly investigated in England\textsuperscript{275}. Patients are only eligible for this service if they are regular patients of a pharmacy (patients receiving more than one medicine from a single pharmacy for three consecutive months). As such, pharmacists have been incentivised to act as gatekeepers to GP care for medication-related problems. This might be an important explanation for the finding that patients with MRH that had a regular community pharmacist were more likely to access medical care. Nevertheless, the data was saturated with 95% of MRH patients reporting a regular community pharmacist. Therefore, whilst a regular community pharmacist was a statistically significant predictor of healthcare access, there is considerable uncertainty of this relationship (adjusted OR 4.2, 95% CI 1.4-12.7, p<0.01) and the finding should be interpreted cautiously.

The costs of MRH to the health service in England have seldom been explored and the PRIME study is the first that specifically analyses the costs of MRH in the older population \textsuperscript{103,104,277}. The results of this PRIME study cost-analysis demonstrates a considerable financial burden on the NHS in England. Over an 8 weeks period, the cost of NHS use for MRH in the PRIME cohort was £225,747. Hospital admissions were the core cost, with GP consultations relatively inexpensive despite their number. The cost analysis performed and reported in this chapter pertains to the direct costs of consultation time and resource use, and excludes ‘indirect’ costs associated with wasted medicines, social care provision, and loss of productivity costs for informal care givers (e.g. employed relatives). Based on the number of hospital admissions in England, we extrapolated this data to estimate a cost of £396 million across the NHS from MRH occurring post-discharge. Based on the national
NHS expenditure in the 2014/15 financial year of £118.5 billion, MRH post-discharge in older adults represented 0.33% of the total healthcare costs in England\textsuperscript{22}. At least £50 million of this overall cost is preventable, however preventable costs are likely to be greater considering many MRH cases were classified as ‘possibly’ preventable. Therefore, if we consider the potentially avoidable total healthcare costs attributable to MRH, up to 0.2% (£240 million out of £118.5 billion expenditure) of NHS expenditure could be spent elsewhere if preventable MRH can be reduced\textsuperscript{22}. To put this national sum into better perspective, in the same financial year 2014/15, £240 million could have funded the annual salary of an additional 2649 GPs in the NHS\textsuperscript{278}.

A recent systematic review of the financial costs of ADE in all age groups identified 20 studies that evaluated the MRH costs from all drug groups, as opposed to specific drugs\textsuperscript{103}. Only one study, conducted in the Netherlands, evaluated costs specific to an older population (65 years and over)\textsuperscript{247}. The Hospital Admission Related to Medicines (HARM) study by Leendertse et al (2008)\textsuperscript{183} was a nationwide prospective case-control study with similar methods for defining MRH and ascribing causality to those of the PRIME study (i.e. including harm from ADR, non-adherence and medication error, and using expert judgement in conjunction with an algorithm). The rate of MRH associated hospital admissions was 5.6% over a 40 days observation period, whilst 2.6% of all acute admissions were due to preventable MRH. The average cost of one preventable hospital admission due to MRH in this Dutch study was €5637, and extrapolated to the Netherlands as a whole the authors estimated an annual cost of €55.6 million in that country. Considering Europe more broadly, in 2008 the European Commission estimated ADRs alone to cost member states €79 billion annually (direct and indirect costs)\textsuperscript{279}. More broadly for comparison, the cost of NHS resource use in England secondary to unintentional injury e.g. falls, road traffic accidents, sporting injury in adults over a one-year follow up post-injury episode was estimated at £1.5 billion\textsuperscript{280}. Approximately the same proportion of cost was due to hospital readmission (87%) and primary care consultation (10%) as in the PRIME study.
However, unlike many other areas of research, data on health system costs are particularly difficult to generalise to other countries given the variations in pricing of resources\textsuperscript{242} and complexities of health system payment and reimbursement across countries\textsuperscript{104}. One large prospective study in the UK by Pirmohamed \textit{et al} (2004) analysed data of 18,800 patients aged 18 years and over admitted to two hospitals, and determined the costs of hospital admission associated with MRH\textsuperscript{8}. Calculations based on the average length of stay and hospital bed-day costs of patients with MRH were used to estimate an annual MRH cost of £466 million to the NHS\textsuperscript{8}. Based on the data from this study by Pirmohamed \textit{et al} (2004), in 2015 the National Institute for Health and Care Excellence (NICE) estimated the cost of preventable hospital admissions in England caused by MRH at £530 million.\textsuperscript{28} The work I have conducted built on this cost estimate from a decade ago, to update cost estimates of MRH to the NHS and consider both primary and secondary care costs. The cost estimate, stratified by preventability, provides policy makers with a better indication of the scale of the cost impact and of the level of financial investment to address the problem that might return a net financial saving.

\section*{6.4.3 Future implications}

The results reported in the chapter are based on incidence, resource use and cost data from 2014. To explore how the costs of MRH might have changed since this time in the NHS and change in the future, there are various factors to consider (figure 6.3). As is shown in figure 6.3. there are factors that are likely to increase costs and others that may reduce the costs, however many of these are challenging to quantify e.g. increased knowledge of MRH amongst prescribers\textsuperscript{281}, or increased health literacy of patients and care givers\textsuperscript{282}. Several drivers of increased cost in the future are more readily quantifiable. For instance, the number of adults aged 65 years and older in England was predicted to increase by 20\% between 2014 and 2024\textsuperscript{67}, and by 2025 more than one in five people in England will be over the age of 65 years\textsuperscript{283}. The number of hospital admissions of adults aged 65-84 years has seen the greatest increase over the last decade, increasing from 4.3 million to 6.3 million (almost 50\% rise). In England, a retrospective analysis of over 400,000 adult patients
found that patients with multimorbidity experienced 2.5 times the usage of health services over a 4-year follow-up than those without, 79% of all prescriptions were to multimorbid patients, and 53% and 56% of GP consultations and hospital admissions respectively were for multimorbid patients. Clearly a rapidly ageing population, with an increased prevalence of multimorbidity and polypharmacy, is likely to increase the absolute number of MRH episodes and avoidable health service use.

In England between 1990 and 2010, the number of older adults regularly using 5 or more medicines increased four-fold, from 12% to 49%\textsuperscript{23}. The number of older adults using no medicine decreased from 20% to 8%\textsuperscript{23}. And the use of cardiovascular medicines increased by 230% in this population. The requirement for and positive impact of this increased treatment is debated widely\textsuperscript{11,229}. This substantial increase in medicines use is strongly related to over-diagnosis of disease that will have no symptomatic impact on patients, the lowering of thresholds for diagnosis of long-term conditions such as chronic kidney disease, diabetes mellitus and hypertension, and the addition of many new diseases to ‘disease formularies’ e.g. the Diagnostic and Statistical Manual of Mental Disorders update in 2013\textsuperscript{10,284}. Disclosed and undisclosed financial conflicts of interest amongst experts that develop guidelines for the diagnosis and management of disease is an important concern for current and future patient safety\textsuperscript{285}. Although the conflicts of interest described have been primarily identified in the North American setting, the practice of medicine in the UK is not isolated from that of the US. Nonetheless, an increasingly visible body of experts are calling for the rationalisation of medicines use and reconsideration of low thresholds for disease diagnosis and treatment\textsuperscript{286}. The ‘preventing overdiagnosis’ movement was founded in 2013 through collaboration between reputable healthcare, academic and patient organisations from the UK and the US including the British Medical Journal, The Dartmouth Institute, and The Centre for Evidence Based Medicine, University of Oxford (www.preventingoverdiagnosis.net). Furthermore there is a strengthening literature base recognising the significant flaws in what is accepted as evidence from supposedly ‘gold-standard’ clinical trials\textsuperscript{17,108,118}. Indeed, the traditional model of ‘evidence-based medicine’ has been called into question given its bias towards the randomised-controlled trial that fails to provide real-world evidence that is useful at the level of the individual patient\textsuperscript{118}. 


Therefore, although unquantifiable, a shift is emerging in UK clinical practice towards more individualised care less focused on single disease management\textsuperscript{287}. This shift is further supported by an emerging evidence base for ‘deprescribing’ medicine in older adults, particularly those that are frail,\textsuperscript{288,289} and increased awareness of the harms associated with overtreatment\textsuperscript{56,59}.

Figure 6.3 Factors likely to impact on the cost of MRH to the NHS in the future

- Number of older adults with multimorbidity
- Number of hospital admissions
- Use of polypharmacy
- Diagnostic thresholds and increasing number of disease classifications
- Reduction in social care provision
- Cost of medical consultation and hospital bed-day
- Cost of social care
- Cost of lost productivity in provision of informal care by employed relatives/friends
- Prescriber knowledge of MRH and ‘deprescribing’
- Social prescribing
- Cost of certain medicines that come off-patent
- Health literacy of patients and care givers
- Use of hospital and community pharmacists to review medicines
- Consultation time of pharmacists, advanced nurse prescribers, paramedics instead of General Practitioners as allied health professionals increasingly used in primary care service provision
- Increased uptake of private healthcare insurance schemes
6.4.3 Limitations

The results I report in this chapter give a strong indication of the healthcare use of older adults with MRH post-discharge in England. However, there are several limitations to recognise. It is not possible to entirely attribute healthcare access to MRH given the complex pathway from the incidence of an adverse health event to medical consultation, which is influenced by patient, provider and policy level determinants. This may have led to an overestimation of the healthcare costs we have calculated. Nonetheless, data on hospital readmission, accounting for 93% of costs, were captured prospectively with MRH deemed to have primarily caused the admission by both the research pharmacist and medical consultant overseeing the patient’s care. Furthermore, the most conservative costings were used where uncertainty existed e.g. A&E visits costed with ‘no investigation or treatment’.

Although this was a relatively large, multicentre UK study, the extrapolated costs of MRH to the NHS in England should be interpreted as a crude approximation. The incidence and types of MRH are based on the 1116 patients and five hospitals involved in the PRIME study, and may not reflect the pattern of MRH and health care access elsewhere in England. Furthermore, hospital readmissions that occurred over the weekend were not captured if the patient was discharged during the same weekend.

The data are limited to only analyse patient-related factors that influenced healthcare access. There are provider-level factors that influence access e.g. enhanced GP services to proactively manage frailer patients, which have not been explored.

Whilst the direct cost of MRH to patients has been evaluated in this study, this is a gross cost. A net cost, obtained within a cost-benefit analysis, would compare the benefits conferred on the health of a patient from the medicine (and health service utilisation avoided secondary to improved health) against the cost of MRH. This is incredibly challenging to achieve as the benefits of a high proportion of medicines used in older adults are at a population level and are of a preventative nature such that benefit is elicited over periods of time (often several years). This is the concept of Numbers Needed to Treat (NNT) i.e. treating ‘x’ individuals for ‘y’ years will
prevent one event. The criticisms of this approach are that it is a utilitarian approach, where a majority risk MRH (and changes to their quality of life through taking medicines for the long-term) for a minority that will experience benefit. Let us consider an example. If 100 patients are to take a daily antihypertensive to maintain low BP with a NNT of 33 over 5 years to prevent a cardiovascular event or death, then 3 potentially life-threatening events will have been prevented at 5 years from 100 people remembering to take a tablet every morning for 5 years. Ninety-seven of these people will have experienced either no health benefit or harm over this period. Whilst the reduced blood pressure acts over the five-year timeframe to prevent an event, the patient experiences no palpable benefit in the meantime. However, they may well experience light-headedness or constipation daily. Hence the harm is experienced very clearly at an individual level, whereas the benefits of many medicines are based on population level data. Furthermore, this utilitarian medical practice fails to appreciate the fact that the randomised trials upon which the benefits of medicines are elicited are under controlled conditions where patients are monitored and motivated to adhere. However, in the ‘real-world’ it has been shown that 30% of older adults are not fully adherent to medicine for long-term use, just 10 days following its prescription.

6.5 Conclusions

A majority of older people that experience MRH post-discharge access healthcare. Those that do not have less morbidity, fewer medicines, greater muscle strength, higher cognition and functional independence. They are also more likely to be living with others, and have higher socioeconomic status. Living in an urban setting and having a regular pharmacist were found to be independent predictors of healthcare access, along with markers of frailty and poorer cognition. The cost of healthcare utilisation secondary to MRH is large, a considerable proportion of which is preventable. Thus, effective interventions to reduce preventable MRH post-discharge could free up substantial NHS resource for uses other than that of iatrogenic harm.
CHAPTER 7.
Predicting risk: Can doctors identify patients at risk of MRH?
Chapter Summary

Medication-related harm (MRH) is increasing in the context of polypharmacy and ageing populations globally. The post-discharge period is high risk for the incidence of MRH, and results in avoidable healthcare use. In resource-limited health systems, interventions to reduce this risk cannot be universal and need to be targeted at high-risk patients to enhance cost-effectiveness. This chapter used the PRIME multicentre prospective cohort study to investigate whether doctors organising discharge for patients can predict which older patients will experience MRH requiring healthcare post-discharge. The chapter also examines whether clinical experience and level of confidence in MRH prediction influences the accuracy of the prediction. Finally, the factors that doctors believe are influential in the incidence of MRH are explored.

Doctors discharging patients (predominantly junior doctors) were asked to complete structured questionnaires to predict MRH alongside some free text boxes to provide rationale for their predictions. Data of 1066 patients (83% of the total PRIME study cohort) who had both a completed prediction questionnaire on discharge and an 8-week follow-up were analysed. Patients in this sub-study had a median age of 82 years and 58% were female. Most predictions (85%) were made by junior doctors with less than 5 years’ clinical experience. Using logistic regression models, no statistically significant relationship was found between doctors’ predictions and post-discharge MRH (OR 1.10, 95% CI 0.82-1.46, p=0.53), irrespective of years of clinical experience. Doctors’ predictions were more likely to be accurate when they reported higher confidence in their prediction, particularly in predicting MRH-associated hospital readmissions (OR 1.58, 95% CI 1.42-1.76, p<0.001). Doctors reported a range of clinical, social and psychological factors as influencing their predictions, some of which were evidence based and others that have high face validity but warrant future investigation. Enhancing clinical pharmacology and therapeutics teaching in the medical curriculum might provide one way forward to enhance doctors’ ability to predict MRH. Advanced statistical modelling on a large data set to develop and internally validate a risk prediction tool is a logical next step in improving MRH risk prediction.
7.1 Introduction

Previous chapters in this thesis have described my work to identify the burden of MRH to the NHS in England. This harm is unlike other iatrogenic harm; medicines are the most commonly used treatment in health systems across the world and patients do not expect to be harmed from treatment and are certainly not well informed and consented as is the case for surgery. Four patients died secondary to MRH in the PRIME study (chapter 5) and 8% of patients were readmitted to hospital, therefore the significance of the risk of iatrogenic harm from medicines is not incomparable to that of surgical procedures. Nonetheless, patients are clearly consented for surgical procedures in England and risk stratification is a primary step in reducing the harms from anaesthesia and surgery. Risk stratification and medicines optimisation are two priorities for the NHS in England to improve the cost-effectiveness of patient care and reduce the incidence of avoidable harm.291,292 Currently there are no risk prediction tools to identify high-risk patients for MRH post-discharge, and the success of pharmacist interventions to reduce MRH and hospital readmission has been inconsistent.76,293–295 In the NHS, doctors (particularly junior doctors) are key professionals in ensuring a safe hospital discharge through careful and informed coordination of patient care from hospital to the community.296 Junior doctors most commonly prepare patient discharge summaries that include details of the admission diagnosis, inpatient investigations, and prescribed medications to be continued at home. Doctors prescribing discharge medications and communicating with GPs through discharge summaries should be familiar with the patient’s clinical state (e.g. renal function, cognition, comorbidities) and social environment (e.g. support with medicines). In addition, chapter 5 showed that adverse drug reactions (ADR) are the most common MRH and are usually predictable from the pharmacological action of the drug (i.e. type ‘A’ reactions).8,73. Therefore, one might reasonably expect doctors to be well situated healthcare professionals to predict patients at high risk of MRH following hospital discharge.

This chapter reports my work to test a hypothesis that discharging doctors can identify older patients at high risk of MRH post-discharge. The focus was on clinically
significant MRH i.e. MRH requiring healthcare use. This work also investigates whether doctors’ years of clinical experience influences their ability to predict MRH accurately, and whether a doctor’s confidence in their prediction is associated with increased accuracy. Finally in this chapter, a thematic analysis that I conducted to understand the factors that doctors held to be important in influencing their predictions of MRH is reported.

7.2 Methods

The general methods for the PRIME study, from which data is used for this chapter, are described in detail in chapter 4.

Around the time of or just following a patient’s hospital discharge, a research nurse asked the discharging doctor to complete a questionnaire (see appendix 5). On this questionnaire, the discharging doctor was asked to anonymously predict the likelihood of their patient experiencing MRH requiring healthcare utilisation (1. hospital admission, and, 2. community healthcare) in the first 8 weeks following discharge. Doctors were asked to classify their prediction based on recognised categories in this research area: doubtful, possible, probable or definite. Predicting a likelihood for a given consequence (MRH serious enough to seek healthcare) to estimate risk is based on the National Patient Safety Agency risk model matrix. Participating doctors also assigned a confidence rating to their judgements from ‘little or no confidence’ to ‘virtually certain’ using a six-point Likert scale: 1) little or no confidence; (2) slight to moderate confidence; (3) less than 50% confidence but a close call; (4) more than 50% confidence but a close call; (5) strong confidence; (6) virtually certain. Doctors provided information on their level of seniority according by their medical grade (e.g. foundation year one, foundation year two, core trainee, registrar, consultant). This information was grouped into the following categories of clinical experience; less than one year (reflecting foundation year one), 1-4 years (reflecting senior house officer) and more than 4 years (reflecting registrar or consultant). Discharging doctors had the opportunity to provide some free narrative to give their rationale for their prediction. This narrative was coded by myself and Dr Jennifer
Stevenson (clinical pharmacy research fellow) through immersion in the data. Based on this coding of the data, major themes and sub-themes were drawn to explain the factors that discharging doctors considered in the process of making their prediction of whether a patient was likely to experience MRH post-discharge. Any disagreements were resolved through discussion.

Given the regular rotation of junior doctors, there was a need to provide ongoing information about the study. As a part of the induction of new doctors joining the participating medical wards, the doctors were given information about their requested involvement in completing questionnaires and it was reiterated that they should not complete questionnaires if unfamiliar with the patient. In addition to this, research nurses conducting the questionnaires were trained to confirm that only doctors with knowledge of the patient’s case history were requested to complete the questionnaire.

7.2.1 Statistical Analysis

To describe the baseline characteristics of the patient population that formed part of this study, the distribution of variables was examined by plotting histograms and used in conjunction with the Kolmogorov-Smirnov test for normality. The median and interquartile range for continuous variables was calculated. For analyses, patients that did not have a doctor’s prediction or that were lost to follow-up i.e. no MRH outcome information at 8-weeks were excluded. The baseline characteristics of the patient cohort included in the analysis and those patients excluded was compared using the Mann-Whitney U-test for continuous, non-normally distributed variables. To compare categorical variables, Fisher’s Exact Test was used.

The relationship between the discharging doctors’ prediction of MRH and the observed outcome of MRH was analysed using a logistic regression model. Patients were grouped as having experienced MRH is they had a possible, probable or definite event. Consistent with this, doctors’ predictions of possible, probable and definite MRH were grouped together as a prediction that MRH will occur. A sensitivity analysis using a logistic regression model that only included probable and definite MRH predictions and events was conducted to investigate any impact on the
main results of the inclusion of ‘possible’ cases in our categorization of MRH. Similarly, a sensitivity analysis was conducted including only ADRs (excluding harm only due to non-adherence and medication error) to determine any effect of definition.

The sensitivity, specificity, positive and negative predictive values, and the Area under the Receiver Operating Curve (AUROC) were also calculated to quantify the discriminatory ability of the doctors’ predictions. The sensitivity and specificity describe the proportion of those that experienced (or did not experience) MRH that had predictions concordant with this outcome i.e. true positives and true negatives. The positive and negative predictive values reflect the proportion of ‘MRH’ and ‘no MRH’ predictions that were found to be accurate once the outcome was known i.e. truly did or did not have MRH for positive and negative predictive values respectively. The AUROC (also referred to as the c-statistic) is a measure of the ability of doctors predictions to discriminate between high and low risk patients, with a value of 0.5 representing no discrimination and a value of 1 representing perfect discrimination.

Using logistic regression, the influence of the years of clinical experience of doctors, and the confidence doctors placed in their predictions, were evaluated. Likelihood ratio tests were conducted to compare models using level of confidence as an ordered categorical variable and as a linear term. All models were controlled for site of patient recruitment to limit confounding due to differences in healthcare processes or culture at the different participating hospital trusts.

A p-value of <0.05 was taken as statistically significant. All statistical analysis was conducted in Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).
7.3 Results

7.3.1 Patient characteristics

The PRIME study recruited a total of 1280 older adults at hospital discharge to follow up for 8-weeks, however for this sub-analysis the data of 1066 patients was analysed. Seventeen patients (1.3%) died with no follow up, and 197 (15.4%) patients either did not have a prediction of MRH or did not have an 8-week follow up. The baseline characteristics of the sample are shown in Table 1. The median age of the patients was 82 years (IQR 75.6-87.0), and 58% were female. The median score on the Charlson comorbidity index was 2 (IQR 1-3), and the median number of drugs prescribed at discharge was 9 (IQR 7-12).

From the sample of 1066 patients, 315 (29.5%) patients experienced MRH requiring healthcare (emergency department attendance, hospital readmission, outpatient consultation, GP consultation including out of hours), in the 8 weeks post-discharge.
### Table 7.1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included patients (n=1066)</th>
<th>Excluded patients (n=214)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (IQR), years</strong></td>
<td>82.0 (75.6-87.0)</td>
<td>80.2 (74.3-85.7)</td>
<td>0.008</td>
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<tr>
<td><strong>Gender, n (%),</strong></td>
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<tr>
<td>Women</td>
<td>619 (58.1)</td>
<td>126 (58.9)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>447 (41.9)</td>
<td>88 (41.1)</td>
<td>0.879</td>
</tr>
<tr>
<td><strong>Hospital stay, median (IQR), days</strong></td>
<td>7 (3-14)</td>
<td>7 (3-13)</td>
<td>0.383</td>
</tr>
<tr>
<td><strong>Number of Charlson Index comorbidities (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>521 (48.9)</td>
<td>108 (50.5)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>545 (51.1)</td>
<td>106 (49.5)</td>
<td>0.708</td>
</tr>
<tr>
<td><strong>Selected comorbidities, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>582 (54.6)</td>
<td>115 (53.7)</td>
<td>0.822</td>
</tr>
<tr>
<td>CLD</td>
<td>310 (29.1)</td>
<td>72 (33.6)</td>
<td>0.191</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>263 (24.7)</td>
<td>59 (27.6)</td>
<td>0.388</td>
</tr>
<tr>
<td>Diabetes</td>
<td>255 (23.9)</td>
<td>45 (21.0)</td>
<td>0.378</td>
</tr>
<tr>
<td>IHD</td>
<td>212 (19.9)</td>
<td>50 (23.4)</td>
<td>0.265</td>
</tr>
<tr>
<td>CKD</td>
<td>146 (13.7)</td>
<td>28 (13.1)</td>
<td>0.913</td>
</tr>
<tr>
<td>CCF</td>
<td>143 (13.4)</td>
<td>27 (12.6)</td>
<td>0.826</td>
</tr>
<tr>
<td>Depression</td>
<td>92 (8.6)</td>
<td>15 (7.0)</td>
<td>0.500</td>
</tr>
<tr>
<td>Dementia</td>
<td>51 (4.8)</td>
<td>6 (2.8)</td>
<td>0.274</td>
</tr>
<tr>
<td><strong>Charlson Index score, median (IQR)</strong></td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>0.385</td>
</tr>
<tr>
<td><strong>Barthel Index Score, median (IQR)</strong></td>
<td>17 (13-20)</td>
<td>18 (14-20)</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>Number of discharge medicines, median (IQR)</strong></td>
<td>9 (7-12)</td>
<td>9 (7-12)</td>
<td>0.202</td>
</tr>
<tr>
<td><strong>Multicompartment compliance aid, n (%)</strong></td>
<td>351 (32.9)</td>
<td>63 (29.4)</td>
<td>0.337</td>
</tr>
<tr>
<td>Discharge to care home, n (%)</td>
<td>29 (2.7)</td>
<td>9 (4.2)</td>
<td>0.267</td>
</tr>
<tr>
<td>Living alone after discharge, n (%)</td>
<td>531 (49.8)</td>
<td>100 (46.7)</td>
<td>0.498</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test for continuous variables and Fisher’s Exact test for categorical variables.
IQR, interquartile range; CLD, chronic lung disease; IHD, ischaemic heart disease; CKD, chronic kidney disease; CCF, congestive cardiac failure
7.3.2 Discharging doctors

A majority of MRH predictions (n=595, 55.8%) were made by doctors with less than one full year of clinical experience post-medical qualification i.e. foundation year one doctors or doctors with 1-4 years’ clinical experience i.e. senior house officer level (n=306, 28.7%). The remaining 11.8% (n=126) predictions were made by senior doctors of five or more years’ clinical experience i.e. registrar or consultant grade. The seniority grade of the doctor was unknown for 3.7% (n=39) predictions.

7.3.3 Accuracy of Predictions

Doctors accurately predicted the outcome (MRH or no MRH) in 469 out of 1066 patients (44%). Doctors accurately predicted MRH would occur in 204 out of the 315 MRH cases (64.8%), and that MRH would not occur in 265 out of 751 patients (35.2%) that did not experience MRH. The sensitivity of doctors’ predictions was 0.65 and specificity was 0.35. The positive predictive value 0.30 and the negative predictive value 0.70. The AUROC (or c-statistic) was 0.50, which demonstrates no predictive discrimination between patients that did or did not experience MRH.

Using logistic regression models, there was no relationship between the doctors’ predictions and MRH outcome (odds ratio (OR) 1.10, 0.82 to 1.46, p=0.53) (Table 2). A sensitivity analysis to determine whether exclusion of possible cases of MRH and doctors’ predictions affects this relationship demonstrated no meaningful difference (OR 0.90, 95% CI 0.53-1.52, p=0.68). A further sensitivity analysis to determine if doctors could correctly predict ADRs, rather than the broader definition of MRH (includes harm from non-adherence and medication error), also demonstrated no significant relationship (OR 0.91, 95% CI 0.64-1.28, p=0.57).

7.3.4 Influence of doctor’s seniority and confidence

There was no significant difference in predictive accuracy between doctors with varying years of clinical experience (<1 year, 1-4 year, >4 years) (see Table 2). The results do however show that a higher confidence placed by doctors in their own MRH
predictions (‘little or no confidence’ through to ‘virtually certain’) was associated with a more accurate prediction (see Table 3). Increasing confidence levels in doctors’ predictions of MRH leading to hospital readmission was associated with 58% greater odds of a prediction with higher accuracy (OR 1.58, 1.42 to 1.76, p<0.001). Increasing confidence was also associated with the accuracy of doctors’ predictions of MRH leading to community healthcare use, however the size and strength of the association were less than that for predicting hospital readmission (OR 1.14, 1.03 to 1.26, p=0.009).

Table 7.2 Relationship between discharging doctors’ predictions and medication-related harm (MRH) by (a) all doctors (b) level of clinical experience†

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Discharging doctor prediction of MRH (Yes vs No)</td>
<td>1.10</td>
<td>0.82 – 1.46</td>
<td>0.527</td>
</tr>
<tr>
<td>(b) &lt;1-year experience</td>
<td>1</td>
<td>0.88 – 1.98</td>
<td>0.181</td>
</tr>
<tr>
<td>1–4 years</td>
<td>1.32</td>
<td>0.88 – 1.98</td>
<td>0.181</td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>1.14</td>
<td>0.58 – 2.23</td>
<td>0.709</td>
</tr>
</tbody>
</table>

†(a) based on 1066 predictions; (b) based on 1028 predictions
Possible, probable and definite classifications for predictions and outcomes grouped as affirmative of MRH occurrence

Table 7.3 Relationship between discharging doctors level of confidence in their prediction of (a) hospital readmission associated with MRH, and (b) community health service use associated with MRH, and the accuracy of the prediction†

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (OR)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Level of confidence in prediction of MRH readmission</td>
<td>1.58</td>
<td>1.42 - 1.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(b) Level of confidence in prediction of MRH community health service use</td>
<td>1.14</td>
<td>1.03 - 1.26</td>
<td>0.009</td>
</tr>
</tbody>
</table>

†(a) based on 1062 predictions; (b) based on 1053 predictions
7.3.5 Themes influencing doctors MRH predictions

Four main themes were elicited from the free text narrative completed on the questionnaire by doctors to explain the rationale for their MRH predictions. The coding of the text was categorised into themes around specific medication-related factors, social support and function, cognition and adherence issues, and clinical complexity. The main themes, sub-themes and selected illustrative quotes elicited are shown in Table 7.4. Out of the 1066 completed questionnaires, medication-specific factors were given as a rationale in 726 (68.1%) predictions of the likelihood of MRH. Social support and functional independence (or lack of) were stated as factors influencing doctors’ predictions in 174 (16.4%) completed questionnaires. Cognition and adherence issues were described as reasons for the predictions given by doctors in about one-third of patients (327 completed questionnaires, 30.7%). Finally, the clinical complexity of the patient was mentioned as a factor influencing the likelihood of MRH on 154 questionnaires (14.4%).
Table 7.4 Thematic analysis of factors described by doctors as influencing their MRH predictions

<table>
<thead>
<tr>
<th>Main themes</th>
<th>Sub-themes</th>
<th>Illustrative quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication-specific factors</strong></td>
<td>Polypharmacy</td>
<td>'multiple medications’&lt;br&gt;‘they are on a plethora of medication’&lt;br&gt;‘meds reviewed several times and several have been stopped. Meds are long term’&lt;br&gt;‘Antihypertensives. Zopiclone prescription - addictive meds + polypharmacy’</td>
</tr>
<tr>
<td>Medication changes</td>
<td></td>
<td>'no change to medication’&lt;br&gt;‘one new drug added monitored whilst inpatient with no side effects’&lt;br&gt;‘few meds, none new’</td>
</tr>
<tr>
<td>Drug-drug or drug-disease interaction</td>
<td></td>
<td>'ramipril and ibuprofen – AKI risk’&lt;br&gt;‘prednisolone plus spironolactone increases risk of hyperkalaemia’&lt;br&gt;‘diabetic and on high dose steroids. Likely to have difficult diabetic control’</td>
</tr>
<tr>
<td>Past history of ADR</td>
<td></td>
<td>'did have bradycardia secondary to diltiazem’&lt;br&gt;'No change to meds, no previous admissions due to meds’</td>
</tr>
<tr>
<td>High risk medicines</td>
<td></td>
<td>'warfarin high risk in older patients with falls risk’&lt;br&gt;‘pain medication has high risk of side effects’&lt;br&gt;‘benign list of meds’&lt;br&gt;‘initiation of insulin’</td>
</tr>
<tr>
<td>Duplicate medications of same class</td>
<td></td>
<td>‘Added in a third antihypertensive’&lt;br&gt;‘on multiple diuretics’</td>
</tr>
<tr>
<td><strong>Social support and function</strong></td>
<td>Co-habitants</td>
<td>'lives with daughter who will assist with medications’&lt;br&gt;‘Supportive family. Supportive family would notice any changes in patient’&lt;br&gt;‘lives alone’</td>
</tr>
<tr>
<td>Carers</td>
<td></td>
<td>'lives with husband as main carer’&lt;br&gt;‘discharged with package of care’&lt;br&gt;‘Her niece was present with warfarin counselling, plus having district nurse help’</td>
</tr>
<tr>
<td>Functional independence</td>
<td></td>
<td>‘patient seemed very able to cope with medication’&lt;br&gt;‘Been self-administering medications for a long time’&lt;br&gt;‘Bed bound’&lt;br&gt;‘increasing fraility’&lt;br&gt;‘independent of ADL’s’</td>
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</tbody>
</table>
Table 7.4 Cont’d. Thematic analysis of factors described by doctors as influencing their MRH predictions

<table>
<thead>
<tr>
<th>Main themes</th>
<th>Sub-themes</th>
<th>Illustrative quotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition and adherence issues</td>
<td>Past history of adherence</td>
<td>‘known not to comply with medication’</td>
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<tr>
<td></td>
<td></td>
<td>‘Patient has history of overdose’</td>
</tr>
<tr>
<td></td>
<td>Health literacy</td>
<td>‘understands medications and indications’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘very aware of medical issues and good understanding of meds’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>‘very good insight into his medical care needs’</td>
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<tr>
<td></td>
<td></td>
<td>‘unsure if parents fully understands his medication - compliance seems variable pre-admission from talking to the patient’</td>
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<tr>
<td></td>
<td>Use of medication compliance aid</td>
<td>‘has NOMAD’</td>
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<tr>
<td></td>
<td></td>
<td>‘as a blister pack decreasing chance of error’</td>
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<tr>
<td></td>
<td>Cognitive impairment</td>
<td>‘no cognitive issues’</td>
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<tr>
<td></td>
<td></td>
<td>‘no dementia’</td>
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<td></td>
<td></td>
<td>‘memory impairment’</td>
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<td></td>
<td></td>
<td>‘vascular dementia’</td>
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<td></td>
<td>Educational competence</td>
<td>‘sensible man’</td>
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<td></td>
<td></td>
<td>‘intelligent lady’</td>
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<tr>
<td></td>
<td></td>
<td>‘Very coherent and lucid, switched on patient’</td>
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<tr>
<td></td>
<td></td>
<td>‘well educated’</td>
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<tr>
<td></td>
<td></td>
<td>‘Bright articulate’</td>
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<tr>
<td></td>
<td>Clinical complexity and monitoring</td>
<td>‘asked GP to repeat bloods to ensure renal function stable’</td>
</tr>
<tr>
<td></td>
<td>Medical follow-up post-discharge</td>
<td>‘Patient due to have follow up at RACOP’</td>
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<td></td>
<td></td>
<td>‘Unless patient is actively reviewed in community she may come to harm’</td>
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<td></td>
<td>Multimorbidity and frailty</td>
<td>‘multiple comorbidities’</td>
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<td></td>
<td></td>
<td>‘Frailty, poor mobility and co-morbidities’</td>
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<td></td>
<td>High risk comorbidity</td>
<td>‘cancer puts her at risk of further medication problems’</td>
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<td></td>
<td></td>
<td>‘renal impairment and CCF necessitating caution’</td>
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<tr>
<td></td>
<td>Patient anxiety</td>
<td>‘Very anxious patient. Anxiety related - probably not from actual medicines related harm but from his perceived harm related to medicines’</td>
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<td></td>
<td></td>
<td>‘Less likely actual harm than perceived harm as anxious individual’</td>
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7.4 Discussion

Risk prediction is a crucial strategy to use limited healthcare resources cost-effectively. The main objective of my work described in this chapter was to determine the reliability of discharging doctors’ clinical judgement as an MRH risk stratification tool. This is the first study to address the question of whether clinical judgement is a sufficient tool to predict MRH in older adults. Experts have previously called for such research.299 The study focused on the judgement of doctors (rather than other health professionals) given their primary role in planning and coordinating discharge, prescribing medicine at hospital discharge, and communication with patients’ GPs through discharge summaries. Discharging doctors are well-situated to intervene by highlighting medication concerns on a discharge summary or altering medicine lists in high-risk individuals. The study results demonstrate that clinical judgement alone is not a reliable predictor of post-discharge MRH in older patients. Furthermore, this finding does not appear to be influenced by the seniority of the discharging doctor. It is notable, however, that when the discharging doctor had stronger confidence in their prediction, it was more likely to be a correct prediction.

A majority of doctors that participated in completing this questionnaire survey were junior doctors (85%). This reflects the fact that junior doctors are the members of the medical team most usually responsible for facilitating patient discharges in the NHS.

7.4.1 Comparison with previous work

There are no previous studies of clinical prediction of medication harm that can be used to draw upon to directly to compare my findings.

It is surprising that much effort has been invested in the development of statistically generated risk prediction models112,300, and yet the basic question of whether clinical judgement might suffice has remained unanswered. A recent systematic review of risk prediction models to predict MRH in hospitals found that none of the tools were suitable for routine clinical implementation300.

There have however been studies investigating risk prediction by doctors in related areas. A study in the United States evaluated the ability of doctors to predict 30-day hospital readmission in a sample of 164 older adults at the point of hospital discharge.
The US study had similar findings to the results of the study reported in this chapter; doctors showed poor ability, irrespective of grade seniority, to discriminate between patients that were readmitted and those that were not (AUROC 0.59 for junior doctors, and AUROC 0.58 for senior doctors). The study authors speculated that the heterogeneity of the older population in conjunction with the complex interplay between clinical and social factors that drive hospital readmission could explain these findings. The drivers of MRH are comparably complex, with a multitude of recognised risk factors across biological, psychological and social domains, and is one explanation for doctors showing poor ability to predict MRH. Using literature searching, Nominal Group Technique and Delphi consensus, a multidisciplinary expert panel in Switzerland reported 27 risk factors for medication related problems (including behavioural, sensory, drug-specific, disease-based and physiological) considered as important through a combination of literature.

Nonetheless an important contrast from predicting all-cause readmission, as investigated in the study by Allaudeen et al (2011), is that many MRH episodes can be predicted from a strong knowledge of clinical pharmacology (i.e. ‘type A’ ADRs). Enhancing clinical pharmacology and therapeutics (CPT) knowledge within the medical training curriculum has been advocated for in the UK and in other Western healthcare systems, and is elaborated on later in this discussion section. This is gaining increasing importance with ageing populations globally, and the rapid increase in polypharmacy and adverse drug reactions in the older population.

Comparing the findings of this chapter with other studies specifically focussed on the hospital discharge period, a study in Italy explored the ability of 11 consultant doctors to predict various discharge outcomes (global function, length of stay, discharge destination) of older patients. The results showed poor association between predicted and observed outcomes, although predictions were found to be more accurate where patients fell into extreme categories i.e. very poor or very high level of function based on the Barthel Index, or very short and very long lengths of stay in hospital. The authors of the study suggested these results could indicate poorer prognostic accuracy amongst doctors when a patient’s clinical picture is uncertain as opposed to ‘black or white’. This reasoning resonates with the finding in this chapter.
that predictions made with stronger confidence (where MRH risk might have been felt to be clearer cut) were more likely to be accurate.

An area of clinical prediction in older patients that has been much more extensively explored is survival in terminally ill patients. A recent systematic review of clinical prediction of survival in palliative patients, which included 42 studies and 12000 predictions, found no evidence that clinicians can consistently predict the extent of survival in palliative care patients. The review also showed that the level of clinical experience of the individual making the prediction does not improve the prognostic accuracy. Interestingly, the systematic review of clinical prediction in palliative patients included two studies where predictions were made by a multidisciplinary team, and these demonstrated greater prognostic accuracy than individual clinical prediction. Multidisciplinary predictions in the context of predicting MRH would be a worthwhile area for future research. Combining the doctor’s clinical knowledge, with pharmacist expertise on medication safety and management including drug interactions, contraindications, adherence and monitoring, and insight from nurses on the patient’s social environment, could lead to more accurate identification of high-risk patients.

There is no previous literature around confidence and predicting adverse medical outcomes to specifically draw upon to support or contrast this chapter’s findings. One US study used hypothetical medical cases, ranging in degree of clinical complexity, to examine the relationship between diagnostic confidence and accuracy in a sample of doctors. The results showed poor calibration between doctors’ confidence and diagnostic accuracy, identifying a misplaced confidence when diagnosing more complex cases. The ‘confidence-accuracy’ relationship has been little explored within clinical medicine and is another area that warrants further research.

7.4.2 Factors reported by doctors as influencing their MRH predictions

Although my findings indicate that discharging doctors cannot reliably predict MRH, the factors that influenced their predictions were sensible based on existing literature.
Common risk factors cited by doctors were polypharmacy, cognitive impairment, renal disease, past ADRs, specific medicine types e.g. antithrombotics and insulin, and drug interactions. These are established risk factors for MRH\textsuperscript{112,310,311}. It was an interesting finding that doctors’ predictions were often influenced by the level of functional dependence and frailty of a patient. There have been few studies that have explored the relationship between frailty and MRH, and results have been mixed \textsuperscript{312,313}. Indeed, one of these studies based on older US veterans found that higher functional dependence was indeed protective against MRH \textsuperscript{312}. This finding was likely due to the additional assistance with medicines that dependent patients received.

Discharging doctors also identified support (both formal and informal) and medication compliance aids (e.g. blister packs) as protective factors against MRH. Adherence may be influenced by social support through prompting (or administering), but social support may also act as a valuable safety net. For instance, a carer might recognise a health deterioration that could be associated with medication and seek healthcare. Doctors commonly recorded medication compliance aids as a protective feature for a patient upon discharge, however evidence suggests that the protective ability of medication compliance aids is over-estimated \textsuperscript{314,315}. The qualitative study I conducted, was reported in chapter 3, similarly found that whilst some older adults found medication compliance aids helpful, others felt that there was a loss of autonomy with them and that they could be confusing and cumbersome to use\textsuperscript{316}.

Many doctors commented on the health literacy of a patient as an important feature in predicting whether a patient was likely to experience MRH requiring healthcare. Health literacy is defined as ‘the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions’ \textsuperscript{317} As described in chapter 3, older patients identify a lack of knowledge about medicines and poor understanding of treatment aims as key problems related to medicines use \textsuperscript{316}. Surprisingly, only one study has investigated whether low health literacy in older adults predicts the incidence of MRH \textsuperscript{318}. This was a community-based prospective study with a one-year follow up of 310 retired US veterans. The results demonstrated a trend towards a relationship between low health literacy and MRH, however the study was underpowered and the results did not reach statistical significance. Medication adherence has been more closely studied
in relation to health literacy. A systematic review found some evidence for a linear relationship between health literacy and medication adherence in older people, although a relationship was not consistently seen across studies. The inconsistency between studies might be explained by a ‘U-shaped’ relationship; those with lower health literacy are found to unintentionally non-adhere to medicine, whilst those with higher health literacy have been found to intentionally non-adhere as a protective strategy towards medicines perceived to be problematic.

7.4.3 Implications for medical education and MRH risk prediction

As alluded to earlier, a potential explanation for the findings reported in this chapter is poor CPT knowledge amongst doctors. Compared with diagnostic-related teaching, CPT has been a neglected area of the medical curriculum in the UK and more widely (2-3% of medical education). Yet, much of the day-to-day work of a junior doctor is the prescribing and monitoring of medicines. A recent systematic review and large European survey of final year medical students have both shown that junior doctors are underprepared for their prescribing responsibilities, and pharmacovigilance is an area in particular need of improvement. Academics, hospital doctors, and medical students have called for increased CPT training in the medicine curriculum. This is increasingly important as the population ages, and are prescribed more medicines. A national prescribing safety assessment for medical students in the UK, within which ADR is a key section, was introduced in 2014 and is expected to increase the visibility of CPT within medical school curriculums. Whilst an evaluation of this initiative has demonstrated its feasibility, an impact assessment on CPT integration in medical school curriculums, prescribing safety, and knowledge of ADRs is needed. A welcome development is the General Medical Council’s new 2018 guidelines for medical schools, ‘Outcomes for Graduates 2018’, which makes it incumbent upon medical schools to equip doctors with the professional skills ‘to prescribe medications safely, appropriately, effectively and economically and be aware of the common causes and consequences of prescribing errors’. Increased education in CPT could enable future doctors to better predict MRH, and therefore target high-risk patients for additional medicines.
support and monitoring in the community post-discharge. Nonetheless it is important to acknowledge that ADRs in the very old population can present atypically and be mistaken as manifestation of frailty, such as chronic constipation and regular falls. Therefore doctors must remain vigilant to this, alongside increases in CPT knowledge. The enhanced training in medical prescribing, directed by the UK General Medical Council (GMC), is to be welcomed. However, the focus has been more on appropriate prescribing for single diseases, rather than within a context of safer prescribing in multimorbidity and frailty as is commonly found in Geriatrics. The lack of emphasis on multimorbidity within clinical guidelines until very recently has perhaps contributed to this, but this should change with greater recognition that a single-disease model of management is inappropriate in Geriatrics.

A considerable proportion of MRH is attributable to poor adherence (23% of MRH in the PRIME study) and medication errors (5% in the PRIME study) (reported in Chapter 5). Qualitative work has shown that GPs value pharmacists’ expertise on adherence-related and medication management issues, particularly in older patients. Shared learning initiatives between doctors and pharmacists might also enhance knowledge amongst doctors of adherence and medication management problems and increase their ability to predict these issues in their patients. Less conventional educational approaches may also be valuable towards doctors developing a broader knowledge of the determinants of MRH and reducing its burden; a study of third year medical students in the United States found that experiential learning methods by direct involvement in patient care at the point of discharge and subsequent community follow-up enhances knowledge of medication-related problems in the post-discharge period. Whether increasing awareness of medication-related problems or additional pharmacology training translates into reductions of adverse events remains to be explored.

Having shown that clinical judgement alone is insufficient to predict which older patients will experience MRH requiring healthcare following hospital discharge, a statistical approach to MRH risk prediction that overcomes some key methodological limitations of previous attempts is warranted. In the next chapter I will describe
my work to develop and validate a risk prediction tool for use at the point of discharge of older adults, which could supplement clinical judgement to identify patients at highest risk of MRH. Further exploration of some risk factors mentioned by doctors as influencing their predictions is warranted. Doctors considered a range of seemingly appropriate factors in making their judgements, however, some of these factors including frailty and health literacy have been poorly investigated in the context of MRH. There is a need for further study of these important concepts to explore their relationship with MRH risk.

7.4.4 Limitations

Although 1066 predictions were analysed, doctors are commonly discharging multiple patients over a given time and thus a doctor may have contributed more than one prediction to our results. This could have introduced bias through a clustering effect, decreasing standard errors leading to narrower confidence intervals and smaller p-values. However, the four-monthly rotation of junior doctors in combination with a two-year study period on multiple wards of five hospitals ensured a wide breadth of participation.

Although the results show that the years of clinical experience of the discharging doctor did not influence the accuracy of predictions, only 126 (12%) predictions were by doctors of very senior grade (registrar or consultant) and therefore this finding should be interpreted with caution. Within the registrar grade respondents’ information pertaining to their specific year of specialist training was not collected, and therefore it is possible that a difference exists in the accuracy of MRH prediction within this specialist grading. Nevertheless, discharge documentation is usually by junior doctors (below registrar level) and this study reflects that as 85% of respondents in this study were below registrar level.

Prompting the discharging doctor to consider the potential medication risk for each patient may have led to changes in behaviour (‘the Hawthorne effect’), biasing the patient discharge process e.g. increased efforts to reduce potential harm by adjusting discharge medications or post-discharge support. To minimise this potential bias, the doctor’s prediction was requested as close as possible to the patient’s actual
hospital discharge or soon thereafter. Similarly, the behaviour of discharged patients may have been influenced by their participation in the study. A heightened awareness of potential adverse effects of medicines might have prompted increased attention to medicines-related information and usage instructions, or higher likelihood of seeking healthcare if MRH was suspected. However, this increased knowledge may also have enabled patients to attribute and report MRH more accurately when interviewed at their 8-week follow-up.

Doctors were only asked for brief reasoning for their clinical judgements, and therefore it is possible that there are some additional important themes that have not been identified. Nevertheless, given the relatively large number of patients, one could reasonably expect that key themes which discharging doctors believed to influence the risk of MRH would have been captured.

7.5 Conclusions

In conclusion, my findings indicate that doctors (predominantly junior doctors) cannot reliably identify older patients that experience MRH requiring healthcare following hospital discharge. This might reflect a combination of insufficient CPT knowledge amongst doctors, and, the challenges in discerning complex biopsychosocial risk factors associated with MRH. Doctors recorded a wide range of factors, including clinical, social and psychological, that influence their risk prediction of MRH. This has highlighted the need for further quantitative study of some important potential risks such as low health literacy and frailty. Efforts to improve MRH risk prediction might benefit from the development of a predictive tool using statistical methods; work which I have performed and will describe in the next chapter. However, statistical prediction cannot and should not replace the importance of clinical intuition and judgement. Therefore, statistical work to improve MRH risk prediction should happen in conjunction with increased CPT education for doctors and interdisciplinary collaboration with pharmacists.
CHAPTER 8.
Predicting risk: Development and validation of the PRIME tool
Chapter Summary

This chapter reports the development and internal validation of a risk prediction tool (PRIME tool) that can predict the risk of an older person experiencing MRH following hospital discharge. The need for the development of such a tool is demonstrated by the high clinical, economic and human burden of MRH following hospital discharge. Crucially, it was shown in chapter 7 that a reliance on the ability of discharging doctors to predict MRH is unreliable. The primary outcome of the PRIME tool is the predicted absolute risk of MRH within 8 weeks of discharge requiring healthcare use. Candidate variables for prognostic modelling were selected by a combination of existing literature (Chapter 2), qualitative work with older adults (Chapter 3), and the expert judgement of a panel of clinicians and academics. Multivariable logistic regression with backward elimination, based on Akaike’s Information Criterion, was used to develop the tool. Following logistic regression modelling, eight variables measured at hospital discharge were included in the final prediction tool; age, gender, antiplatelet drug, sodium level, antidiabetic drug, past ADR, number of medicines, living alone. The performance of the tool was evaluated by its discrimination and calibration. The tool had a discrimination C-statistic of 0.69 and showed good calibration. The tool was subsequently internally validated using a bootstrap resampling method which adjusted the model for optimism resulting in a discrimination c-statistic of 0.66. Given the complexity of MRH in older adults, the face validity of the tool should be high with the inclusion of demographic, clinical, biochemical and social variables. The PRIME tool could offer value to clinicians by enhancing medicines optimisation for older adults and targeting support following discharge to those at highest risk. For healthcare policymakers, the tool may be one pivotal step in targeting community resources at high risk individuals to reduce avoidable healthcare use due to MRH. Prior to routine clinical use the tool requires testing in new population settings i.e. external validation.
8.1 Introduction

Risk prediction is needed in healthcare to target limited resources at those most likely to benefit\(^{291}\). Healthcare use due to MRH is increasing\(^{27,222}\) and puts avoidable pressure on healthcare systems challenged with limited resources to support an ageing population\(^{16,336}\). The need for the development of a tool to predict the risk of MRH post-discharge is evidenced throughout this thesis by the high clinical, economic and human burden of MRH post-discharge in the NHS. This thesis has shown that, in England, 28% of older adults (\(\geq 65\) years) use health services due to MRH within the 8 weeks following hospital discharge, at an estimated annual NHS cost of £400 million\(^{337}\). The analyses in chapter 7 demonstrated that clinical judgement of discharging hospital doctors has insufficient accuracy to be relied upon for identification of high risk patients. Targeted reduction of MRH during transitions of care such as hospital discharge is a priority for the World Health Organisation and UK Government\(^{29,66}\).

Risk prediction supports clinical decision making and informs patient choice. Some risk prediction tools have transformed the provision of healthcare such as the QRisk tool for cardiovascular 10-year risk\(^{338}\), or, the CHA2DS2-VASc score to assess the risk of stroke\(^{339}\).

Despite the post-discharge period conferring the highest risk of MRH to older patients\(^{31,182,337,340}\), there are no tools to quantify this risk\(^{112}\) and target intervention at the most vulnerable patients. A key recommendation in a position statement from the International Group for Reducing Inappropriate Medication Use and Polypharmacy is to ‘develop tools that can aid the detection and management of drug adverse effects’\(^{341}\).

The objectives of the work presented in this chapter were to:

1. develop a risk prediction tool from the PRIME study data to identify older patients at high risk of MRH requiring healthcare use within 8-weeks post-discharge.
2. to internally validating this risk prediction tool
8.2 Methods

8.2.1 Patients and sample size

I developed the PRIME risk prediction tool using data from the PRIME multicentre, prospective cohort study. The general methods for this study were explained in detail in chapter 4. This chapter is reported in accordance with the TRIPOD statement\textsuperscript{342} (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis).

A sample size calculation was performed assuming a sensitivity of 80% with a 95% confidence interval width of 5% and based on an MRH prevalence rate of 30\%\textsuperscript{193,194}. The nomogram designed by Carley \textit{et al} (2005)\textsuperscript{195} and based on the work of Buderer \textit{et al} (1996)\textsuperscript{196}, suggested recruitment of 1500 patients (as detailed in Chapter 4). This calculation was based on an anticipated split-sample validation method, where the recruited population would be split in half to form a ‘derivation cohort’ for developing a risk prediction model and the other 50% cohort forming the validation cohort. More recently ‘bootstrap’ resampling methods have demonstrated less bias during out-of-sample validation compared with a split-sample approach\textsuperscript{197}, ensuring that data from the full recruited population is used to develop the model. The bootstrap methodology was therefore adopted for the validation in this study. Based on this revised approach, the sample size for the development of the risk prediction model of n=818 was adequate.

8.2.2 Outcome definition

The risk prediction model was developed to predict MRH requiring healthcare within 8-weeks of hospital discharge. Healthcare use included primary, secondary or tertiary consultations related to MRH as described in chapter 6. Where MRH was suspected it was classified using the Naranjo algorithm\textsuperscript{110} alongside the judgement of an endpoint committee (a Professor of Geriatrics, Professor of clinical pharmacy, and two consultant Geriatricians independent of data collection) as ‘possible’, ‘probable’ or ‘definite’. If there was no evidence of MRH, this was classified as ‘doubtful’. To
eliminate uncertainty and strengthen the external validity in the development of the PRIME model, a decision was made to exclude patients with MRH that was ‘possible’ or ‘probable’. In addition to this, patients with MRH who did not require healthcare use were also excluded. A flow diagram is presented in figure 8.1 to show how the recruited cohort was streamlined to patients included for the development of the risk prediction model. The cohort included for the model development was 119 patients with definite MRH requiring healthcare and 699 patients that did not experience MRH.
Figure 8.1 Patient flow diagram for cohort that was included in model development.

Patients recruited (n=1280)

Lost to follow-up
- Death before follow-up (n=17, 1%)
- No patient interview, GP records or hospital re-admission (n=147, 12%)
- Missing key information on discharge medicines (n=4, 0%)

Complete follow-up (n=1112)

Patients experienced:
- possible MRH
- probable MRH, or
- definite MRH (n=413, 37%)

Patients did not experience MRH (n=699, 63%)

Patients with definite MRH requiring healthcare (n=119, 29%)

Patients with:
- possible MRH
- probable MRH, or
- definite MRH not requiring healthcare (n=294, 71%)

Hospital readmissions (n=20)

GP consultations (n=101)

Other consultations (n=9): A&E (n=4), Out-of-Hours (n=1), Outpatient (n=4)
8.2.3 Selection of candidate predictors

Candidate variables for the development of the PRIME tool were selected with the support of three methods. The first influence was the existing published literature on risk prediction tools in the area of MRH and epidemiological data on MRH post-discharge (detailed in chapter 2). The second influence was three round-table expert meetings to identify candidate predictors, prior to any data analysis, based on clinical relevance and practicality of routine measurement (including two Professors of Geriatrics, two consultant Geriatricians, one professor of Pharmacy, one Pharmacy research fellow and one Geriatrics research fellow). The third influence was the qualitative exploration of MRH risk factors from the patient and carer perspective (detailed in chapter 3). During this early process of selecting candidate variables, data collection from the PRIME study had not finished and therefore the total number of MRH cases was not known. Therefore, Peduzzi et al’s guidance to limit the number of variables for model development to a ratio of 10 events per variable was not applicable at this point. Thus, initially, no upper limit was placed on the number of candidate variables. All candidate variables were selected based on clinical relevance. Once the number of patients that experienced MRH was known following study completion and data analysis (chapter 5), a systematic process of reducing the initial list of candidate variables took place which is further described in the results below.

8.2.4 Statistical Analysis

All statistical analysis was conducted in Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

8.2.4.1 Model development

The primary outcome was whether a person experienced MRH requiring healthcare use and is thus a binary variable. Backward elimination was used based on the Akaike’s Information Criterion (AIC) to exclude variables that were not contributing sufficient predictive information in the multivariable logistic regression model (the
AIC is a predictive metric that equates to the elimination of variables with p-value ≥ 0.157). The AIC was chosen as the selection statistic as it balances the risk of overfitting a model to the derivation data and introducing misspecification error from trimming potentially meaningful variables, whilst penalising the inclusion of redundant variables contributing little predictive information in order to generate a parsimonious model346. Two variables (age and sodium level) were centered on their mean values to make the interpretation of the intercept easier and meaningful. In the model equation, the intercept can be interpreted as the predicted risk of MRH if all the continuous explanatory variables are set to 0 (and the categorical variables held at their baseline values), a value which is infeasible for continuous variables such as age and sodium level. Therefore by centering these two variables, the intercept in the model equation would indicate the predicted risk of MRH with plausible values for age and sodium level.

A final model of eight predictors was obtained after backward elimination and a risk equation for predicting the log odds of MRH was formed by summing the estimated β-coefficients (obtained from fitting multivariable logistic regression) and their corresponding observed predictor (among the 8 predictors) plus the intercept. The predictors were assessed for multicollinearity by calculating the Variance Inflation Factor (VIF) to identify whether variances of the estimated coefficients were inflated347.

8.2.4.2 Evaluating Model Performance

The performance of the model was evaluated by assessing its discrimination and calibration, using the Area Under the Receiver-Operating-Characteristic curve (c-statistic) and a calibration plot respectively. The c-statistic is a measure of the ability of the risk prediction model to discriminate between high and low risk patients, with a value of 0.5 representing no discrimination and a value of 1 representing perfect discrimination298. The Hosmer-Lemeshow goodness-of-fit statistic was also calculated as an additional indication of the acceptability of the model’s calibration298.
8.2.4.3 Bootstrap correction of model optimism and validation

Bootstrapping is recommended when an external cohort of patients is unavailable to estimate the performance of the prediction model\textsuperscript{348–351}. Bootstrapping is a statistical method that can be used for internal validation of risk prediction models, and corrects measures of predictive performance (e.g. c-statistic) for model optimism. It is a resampling method that is used to randomly generate data (data for subsets of patients) from the original (master) dataset with replacement (patients can be selected multiple times). The bootstrap sample is the same size as the original sample. One-hundred bootstrap samples were drawn from the derivation data, and in each sample, a prediction model was developed and used it to compute an estimate of model optimism through the following two steps. First, the ‘bootstrap model’ was fitted on the same bootstrap sample to obtain a quantitative measure of apparent performance. The bootstrap model was then fitted to the original dataset to obtain an ‘out-of-sample’ estimate of performance. The difference between the apparent performance and the out-of-sample performance is defined as the optimism of model. This process was repeated 100 times, after which the final model optimism is then the average of the optimism values calculated in the bootstrap iterations. This average is then subtracted from the apparent model performance measure, to obtain an optimism-corrected model performance. The linear shrinkage factor for the estimated beta-coefficients of the predictors in the model are derived from the average of the calibration slopes over the bootstrap iterations. ‘Shrunk’ coefficients are calculated by multiplying the original regression coefficients by the shrinkage factor (which has a value between 0 and 1). The intercept was then re-estimated based on the shrunken beta coefficients to generate the final model equation. This method of coefficient shrinkage corrects for selection bias that may occur during backwards elimination (as predictors with larger coefficients by chance are more likely to be selected than predictors that by chance had smaller coefficients).\textsuperscript{352}
8.2.4.4 Missing Data

Two variables that were selected as candidate predictors for the final model development had considerable missing data (>5%); estimated Glomerular Filtration Rate (eGFR) had 56 (6.8%) missing values, and hand grip strength had 100 (12.2%) missing values. These values were replaced under a missing at random assumption by Multiple Imputation by Chained Equations (MICE) based on all candidate predictors\textsuperscript{353}. For each variable 10 imputed datasets were created and Rubin’s rules were used to obtain an overall estimate\textsuperscript{353}.

8.3 Results

8.3.1 Patient characteristics

As shown in the patient flow diagram (figure 8.1) 119 patients experienced ‘definite’ MRH requiring healthcare use within 8-weeks following hospital discharge (an incidence of 107 patients per 1000 discharged), and 699 patients did not experience MRH. The model derivation cohort therefore included 818 patients with either ‘definite’ MRH requiring healthcare use or no MRH. Baseline characteristics of this selection of patients are shown in table 8.1. The mean age of patients included in the model development was 81 years (SD 7.7, range 65-103). Approximately half (51%) the cohort had two or more Charlson Index comorbidities\textsuperscript{163}. Patients had an average length of stay of one week (median 7, IQR 3-13 days). Patients were discharged with a mean of nine medicines (SD 4.1, range 0-27).
Table 8.1 Baseline characteristics of patients included for the model development

<table>
<thead>
<tr>
<th>Key Characteristics</th>
<th>Patients for model development (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>81.2 (7.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>464 (56.7)</td>
</tr>
<tr>
<td>Length of hospital stay, median (IQR), days</td>
<td>7 (3-13)</td>
</tr>
<tr>
<td>Charlson Index comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>398 (48.7)</td>
</tr>
<tr>
<td>≥2</td>
<td>420 (51.3)</td>
</tr>
<tr>
<td>Barthel Score, median (IQR)</td>
<td>18 (13-20)</td>
</tr>
<tr>
<td>Number of medicines, mean (SD)</td>
<td>9.1 (4.1)</td>
</tr>
<tr>
<td>Past ADR, n (%)</td>
<td>252 (31.1)</td>
</tr>
<tr>
<td>Medication compliance aid e.g. dosette box, n (%)</td>
<td>274 (33.5)</td>
</tr>
<tr>
<td>Discharge to care home, n (%)</td>
<td>28 (3.4)</td>
</tr>
<tr>
<td>Living alone after discharge, n (%)</td>
<td>391 (47.9)</td>
</tr>
<tr>
<td>IQR, interquartile range; ADR, adverse drug reaction.</td>
<td></td>
</tr>
</tbody>
</table>

8.3.2 Model development and performance

Twenty-five candidate variables were initially identified for the model development, prior to completion of the study and therefore knowledge of the number of MRH cases. With 119 ‘definite’ MRH cases that required healthcare use, the number of candidate variables was reduced from 25 to 12 for an events-per-variable ratio as recommended by Peduzzi et al to minimise model performance bias (10 events for each variable included in the regression model, therefore 12 variables for 119 MRH cases). Univariable analysis was not used to identify any candidate predictors to eliminate the possibility of including variables by statistical chance. Three of the 25 variables (albumin level, C-reactive protein, white cell count) were excluded due to substantial missing data (>20%). Two variables (change in accommodation after discharge and hepatic impairment) were excluded due to insufficient prevalence in the cohort (<10%). One variable (cardiovascular drug on discharge) was excluded due to saturated prevalence in the cohort (>80%). The remaining 19
variables were taken forward for potential inclusion in the final multivariable analysis, and 12 predictor combinations were trialled to obtain a parsimonious model with optimal performance and stability. Models were examined for evidence of multicollinearity, and where demonstrated the variable contributing the least predictive value was excluded. The iterative procedure resulted in the exclusion of a further seven variables (regular falls, Barthel Index score, addition of a new drug, opiate drug, anticoagulant drug, abbreviated mental test score, depression on screening). The 12 predictors included in a final multivariable model to generate the PRIME tool are shown in table 8.2.
Table 8.2 Selected candidate predictors to derive the risk prediction model

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Data source and measurement</th>
<th>Prevalence‡</th>
<th>Unadjusted odds ratio (95% CI) on univariable analysis</th>
<th>Adjusted odds ratio (95% CI) on multivariable regression‡</th>
<th>β coefficients of variables included in model</th>
<th>P-value in multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Self-report and medical records</td>
<td>81.2</td>
<td>1.03 (1.00-1.06)</td>
<td>1.03 (1.00-1.05)</td>
<td>0.025</td>
<td>0.078</td>
</tr>
<tr>
<td>Gender (reference female)</td>
<td>Self-report and medical records</td>
<td>43.3 (M) 56.7 (F)</td>
<td>0.57 (0.38-0.86)</td>
<td>0.67 (0.43-1.04)</td>
<td>-0.398</td>
<td>0.075</td>
</tr>
<tr>
<td>Past ADR†</td>
<td>Self-report and medical records</td>
<td>31.1%</td>
<td>1.79 (1.20-2.67)</td>
<td>1.61 (1.06-2.45)</td>
<td>0.477</td>
<td>0.026</td>
</tr>
<tr>
<td>Antiplatelet drug</td>
<td>Discharge summary and medical records. Drugs coded B01AC on WHO-ATC system</td>
<td>43.3%</td>
<td>1.78 (1.20-2.63)</td>
<td>1.67 (1.11-2.53)</td>
<td>0.515</td>
<td>0.014</td>
</tr>
<tr>
<td>Antidiabetic drug</td>
<td>Discharge summary and medical records. Drugs coded A10A or A10B on WHO-ATC system</td>
<td>19.7%</td>
<td>1.89 (1.22-2.94)</td>
<td>1.81 (1.12-2.91)</td>
<td>0.591</td>
<td>0.016</td>
</tr>
<tr>
<td>Living alone‡</td>
<td>Self-report and medical records</td>
<td>47.9%</td>
<td>1.61 (1.08-2.38)</td>
<td>1.49 (0.98-2.27)</td>
<td>0.397</td>
<td>0.064</td>
</tr>
<tr>
<td>Sodium level§ (mmol/l)</td>
<td>Last recorded inpatient biochemistry prior to discharge</td>
<td>137</td>
<td>0.97 (0.93-1.01)</td>
<td>0.96 (0.92-1.00)</td>
<td>-0.042</td>
<td>0.069</td>
</tr>
<tr>
<td>Number of medicines</td>
<td>Discharge summary and medical records. Total number of medicines at discharge</td>
<td>9</td>
<td>1.08 (1.04-1.13)</td>
<td>1.06 (1.00-1.11)</td>
<td>0.056</td>
<td>0.033</td>
</tr>
<tr>
<td>Hand grip strength (kg)</td>
<td>Southampton Protocol for Adult Grip strength Measurement using the JAMAR Hydraulic Hand Dynamometer§</td>
<td>25.6 (M) 14.3 (F)</td>
<td>0.98 (0.96-1.00)</td>
<td>Eliminated from model (P&gt;0.157)</td>
<td>N/A</td>
<td>0.911</td>
</tr>
<tr>
<td>Medication compliance aid</td>
<td>Blister pack or dosette box on discharge</td>
<td>33.5%</td>
<td>1.54 (1.03-2.29)</td>
<td>Eliminated from model (P&gt;0.157)</td>
<td>N/A</td>
<td>0.302</td>
</tr>
<tr>
<td>Renal impairment (eGFR &lt;60 mL/min/1.73 m²)</td>
<td>Last recorded inpatient biochemistry prior to discharge</td>
<td>41.9%</td>
<td>1.67 (1.13-2.47)</td>
<td>Eliminated from model (P&gt;0.157)</td>
<td>N/A</td>
<td>0.216</td>
</tr>
<tr>
<td>Number of Charlson Index comorbidities</td>
<td>Discharge summary and medical records. Total number of diseases defined by Charlson Index§</td>
<td>48.7% (&lt;2) 51.3% (≥2)</td>
<td>1.12 (0.95-1.31)</td>
<td>Eliminated from model (P&gt;0.157)</td>
<td>N/A</td>
<td>0.403</td>
</tr>
</tbody>
</table>

†Percentage of patients for categorical predictor or average value for continuous predictor. ‡Incomplete data for predictors; renal impairment (n=56) hand-grip strength (n=100), past ADR (n=7), sodium level (n=4), lives alone (n=2). §Based on backwards elimination based on Akaike’s Information Criterion (P>0.157). eGFR, Estimated Glomerular Filtration Rate; F, Female; M, Male.
Once these 12 variables were entered into the multivariable analysis, some predictors were removed in a stepwise process from the model by backward elimination using the AIC (equating to p=0.157)\textsuperscript{345}. This resulted in a final risk prediction model of eight variables: age, gender (female=0), antiplatelet drug (antiplatelet on discharge=1), sodium level, antidiabetic drug (antidiabetic on discharge=1), past history of ADR (past ADR=1), number of discharge medicines, and living alone (living alone post-discharge=1).

The equation for the PRIME tool is as follows (see figure 8.2 for examples of clinical application):

\[
\text{Risk score} = -2.384 + 0.85 \times (0.025(\text{age}-81) - 0.398(\text{gender}) + 0.515(\text{antiplatelet drug}) - 0.042(\text{sodium}-137) + 0.591(\text{antidiabetic drug}) + 0.477(\text{past ADR}) + 0.056(\text{number of medicines}) + 0.398(\text{living alone}))
\]

No multicollinearity was demonstrated in this model (mean VIF=1.07). The apparent discrimination of the model was AUC 0.69 (95% CI 0.64-0.74) (figure 8.3). For comparison, the number of medicines alone discriminated between higher and lower risk patients with AUC 0.61 (95%CI 0.55-0.66).

The optimism of the model’s discriminatory performance was 0.028, calculated as the average difference between model discrimination in the bootstrap dataset and the discrimination of the bootstrap model in the original dataset over 100 bootstrap iterations. The optimism adjusted model discrimination is AUC 0.66 (95% CI 0.61-0.71).

The calibration i.e. the level of agreement between predicted and observed risk probabilities was good (figure 8.4). The Hosmer-Lemeshow goodness-of-fit statistic was 5.47, with 8 degrees of freedom, \( P = 0.71 \) indicating no evidence of statistically significant difference between the observed and expected values. A uniform shrinkage factor of 0.85, derived from the average of the calibration slopes of the bootstrap iterations, was applied to predictor coefficients to adjust the risk prediction model for optimism.
Figure 8.2 Clinical examples of PRIME tool application to calculate patient MRH risk

**Model equation for risk score** = -2.384 +0.85 x (0.025(age-81) - 0.398(gender) + 0.515(antiplatelet drug) - 0.042(sodium-137) + 0.591(antidiabetic drug) + 0.477(past ADR) + 0.056(number of medicines) + 0.398(living alone)

**Individual estimated risk of MRH (%)** = (1/1+e^{-risk score})*100

**Case Example 1.**

Mr B is 85 years old and was hospitalised for a community-acquired pneumonia. He lives with his daughter in a bungalow. He has a past medical history of a stent following a myocardial infarction, hypertension, osteoarthritis, and benign prostatic hypertrophy. His discharge medications include clopidogrel, atorvastatin, atenolol, ramipril, tamsulosin, paracetamol, codeine phosphate, macrogol and four days of co-amoxiclav to complete an antibiotic course. His last sodium level was 130mmol/l.

**Risk score** = -2.384 +0.85 x (0.025(85-81) + -0.398(1) + 0.515(1) + -0.042(130-137) + 0.591(1) + 0.477(0) + 0.056(9) + 0.398(0)

**Individual estimated risk of MRH (%)** = (1/1+e^{-1.52})*100

Mr B’s absolute risk of experiencing MRH requiring healthcare use over the next 8-weeks is estimated at 18%

**Case Example 2.**

Mrs V is 78 years old and was hospitalised following a fall and fractured neck of femur. She lives alone in sheltered accommodation. She has a past medical history of poorly controlled type 2 diabetes, hypertension, moderate stage chronic kidney disease and depression. Her discharge medications include gliclazide, sitagliptin, doxazosin, losartan, mirtazapine, zopiclone, paracetamol, oxycodone, senna, adcal D3, alendronate, and omeprazole. Her last sodium level was 132mmol/l. Mrs V recalls seeing her GP with swollen ankles last year, which improved after her amlodipine was stopped.

**Risk score** = -2.384 +0.85 x (0.025(79-81) + -0.398(0) + 0.515(0) + -0.042(132-137) + 0.591(0) + 0.477(1) + 0.056(12) + 0.398(1)

**Individual estimated risk of MRH (%)** = (1/1+e^{-0.435})*100

Mrs V’s absolute risk of experiencing MRH requiring healthcare use over the next 8-weeks is estimated at 39%
Figure 8.3 PRIME prediction tool compared with number of medicines alone to discriminate patient risk of MRH

Figure 8.4 Calibration plot across tenths of predicted risk of MRH
8.4 Discussion

The PRIME tool is the first tool to predict the absolute risk of an older person experiencing medication harm in the post-discharge period; the risk of MRH in this transition period is approximately three times greater than the inpatient or ambulatory setting\textsuperscript{31,182,337,340}. The tool derived from a large multicentre, prospective study\textsuperscript{337,340} that is methodologically advanced compared with prior studies. A real-world patient-centered definition of MRH was used, patient interviews provided data alongside GP records and hospital readmissions, a multistage MRH verification process was employed, and all tiers of medical care associated with MRH were evaluated. The prediction tool consists of eight variables routinely collected in hospital (age, gender, antiplatelet drug, sodium level, antidiabetic drug, past ADR history, number of medicines, and living alone).

This tool has major potential to support the WHO’s Global Patient Safety challenge to reduce MRH by 50\%\textsuperscript{356} by (1) targeting medicines optimisation to those that at highest-risk, (2) better informed discussions with patients about medication safety, and (3) enabling clinicians to more accurately evaluate the risk of polypharmacy for individual patients.

8.4.1 Comparison with other studies

This is the first risk prediction tool developed for application to the high-risk transition of care following hospital discharge; indeed the risk of MRH in this transition period is approximately three times greater than other settings\textsuperscript{31,182,337,340} (i.e. inpatient or ambulatory setting). Other MRH tools have been developed primarily to predict inpatient MRH (see appendix 6). The PRIME tool’s discrimination and calibration\textsuperscript{298,357} is comparable with these (PRIME c-statistic 0.66 vs c-statistics of other tools e.g. ADRROP\textsuperscript{358} (0.59), GerontoNet\textsuperscript{165} (0.70), PADR-EC\textsuperscript{257} (0.67), BADRI\textsuperscript{164} (0.73), Trivalle\textsuperscript{359} (0.70). The PRIME tool displayed good calibration, whilst other tools to predict MRH have not reported this important measure, with exception of BADRI (Hosmer Lemeshow p=0.757, calibration plot not reported)\textsuperscript{164112}.

The PRIME tool provides an absolute patient risk of MRH, whereas other tools indicate a relative patient risk based on scoring systems that round predictor odds ratios to the
nearest integer. Whilst one can appreciate the merit in making a tool as simple as possible for routine clinical use, it can lead to imprecision in calculating patient risk. Finally, the PRIME tool was developed based on ‘definite’ harm that resulted in healthcare use.

8.4.2 Predictors in the model

The PRIME tool includes a combination of demographic (age, gender), medication-specific (number of medicines, antiplatelet drug, antidiabetic drug, past ADR), biochemical (sodium level) and social predictors (living alone). This comprehensive set of patient information reflects the complexity of predicting MRH and healthcare use. The selection of candidate variables was grounded in clinical expertise and further informed by patient experience of MRH. Therefore, one would expect the tool to hold a high degree of face validity amongst both clinicians and patients. Most of the variables in the tool have been previously demonstrated to be associated with MRH and/or unplanned healthcare utilisation in older adults. Few studies have investigated living alone as a risk factor for MRH. The study detailed in this chapter substantiates self-reported evidence of adverse outcomes in older adults living alone following hospital discharge. The informal support from co-habiting family could facilitate medicine adherence and promote early recognition and management of MRH.

The data presented in this chapter extends the pool of evidence for poor outcomes associated with low sodium levels, including the post-discharge setting. Even mild and asymptomatic hyponatremia is associated with attention deficits, postural instability, and falls. This might contribute to patients being less receptive to medicines information around discharge, and less able to tolerate common ADRs such as dizziness without serious consequences.

8.4.3 Implications for practitioners and policy makers

The average number of medicines used by older adults has been increasing rapidly over the last two decades. Despite the potential benefits, this thesis has presented the substantial clinical, economic and humanistic burden of MRH in older
adults. The PRIME tool is unique in estimating a patient’s absolute risk of MRH. Geriatricians have highlighted the limitations of risk stratification that arbitrarily divides patients into categories of relative high and low risk; these approaches fail to inform a clinician whether a patient’s risk is so high that the harm of prescribing outweighs the benefit, or so low that monitoring is not required. Absolute patient risk can inform a more personalised approach to medication-related decisions; literature indicates that the use of probabilities is necessary for a comprehensive understanding of health risk.

Healthcare use due to MRH is increasing and adds avoidable pressure to healthcare systems that are grappling with limited resources to support an ageing population. Emergency hospital admissions in older adults in England are projected to reach 3 million by 2020, a rise of 36% from 2012. This anticipated demand for healthcare is unlikely to be met entirely through an increase in resources and capacity, and therefore reducing avoidable healthcare use is of increasing importance. Risk prediction is a necessary step towards efficiency by targeting limited healthcare resources at those most likely to derive benefit. As shown in chapter 7, clinical judgement of physicians is insufficient on its own to identify older adults at high risk of MRH. The PRIME tool can offer value by supplementing clinical judgement to identify patients at high risk of serious MRH, for whom discharge drug lists could be further scrutinised and additional medication support in the community offered. The PRIME model could be useful to streamline resource use in clinical practice as the current targeting of interventions to reduce post-discharge MRH is either lacking or not based on reliable evidence. This absence of risk stratification may have contributed to the poor cost-effectiveness of certain previously tested interventions to reduce post-discharge harm, in spite of strong face validity.

The tool could be integrated into electronic discharge systems and used to increase vigilance to medications prescribed at hospital discharge (see appendix 7). The information could be communicated with primary care in real-time as part of the electronic discharge summary, enabling support in the community to be targeted at high-risk individuals. This might enhance the cost-effectiveness of the UK Government’s £100 million medicines optimisation programme of introducing clinical pharmacists into General Practice nationally by 2021.
8.4.4 Limitations

The tool has not yet been externally tested and evaluated for impact. However, the large cohort investigated in this study using a multicentre, prospective design, in conjunction with a robust approach to MRH verification, and adjustment for model optimism, lends the PRIME tool to favourable re-testing.

Whilst the model performance is not dissimilar to other tools for predicting complex outcomes e.g. stroke\textsuperscript{339}, certain cancers\textsuperscript{376}, and hospital readmission\textsuperscript{377,378}, the impact of false negatives and false positives must be carefully considered given a modest discrimination. Nevertheless, a false positive would ultimately result in increased medication scrutiny.

Developing a tool that predicts MRH requiring healthcare use, as opposed to MRH irrespective of healthcare use, enhances the clinical significance of the predicted risk. However, it is acknowledged that the drivers for healthcare use are complex and can only be explained in part by the severity of a condition. Nonetheless, healthcare use is a widely adopted proxy for injury severity given its objectivity and comparability.

8.5 Conclusions

In conclusion, the PRIME tool offers an approach to identifying older patients at high (and low) risk of MRH requiring healthcare use following hospital discharge. The tool comprises eight variables that are routinely collected in clinical practice, and has potential to be implemented into electronic hospital discharge systems. Following internal validation, the tool shows moderate discrimination between high and low risk patients, and good calibration. The tool requires external validation in a setting independent of that which was used to collect data for the development of the tool. If this next phase of validation is successful, then the tool would represent an essential adjunct to clinical judgement for the targeting of medicines optimisation interventions.
CHAPTER 9.

Discussion and future directions
9.1 Main findings and implications

The research reported in this thesis aimed to investigate the impact of MRH in older adults following hospital discharge. The studies conducted identified a very high clinical and economic burden of MRH in England. This warranted the latter parts of my investigation to examine whether MRH could be predicted so that interventions to reduce MRH can be targeted at high risk patients. The work presented in this thesis includes data from a systematic review, a qualitative study and quantitative study to capture a complete picture of the extent and implications of MRH in the post-discharge period, for patients and the NHS. It is my intention that these findings will inform the response from clinicians, educational establishments and policy-makers to the WHO’s target of reducing severe, avoidable MRH by 50% by 2022.

The systematic review investigated prior studies internationally of the incidence, severity, preventability and risk factors for MRH in older adults following hospital discharge. Only eight studies had investigated this problem and no studies had been conducted in England. Substantial methodological heterogeneity across multiple domains of the studies resulted in a wide reported MRH incidence, from 0.4% to 51.2% of discharged patients. This systematic review clearly identified the need for a large prospective study to provide robust data on the epidemiology of the MRH during this critical juncture of healthcare.

Whilst the quantitative data was crucial to gather, a qualitative study was conducted to first and foremost understand the scope of the MRH burden from the lived experience of older patients. As Barry & Levitan (2012) eloquently stated in a perspective piece on patient-centered care in the New England Journal of Medicine, ‘If we can view the health care experience through the patient’s eyes, we will become more responsive to patients’ needs and, thereby, better clinicians’. The qualitative research involved a mixture of focus groups and semi-structured interviews to support the recruitment of both functionally independent older people, and those
that are housebound and rarely get their voices heard. The participants described their experiences of MRH in the context of a fragmented health system, impractical packaging, information and formulation of medicines, challenges of getting support for medication problems, and, implicit trust that medicines will do more good than harm because a doctor prescribes them. The qualitative study demonstrated that older people feel particularly vulnerable around the transition of care from hospital back into the community, describing their reduced capacity to comprehend information during pressured discharge circumstances and a lack of integrated follow-up care in the community.

The PRIME multicentre, prospective cohort study was designed to collect robust epidemiological data on MRH post-discharge in adults aged 65 years and above. One thousand two hundred and eighty older adults with a median age of 82 years were recruited from five different hospitals in South England. Based on an eight-week follow-up by research pharmacists, 37% of patients had experienced MRH. A high proportion of cases were classified as serious in nature (81%), and four patients died from events that were attributable to their medicines. These deaths were the ‘tip of the iceberg’, with many others experiencing disability and reduced quality of life because of MRH. More than half of the patients that experienced MRH had events that were potentially preventable, offering huge scope for improvements in patient safety. By frequency, antihypertensive medicines were associated with the greatest burden of harm accounting for one in five events. However, there were almost double the prescriptions for antihypertensive medicines compared with any other class of medicine. This is a notable finding because the evidence for using antihypertensives in multimorbidity is limited, and more than half of the patients’ followed-up in the PRIME study had two or more serious comorbidities (based on the Charlson Index). The medicine classes associated with the highest risk of MRH were opiates, antibiotics, and benzodiazepines although the risk from opiates was striking. Four in ten patients that were prescribed an opiate or opiate-like medicine at discharge experienced a harmful event. A significant proportion of patients were using opiate medicines for analgesia in musculoskeletal problems. This is generally
an inappropriate indication\textsuperscript{214,379,380}, and should capture the attention of prescribers in the NHS.

Whilst the NHS is struggling to meet demand, with hospitals at full capacity and GPs facing unprecedented pressures with surgeries unable to recruit and many closing down\textsuperscript{224}, the waste of precious resources due to avoidable MRH must be tackled. Analysis of healthcare utilisation due to MRH in the PRIME study found that 29\% of discharged patients used health services due to MRH, including 50 avoidable hospital admissions and 135 avoidable GP consultations in a period of eight weeks. Using the Department of Health and Social Care’s National Tariff, the cost of post-discharge MRH in older adults was estimated to cost the NHS £396 million annually, of which £243 million is potentially preventable. To give this cost some perspective, the Department of Health and Social Care recently announced an investment of £110 million over five years to introduce the expertise of pharmacists to optimise medicines use across a 40\% coverage of GP surgeries in England. If £243 million NHS cost from preventable MRH could be saved over one year and reinvested, it would meet the financial investment needed to cover the outstanding 60\% of GP surgeries that will not have medicines optimisation support from a clinical pharmacist.

In a resource-limited healthcare system, risk stratification is paramount to target intervention at those most likely to derive benefit\textsuperscript{291}. Hence, determining how best to identify high risk patients is a necessary step to prevent MRH from occurring. The two main options for stratifying the risk of MRH in patients are either by clinical judgement or the development of a statistical model using a data\textsuperscript{381}. The study presented in chapter 7 showed that there was no relationship between discharging doctors’ predictions of MRH and patient MRH, irrespective of clinical experience. Most predictions (85\%) were made by junior doctors with less than 5 years’ clinical experience, reflecting the fact that junior doctors most usually organise the medical aspects of a patient’s discharge. A qualitative analysis of the factors that doctors described to influence their risk predictions provides insight into new variables that should be explored in relation to MRH. The level of health literacy that a patient showed and the presence of frailty were two variables that have been poorly investigated within existing MRH literature and warrant further research.
The research presented in the thesis concluded with the development and internal validation of a statistical model (the PRIME tool), which estimates the absolute risk of a patient experiencing MRH requiring healthcare use within eight weeks post-discharge. Whilst the model’s performance after internal validation and correction for optimism was modest (c-statistic 0.66), the methods used were superior to related tools designed for predicting inpatient MRH and the outcome that the PRIME tool predicts is of high clinical relevance (MRH requiring healthcare use). The PRIME tool contains nine routinely collected variables from clinical (number of medicines, antiplatelet drug, antidiabetic drug, sodium level, history of ADR), social (living alone) and demographic (age, gender) domains. It has potential to be integrated into electronic discharge systems to alert hospital prescribers and GPs of high-risk patients. Importantly, the presentation of a personalised percentage risk can offer patients new information that can better involve them in decisions about their medication regimen and requirements for post-discharge medication support.

The data required for the tool could be retrieved in an automated procedure from electronic patient records. The Government has set out its ambitions for a paperless NHS by 2020, where all patient care records are ‘digital, real-time and interoperable’. The PRIME tool would integrate into such a system, and make the risk of MRH far more visible to clinicians and patients during transition of care. This is necessary given existing evidence shows both patients and clinicians overestimate the benefits of medical treatment, and underestimate the harms.

9.2 Future directions

9.2.1 Involving patients in medication-related decisions

The involvement of patients in decisions about their medication is a moral and practical imperative. As the qualitative study reported in chapter 3 showed, older adults identify a lack of knowledge about medicines and poor understanding of treatment aims as key problems related to medicines use. Patient involvement can be a crucial determinant of whether the balance of risk to benefit of prescribing a
medicine tilts one way or another\textsuperscript{144}. Therefore, if a doctor’s duty is to ‘first, do no harm’ then involving patients as partners in the decisions made about their medicines is a duty. Indeed, within the GMC’s 2018 ‘Outcomes for Graduates’ medical schools are required to equip new doctors with competencies in collaborative medication-related decision making\textsuperscript{331}. The guidance states that newly qualified doctors must be able to:

- carry out an assessment of benefit and risk for the patient of starting a new medication taking into account the medication history and potential medication interactions in collaboration with the patient and, if appropriate, their relatives, carers or other advocates

- provide patients, their relatives, carers or other advocates, with appropriate information about their medications in a way that enables patients to make decisions about the medications they take

- agree a medication plan with the patient that they are willing and able to follow

Based on this new GMC guidance, training medical students to collaborate with patients and carers in medication related decisions is now a requirement of medical schools. However, it is also incumbent upon Government to promote the health literacy of patients and the public to empower their meaningful involvement in such decision making\textsuperscript{64,384}. This has major potential to reduce MRH. The involvement of patients in decisions about their medical care is enshrined in law under the National Health Service Act 2006 applied by the Health and Social Care Act (2012)\textsuperscript{385}. The legislation under 14U reads,

‘Each clinical commissioning group must, in the exercise of its functions, promote the involvement of patients, and their carers and representatives (if any), in decisions which relate to – (a) the prevention or diagnosis of illness in the patients, or (b) their care or treatment.’ \textsuperscript{385}
Health literacy is defined as ‘the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions’. Figure x shows selected determinants of health literacy in the older adults, the different contexts within which the determinants facilitate health literacy, and the positive outcomes of improving health literacy. This figure is a simplified, adapted version of an established conceptual model of health literacy.

Figure 9.1 Conceptual model of the determinants, contexts and outcomes of health literacy in older adults

Adequate health literacy might reduce MRH through several processes; (1) enabling a shared medication related decision with the prescriber (2) enabling the individual to consider the health and treatment related information they have been provided by the prescriber and have the confidence to ask questions whilst obtaining the medicines from a pharmacist (3) interpreting the instructions for usage accurately and correctly adhering to the medicine (4) recognition of adverse events
prompting appropriate health-seeking behaviour. Thus, promoting health literacy represents a strategy to empower patients to seek out information and increase autonomy over their health\textsuperscript{387,388}. Patients should be encouraged to question decisions that they deem unsafe, whether this be related to diagnosis or treatment. The paternalistic approach to the doctor-patient relationship is outdated, and shared decision making may indeed provide protection against litigation when MRH occurs. This is of particular importance in the older population given the tenuous evidence for many commonly prescribed medicines, especially in patients with multimorbidity \textsuperscript{15}. Engaging with patient’s therapeutic preferences can provide a powerful counter-measure to polypharmacy provoked by guidelines focused on single-disease management. For instance, a qualitative exploration of the therapeutic priorities of patients with both hypertension and falls risk showed that patients with multimorbidity were less likely to prioritise a blood pressure reduction above the increased risk of MRH \textsuperscript{389}.

Nevertheless, there is a paucity of published data specifically investigating health literacy as a determinant of MRH, and future work in this area may prove fruitful to better understanding of the causal pathways leading to MRH in older adults.

Healthcare providers, through the leadership of clinical commissioning groups, should facilitate open talks by healthcare professionals aimed at a public audience, and closer public engagement. Much of this work is done by local public health departments but, following public health’s removal from the NHS to the local authority, public health departments have had their budgets cut year on year since 2015\textsuperscript{390}. There is increasing pressure to demonstrate the cost-effectiveness of any work. Therefore, initiatives that have poorly quantifiable output risk being neglected. The benefits of empowering older adults to have more meaningful involvement and autonomy over their health is not easily quantifiable, but is crucial to the efficient use of healthcare resources and should be prioritised.
9.2.2 Improving processes around hospital discharge

Key features of a safe hospital discharge include timely and comprehensive information transfer from the hospital to primary care, a patient discharge plan that encompasses medicines reconciliation, patient education that is comprehensible, and community follow-up. Follow-up in the community to reduce adverse outcomes can be with a specialist nurse rather than a GP, and previous studies have shown this to be cost-effective. A randomised controlled trial of older patients in Denmark investigated the effectiveness of community follow-up one week, three weeks and eight weeks post-discharge. The follow-ups were conducted by GPs and district nurses, with the first visit being a structured home visit. The study found that patients receiving the follow-up intervention were significantly more likely to adhere to their medicines at 3 months follow up and had a reduced incidence of hospital readmission at 6 months post-discharge. Of course, such an intervention is resource intensive and impractical for every older person that is discharged from hospital. The PRIME tool offers a resource during the discharge process for targeting interventions at patients with high risk of MRH requiring healthcare use. This tool is unique for multiple reasons. It was developed from prospectively collected data in a large population of older adults from multiple hospitals. Only MRH events that were determined to be definitely attributable to medicine, and resulted in the use of healthcare were included in the development of the tool. This enhances both the tool’s precision and clinical significance. The variables included in the tool were selected first and foremost through clinical expertise, substantially reducing the introduction of variables that appear important through ‘statistical chance’. Finally, the tool was internally validated and corrected for optimism through an advanced statistical procedure i.e. bootstrap. Now, however, the tool requires prospective testing in a different setting from that which was used for the PRIME study, and work has already commenced on this front. Work is in progress with research groups in Australia and Qatar for an external validation phase for the PRIME tool. During the external validation phase, it is intended that data on the health literacy of patients will be collected to examine whether this is a determinant of MRH and whether it can enhance the performance of the PRIME risk prediction tool.
The quality of communication between secondary and primary care around hospital discharge requires improvement. Kattel et al’s (2016) systematically reviewed studies that examined the quality of transfer information at discharge. The review found that a median of 60% of discharge summaries provided results of diagnostic tests, 25% provided information on pending tests, 78% provided information on discharge medications and 42% on follow-up plans. For 1 in 12 discharged patients, the patient’s hospital discharge summary is never received by the primary care provider. When discharge summaries are available they often lack key information necessary for providing continuity of care. For instance, even where details regarding medication changes during hospital admission are provided, the actual information communicated is frequently inaccurate. Reducing the workload of junior doctors is an intervention that has been shown to significantly improve the quality of discharge summaries. And insufficient opportunities for junior doctors in hospital to communicate with patients’ post-discharge (ie. in clinics, and home visits) is associated with the perception of less responsibility for the safe transition of patient care back into the community. For junior doctors training in hospitals to get a clearer insight of community healthcare, perhaps a brief but mandatory placements within General Practice would enhance their awareness and sense of responsibility for a patient’s transition of care.

9.2.3 Tackling the culture of medicines overuse

Whilst the concept of ‘evidence-based medicine’ and the gold-standard RCT were revolutionary when we consider some historical treatment modalities e.g. bleeding and purging in the era of humours, the pedestal that EBM occupies is increasingly being debated. The ‘controlled’ in RCTs is an obvious problem as in practice medical treatment happens in the real-world, not under tightly regulated and monitored conditions with highly selected participants. Therefore whilst an RCT may demonstrate the efficacy of a treatment, it does not confirm the effectiveness of a treatment. Pragmatic trials are needed, following phase 3 trials, at the
postmarketing phase of evaluation. However, such trials require substantial financial resource and the pharmaceutical industry is unlikely to welcome a responsibility to demonstrate ‘real-world public health value’. Governments may need to invest for an overall public health benefit through closer involvement in industry-sponsored trials, influencing patient-centered end-points, full data transparency and pragmatic phase IV (postmarketing) trials.

The harms of overdiagnosis and overtreatment should be better communicated through generating good evidence, as the PRIME study results have shown. Where profit are to be made, malign methods have been used to convert risk factors into disease labels, to push the medicalisation of society. Healthcare leaders down to medical students must resist these attempts in the interests of preserving the trust of our patients and the four principles of medical ethics; respect for autonomy, beneficence, non-maleficence, and justice. The medical profession must trust in their role as physicians (‘healers’) not merely prescribers, and within this armoury is care, compassion and advice as treatment in and of themselves. Finally, medicines are an essential and invaluable tool that doctors are privileged to be the gateway of. Doctors must be precise with the medicines used, that is the right medicine, for the right person at the right time. Medical training is established in teaching about use of the right medicine, but rarely about the right person and the right time. However, the right medicine is non-existent if it’s not in the right person or at the right time.

9.2.4 Medical Education

The importance of improving prescribing practices globally was emphasised 30 years ago at a WHO conference titled ‘The rational use of drugs’ (Nairobi, 25-29 November 1985). A key recommendation that came out of this was ‘better information, proper training and continuing training throughout the health worker’s career, from the most senior medical prescriber to the humble non-professional village health worker’
The recently published GMC outcomes for new doctors states that graduates should be competent to

- detect and report adverse medication reactions and therapeutic interactions and react appropriately by stopping or changing medication

- monitor the efficacy and effects of medication and with appropriate advice from colleagues, reacting appropriately by adjusting medication, including stopping medication with due support, care and attention if it proves ineffective, is no longer needed or the patient wishes to stop taking it

- recognise the risks of over-prescribing and excessive use of medications and apply these principles to prescribing practice

These outcomes will undoubtedly increase the visibility and volume of CPT education in the medical school curriculum. As discussed in chapter 7, CPT has traditionally been a neglected component of medical training and the problems associated with this are evident. Alongside knowledge about and monitoring for ADR, adherence related issues must also be considered and addressed where possible. A considerable proportion of MRH in the PRIME study arose from poor adherence to medication (23%). Whilst many medicines might indeed be appropriate to suit a diagnosis, they are inappropriate for the individual if they are not going to correctly adhere to the prescription. Not only does poor adherence cause harm to many patients, but it is an immense waste of healthcare resource. It has been estimated that there £300 million worth of medicines are wasted in England each year. Table 9.1 describes some key adherence related issues that hospital doctors should consider when preparing the discharge of older patients, and offers some potential solutions to the problems.
Table 9.1 Common barriers to medication adherence and possible solutions

<table>
<thead>
<tr>
<th>Common barriers to adherence</th>
<th>Potential solutions</th>
</tr>
</thead>
</table>
| Forgetfulness                | 1. Simplify medication regimen  
                               | 2. Consider a medication compliance aid e.g. blister pack  
                               | 3. Encourage carer or family involvement in supporting compliance |
| Patient beliefs about        | 1. Explore ideas, concerns, expectations and establish shared  
medication use                | treatment goals  
                               | 2. Signpost to reliable sources of information |
| Practical difficulty with    | 1. Consider most appropriate formulation and administration aid to  
medication use                | reduce difficulties (consult pharmacist as required)  
                               | 2. Simplify pill regimen and pill burden |
| Adverse drug reactions       | 1. Ensure sufficient and comprehensible provision of information  
                               | regarding common side-effects  
                               | 2. Monitor and re-evaluate benefit and harms of new prescription at  
                               | regular intervals |

High risk prescribing can be defined as the use of drugs where the risk of adverse events outweighs the clinical benefit\textsuperscript{204}. The appropriateness of medication in older people is an important predictor of quality of life \textsuperscript{404}. Explicit lists of inappropriate medicines, such as the Beers Criteria discussed in Chapter 5 or the STOPP criteria, have merit for education and research purposes\textsuperscript{405} but in routine clinical practice are burdensome to use due to their length and absence of individual context\textsuperscript{201,215,406}. Instead, training should focus on harnessing the clinical acumen of prescribers to ensure that the medicines are initiated appropriately. The BEGIN algorithm, developed by myself and colleagues using existing literature and expert opinion in Geriatrics and clinical pharmacy, offers prescribers a simple method to focus their decision-making process and ensure that the right medicine is prescribed to the right person at the right time (figure 9.2). The BEGIN algorithm has been incorporated into the medical school teaching at Brighton and Sussex Medical School, and is given mention in the Royal College of General Practitioner’s e-learning module on safe prescribing.
9.3 Limitations

Within each data chapter of this thesis, limitations of the work have been discussed. Here I will briefly consider some of the broader limitations of the work presented.

First and foremost, my research has entirely focused on the harms of medicine with no investigation of the benefits that the medicines provided to the participants. Medicines have, and undoubtedly will, continue to prevent illness, cure illness, and maintain stability in illness. However, there has been an imbalance in research (and therefore clinician and patient opinion) of the benefits and harms of medicine. Because medicines are so often used for the prevention of disease, it is hugely
challenging to design a study to compare the benefits and harms of medicine at the level of the individual. The individual can encounter the adverse effects of medicine on a day by day basis, but the benefit of preventing a major disease may not be realised for years (or indeed ever known). The benefit for preventative medicines can only be observed at the population level through an observed reduction in the incidence of disease. The purpose of the programme of work presented in this thesis was not to compare or disregard the benefits of medicine, but to generate robust information on some of the harms of medicine in older adults at a critical time-point in their healthcare journey. Furthermore, to develop an approach to identify more susceptible patients in whom this harm can potentially be prevented.

The work presented is limited to patients in England, and of course the use of medicines is far less liberal in resource-poor settings, and specific groups of people in non-universal healthcare systems. The generalisability of the PRIME tool will be examined in future work. Nonetheless, ageing societies is a global phenomenon (with exception of some African nations) and the availability of medicines is increasing across global settings and cultures. Therefore, whilst the findings reported in this thesis may not be applicable to all settings, certainly the broader lessons of the potential harms of medicine use in older populations in the post-discharge period can inform policy development and practice internationally.

Clinical judgement informed the decisions of whether an adverse event was attributable to medicine. Whilst there is some inherent subjectivity in this process, clinical judgement supplemented the validated Naranjo algorithm and information in the BNF and SPC. The purpose of the end-point committee reviewing and verifying all cases of MRH was to standardise these judgements. In real-life clinical practice, it is the judgement of practicing clinicians that determines whether harm is iatrogenic or due to a underlying disease or condition. Therefore, including the clinical judgement of practicing clinicians was important for the study findings to reflect real-life.
Medication errors that caused harm were included in the PRIME study, however no attempts were made to identify errors where they were not reported during follow-up. Therefore, it is likely that some errors leading to harm were misclassified as ADRs or adherence-related. Nonetheless, recent work has shown that a very small proportion of medication errors in England and internationally result in actual harm.\(^{220,407}\)

Finally, the PRIME tool has not been externally validated which is an imperative stage before steps can be made towards implementation in clinical practice. Alongside the tool’s performance in an external setting, the usability and face validity of the tool must be tested. The external validation of the PRIME tool is in progress. The tool generates an estimate of an absolute patient percentage risk of MRH requiring healthcare within eight weeks of hospital discharge. The threshold of risk at which intervention should and could be implemented is context specific. It would be arbitrary for thresholds of high and acceptable risk to be set as it will depend on the acceptability of MRH to patients and healthcare providers within the healthcare setting that it is being employed. Furthermore, a threshold will need to be dependent on available resources to provide medication-related support in any specific setting. It is also acknowledged that use of the tool could result in unexpected adverse outcomes, such as the under treatment of patients. These unintended effects will be monitored, with parallel ethnographic work to explore how clinicians, patients and care processes respond to the new information that the PRIME tool delivers.

**9.4 Conclusions**

In 1976, Ivan Illich asserted ‘A vast amount of contemporary clinical care is incidental to the curing of disease, but the damage done by medicine to the health of individuals and populations is very significant. These facts are obvious, well documented, and well repressed.’\(^{3}\) Forty years on from this, in 2017, the WHO launched a global patient safety campaign ‘Medication without harm’\(^{356}\). I sought to
investigate the impact of MRH in older adults following hospital discharge, and whether this harm could be predicted. In England, this research has shown that MRH poses a very significant burden to patients and carers. This has serious implications on both human and financial resources within the NHS. This harm is predictable using a combination of clinical, demographic, and social patient indicators. Clinical judgement of doctors alone is likely to be insufficient to identify high-risk patients, however could in the future be supplemented with the PRIME risk prediction tool to make safer medication-related decisions in collaboration with patients. Whilst Illich was undeniably radical in his criticism of the medical profession, the facts are obvious and the profession can choose to heed this knowledge and protect the trust of patients or neglect them at its peril.
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Appendices

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Appendix 2. Participant information sheet for qualitative study - chapter 3
Appendix 3. Interview topic guide for qualitative study - chapter 3
Appendix 4. Advertisement for recruitment to qualitative study - chapter 3
Appendix 5. Questionnaire completed by discharging doctors – chapter 7
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Appendix 7. Potential interface for implementation of PRIME tool – chapter 8
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<td>Incidence of MRH:</td>
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<td>Incidence by severity of MRH:</td>
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<td>Number of events:</td>
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<td>Type of MRH events (+ by system if applicable):</td>
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<tr>
<td>Risk of MRH by drug class (frequency of events caused by one class)</td>
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<td>Reported risk factors for MRH</td>
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<td>Funding sources</td>
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<td>Additional Notes</td>
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</table>
Appendix 2.

“Medicines and more medicines” (M&Ms)
Older people and medication-related problems research
Participant Information Sheet

This project is a partnership between Brighton and Sussex Medical School, University of Brighton and Age UK Brighton and Hove. The key aim of this project is to get a better understanding of medication problems that are experienced by older people.

We would like you to participate in a discussion group of older people about your views and experiences of medication-related problems. We are particularly interested in understanding the medication problems that arise following a hospital admission. After we have collected people’s views and experiences, we will produce a report that local organisations interested in the health of older people can use to gain a better understanding about the issues.

We expect that the discussion should not last more than an hour and a half but want to stress that you are free to leave the group at any point without giving a reason.

We would like to record the discussion in the group as this will help us make sure we have properly understood what has been said.

We will ensure that everything you tell us will be treated in the utmost confidence and we will not pass personal information on to anyone else. The only exception would be if this information raises serious concerns about your own safety. In such a case we may need to contact somebody who can help. We will also request that you keep any personal experiences of others that are heard during the discussions confidential.
The discussion group will be held at the main building of Age-UK Brighton & Hove. We will cover any transport costs you may incur in order to take the time to talk to us. Refreshments will be provided.

This research is part of a PhD project of Dr Nikesh Parekh. Nikesh is a medical doctor, however will be conducting the discussion in his research role. Therefore he will not be able to discuss any personal medical queries with you.

If you would like to talk to Nikesh to find out more about this project you can call him on 01273 523362. For more detailed information, please continue reading.

1. **What is the purpose of the study?**
   The purpose of this study is to explore the views and experiences of older people about medication-related problems that occur following discharge from hospital. We hope that health professionals can use the findings from the research to reduce the risk of medication problems for older people in the future.

2. **Who is organising and funding the research?**
   The research is funded by the Community Universities Partnership Programme from the University of Brighton

3. **Why have I been invited?**
   You have been invited to participate because you have reached the age of 65 and take regular medicine and have experienced being discharged from hospital in older age.

4. **Do I have to take part?**
   No. It is up to you to decide whether or not you wish to join the study. If you agree to take part, we will ask you to sign a consent form on the day of the group discussion.

5. **What will happen to me if I take part?**
   You will be invited to attend a day-time group discussion involving 6-8 people, and it is expected to last approximately one hour and a half. In this discussion, you will be encouraged to share your views and experiences of medication related problems in the transition period following a hospital discharge. As a token of our appreciation, we will offer you a shopping voucher for Marks & Spencer.
7. Are there any possible disadvantages or risks of taking part?
   Discussing personal experiences of health care might be upsetting. However, you will be in a safe environment to discuss sensitive issues and all personal information will remain entirely confidential as outlined in the next point.

8. What about confidentiality?
   All the information about your having taken part in this study and all information collected during the course of the research will be stored securely and will be kept strictly confidential. The only exception to this will be if any information raises concern for your wellbeing, safety and management. In such a case, this information will be discussed with Dr Khalid Ali (Consultant Physician, Brighton and Sussex University Hospitals Trust), Dr Beatrice Gahagan (Age-UK wellbeing manager), and another appropriate health care professional if necessary (for example, your GP).

9. What will happen if I don’t want to carry on with the study?
   You are free to withdraw at any time and without giving a reason. We will also be happy to discuss with you what will happen to any data that has been collected up to the point of your withdrawal from the study.

10. What will happen to the results of the research study?
    The results of the study will be written in to a study report, which will be sent to you, and published in a scientific journal. We also hope to hold an event for local health professionals to discuss medication problems in older people and the results from this study would be presented.

11. Who has approved this study?
    This study has received ethical approval from the Brighton and Sussex Medical School Research Governance and Ethics Committee (BSMS RGEC)

12. Who can I direct a complaint to?
    If you have a complaint about any aspect of this study, you should ask to speak with Dr Khalid Ali (Consultant Physician, Brighton and Sussex University Hospitals Trust) who will do his best to answer any questions and address any concerns or other problems (contact details of Dr Khalid Ali are provided below)

    For any further information, please do not hesitate to call our research team
Appendix 3.
Medication-related problems project
INTERVIEW TOPIC GUIDE

<table>
<thead>
<tr>
<th>Headings</th>
<th>Prompts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opening</strong></td>
<td>Icebreaking comments, eg weather, the journey etc</td>
</tr>
<tr>
<td>Thank you for agreeing to take part</td>
<td>Acknowledge ‘medication use and problems’ a complex topic;</td>
</tr>
<tr>
<td></td>
<td>we want to understand your professional experience of older people experiencing difficulties with their medications during the transition from hospital to home after an admission.</td>
</tr>
<tr>
<td></td>
<td>No right or wrong answers – want to explore some of your thoughts and understand your experience.</td>
</tr>
<tr>
<td></td>
<td>I will be jotting down some notes on the sheet and I’ve got some prompts which I will refer to</td>
</tr>
<tr>
<td><strong>Introduce topic</strong></td>
<td>The things we want to cover in this interview</td>
</tr>
<tr>
<td></td>
<td>We are expecting it to take about an hour.</td>
</tr>
<tr>
<td><strong>About you?</strong></td>
<td></td>
</tr>
</tbody>
</table>

Researcher:
It would be helpful to know a bit about you and your general health and well-being.

**Recent hospital admission**

Illness?

Explain and acknowledge it may be difficult to recall.

What events led to hospital admission?

Experience of using medicines for illness in hospital? Positives and negatives.

**Preparing to leave hospital**

Events leading to being aware/informed of ‘hospital discharge’

Feeling ready to leave the hospital setting?

Support for medication use

Information about medicines to be continued at home –

How do you spend your time—can you tell me about a typical day / week?

How do you feel your general health is?
Initial 48 hours back at home

which medicines and for what benefit?

Changes from medicines prior to admission

Hospital staff checking participant’s understanding of medicines to take home (ideas, concerns, expectations)

How did you feel to be back at home? (ideas, concerns, expectations)

Support (hospital, GP, pharmacy, local organisations, family, friends, carers)

Supply of required medication

Medication recognition
<table>
<thead>
<tr>
<th>Ability to remember medication-related information provided (if provided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readability of instructions</td>
</tr>
<tr>
<td><strong>Medication usage</strong></td>
</tr>
<tr>
<td>Managing packaging (blister, dosette, or standard packaging)</td>
</tr>
<tr>
<td>Counting/confirming/adjusting dosage</td>
</tr>
<tr>
<td>Taking medication (sticks, taste, size, quantity)</td>
</tr>
<tr>
<td><strong>Benefits and harms</strong></td>
</tr>
<tr>
<td>Feelings about taking the medicine (short-term / long-term)</td>
</tr>
<tr>
<td>Improvements in well-being</td>
</tr>
</tbody>
</table>
After 48 hours back at home

- Adverse effects (expected or unexpected)
- Impact on quality of life (timings and remembering to take medicine, socializing, adverse feelings)
- Need for help (advice, follow-up, hospital or GP)
- Changes to medicines (reasons)
- New practical difficulties (supply, handling, consuming)
- New avenues of support for medication understanding and use

Benefits and harms
Feelings about taking the medicine (short-term / long-term)

Improvements in well-being

Adverse effects (expected or unexpected)

Impact on quality of life (timings and remembering to take medicine, socializing, adverse feelings)

Need for help (advice, follow-up, hospital or GP)

Level of involvement in decision making about medication-related issues that participant desires

Extent to which participant engaged in medication-related decisions
Opportunity for involvement offered by health practitioner?

Any aspects not covered from identified themes

You have said a lot about ... but haven’t mentioned ....

My reflections on the interview (please include any observations, e.g. body language)
Appendix 4.

“Medicines and more medicines” (M&Ms)
Older people and medication problems focus group

Invitation to Tai Chi group members

Aged 65 years or over?

Had an admission to hospital in the last couple of years?

Taking regular medication?

If so, we would love to talk to you after your Tai chi class.

Age UK Brighton and Hove are working on a study concerning older peoples’ experiences of medicines. The key aim of this project is to get a better understanding of medication problems from the perspective of older people.

If you would like to take part along with other members of your Tai Chi group, we will be holding a discussion group here after the Tai Chi session on:

Friday 21st October after the Tai Chi class, from 12.15 -1.45 p.m.

Refreshments will be provided along with a small gift as a token of our appreciation.

Please read the detailed information attached if you are interested and let us know if you would like to take part by completing the contact sheet provided giving your name, address and telephone number.

We will contact you before the event to answer any questions you might have and to let you know more details.
### Appendix 5.

#### Junior Doctors Post discharge risk rating

<table>
<thead>
<tr>
<th>Date completed</th>
<th>Doctors Grade</th>
</tr>
</thead>
</table>

1) Thinking about this patient in the 8 weeks after discharge, how likely is it that they will be admitted to hospital due to medication related harm?

- [ ] Doubtful (do not expect to happen)
- [ ] Probable (will probably happen)
- [ ] Possible (might happen)
- [ ] Definite (will undoubtedly happen)

2) Please give brief reason(s) for the likelihood and you have chosen:

3) How confident are you in this answer?

- [ ] Little or no confidence
- [ ] >50% confidence but a close call
- [ ] Slight to moderate confidence
- [ ] Strong confidence
- [ ] <50% confidence but a close call
- [ ] Virtually certain

4) Thinking about the patient in the 8 weeks after discharge, how likely is it they will access healthcare in the community due to medication related harm?

- [ ] Doubtful (do not expect to happen)
- [ ] Probably (will probably happen)
- [ ] Possible (might happen)
- [ ] Definite (will happen)

5) Please give brief reason(s) for the likelihood and you have chosen:

6) How confident are you in this answer?

- [ ] Little or no confidence
- [ ] >50% confidence but a close call
- [ ] Slight to moderate confidence
- [ ] Strong confidence
- [ ] <50% confidence but a close call
- [ ] Virtually certain
## Appendix 6.

<table>
<thead>
<tr>
<th>Study</th>
<th>Derivation cohort</th>
<th>ADR inclusion by causality</th>
<th>Verification</th>
<th>Model development</th>
<th>Predictors</th>
<th>Validation</th>
<th>Model performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>McElnay (1997) Tool to predict unplanned hospital admission due to ADR</td>
<td>929 [149 events]. Unknown if EPV guidance followed.</td>
<td>Probable (Naranjo score 4-8) or definite events (≥9)</td>
<td>Unclear</td>
<td>Backwards elimination (p&lt;0.05)</td>
<td>(1)Digoxin, (2)Antidepressants, (3)COPD, (4)Angina, (5)Gastrointestinal complaint, (6)Abnormal potassium, (7)Patient belief that medicine influenced hospital admission</td>
<td>Split-sample validation (n=204). 37 events in validation cohort</td>
<td>C-statistic NR. Calibration NR. Using cut point of p&gt;0.3</td>
</tr>
<tr>
<td>Nair et al (2016) (PADR-EC) Tool to predict unplanned hospital admission due to ADR</td>
<td>768 [115 events] EPV guidance not met.</td>
<td>Probable (Naranjo score 5-8) or definite events (≥9)</td>
<td>Pharmacist only</td>
<td>Multivariable logistic regression model with score based on predictors p&lt;0.05</td>
<td>(1)Number of antihypertensives (1-2 = 3 points, ≥3 = 5 points), (2)Dementia, (3)Renal failure, (4)Drug changes in last 3 months, (5)Use of anticholinergic medication</td>
<td>Validation in neighbouring hospital (n=240). 30 events in validation cohort</td>
<td>0.67 (0.56-0.78) Calibration NR</td>
</tr>
<tr>
<td>Tangisuran (2009) (BADRI) Tool to predict in-hospital ADR</td>
<td>690 [86 events]. EPV guidance not met.</td>
<td>Possible, Probable or definite events (Hallas algorithm)</td>
<td>Physician and pharmacist</td>
<td>Backwards elimination (p&lt;0.1) and forwards selection</td>
<td>(1)Hyperlipidaemia, (2)Number of drugs (≥28) (3)Hypoglycaemic agent, (4)High WCC on admission, (5)Length of stay≥12 days</td>
<td>Validation in sample (n=483) from 4 European countries with 56 events</td>
<td>0.73 (0.66-0.80) Calibration acceptable</td>
</tr>
<tr>
<td>Trivalle (2011) Tool to predict in-rehabilitation ADE</td>
<td>505 [152 events]. Unknown if EPV guidance followed</td>
<td>At least probable events included. No validated tool used to assess causality.</td>
<td>Physician and pharmacist</td>
<td>Backwards elimination (p&lt;0.05)</td>
<td>(1)Number of drugs (7-9 = 6 points, 10-12 = 12 points, ≥13 = 18 points), (2)Antipsychotic drug, (3)Anticoagulant drug</td>
<td>Bootstrap internal validation</td>
<td>0.70 (0.65-0.74) Calibration NR</td>
</tr>
<tr>
<td>Onder (2010) (GerontoNet) Tool to predict in-hospital ADR</td>
<td>5936 [383 events] EPV guidance met</td>
<td>Probable (Naranjo score 5-8) or definite events</td>
<td>Physician only</td>
<td>Backwards elimination (p&lt;0.1)</td>
<td>(1)≥4 comorbidities, (2)eGFR&lt;60mL/min (3)Heart failure, (4)Liver disease, (5)Previous ADR, (6)Number of drugs (3-7 = 1 points, 8 = 4 points)</td>
<td>Validation in sample (n=483) from 4 European countries with 56 events</td>
<td>0.70 (0.63-0.78) Calibration NR</td>
</tr>
<tr>
<td>O’Mahony (2018) (ADRRP) Tool to predict in-hospital ADR</td>
<td>1687 [number of events NR] Unknown if EPV guidance followed</td>
<td>Probable or definite events based on WHO-UMC criteria</td>
<td>Physician only verified events.</td>
<td>Backwards elimination (p&lt;0.1)</td>
<td>(1)Female gender, (2)Age≥70, (3)eGFR&lt;30mL/min/1.73², (4)Assistance with an ADL, (5)≥4 comorbidities, (6)Liver disease, (7)Number of STOPP criteria drugs (1=3 points, 2=6 points), (8)≥1 fall in last year</td>
<td>Split-sample validation n=530 [number of events NR]</td>
<td>0.59 (0.53-0.65) Calibration NR</td>
</tr>
</tbody>
</table>

WCC: White Cell Count; NR: Not Reported; EPV: Events per Variable; eGFR: estimated Glomerular Filtration Rate
Appendix 7.

PRIME prediction tool

Yes = 1, No = 0

Age: 78
Male: 0
Antiplatelet drug: 0
Sodium level (mmol/l): 132
Antidiabetic drug: 1
Past adverse drug reaction: 1
Number of medicines: 12
Living alone: 1

RISK of medication harm requiring healthcare within 8 weeks: 39%
Peer-reviewed publications

Chapter 2


Chapter 3


Chapter 4


Chapters 5&6


Chapter 7


Chapter 9

