DEVELOPMENT OF A MODEL PREDICTING 30-DAY READMISSION USING PRESCRIPTION INFORMATION FROM THE MEDICAL SHORT STAY UNITS OF ONE NHS TRUST

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Abstract

Emergency readmission is defined within the NHS as an emergency admission to hospital within 30 days of discharge. Excess readmissions are undesirable in terms of care quality and efficiency; yet, despite financial incentives for improvement, reports of increasing readmission rates continue. There is evidence that pharmacist intervention can prevent medication errors, discrepancies and adverse drug events; which can each contribute to readmission. The purpose of the work in this thesis was to develop a model based on routinely collected prescription information to enable the pharmacy team to estimate readmission risk in the clinical setting, thereby facilitating appropriate prioritisation of potentially preventative intervention.

A multiple logistic regression model for estimating readmission risk using routinely recorded prescription information among patients discharged home from the medical short stay units of one NHS Trust was developed, and survival analysis was undertaken to characterise readmission behaviour in relation to the predictors.

The readmission rate was 18% (220/1240). Readmission risk increased with increasing age and polypharmacy: each additional medicine prescribed increased the odds of readmission within 30 days by eight per cent and each additional year of age increased the odds of readmission within 30 days by two per cent. Each additional medicine prescribed decreased the time to readmission by seven per cent and each additional year of age decreased the time to readmission by one per cent. Over one-third of readmissions occurred within one week (73/200) and more than half (114/200) occurred within two weeks, supporting that identification of those at risk and intervention to prevent readmission should be provided promptly. The predictive model developed is suitable for application on admission and could therefore enable clinicians to identify the patients most likely to require intervention to prevent readmission before they are discharged home from hospital, thereby maximising the time available to organise and/or provide the necessary support. Although the logistic regression model improved accuracy by 36% compared to indiscriminate intervention whilst identifying 70% of patients who would be readmitted, it had relatively weak discriminative capability (c-statistic 0.637). It may be the case that clinical intuition is as effective for predicting readmission and further research should be undertaken to confirm whether this is the case.

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Glossary

Term	Definition
Adherence (medication)	Whether a patient uses their medication in accordance with their prescription
Ambulatory Care Sensitive Condition	Condition for which effective community care can help to prevent the need for hospital admission
Anticholinergic (antimuscarinic)	The blockade of acetylcholine and its action upon muscarinic receptors resulting in side effects commonly including dry eyes, dizziness, sedation, confusion, delirium, and falls
Anticipatory medication	Used to manage symptoms commonly experienced during the end of life
C-statistic	Area under the ROC curve (AUC), representing a predictive model's discrimination
Calibration	Represents agreement between a model's predictions and the observed outcomes over the entire range of probability values
Candidate predictor	An independent variable which may have potential to predict the value of the dependent variable
Care transition	Moving from one care setting to another
Charlson Comorbidity Index	Predicts one-year mortality based on comorbid conditions (Charlson, Pompei, Ales, & MacKenzie, 1987)
Commissioning for Quality and Innovation	Providers are reimbursed by commissioners subject to achieving locally-agreed quality improvement targets (NHS England, 2016)
Comorbidity	The presence of two (or more) long term conditions
Correlational research	Observational research to identify relationships between naturally occurring variables

Term	Definition
Discrepancy (medication)	A lack of agreement or incompatibility between medication regimens across the care transition
Discrimination (statistics)	A model's ability to separate those who will and will not experience the outcome of interest
Familywise error rate	The probability of type I error in a set of tests on the same data
High risk medicines	As defined in the Medicines Use Review service specification
Hosmer-Lemeshow	Test for a logistic regression model's goodness of fit (see page 152)
Hospital A	Calderdale Royal Hospital
Hospital B	Huddersfield Royal Infirmary
Hospital Episode Statistics	A database containing details of all admissions to NHS hospitals in England
Hospital utilisation/reutilisation	Hospital attendance, whether emergency department visit or resulting in admission
Index admission	The original admission (typically preceding a readmission or rehospitalisation)
LACE Index	Predicts readmission or death within 30 days on the basis of length of stay, acuity of admission, comorbidity and emergency department visits (van Walraven et al., 2010a)
Listwise deletion	Cases are eliminated from analyses if values are missing for any variable; only cases with a complete set of data are included
Long term condition	A condition that cannot be cured but is controlled by medication and/or other treatment/therapies (longstanding condition/disease/illness)

Term	Definition
Medicare	A USA state-based health insurance program for people aged 65 years of age or over and people under 65 with certain disabilities or end-stage renal disease
Medicaid	A USA state-based health coverage program for people on low incomes
Medication/medicines optimisation	A person-centred approach to ensure people use their medicines safely and effectively to achieve the best possible outcomes
Medication/medicines reconciliation	The process of obtaining a complete and accurate list of patient's current medication to identify any discrepancies
Multidisciplinary	Involving multiple disciplines in a clinical setting
Multi-morbidity	The presence of multiple medical conditions
NHS Outcomes Framework	Framework setting out the national outcome goals used to monitor the progress of NHS England. Its indicators provide national level accountability for the outcomes the NHS delivers
Non-parametric	Not relying on the assumption that the sampling distribution takes a particular form (typically a normal distribution)
One-stop dispensing strategy	Non-stock medicines for inpatients are dispensed so that they are suitable for issue against a discharge prescription in the clinical setting where appropriate
Pairwise deletion/exclusion	Maximises the data included in analysis by limiting elimination to cases for which the necessary combination of values are not available irrespective of whether values are missing from other variables for the case
Parametric	Relying on the assumption that the sampling distribution takes a particular form (typically a normal distribution)
Parsimony	Balancing simplicity with effectiveness

Term	Definition
PASWEB	The Trust's electronic patient administration system
Pharmaceutical intervention	Practical intervention by the pharmacy team
Polypharmacy	The use of multiple medicines
PRN (*pro re nata*)	When required
Quality of care	The extent to which care delivered meets expected standards
Quantitative	Involving application of deductive reasoning to test objective theories by examination of relationships between variables
Reablement	Reablement helps people with poor health accommodate their illness by learning or re-learning the skills necessary for daily living by the use of services such as community health services, social care, home adaptations, and extra-care housing
Readmission	Emergency admission within 30 days of discharge as defined in the 2016/17 National Tariff (Monitor, 2016), unless otherwise specified
Regression to the mean	A phenomenon in which outlying initial observations tend to precede observations that are closer to the average
Rehospitalisation, repeat admission	Admission subsequent to a prior admission, but not necessarily within the readmission period
Receiver operating characteristic curve	A plot of a model's sensitivity in relation to specificity, representing its discrimination
Sensitivity	A model's ability to identify those who would experience the outcome of interest
Specificity	A model's ability to identify those who would not experience the outcome of interest
Type I error (false positive)	Identifying a relationship that is not significant as significant

Term	Definition
Type II error (false negative)	Incorrectly identifying a relationship that is significant as non-significant
Winter pressures	Increased demand for NHS services during the winter months
30-day emergency readmission rule	As defined in the *Payment by Results Guidance for 2012-13* (Department of Health, 2012b)

Abbreviations

Abbreviation	Full term
ACB	Anticholinergic Cognitive Burden
ACEi	Angiotensin-converting enzyme inhibitor
ACGs	Adjusted Clinical Groups
ACSC	Ambulatory care sensitive condition
ADLs	Activities of daily living
ADR	Adverse drug reaction
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AUC	Area under the curve
*b*s	Parameter estimates
BNF	British National Formulary
CAD	Coronary artery disease
CAG	Confidentiality Advisory Group
CAP	Community acquired pneumonia
CCG	Clinical Commissioning Group
CCI	Charlson Comorbidity Index
CHF	Congestive heart failure
CHFT	Calderdale and Huddersfield NHS Foundation Trust (the Trust)
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPHR	Cox Proportional Hazards Regression

Abbreviation	Full term
CQUIN	Commissioning for Quality and Innovation
CV	Cardiovascular
DH	Department of Health
DPD	Doses prescribed per day
ECG	Electrocardiogram
ED	Emergency Department / Accident & Emergency
EDS	Electronic discharge summary
EDMS	Electronic discharge medication summary
EF	Ejection fraction
EHR	Electronic health record
ENT	Ear, nose and oropharynx
ERA	Elder Risk Assessment
GI	Gastro-intestinal
GP	General Practitioner
GU	Genitourinary
HbA1c	Glycated haemoglobin
HES	Hospital Episode Statistics
HF	Heart failure
HL	Hosmer-Lemeshow Test
HR	Hazard ratio
HRM	High risk medicine (MUR)
IQR	Interquartile range
IRAS	Integrated Research Application System
KMSA	Kaplan-Meier Survival Analysis
LOS	Length of stay
LTC	Long term condition
MCA	Multi-compartment compliance aid

Abbreviation	Full term
MCAR	Missing completely at random
MSK	Musculoskeletal
MSSU	Medical Short Stay Unit
MUR	Medicines Use Review
NA	Not applicable
NHS	National Health Service
NMS	New Medicines Service
NP	Not presented
NS	Not significant
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PbR	Payment by Results
PSIE	Agency for Healthcare Research and Quality Patient Safety Indicator event
PTSD	Post-traumatic stress disorder
ROC	Receiver operating curve
RPS	Royal Pharmaceutical Society
SD	Standard deviation
SE	Standard error
The Trust	Calderdale and Huddersfield NHS Foundation Trust
THIS	The Health Informatics Service
TMUR	Targeted Medicines Use Review
UK	United Kingdom
USA	United States
VIF	Variance Inflation Factor

Chapter 1 Introduction

1.1 Readmission in the NHS

The National Health Service (NHS) in England defines emergency readmission as any emergency admission that happens within 30 days of discharge and has a national price[1] (Monitor, 2016). Published rates of readmission vary, but it has frequently been reported that readmission rates have risen over recent years: in 1998/9 fewer than 8% of NHS inpatients in England were readmitted within 28 days, compared to just over 10% in 2006/7 (Zerdevas & Dobson, 2008). Blunt, Bardsley, Grove, and Clarke (2014) observed that 7% of hospital discharges in England between 2004 and 2010 resulted in readmission within 30 days; this was associated with an average monthly increase of 0.01%. Billings et al. (2012) identified a 30-day readmission rate of 12% in a sample of one-tenth of all hospital admissions in England in 2008/9, and it was reported that the national readmission rate had increased from 9.5% in 2002/3 to just under 12% in 2011/12 when emergency readmission within 30 days was introduced to the *NHS Outcomes Framework*[2] in December 2013 (Health & Social Care Information Centre, 2013a). A recent analysis of Hospital Episode Statistics (HES)[3] reported that although the number of readmissions increased by almost one-fifth between 2010/11 and 2016/17, half of this was accounted for by increasing admissions; the emergency readmission rate increased from 7.5% in 2010/11 to 8.0% in 2016/17 (Morris, 2018). Additionally, a national analysis of emergency readmission in England between 2006 and 2016 reported that risk-adjusted readmission rates had remained relatively stable at

[1] Payment due to the provider to cover the cost of care according to the NHS Operating Framework National Tariff (other prices are set locally)

[2] NHS Outcomes Framework sets out the national outcome goals that the Secretary of State uses to monitor the progress of NHS England and its indicators provide national level accountability for the outcomes the NHS delivers

[3] A database containing details of all admissions to NHS hospitals in England

around 6.6%; although, variation was observed between subgroups, with increases in the rates of some types of readmission being effectively balanced by reductions in others: readmissions following emergency admissions increased from 11.7% in 2006/7 to 12.7% in 2015/16 (Friebel, Hauck, Aylin, & Steventon, 2018).

1.1.1 Introduction of readmission as an outcome measure

Acheson and Barr (1965) originally proposed readmission rate as an appealing potential index of medical care quality based on outcome rather than process. Ease of measurement is a key appeal of readmission as an outcome measure (Benbassat & Taragin, 2013): the *NHS Outcomes Framework Indicator Quality Statement* for *emergency readmissions within 30 days of discharge from hospital* states that the indicator has no additional cost implications or burden to the health service due to making use of existing data (Health & Social Care Information Centre, 2014b). It was suggested in the Nuffield Trust's report *Trends in emergency admissions in England 2004-2009* that regulators should develop ways of assessing the quality of care across different providers, and consider using avoidable emergency admissions to indicate the adequacy of coordinated care (Blunt, Bardsley, & Dixon, 2010). The King's Fund report *Older people and emergency bed use: Exploring variation* (2012) identified that areas with well-developed, integrated services for older people had lower rates of hospital bed use, and that areas with low bed use also delivered good patient experience and had lower readmission rates (Imison, Poteliakhof, & Thompson, 2012). Readmission is considered undesirable in terms of:

- patient experience (Carter, Ward, Wexler, & Donelan, 2018; Friebel, Dharmarajan, Krumholz, & Steventon, 2017; Lawrie & Battye, 2012)
- quality of care (the extent to which care delivered meets expected standards)
- financial efficiency and/or consequences to the NHS (Department of Health, 2011)

Liberating the NHS encouraged improvement in outcomes by delivering safer, more effective care and providing a better experience for patients (Department of Health, 2010a),

and it is a target within the NHS is to reduce readmissions to the minimum possible (Health & Social Care Information Centre, 2013c). The Department of Health (DH) published a revision to the *National Health Service Operating Framework National Tariff* to cover reablement[4] and post-discharge support in June 2010, with hospitals apportioned responsibility for patients for 30 days after discharge (Department of Health, 2010b). From December 2010, emergency readmissions ceased to attract full reimbursement for hospital trusts from commissioning bodies when it was deemed that they had not provided sufficient quality of service or adequately prepared patients for discharge. The 30-day emergency readmission rule was incorporated into the NHS *Payment by Results (PbR) Guidance for 2011-12* (Department of Health, 2011), with reference to a decade of increasing readmission rates. The intention was to provide an incentive for hospitals to reduce avoidable readmissions by investing in better discharge planning, more collaborative working and better coordination with community and social care providers (Monitor, 2016). Reimbursement for emergency readmissions following non-elective admissions was subject to locally agreed thresholds which were set to deliver at least a 25% reduction compared to the previous year, although exceptions were made when clinical audit identified that the rate was already in line with best practice or only a lesser reduction was achievable. Payment was to be declined for emergency readmissions following elective admissions unless defined exclusion criteria, intended to prevent payment from being withheld in scenarios for which it was not considered fair or appropriate, were met (NHS Improvement, 2016). The excluded conditions were:

- conditions not under the national tariff (including adult mental health)
- maternity and childbirth
- cancer, chemotherapy and radiotherapy
- children under four years of age

[4] Reablement helps people with poor health accommodate their illness by learning or re-learning the skills necessary for daily living by the use of services such as community health services, social care, home adaptations, and extra-care housing

- multiple trauma, road traffic accidents
- patients who had self-discharged against clinical advice
- transfers from other providers
- cross border activity

In addition to the defined exclusions, commissioners were free to reimburse providers for readmissions that were clearly unrelated to the original admission (Department of Health, 2011).

It was estimated that the 30-day emergency readmission rule could cost NHS hospitals between £584 million and £790 million in lost income; £4 million per trust on average (NHS Confederation, 2011; Sg2, 2011). Trusts were encouraged to collect and analyse readmission data to understand the clinical conditions and practices, and patient characteristics driving readmissions in order to develop initiatives for improvement (Sg2, 2011). The DH acknowledged feedback from NHS colleagues in the *PbR Guidance for 2012/13* (Department of Health, 2012b) that the policy had been difficult to operate locally resulting in an unacceptable level of national variation in implementation. As a result, simpler rules were introduced. Differentiation between readmissions following elective and emergency admissions was no longer necessary unless it was required by the locally agreed thresholds for non-payment, and a proportional reduction was no longer prescribed. Thresholds were instead based on the clinical review of a sample of readmissions for avoidability. The exclusion criteria were altered so that patients receiving renal dialysis and following organ transplant replaced admission due to multiple trauma and road traffic accidents, and the rules remained the same according to the 2016/17 National Tariff (Monitor, 2016); this is the definition of readmission adopted in this thesis. Emergency readmission within 30 days of discharge first appeared in the *December 2013 NHS Outcomes Framework* as an indicator concerned with progress in helping people to recover as effectively as possible (Health & Social Care Information Centre, 2013a), and readmission rate has served as a benchmark by which providers and commissioners can

detect differences not only between services, but within the same service over time, ever since.

1.1.1.1 The Trust's goal

Recognising that readmission to hospital can be distressing for patients and add a significant cost to healthcare, as well as acknowledging that income would be reduced due to the introduction of the policy of non-payment (Calderdale and Huddersfield NHS Foundation Trust, 2013b), Calderdale and Huddersfield NHS Foundation Trust (the Trust) set a goal to reduce readmissions by a third every year for three years (Calderdale and Huddersfield NHS Foundation Trust, 2013a) and the pharmacy department commissioned the research reported in this thesis to explore the pharmacy team's potential contribution towards this goal.

1.2 Readmission outside of the UK

Various readmission reduction policies have been implemented in countries around the world, including Australia, Canada, Denmark, Germany, New Zealand and the United States of America (USA) (Goldfield, 2010; Kristensen, Bech, & Quentin, 2015). The USA (Centers for Medicare[5] and Medicaid[6] Services, CMS) and United Kingdom (UK) have in common that their policies for readmission reduction involve financial penalties for hospitals; conversely, Denmark's policy involves financial incentive. Although the UK introduced public reporting of readmissions around ten years before the USA, the financial aspect of the readmission reduction policies were introduced simultaneously in 2011 (UK) and 2012 (USA) (Kristensen et al., 2015). The CMS introduced the *Hospital Readmissions Reduction Program* to improve health care quality and population health, and reduce the costs of health care. In contrast to

[5] A USA state-based health insurance program for people aged 65 years of age or older, people under 65 years of age with certain disabilities or end-stage renal disease

[6] A USA state-based health coverage program for people on low incomes

UK policy, the USA limits applicable readmissions to those following admission for just seven conditions; four of which have been added over recent years:

- Acute myocardial infarction (AMI)
- Chronic obstructive pulmonary disease (COPD)
- Heart failure (HF)
- Pneumonia
- Total hip arthroplasty
- Total knee arthroplasty
- Coronary artery bypass graft surgery (U.S. Centers for Medicare and Medicaid Services, 2019)

In contrast to the UK system of clinical review to establish the proportion of avoidable readmissions and inform a local threshold for non-payment, avoidability is inferred by the nature of the applicable conditions under the USA system and hospitals with higher than average readmission rates are penalised by a proportional payment reduction.

1.3 Readmission rate calculation

Variability in readmission rate is influenced not only by fluctuation in the frequency of the event, but also by variation in its definition and by discrepancies in its calculation (Clarke, 2004). Readmission rates should represent the proportion of hospital discharges that are followed by an unplanned admission within the relevant interval, 30 days in NHS terms, among those at risk. Denominator inflation commonly occurs by the inclusion of patients who died during admission (e.g. by calculating readmissions based on admissions rather than discharges) or within the observation period (the duration of which also varies between studies); indeed the PbR methodology does not describe accounting for whether patients die within the observation period. However, their inclusion in the calculation results in underestimation of readmission rates. Furthermore, not accounting for associated mortality rates can mask any interaction between mortality and readmission rates as outcome measures (Fischer et al., 2014; Laudicella, Donni, & Smith, 2012); improvement in

readmission to the detriment of mortality does not represent success, and vice-versa. Similarly, it is necessary to account for patients transferred as inpatients elsewhere or discharged to intermediate care, as these do not represent genuine discharges; some studies have gone further by excluding those discharged to nursing homes and/or hospices/under palliative care on the basis that differences in patient characteristics and/or the processes of subsequent care could confound their risk of readmission (Silverstein, Qin, Mercer, Fong, & Haydar, 2008; van Walraven et al., 2010a). Numerator variability is also problematic, often occurring due to the inclusion of elective (planned) readmissions, readmissions following self-discharge (discharge against medical advice), failing to account for readmissions to different hospitals or trusts than the original (index) admission, and sometimes the exclusion of very early readmissions (i.e. categorising same-day readmissions as failed discharges). Patients who are readmitted by choice are distinct from those who are readmitted emergently and it should also be considered that not all deteriorations are related to the care provided during the first admission; furthermore, given the choice, patients who receive substandard care during their initial admission may attend a different hospital subsequently.

1.4 Preventing readmissions

Although preventing avoidable readmissions should represent a positive step towards improving patients' experience irrespective of financial consequence, gauging performance and basing payment on readmission rates has incentivised readmission reduction. Readmission is multifactorial and it is necessary to understand the influencing factors in order to address the problem. The reason for readmission must be causal and modifiable in order for it to be amenable to intervention. Some readmissions are necessary and unavoidable, and it would not be correct to expend resources in an effort to prevent readmissions that are appropriate. Furthermore, it was acknowledged in the *2017-19 National Tariff* that the best course of care for a patient may involve discharge from hospital despite the risk of readmission within 30 days, provided that appropriate information and

community care are provided (NHS Improvement, 2016). Goldfield (2010) highlighted four components in order to sustain a reduction in avoidable readmissions:

1. A tool to identify avoidable readmissions to hospital
2. A strategy to improve quality to decrease the number of readmissions
3. Payment incentives to encourage commitment to reducing readmissions
4. Public reporting any information relevant to hospital readmissions

Although the policy for non-payment for readmission and adoption of readmission rate as an outcome indicator incorporate payment incentives and benchmarking at a national level, identification of avoidable readmissions and the strategy for improvement require appropriate local management to ensure health systems utilise NHS resources rationally to help patients to recover as effectively as possible.

1.4.1 Identifying those at risk

Considering that hospital performance is gauged by, and payment based on, readmission rates, acceptable rates ought to be risk-adjusted according to known influential factors present in the populations that hospitals serve; it is known that some of the reported increases in readmission rates can explained by changes in admission rates and case-mix over time (Friebel et al., 2018; Morris, 2018; Zerdevas & Dobson, 2008), and that comparisons can be confounded by inadequate correction for case-mix and competing outcome measures such as mortality and length of stay (Fischer et al., 2014; Laudicella et al., 2012); indeed, what to risk-adjust for can be contentious. For example, if advancing age represents poor adherence to medication, then adjusting for age would correct for a potential deficit in support to maximise adherence (Benbassat & Taragin, 2000). Similarly, Friebel et al. (2018) questioned the appropriateness of the common practice to risk-adjust for socioeconomic status, given that it could reflect the quality of health care accessible to those living in more deprived areas. Additionally, to ensure cost effective utilisation of health service resources, providers need to be able to accurately determine patients' readmission risk so that effective intervention can be targeted to those who are the most

likely to benefit (Blunt et al., 2014; Curry et al., 2005; Haas et al., 2013). Predictive modelling was identified as the preferred technique for identifying patients at risk of readmission in a King's Fund report (Curry et al., 2005). Predictive models are considered appealing because they may be implemented quickly and at a low cost (Amarasingham et al., 2010), however, some have been described as impractical for clinical application (Billings et al., 2012; Bottle, Aylin, & Majeed, 2006) due to the inclusion of sociodemographic variables that are not as readily accessible to clinicians as they are to health care planners (van Walraven et al., 2010a; Zapatero et al., 2012); distinction must be made between readmission predictive models intended for health system-level application (i.e. setting a hospital/health system's anticipated/acceptable readmission rate for the purpose of gauging performance and informing payment) and those for clinical application (i.e. identifying individuals at risk of readmission in order to inform their course of care) (Kristensen et al., 2015; Lindquist & Baker, 2011). van Walraven et al. (2010a) proposed the *LACE* index as a simple model to predict readmission within 30 days in the clinical setting, comprising:

- Length of stay
- Acuity of admission
- Comorbidity
- Emergency department use in the preceding six months

However, the *LACE* index also predicts death within 30 days without discriminating between the two outcomes, and despite the intention for it to be optimised and validated for NHS use (Georghiou et al., 2011), it has been shown to perform poorly in a sample of elderly patients in the UK (Cotter, Bhalla, Wallis, & Biram, 2012). Accurate prediction relies on the correct analysis of reliable, readily available data, generalised to the correct population. van Walraven, Wong, Forster, and Hawken (2013) demonstrated that even seemingly minor differences between samples can be problematic, reporting deterioration in performance of

a predictive risk model on altering the unit of analysis from per patient to per admission. Predictive models must have sufficient sensitivity[7] and specificity[8] to maximise the cost-effectiveness of intervention (Curry et al., 2005). Although risk stratification and knowledge of markers of readmission are useful in identifying patients who are at risk, preventing readmissions requires careful interpretation of the risk identified. Modification of causal factors can prevent readmission; however, effective action in circumstances where markers of readmission are identified is less clear. The ideal strategy for improvement is more complicated than simply targeting those with the highest risk; not only is there evidence that readmissions for patients with moderate risk are equally expensive as readmissions for patients at high risk (Billings et al., 2012), it is also possible that such readmissions are more likely to be preventable (Lindquist & Baker, 2011). What is certain is that prevention needs to cost no more than readmission if a reduction is to be funded under the policy for non-payment without additional investment.

1.4.2 Avoidability

Although not all readmissions are the result of poor care, and not all poor care results in readmission, poor quality care can result in readmission. Individual case review can glean details invaluable to understanding the root cause and avoidability (or preventability) of readmissions. This is important to enable improvement, but too laborious for routine application in clinical practice; yet, automated methods which perform comparably are yet to be seen (Ashton, Del Junco, Souchek, Wray, & Mansyur, 1997; Lindquist & Baker, 2011). Broad categorisations based on patterns in administrative data have been undertaken (Blunt et al., 2014; Halfon et al., 2006), however, the assumption that readmissions involve the same body system as the initial admission is unlikely to be robust (Ashton & Wray, 1996; Blunt et al., 2014; Donzé, Lipsitz, Bates, & Schnipper, 2013b; NHS Confederation, 2011;

[7] Ability to identify those who would experience the outcome of interest

[8] Ability to identify those who would not experience the outcome of interest

Zerdevas & Dobson, 2008); yet, there is evidence that readmissions for the same principal diagnosis as the index admission are more likely to be avoidable (Yam et al., 2010). It has been proven that studies which rely on administrative data deem a greater proportion of readmissions avoidable than studies that consider other sources e.g. clinical records and/or surveys/interviews with patients or clinicians (van Walraven, Bennett, Jennings, Austin, & Forster, 2011a). The proportion of readmissions deemed avoidable varies more than ten-fold, from around 5% to 60% (van Walraven, Jennings, & Forster, 2012a). The *PbR Guidance for 2012-13* contained a summary of a pilot audit of readmission avoidability which reported the average proportion of readmissions deemed avoidable was 25% (Department of Health, 2012b): this seems to represent a reasonable estimate given its recurrence in the literature (van Walraven et al., 2012a). Blunt et al. (2014) identified just five per cent of readmissions were caused by a recognised complication of the original admission, and another quarter were categorised as related to possible suboptimal care; case review was recommended for all such readmissions, and predictive modelling was recommended to target intervention for readmissions representing anticipated but unpredictable hospital care, and those broadly related to the index admission. van Walraven et al. (2011b) identified that around one-third of readmissions within six months were related to medicines, and that around 20% of readmissions within one month were potentially avoidable; unfortunately the proportion of potentially avoidable readmissions within one month was not presented. However, an audit of 30-day readmissions following admission to a UK medical admissions unit identified one in five as related to medication; of these, half were deemed avoidable and another third potentially so (Barry, 2013). Similarly, Witherington, Pirzada, and Avery (2008) reported that over half of medication-related readmissions among elderly patients were avoidable, indicating that avoidability could be relatively high among medicines-related readmissions.

1.4.3 Time to readmission

It is important to consider timing for any intervention intended to prevent readmissions, because intervention must be provided prior to readmission in order to be effective. Emergency readmissions most commonly follow emergency admissions, and the majority of emergency admissions are medical (Zerdevas & Dobson, 2008). Readmissions most commonly occur one day after discharge, and diminish thereafter (Morris, 2018). Witherington et al. (2008) reported that over a quarter of 28-day readmissions among elderly medical patients were within three days of discharge, and in line with national trends for readmission in general, around half occurred within a week (Friebel et al., 2018; Zerdevas & Dobson, 2008). There is a negative correlation between time to readmission and avoidability (Yam et al., 2010); readmissions occurring within the first week have been identified as more likely to be related to the index admission and avoidable (Clarke, 1990; Dobrzanska & Newell, 2006; Heggestad & Lilleeng, 2003; Sg2, 2011). Williams and Fitton (1988) reported the time to readmission due to medication-related problems among elderly patients ranged from one to 23 days, with a median of eight days, indicating that many readmissions for which problems with medication were the primary cause were probably avoidable. Friebel et al. (2018) identified a slight increase in readmissions occurring within a week of discharge, indicating that perhaps a greater proportion of readmissions have been avoidable in recent years. Consequently it is important that intervention to prevent readmission is provided early, and ideally initiated prior to discharge (Amarasingham et al., 2010;Silverstein et al., 2008(Bisharat, Handler, & Schwartz, 2012; Kansagara et al., 2011).

1.4.4 The role of the pharmacy team

Medication is the most common intervention in health care (Health & Social Care Information Centre). The number of prescription items dispensed by community pharmacies in England per person per year increased from 12 to 19 between 2002 and 2012 (Health & Social Care Information Centre, 2013b). The risk of people suffering harm from their medicines increases with polypharmacy (the use of multiple medicines); furthermore,

between one- and two-thirds of patients have an error or unintentional change to their medication regimen when moving from one care setting to another (care transition) (National Institute for Health and Care Excellence, 2015), and such discrepancies could result in readmission (Coleman, Smith, Raha, & Min, 2005). The Royal Pharmaceutical Society (RPS) stated in their report *Keeping patients safe when they transfer between care providers – getting the medicines right* that "Improving the transfer of information about medicines across all care settings should reduce incidents of avoidable harm to patients, and contribute to a reduction in avoidable medicines related admissions and readmissions to hospital" (Royal Pharmaceutical Society, 2012). The discharge prescription is a vital component of communication at the interface between secondary and primary care; primary care relies upon the discharge prescription to ensure continuity of care and inform ongoing prescribing after discharge. The appropriateness, accuracy, completeness and timeliness of the discharge prescription are important factors which have been identified as often lacking in achieving successful care transitions (Care Quality Commission, 2009). Witherington et al. (2008) reported that medication-related problems were the primary cause for one in five readmissions among elderly patients; over two-thirds of readmissions were medication-related, and the majority were considered avoidable. Effective systems and processes can minimise the risk of preventable medicines-related problems such as adverse effects and interactions with other medicines or conditions (National Institute for Health and Care Excellence, 2015). The General Medical Council guidance for prescribing and managing medicines urges doctors to work with pharmacists to review medication and ensure patients are provided sufficient information (General Medical Council, 2013). Difficulty adhering to discharge medication was among the top three contributing issues reported by patients following readmission in the USA (Kangovi et al., 2012). It has been demonstrated that the inclusion of clinical pharmacists in inpatient teams can improve patient outcomes and reduce costs (Gillespie et al., 2009); yet, despite the efficacy of pharmaceutical intervention for outcome measures intermediary to admission and readmission, evidence that pharmaceutical intervention directly reduces readmissions is lacking. It is stated in the RPS'

Professional Standards for Hospital Pharmacy Services that quality pharmacy services strive to optimise patient outcomes through the safe, judicious clinically effective, appropriate and cost effective use of medicines (Royal Pharmaceutical Society, 2014). In addition to hospital pharmacy's traditional supply function, clinical pharmacy services typically involve: medication review, medicines reconciliation, provision of medicines information and professional recommendations for patients and clinicians, and support of safe and effective medicines management including medication adherence. A portion of readmissions will be preventable by the actions of the discharging hospital, with some factors influencing readmission modifiable with the support of the pharmacy team. Knowledge about readmission risk factors and effective intervention should enable the necessary focus for the pharmacy team's efforts towards preventing readmissions. It is conceivable that pharmacists could contribute to minimising avoidable medicines-related readmissions through their routine application of the RPS' four principles of medicines optimisation:

1. Aim to understand the patient's experience
2. Evidence based choice of medicines
3. Ensure medicines use is as safe as possible
4. Make medicines optimisation part of routine practice

Indeed, the *Medicines Optimisation Guidance* specified that the third principle is intended to reduce medicines-related admissions and readmissions to hospitals (Royal Pharmaceutical Society, 2013b).

1.5 Conclusion

Reducing readmissions is an international priority. Predictive modelling is advocated for identifying those at risk of readmission to enable preventative intervention to be efficiently targeted to those most likely to benefit. A portion of avoidable readmissions are medicines-related, and their causes can be mitigated by the actions of the pharmacy team (pharmaceutical intervention).

1.5.1 Research questions, aims and objectives

The research questions, and the study aims and objectives to address them, were:

Question 1: Can the likelihood of readmission within 30 days be determined using prescription information?

Rationale 1: To enable the pharmacy team to identify patients at risk of readmission in the course of their routine duties

Aim 1: To identify whether readmission risk can be reliably determined using routinely recorded prescription data

Objective 1. To identify prescription variables that may be associated with readmission (candidate predictor variables)

Objective 2. To quantify the influence of each of the candidate predictor variables on the risk of readmission

Objective 3. To quantify the adjusted influence, or collective contribution, of candidate predictor variables to the risk of readmission

Objective 4. To develop and validate a predictive model for readmission using prescription information

Question 2: How do predictors of readmission from prescriptions influence the time to readmission?

Rationale 2: To inform the timing of potential intervention to prevent readmissions

Aim 2: To explore the influence of predictors of readmission from prescriptions on the time to readmission

Objective 5. To characterise readmission behaviour depending on predictors of readmission from prescriptions

Objective 6. To quantify the influence of predictors of readmission from prescriptions on the time to readmission

Question 3:	What are the implications of the findings for practice?
Rationale 3:	To inform development and implementation of evidence-based improvements in pharmacy practice
Aim 3:	To consider implications for practice, including how resources to prevent readmissions, particularly pharmaceutical intervention, could be targeted
Objective 7.	To review the study results in the context of the relevant literature and policy
Objective 8.	To provide recommendations for practice and future research

Chapter 2 Literature Review

2.1 Introduction

Having introduced the research topic in Chapter 1, a summary of the relevant literature is presented in this chapter. The literature was reviewed to assess the potential to predict readmission within 30 days of discharge using routinely recorded prescription information.

2.2 Method

2.2.1 Inclusion Criteria

Publications were included in the literature review according to the following criteria:

1. Presentation of original data

2.1. about likelihood of readmission within 30 days and/or

2.2. about the influence of pharmaceutical intervention on readmission within 30 days

3. among adult medical patients.

2.2.2 Search Strategy

The search terms defined in Figure 2.1 were used to search the databases as described in Figure 2.2.

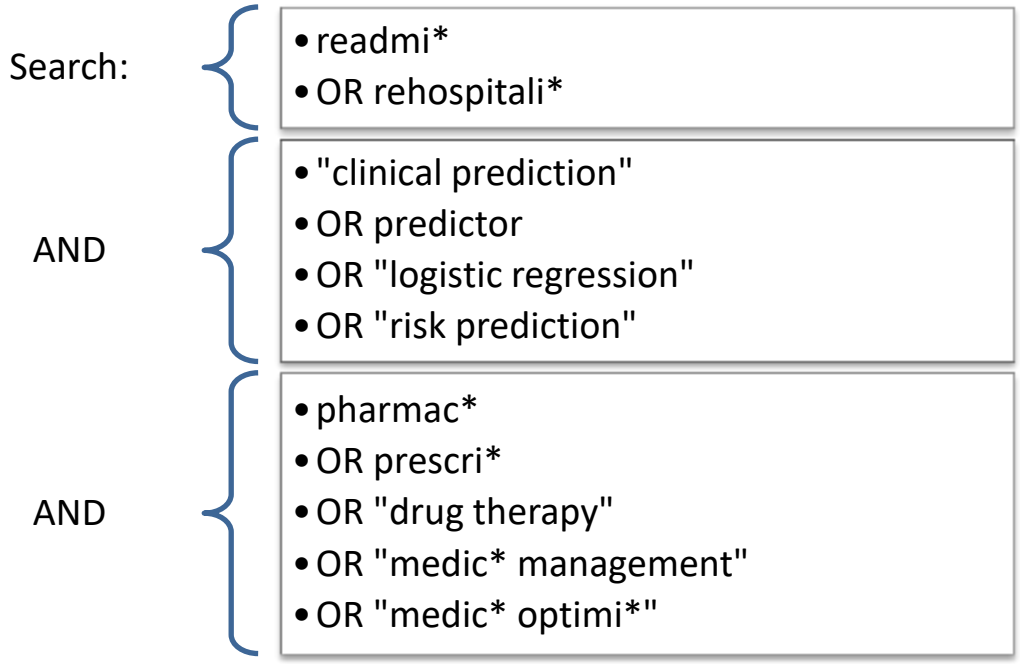

Figure 2.1: Search terms for the literature review

2.2.3 Selection Process

Citations identified by the searches were manually screened for the following in order to identify publications potentially suitable for inclusion in the literature review:

1. duplication and
2. concordance with the inclusion criteria.

Two hundred twenty-eight potentially suitable studies were identified. Of these, 135 were subsequently excluded following review of the abstract and 42 were excluded following further review of the full text; the selection process is described in Figure 2.3. Studies were most often excluded on the basis that they concerned populations other than general medical patients (for example surgical or psychiatric patients), or did not measure 30-day readmission (for example, rehospitalisation over a longer observation period, or admission within 30 days of emergency department attendance). Some were excluded because they reported a composite outcome (for example readmission or death within 30 days); few were disregarded because they did not present relevant original data.

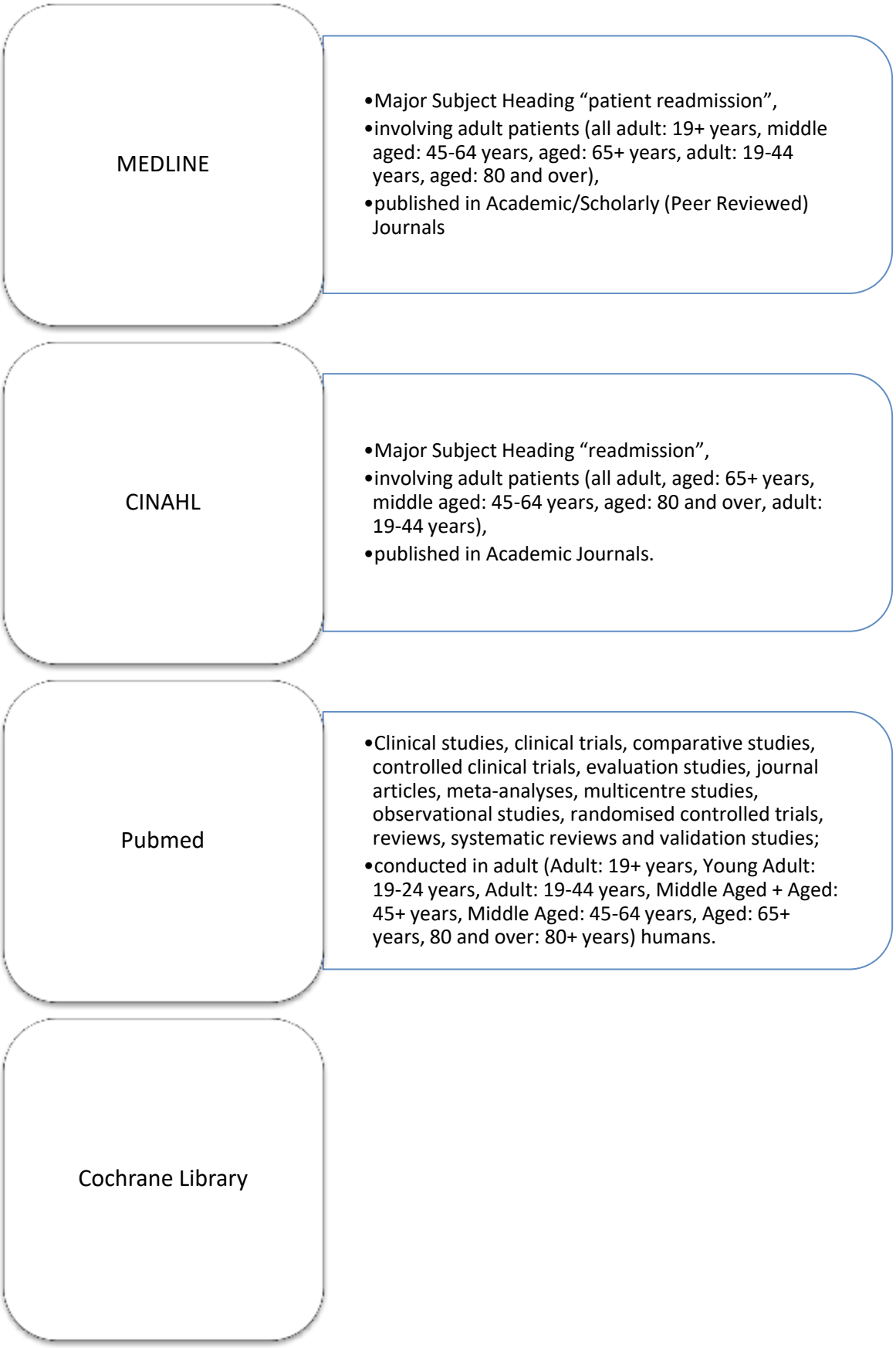

Figure 2.2: Databases searched and filters applied for the literature review

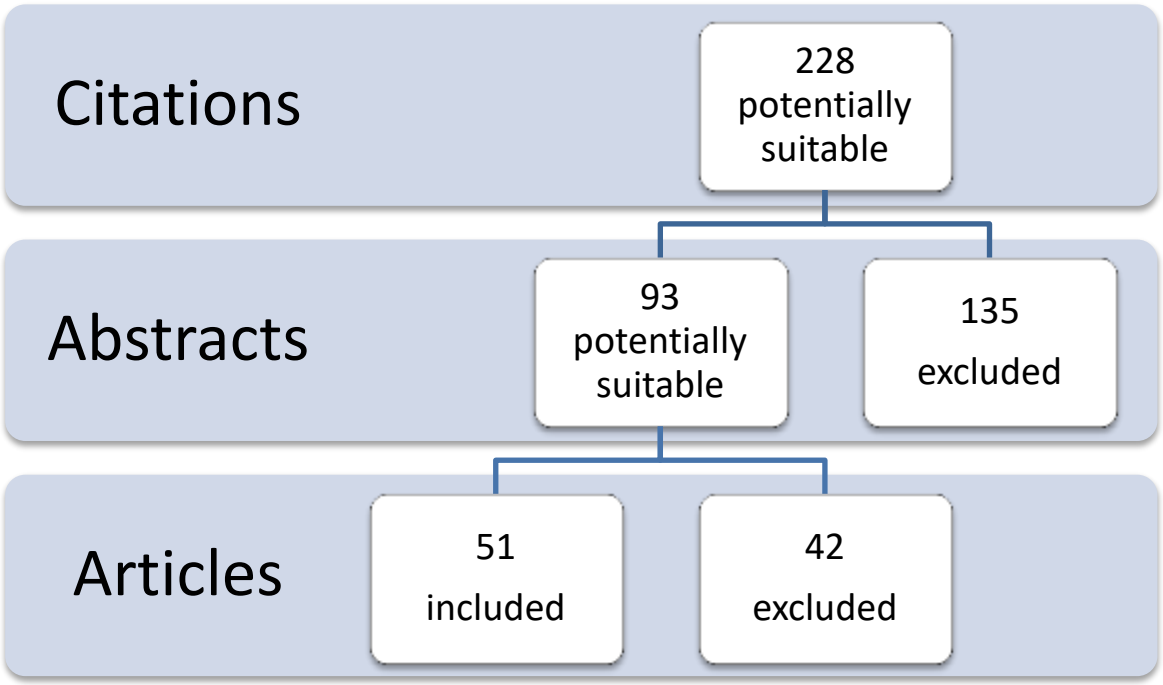

Figure 2.3: Literature review publication selection process

2.3 Results

The key characteristics of the studies included in the literature review are summarised in Table 2.1.

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Arnold, Crouch, Carroll, and Oinonen (2006)	Retrospective cohort study	32 academic hospitals in the United States (USA)	2,130 patients with acute decompensated heart failure (HF)	30-day readmission	Treatment adjusted for potentially confounding variables	Not significant (NS)	Not applicable (NA)	Not applicable
Au, Chan, Chan, and Pang (2002)	Retrospective case-control study	A regional hospital in Singapore	150 cases and 103 controls; elderly* patients	15-day readmission to the geriatric unit	Demographic, medical and social	Number of medical problems and prior admissions	Not presented (NP)	Type 1a

[9] Equivalent to the area under the receiver operating characteristic curve, see also 2.3.6.2 Discrimination. Where c-statistics for both derivation and validation were reported, the validation figure is presented; such optimism-corrected c-statistics are annotated *

[10] See also Table 2.4: Prediction model study types defined by Moons et al. (2015)

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Barbagelata et al. (2000)	Retrospective cohort study	Sub-study of a multinational study	1830 patients who had thrombolytic therapy after acute myocardial infarction (AMI) and had evaluable electrocardiograms (ECGs)	30-day readmission	Q waves	Not significant	Not applicable	Not applicable
Bisharat et al. (2012)	Retrospective case-control study	A medical centre in Israel	292 cases and 290 controls matched for age, sex and primary diagnosis; adult medical patients	30-day emergency readmission to and from general medical, intensive medical and intensive cardiac care	Clinical, epidemiological and socioeconomic variables	Nursing home residence, chronic kidney disease (CKD), length of stay (LOS) of three days or more, hospitalisation in the previous year	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Bollu et al. (2013)	Retrospective case-control study	Hospitals in the USA	812 cases and 1,651 controls; adults aged 40 years and over with chronic obstructive pulmonary disease (COPD)	30-day all-cause readmission to the same hospital	Treatment adjusted for demographics, admission characteristics, diagnoses and severity of illness	Treatment; severity of illness. Gender, age, race, hospital characteristics, diagnoses, admission type, treatment, LOS (all NS)	Not presented	Not applicable
Bottle, Middleton, Kalkman, Livingston, and Aylin (2013)	Retrospective cohort study	30 hospitals across the USA and Europe	6522589 inpatient records	Unplanned readmission to the same hospital within 30 days	Primary diagnosis/procedure; admission characteristics, demographics, comorbidity	Not presented	Not presented	Not applicable
Boulding, Glickman, Manary, Schulman, and Staelin (2011)	Retrospective cohort study	USA hospitals	3746 hospitals	30-day risk standardised readmission rate	Patient satisfaction; hospital clinical performance	Patient satisfaction adjusted for hospital clinical performance	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Bradley, Yakusheva, Horwitz, Sipsma, and Fletcher (2013)	Retrospective cohort study	A major teaching hospital in the USA	5,511 medical and surgical patients. Numerous exclusions including admission <48 hours	30-day unplanned readmission to the same hospital	Patient condition prior to and on discharge adjusted for demographics, insurance status, service assignment and primary discharge diagnosis	Patient condition on day of discharge. Age, gender, insurance status and service assignment (all NS)	0.73*, NP	Type 2a
Charneski, Deshpande, and Smith (2011)	Retrospective cohort study	An urban academic teaching hospital in the USA	11,872 adults (over 20 years of age) admitted to a non-surgical ward and prescribed antibiotic(s)	28-day readmission	Allergy label adjusted for demographic and treatment/services variables	Not significant	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Chu and Pei (1999)	Case-control study	An acute university general hospital in Hong Kong	380 cases and 380 controls matched for age and gender; elderly* patients	28-day emergency readmission	Demographic, socioeconomic, principle and comorbid diseases, and general health status variables	Impairments to activities of daily living (ADLs), income, adverse drug reaction , advanced malignancy, congestive heart failure (CHF), COPD, end-stage renal failure, dysphagia and number of comorbid diseases, living in private old aged home	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
de Bruijne et al. (2013)	Retrospective cohort study	Hospitals across the Netherlands	283,379 hospitalised patients, excluding those in specialised hospitals, obstetrics and Western migrants	Unplanned readmission of at least 24 hours within 30 days of index admission	Demographics, diagnoses, comorbidity, principle intervention, , socioeconomic status	Ethnicity and age	Not presented	Not applicable
Dedhia et al. (2009)	Prospective pre/post study	General medicine wards of three hospitals in the USA	237 elderly* patients admitted to the hospitalist services; 135 during the intervention period	30-day unplanned all-cause readmission rate	Intervention; site	Intervention, adjusted for site	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Eapen et al. (2013)	Retrospective cohort study	USA hospitals providing Get with the Guidelines HF program	30,828 elderly* patients hospitalised for HF	30-day unplanned all-cause readmission	Those available in the electronic health record (EHR)	Laboratory and observation results, age, race	0.59*, NP	Type 2a
Fisher et al. (2013)	Prospective cohort study	Acute Care for Elders Unit of a USA university teaching hospital	111 ambulatory elderly* patients hospitalised with acute medical illness	30-day all-cause, unplanned readmission	Mobility in the week following discharge adjusted for demographics, marital status, comorbidity, LOS, prior mobility/ADLs and severity of illness	Not significant	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Flink, Mochari-Greenberger, and Mosca (2013)	Prospective cohort study	Cardiovascular service of an academic medical centre in the USA	902 patients with diabetes, hospitalised for cardiovascular disease, who participated in a study of caregiving and had glycated haemoglobin (HbA1C) recorded in the previous 12 months; excluding nursing home residents	30-day all-cause readmission	Demographic, comorbidity, admission type and evidence-based prescribing	Glycated haemoglobin (HbA1c), particularly among women; adjusted for demographics, comorbidity, prescribed medication	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Gentry, Greenfield, Slater, Wack, and Huycke (2000)	Retrospective pre/post study	A Veteran Affairs Medical Centre in the USA	7,219 admissions involving infection; 3,570 during interventio n period	30-day readmission for infection rate	Intervention	Not significant	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Gildersleeve and Cooper (2013)	Retrospective cohort study	A semi-rural community hospital in the USA	16,889 adult patients (18 years of age and over), excluding psychiatric and rehab admissions, and discharge against medical advice	30-day readmission to the same hospital	Demographic and clinical	Age, gender, marital status, admission acuity, prior emergency department (ED) visits, over three hospitalisations in the previous year, LOS, insurance status, whether prescribed medication, over six ambulatory medicines (protective), CCI[11]	0.70*, 0.69 to 0.71	Type 2b

[11] The Charlson Comorbidity Index (CCI) predicts one-year mortality based on comorbid conditions (Charlson et al., 1987)

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Godar et al. (2011)	Retrospective cohort study	A USA hospital	969 adult patients (over 17 years of age) admitted with community acquired pneumonia (CAP)	30-day readmission	Demographic and clinical variables relevant for CAP including comorbidity and treatment; each assessed individually.	Age	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Haas et al. (2013)	Retrospective cohort study	A community-focused primary care arm of a large integrated multispecialty group practice	83,187 adult patients (18 years of age and over)	30-day readmission	Adjusted Clinical Groups (ACGs), Hierarchical Condition Categories, Elder Risk Assessment (ERA), Chronic Comorbidity Count, CCI, Minnesota Health Care Home Tiering, and a hybrid of Minnesota Tiering with ERA score	ACG (age, gender, diagnoses)	0.81*, 0.80 to 0.83	Type 4

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Harjai et al. (2001)	Retrospective cohort study	A USA hospital	576 adult patients (21 years of age and over) discharged following admission for HF	30-day HF readmission	Treatment choice; coronary artery disease (CAD), low ejection fraction; demographic	Angiotensin-converting enzyme inhibitor (ACEi) with aspirin (compared to ACEi without aspirin); adjusted for age, gender and race	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Hwang, Li, Gupta, Chien, and Martin (2003)	Prospective case-control study	The general medical service of an urban teaching hospital in Canada	97 cases discharge against medical advice and 97 controls discharged formally, matched for age, gender and primary reason for hospital stay; adult patients (20 years of age and over)	15-day readmission	Demographic, case mix group, LOS, homelessness, general health	Discharge against medical advice	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Jasti, Mortensen, Obrosky, Kapoor, and Fine (2008)	Prospective cohort study; sub-study of another randomised controlled trial	Seven USA hospitals	577 adult patients discharged following admission for CAP; many exclusions applied including index hospitalisations of less than one day or a readmission within 10 days of prior acute hospitalisation	30-day readmission	Sociodemographic and clinical	Education level, employment status, CAD, COPD. Age, CHF, ventricular dysrhythmia, atrial dysrhythmia, asthma, long-term oxygen use, interstitial lung disease, diabetes, pneumonia severity index (all NS)	Not presented	Not applicable
Jenghua and Jedsadayanmata (2011)	Retrospective cohort study	A tertiary care hospital in Thailand	718 patients hospitalised for CHF	30-day all-cause readmission	Not specified	LOS greater than five days	Not presented	Type 1a

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Jiang, Andrews, Stryer, and Friedman (2005)	Retrospective cohort study	Community hospitals across five USA states	130,751 nonmaternal, adult patients (18 years of age and over) admitted for diabetes-related conditions	30-day diabetes-related readmission	Payer status/age and race/ethnicity, adjusted for demographic, socioeconomic, clinical and hospital characteristics, and county health care resources	Race among Medicare (older) patients; demographic, socioeconomic, clinical and hospital characteristics, and county health care resources	Not presented	Not applicable
Johnson et al. (2012)	Retrospective cohort study	A general medicine unit of a USA hospital	4,151 patients	30-day readmission	Additional day's LOS adjusted for demographic characteristics and severity of illness	Not significant	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Jurado Gamez et al. (2013)	Prospective controlled parallel-group study	The pulmonary unit of a tertiary hospital in Spain	35 intervention and 36 control patients under 75 years of age, assigned according to distance from hospital	28-day readmission for COPD exacerbation	Intervention; age, general health, disease severity	Age, partial pressure of oxygen	0.97, NP	Not applicable
Keenan et al. (2008)	Retrospective cohort study	4,669 USA hospitals	1,129,210 Medicare patients* hospitalised with HF	Hospital-level 30-day readmission rate	Claims-based model or medical record-based model	Age, gender, nine cardiovascular and 26 comorbidity variables	0.6*, NP	Not applicable
Lee (2012)	Retrospective cohort study	A teaching hospital in Seoul	11951 patients	28-day readmission	Demographic; treatment, general health and socioeconomic variables	LOS, route of admission, principal diagnosis, department, frequency of outpatient visits (decision tree)	Not presented	Type 2a

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Mather, Fortunato, Ash, Davis, and Kumar (2014)	Retrospective cohort study	A USA teaching hospital	996 elderly* patients admitted for pneumonia	30-day all-cause readmission	The 35 from final Centers for Medicare and Medicaid Services (CMS) medical record Hierarchical Condition Category clinical classification system selection algorithm; marital status, anxiety/depression, prior hospitalisations, and socioeconomic status	Gender, previous admissions, chronic lung disease, cancer, median income, history of anxiety/depression, haemocrit level; age, LOS, nursing home resident, history of HF, renal disease, immunosuppressive therapy, creatinine level, major psychiatric disorders and marital status (all NS)	0.67*, NP	Type 1b

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Mosher et al. (2014)	Retrospective cohort study	129 Veterans Administration hospitals in the USA	122,794 veterans with acute medical admission	30-day readmission	Opioid use adjusted for demographic and clinical variables	Opioid use; admission diagnosis, age, gender, race, income, rural residence, region, CCI, non-metastatic cancer, metastatic cancer, chronic pain, COPD, complicated diabetes, HF, renal disease, dementia, mental health diagnosis other than post-traumatic stress disorder (PTSD), and PTSD	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Nantsupawat, Limsuwat, and Nugent (2012)	Retrospective cohort study	A university medical centre in the USA	103 hospitalisations involving 81 COPD patients	30-day readmission	Demographics, ECG, disease severity; medicines prescribed; test results, health status, inpatient treatment, post-discharge intervention, discharge disposition	CAD and unilateral pulmonary infiltrates; ejection fraction (EF) and follow up call (both NS)	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Nolan and Thomas (2008)	Prospective cohort study	An acute metropolitan hospital in the USA	196 elderly patients (aged 70 years or over) admitted to general medical, aged, or respiratory care, deemed to have intermediate or high risk of functional decline, and able to commence exercise within 48 hours of admission	28-day readmission	Intervention; demographics, clinical complexity	Not significant	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Parker, McCombs, and Graddy (2003)	Retrospective cohort study	A consortium of USA hospitals	6,542 patients admitted acutely excluding maternal, psychiatric, day surgery, and discharge against medical advice	30-day unplanned readmission	Demographics, admission type, diagnosis reference group, comorbidity and pharmacy practice variables	28 comorbidity variables drawn from pharmacy data	0.691, NP	Type 1a
Perimal-Lewis et al. (2013)	Retrospective cohort study	A medical centre in Australia	19,923 general medical patients	28-day readmission	Outlier status adjusted for demographics, comorbidity and duration awaiting a bed in the ED	Outlier status; age, comorbidity, gender, duration awaiting a bed in the ED	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Perkins et al. (2013)	Retrospective cohort study	Hospitals of a health system across one USA state	607 patients admitted for HF with stage 3 to 5 CKD	30-day readmission	Demographic, clinical, laboratory and pharmaceutical EHR variables	23 variables across domains of medical history, active outpatient pharmaceuticals, vital signs, laboratory tests, and recent inpatient and outpatient resource utilisation	0.743*, NP	Type 1b
Pines et al. (2010)	Retrospective cohort study	Two inner city USA hospitals in the same system	1,470 elderly* patients admitted via the ED and discharged within one day	30-day readmission to the same hospitals via the ED	Demographic, general health status and diagnosis	Previous admissions and admission diagnosis of HF. Age, gender, race, four diagnosis codes and six comorbidities (all NS)	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Pouw et al. (2000)	Retrospective case-control study	The Netherlands	14 cases and 14 controls matched for age, gender, month of admission and lung function; admitted with exacerbation of COPD	14-day non-elective readmission	Disease severity and general health status variables	Weight loss during hospitalisation and low Body Mass Index on admission	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Press et al. (2011)	Multiple time series analysis	3,321 USA acute-care non-federal hospitals	3,445,040 Medicare beneficiaries admitted with AMI, CHF, gastro-intestinal bleed or stroke	Change in odds of 30-day all cause readmission in more compared to less teaching-intensive hospitals before and after duty hour reform	Duty hour reform stratified by teaching status and adjusted for patient comorbidities, secular trends affecting all patients (e.g. due to general changes in technology), and hospital-specific fixed effects	Not significant	Not applicable	Not applicable
Reyes Calzada et al. (2007)	Prospective cohort study	Four public hospitals in Spain	425 adult (18 years of age and over) patients admitted with CAP	30-day readmission	Disease severity, treatment	Beta-lactam monotherapy	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Ronksley et al. (2013)	Prospective cohort study	Canada	21,166 adult (18 years of age or older) patients who self-reported having chronic disease and were subsequently admitted to hospital	30-day all-cause readmission	Perceived unmet healthcare need(s) adjusted for demographics, general health, socioeconomic, and domestic variables and survey cycle (time)	Not significant	Not applicable	Not applicable
Rosen et al. (2013)	Retrospective cohort study	Veterans Health Administration, USA	1,807,488 discharges of veterans from acute care	30-day all-cause readmission	Agency for Healthcare Research and Quality Patient Safety Indicator event(s) (PSIEs); adjusted for demographics and comorbidities	PSIEs adjusted for age, gender and comorbidities	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Rothman, Rothman, and Beals (2013)	Retrospective cohort study	3 hospitals across the USA	17,1250 adult (18 years of age or over) medical-surgical and critical care patients discharged home/home healthcare	30-day readmission	Patient condition based on 26 clinical measurements from nursing assessments, vital signs, laboratory results and cardiac rhythms, specifically excluding variables describing 'who' the patient was in order to focus on 'how' they were	Patient condition	0.62*, 0.61 to 0.63	Type 3

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Sakr, Hahn, Donohue, and Ghantous (2008)	Randomised controlled trial	A USA hospital	34 patients presenting to ED with HF and remaining symptomatic despite maximal therapy for at least one hour	30-day HF readmission	Treatment	Treatment	Not presented	Not applicable
Sales et al. (2013)	Randomised controlled trial	One hospital in the USA	70 cases and 67 controls; patients hospitalised for CHF	30-day HF readmission	Intervention; demographics, clinical and general health variables and discharge disposition	Intervention, hypertension; age, gender, comorbidities, medication, New York Heart Association (NYHA) functional class and discharge disposition	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Singal et al. (2013)	Retrospective cohort study	A large safety-net hospital in the USA	836 patients with cirrhosis admitted to hospital	30-day readmission	Medical and socioeconomic variables available within 48 hours of admission	Number of address changes in the prior year, admissions in the year prior, payer status, severity of liver disease, platelet, alanine aminotransferase, haemocrit and sodium levels	0.66*, 0.59 to 0.73	Type 2a
Stevens et al. (2014)	Retrospective cohort study	A tertiary care academic medical centre in the USA	398 patients who had a new central line inserted in hospital	30-day all-cause readmission to the same hospital	Central-line-associated bloodstream infection; demographic, administrative and clinical variables	Not significant	Not applicable	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Tan, Low, Yang, and Lee (2013)	Retrospective cohort study	Wards of the medical department in a tertiary-hospital in Singapore	127,550 adult patients (21 years of age and over)	30-day unplanned readmission	LACE Index[12] of 10 or more, adjusted for demographic and clinical variables	LACE Index of 10 or more	0.70, NP	Type 1a
Thakar, Parikh, and Liu (2012)	Retrospective cohort study	Hospitals across one USA state	6535 adult patients (between 21 and 100 years of age) discharged with primary diagnosis of HF	30-day HF readmission	Acute kidney injury (AKI), CKD; demographic, socioeconomic, treatment, and general health status variables	AKI without CKD, CKD without AKI; age, gender, number of chronic conditions, primary payer, diabetes, valvular heart disease, drug abuse, and psychoses	Not presented	Not applicable

[12] (van Walraven et al., 2010a)

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Torres et al. (2004)	Prospective cohort study	An urban teaching hospital in Spain	93 elderly* patients diagnosed with CAP	30-day readmission	Age, clinical and general health variables, Hospital Admission Risk Profile	Not significant	Not applicable	Not applicable
Weiss et al. (2007)	Prospective cohort study	An urban tertiary medical centre in the USA	113 medical, cardiac or surgical patients discharged home from hospital	15-day readmission	Patient, hospitalisation and socioeconomic characteristics; readiness for discharge, quality of discharge teaching, care coordination, and post-discharge coping difficulty scales	Readiness for discharge	Not presented	Not applicable

Table 2.1: Key characteristics of studies included in the literature review								
Study	**Design**	**Setting**	**Sample**	**Outcome**	**Covariates**	**Final model**	**Performance (c-statistic[9], CI)**	**Analysis type[10]**
Win et al. (2012)	Randomised controlled trial	Multiple USA hospitals	423 black adult (18 years of age or over) patients hospitalised with NYHA class III or IV HF	30-day readmission	Treatment adjusted for baseline differences in clinical characteristics and medication	Treatment adjusted for comorbidities, medication, left ventricular EF and demographic variables	Not presented	Not applicable
* 65 years of age and over								

2.3.1 Purpose

In their systematic review of validated readmission risk prediction models, Kansagara et al. (2011) highlighted that predicting readmission was of great interest not only to identify which patients could benefit most from care transition interventions, but also to risk-adjust rates for the purposes of hospital comparison. Studies included in this literature review were categorised as having been undertaken for the purpose of:

1. Evaluating the care provided in relation to readmission (20)
    - See Figure 2.4
2. Exploring associations between readmission and patient characteristics (16)
3. Predicting individuals' risk of readmission (13)
    - Including those involving model derivation and those involving application or further development of existing models (described in Figure 2.5 and Figure 2.6 respectively)
4. Risk-standardising readmission rates; in other words, determining the expected or acceptable readmission rate for an organisation accounting for case-mix (2)
    - Keenan et al. (2008) developed two models for risk-standardisation of readmission rates for the purpose of public reporting
    - Bottle et al. (2013) produced comparable, risk-adjusted readmission rates for an international sample of hospitals to facilitate collaboration and shared learning

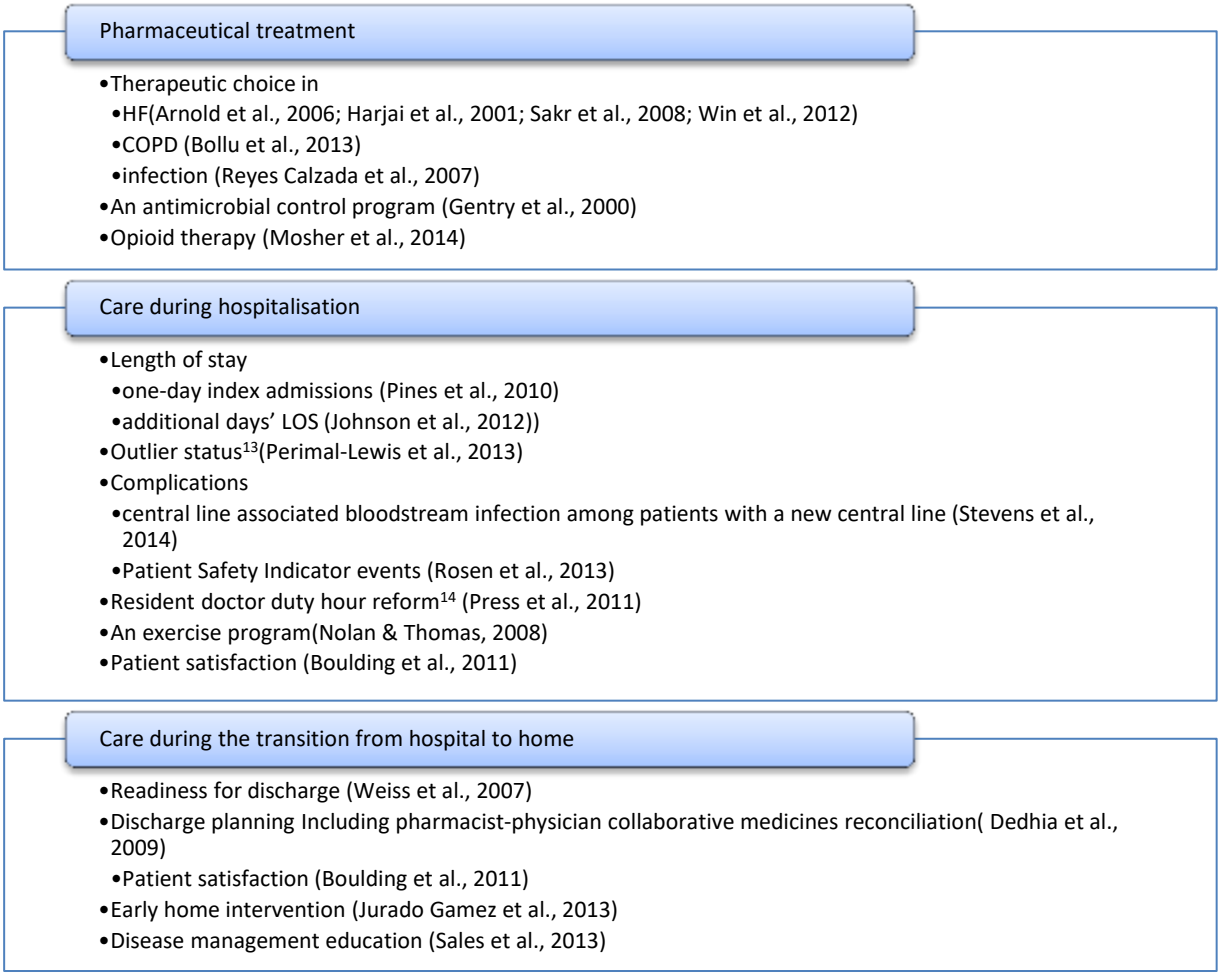

Figure 2.4: Studies included in the literature review that were undertaken for the purpose of evaluating care

Studies exploring associations between readmission and patient characteristics could be grouped into three categories. Those characterising readmission risk according to:

[13] Spending the majority of hospital stay on a ward outside the unit with clinical responsibility for care

[14] Working hour reform introduced standards such as maximum shift length and working week for medicine graduates working as residents within US medical centres (Nasca, Day, & Amis, 2010)

1. demographic factors such as ethnicity (de Bruijne et al., 2013; Jiang et al., 2005) and gender (Flink et al., 2013);
2. physical condition such as functional status (Chu & Pei, 1999; Torres et al., 2004); mobility (Fisher et al., 2013), and body weight (Pouw et al., 2000)
3. and those characterising readmission in cohorts with specific medical conditions or health traits, specifically:
    - CAP (Godar et al., 2011; Jasti et al., 2008),
    - COPD (Nantsupawat et al., 2012),
    - AMI, with and without Q waves (Barbagelata et al., 2000)
    - AKI, with and without CKD (Thakar et al., 2012),
    - antimicrobial allergy (Charneski et al., 2011),
    - general medical patients (Bisharat et al., 2012),
    - chronic medical conditions and unmet health care needs (Ronksley et al., 2013),
    - self-discharge against medical advice (Hwang et al., 2003).

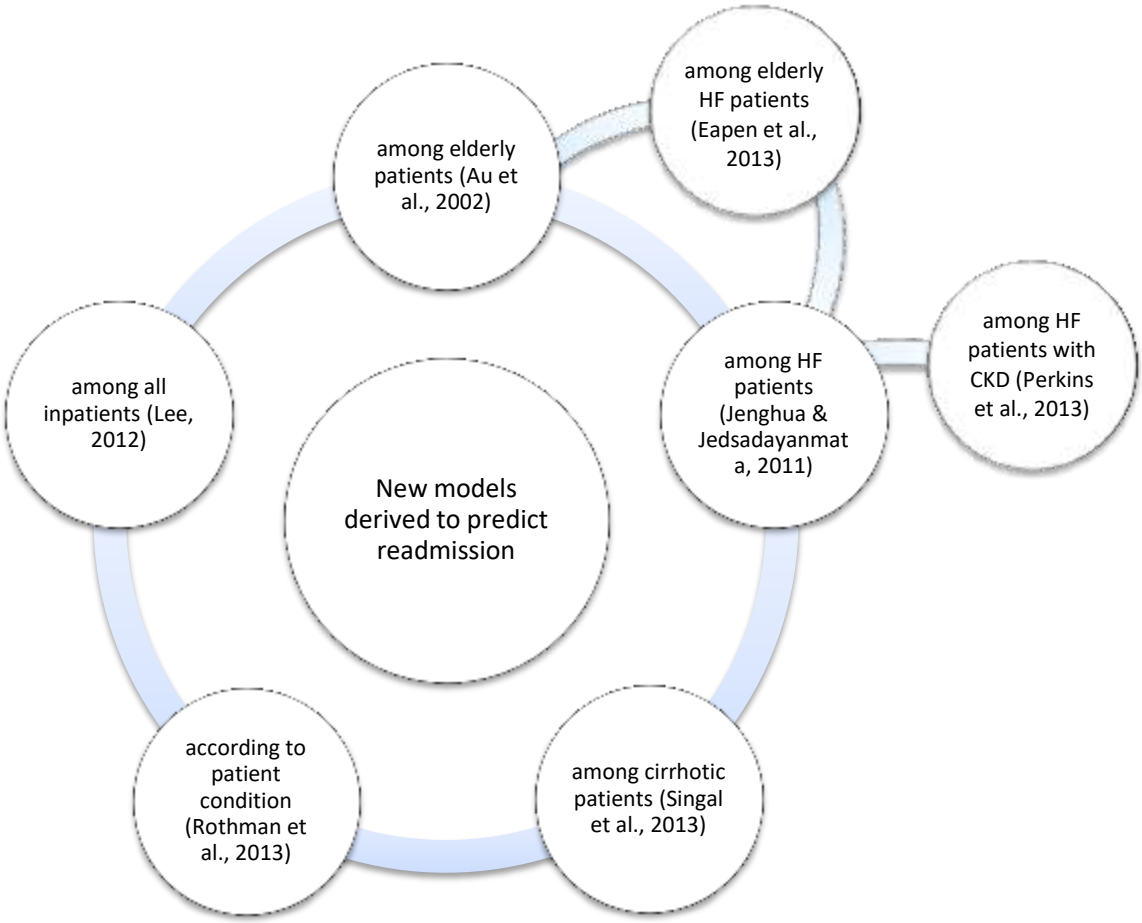

Figure 2.5: Models included in the literature review that were developed for predicting readmission

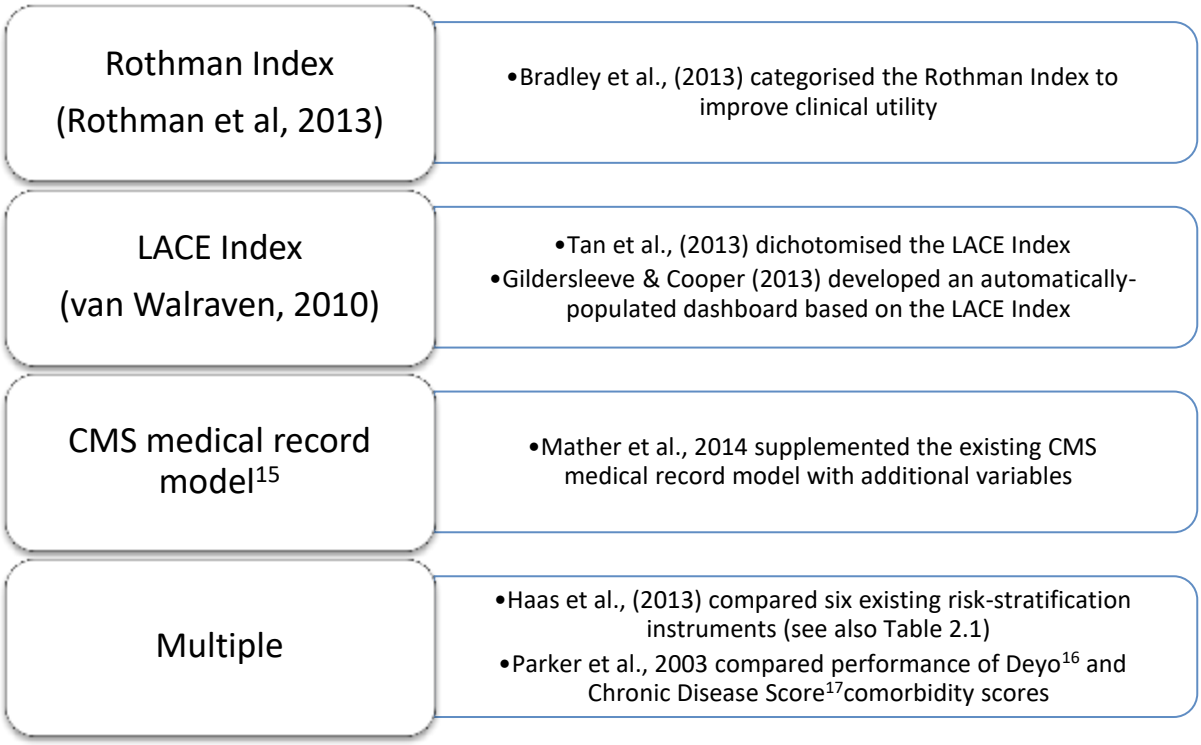

Figure 2.6: Studies included in the literature review which applied and/or further developed existing predictive models

2.3.2 Design and participants

Consistent with the observation of Kansagara et al. (2011), more than two-thirds of studies were retrospective in nature (71%, 36/51), utilising data routinely collected during the delivery of health care. The majority were cohort studies (78%, 40/51); four involved pre/post intervention evaluation. Ten studies involved a control group, of which three described randomisation.

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[15] Cited by Mather et al. (2014) as Lindenauer PK, Normand ST, Drye EE, Lin Z, Goodrich-K, Desai M, et al. Development, validation, and results of a measure of 30-day readmission following hospitalization for pneumonia. J Hosp Med 2011;6(3):142-150

[16] Cited by Parker et al. (2003) as Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-619

[17] Cited by Parker as Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197-203

2.3.2.1 Data source

According to the *TRIPOD Checklist* (Moons et al., 2015), the data source(s) should be specified in a prediction model study. Sources of data for the studies included in the literature review are summarised in Figure 2.7:

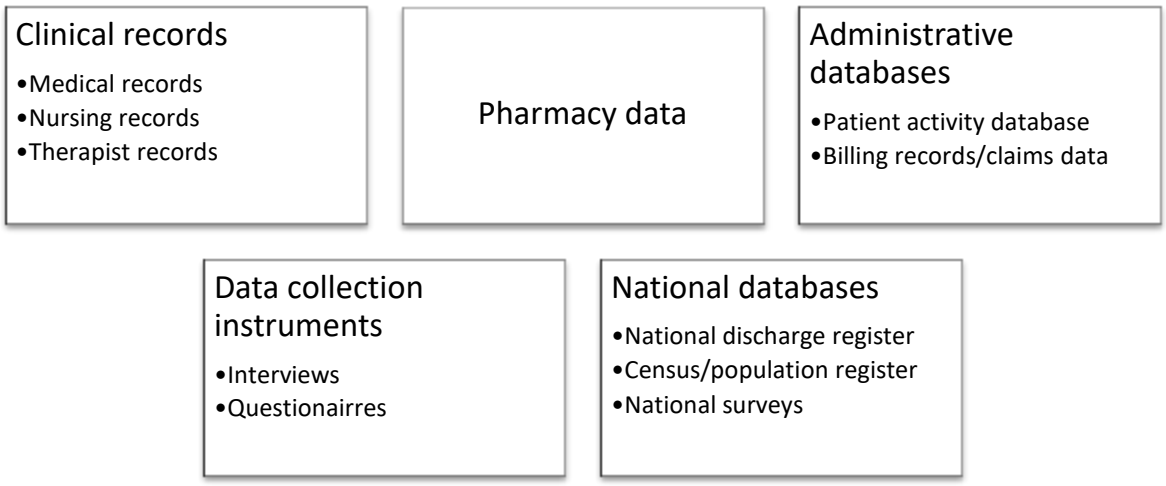

Figure 2.7: Sources of data for studies included in the literature review

Clinical and medical records were the most commonly-cited data sources (15 studies each). Administrative databases were the next most commonly-utilised (11), followed by prospective data collection instruments (8). Studies cited utilising between one and four different types of data source, although they typically had just one (27; 12 had two data sources, three had three data sources, and one had four data sources). Eight studies did not clearly specify the source(s) for their data.

2.3.2.2 Setting

Studies were most commonly:

- undertaken in North America (75%, 38/51)
- involved one site (single-centre; 53%, 27/51)

Single-centre and multicentre studies undertaken in the United States each represented the greatest portion (59%, 16/27 and 78%, 18/23 respectively); studies from the USA accounted for over two-thirds (69%, 35/51) of those included in the literature review. Five

(11%, 5/51) studies were undertaken in Europe and one spanned Europe and the USA; seven studies were undertaken outside of North America and Europe, in Singapore (2), Israel, Australia, China, South Korea and Thailand (1 each).

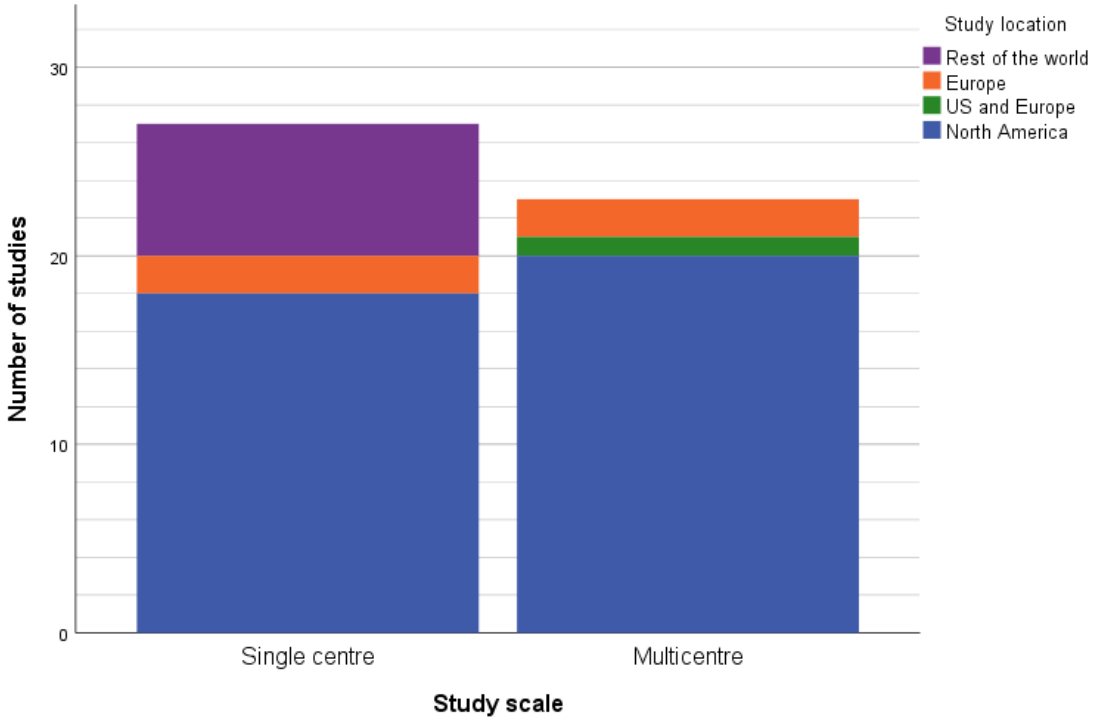

Figure 2.8: Setting for studies included in the literature review

2.3.2.3 Sample size

Sample sizes ranged from 28 to 6522589. The mean sample size was just under 280,000 (279,683; standard deviation, SD 1,061,488); the median was just over 1000 (1233; Interquartile range, IQR 18,033). Figure 2.9 demonstrates that sample sizes were typically between 100 and 999 (39%, 20/51), and that the largest sample sizes were in multicentre studies.

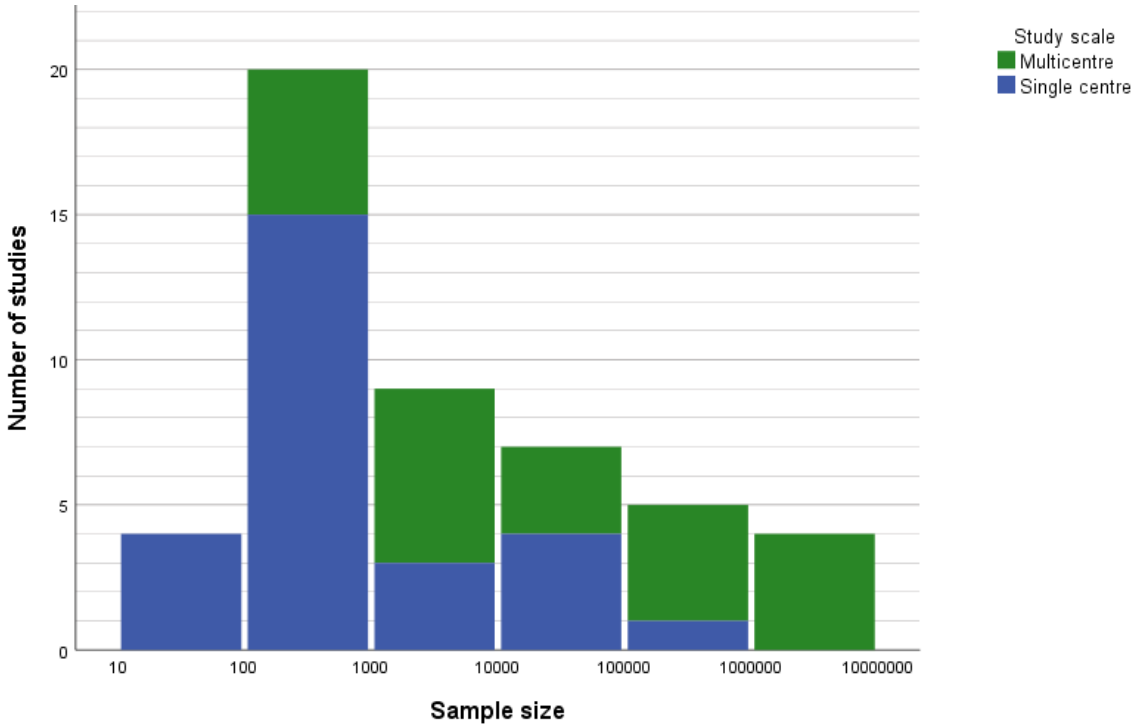

Figure 2.9: Sample sizes for studies included in the literature review

2.3.2.4 Participants

The age group of participants was defined in 69% (35/51) of studies. Cohorts were most commonly limited to adult (21) or elderly (10) patients.

Twenty-eight studies focussed on specific conditions:

1. Heart failure was the most commonly investigated (10), followed by
2. pneumonia (5), then
3. chronic obstructive pulmonary disease (3).

a) Unit of analysis

de Bruijne et al. (2013) discussed the hierarchical data structure applicable to many readmission studies; admissions are nested within patients, and in multicentre studies, within hospitals. Some studies specifically addressed the issue of potential clustering that such a data structure can involve: Lee (2012) specified the subject of analysis was individual patients, and that serial admissions involving the same patient were evaluated individually and included. Rosen et al. (2013) referred to undertaking sensitivity analysis to

account for potential correlation among repeated hospitalisations involving the same patient. Eapen et al. (2013) utilised generalized estimating equations to account for within-hospital clustering, and Keenan et al. (2008) utilised hierarchical generalised linear modelling due to admissions being clustered within the hospitals which served as their unit of inference. Pines et al. (2010) stated clustering was performed at patient level for admission-level models; however it is not clear specifically what technique or procedure this refers to. Bradley et al. (2013) described adjusting standard errors to account for clustering of patients that had additional admissions which were not within 30 days of discharge, having excluded readmissions being cases. Similarly,Godar et al. (2011), Keenan et al. (2008), Press et al. (2011) and Singal et al. (2013) each excluded readmissions being cases in their studies;Dedhia et al. (2009), Jasti et al. (2008) and Mather et al. (2014) excluded admissions subsequent to the index admission as cases in theirs.

In the majority of studies it was not clearly defined whether the unit of analysis was patients or admissions, or how index admissions were identified/defined; the precision of the parameter estimates may be affected for studies in which potential clustering was not accounted for (see also 3.2.2.1 b) Unit of analysis). It was not always clear whether the denominator comprised the number of admissions or discharges; in other words, it was not always stated whether patients who died during admission or transferred elsewhere were accounted for. For example, Nantsupawat et al. (2012) reported that four patients in their study died; however, the denominator appeared unaffected for the analysis of readmission, indicating that the analysis included patients who were not at risk. Perimal-Lewis et al. (2013) acknowledged that death affects the risk of readmission, and referred to re-examining readmission risk data having excluded in-hospital deaths; although not presented, it was reported they were unaltered. Notably, Rosen et al. (2013) excluded admissions which followed death as these represented data error; demonstrating a fundamental drawback of such large-scale studies utilising existing data recorded for other purposes. Bollu et al. (2013), Bradley et al. (2013), de Bruijne et al. (2013), Eapen et al. (2013), Gildersleeve and Cooper (2013), , Jiang et al. (2005), Keenan et al. (2008), Mather

et al. (2014), Mosher et al. (2014), Parker et al. (2003), Pines et al. (2010), Rosen et al. (2013), Singal et al. (2013) and Tan et al. (2013), specifically described excluding patients who died during the index admission. Eapen et al. (2013), Keenan et al. (2008), Mather et al. (2014), Mosher et al. (2014), Parker et al. (2003), Pines et al. (2010) and Sales et al. (2013) described excluding those transferred to acute care.

Some studies specifically excluded short admissions, effectively excluding readmissions related to short LOS:

- Admitted for observation only (Bradley et al., 2013)
- ED overnight admissions (Bisharat et al., 2012)
- Admission less than 24 hours (Dedhia et al., 2009; Jasti et al., 2008)
- LOS less than 48 hours (Bradley et al., 2013)

2.3.3 Outcome

In many studies readmission represented one of a number of outcomes evaluated (Arnold et al., 2006; Barbagelata et al., 2000; Charneski et al., 2011; de Bruijne et al., 2013; Haas et al., 2013; Parker et al., 2003; Reyes Calzada et al., 2007; Rothman et al., 2013; Sales et al., 2013). Bottle et al. (2013) found in their work to risk-adjust LOS, readmission and mortality, that model discrimination was usually poorest for readmission compared to the other outcomes evaluated; this was also the case for Rothman et al. (2013) who achieved much better performance for predicting mortality than readmission.

2.3.3.1 Identifying readmissions

Consistent with the issue of outcomes often being poorly defined in prediction modelling studies, highlighted by Moons et al. (2015); how readmissions were identified was not consistently described among studies included in the literature review, and consequently it was often not clear whether patients who were readmitted to different services/hospitals or those who died during the observation period were accounted for in the numerator. For example:

- Mosher et al. (2014) and Singal et al. (2013) excluded patients who died within 30 days
- Mosher et al. (2014) also excluded those discharged under palliative care; similarly, Pines et al. (2010) excluded those discharged to hospice care.
- Gildersleeve and Cooper (2013) and Tan et al. (2013) each acknowledged patients who died outside hospital during the observation period were not accounted for.
- Eapen et al. (2013) quantified the number of patients who died during the observation period; however, the percentage of readmissions presented indicates that those who died within the observation period were not deducted from the denominator. Similarly, Keenan et al. (2008) quantified patients who died within the observation period and acknowledged that including these in the denominator could be considered treating death as a 'non-event'; nonetheless, their inclusion was justified on the basis readmission was the outcome of interest.
- Arnold et al. (2006) , Bollu et al. (2013), Bradley et al. (2013), Gildersleeve and Cooper (2013), Johnson et al. (2012), Pines et al. (2010), Rothman et al. (2013), Stevens et al. (2014) and Tan et al. (2013) only accounted for readmissions to the same hospital as the index admission/study hospitals. Hwang et al. (2003) accounted for readmissions four local hospitals as well as the study hospital, and were unable to account for care received outside of the system under study; Pines et al. (2010) acknowledged that this could have resulted in underestimation of readmission.
- Singal et al. (2013) identified ability to account for readmissions to 136 surrounding hospitals as a study strength.

Bottle et al. (2013) found that limiting the readmissions included in their study to those to the same hospital as the index admission resulted in the omission of just over 10% for England; the proportion was not known for other countries. Davies, Saynina, McDonald, and

Baker (2013) concluded that same-hospital readmission metrics were limited, and urged caution by those conducting research, quality improvement or comparative applications that do not account for readmissions to other hospitals.

Many studies only included readmissions for the same reason as/reasons related to the index admission (Gentry et al., 2000; Harjai et al., 2001; Jiang et al., 2005; Jurado Gamez et al., 2013; Sakr et al., 2008; Sales et al., 2013; Thakar et al., 2012). Additionally, some studies included only unplanned/emergent readmissions (Bisharat et al., 2012; Bottle et al., 2013; Chu & Pei, 1999; Parker et al., 2003), with Pines et al. (2010) and Tan et al. (2013) specifically including only readmissions through the emergency department; some described only included the first readmission observed (Rosen et al., 2013).

2.3.3.2 Number of readmissions

The number of readmissions observed ranged by more than 250,000 (8 to 262,026). Figure 2.10 demonstrates that between 10 and 999 readmissions were observed for most studies (32/51), and that multicentre studies accounted for the highest number of readmissions:

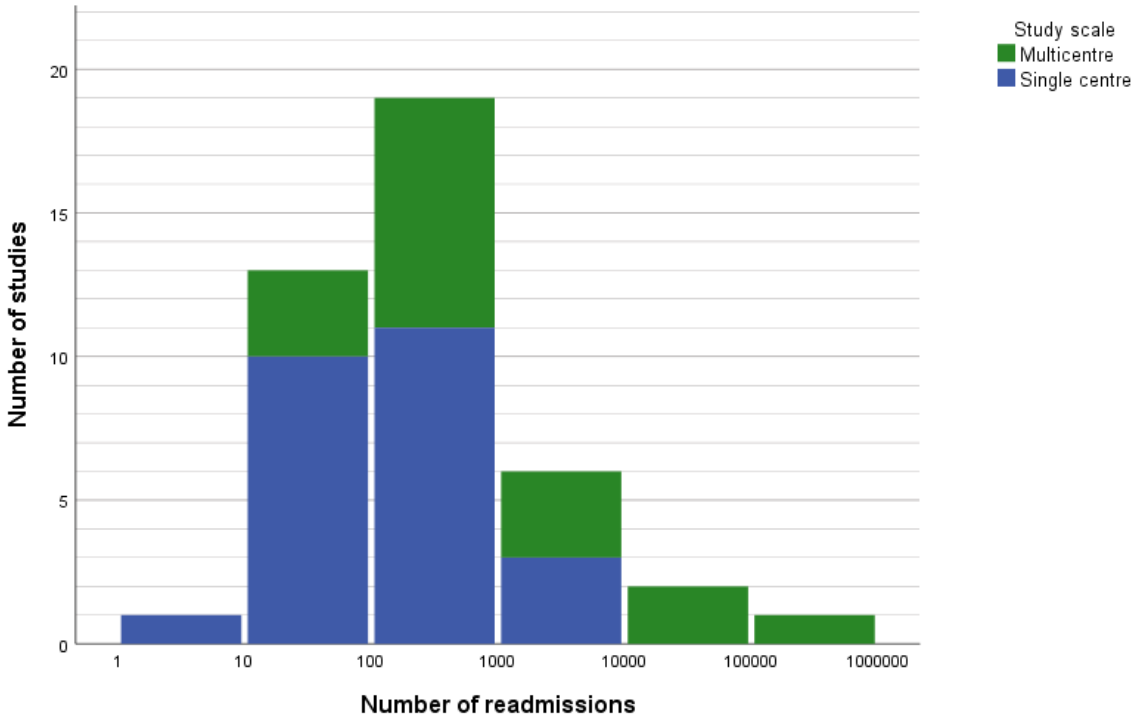

Figure 2.10: Number of readmissions observed for studies included in the literature review

The number of readmissions observed in relation to the sample size ranged from 2 to 59%. Figure 2.11 demonstrates that between 10 and 20% (24/51) participants were readmitted in most studies and confirms that case-control designs accounted for the studies with the highest proportions of readmissions. Bottle et al. (2013) found that USA hospitals had a higher readmission rate than hospitals in Europe: all of the studies included in the literature review that were not case-controlled studies and in which readmissions comprised more than 30% were USA single-centre studies. Excluding case-control studies on the basis of their design, the average proportion of participants readmitted tended to be greater in single centre studies (17%) compared to multicentre studies (13%), and in USA studies (16%) compared to European studies (12%).

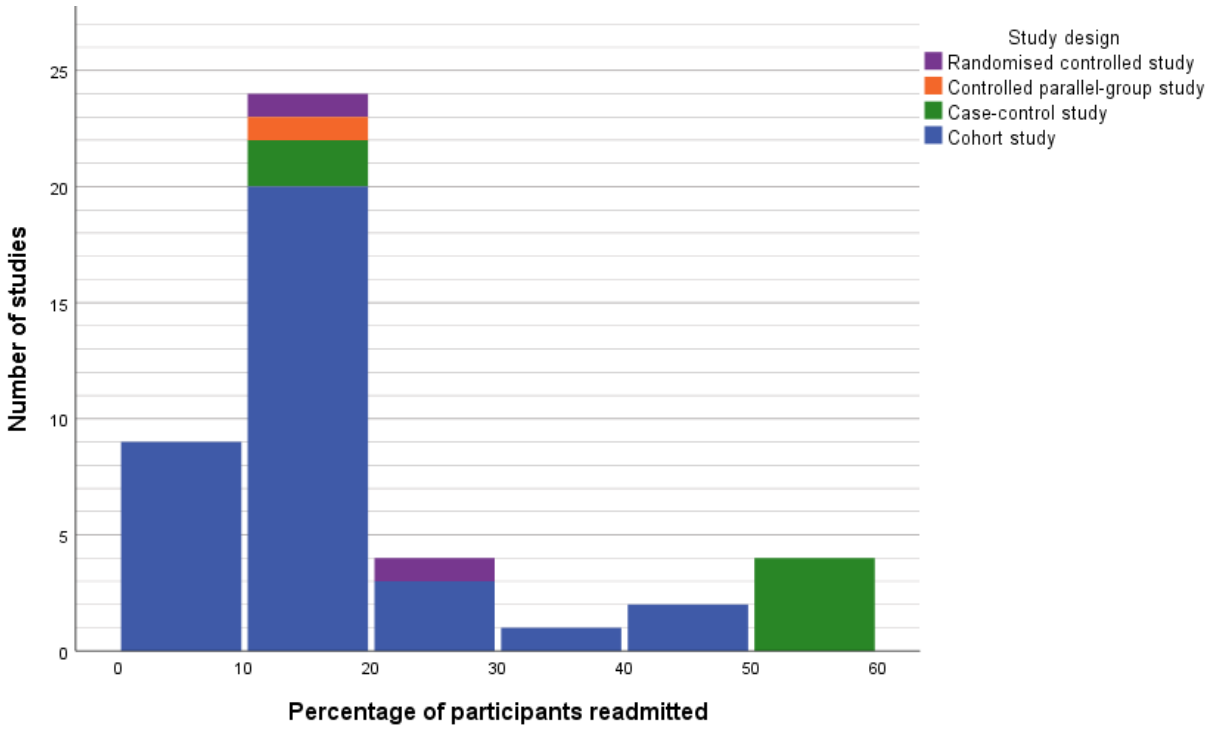

Figure 2.11: Proportion of readmissions for studies included in the literature review

2.3.3.3 Observation period

Consistent with the findings of Kansagara et al. (2011), the observation period was 30 days for the majority of studies (76%, 39/51) included in the literature review. The shortest observation period was 14 days and the longest was 30 days; observation periods of 28 to 30 days accounted for 88% (45/51) of studies included.

2.3.3.4 Time to readmission

Bisharat et al. (2012) reported a mean time to readmission of 12.8 days. Jasti et al. (2008) reported a median time to readmission of eight days (IQR 4 to 13 days), and Singal et al. (2013) reported a median time to readmission of 12 days, with just under 10% of patients readmitted within one week. Mather et al. (2014) presented a Kaplan–Meier curve to demonstrate a uniform distribution of readmissions over the 30 day observation period. Singal et al. (2013) also presented Kaplan-Meier analysis, stratifying readmission behaviour by risk quintile to demonstrate the difference in time to readmission between the highest and lowest risk patients (mean 22.3 days and 27.7 days respectively). Hwang et al. (2003) conducted the most in-depth time to event analysis among the studies included in the literature review, identifying by Cox regression that the readmission behaviour expressed by general medical patients who were discharged against medical advice differed significantly from those who were discharged routinely. Specifically, those discharged against medical advice had an increased risk of readmission within the first 15 days; after which, their readmission behaviour became comparable to those discharged routinely.

2.3.3.5 Reason for readmission

Au et al. (2002) identified that a third of patients had both medical and social issues, yet half were discharged with no adjustment to their previous care system and the majority required readmission due to a medical problem; sepsis was noted to be a factor in half of those admissions concerning a new medical complaint. Almost half (40%%, 4/10) of studies among heart failure patients specifically investigated readmissions for heart failure; Jenghua and Jedsadayanmata (2011) identified CHF as the most common cause of readmission

among CHF patients. Similarly, Bisharat et al. (2012) found that a third of patients were readmitted with the same primary diagnosis as their index admission. Conversely, Jasti et al. (2008) found the majority (74%) of readmissions following admission for community acquired pneumonia were comorbidity-related; the comorbidity most commonly responsible for readmission was cardiovascular disease (37%).

Rosen et al. (2013) identified that the reason for readmission tended to reflect the occurrence of a Patient Safety Indicator event (PSIE) during the index admission, with readmissions following a PSIE being more likely to be due to a complication compared to those which were not preceded by a patient safety event.

2.3.4 Covariates

Moons et al. (2015) set out that in prediction modelling studies predictors should be fully defined, with units of measurement provided for continuous predictors and categories/cut-offs provided for categorical predictors, to ensure that readers could replicate, validate or implement the model. Lee (2012) described risk for readmission as comprising the following factors:

- demographic,
- treatment and clinical, and
- health care utilisation.

Somewhat consistent with this, variables included in studies in the literature review could be categorised as described in Table **2**.**2**:

Table 2.2: Variables included in studies in the literature review					
Demographic	**Domestic**	**Socioeconomic**	**General health**	**Clinical condition**	**Treatment**
Age Gender Race/ethnicity	Marital status/living alone/being a carer Discharge disposition	Health insurance status Employment status Education level Median income Number of recent address changes Homelessness	Functional status, mobility Medical history Comorbidities Prescription Prior utilisation	Nature of admission Diagnosis Severity of disease Physical observations /test results	Intervention LOS Season of admission Hospital characteristics Time taken to send discharge summary

Demographic variables were by far the most commonly-reported:

- Age was presented in 84% (43/51) studies,
- Gender was presented in 80% (41/51) studies, and
- Race/ethnicity was presented in 37% (19/51) studies.

Variables reflecting the care delivered were also commonly reported:

- Treatment i.e. intervention; medication prescribed or procedures performed was reported in 53% (27/51) studies
- Length of stay was reported in 37% (19/51) studies

Variables related to the patient's health status were frequently included. Most commonly:

- Comorbidity was assessed in 65% (33/51) studies,
- Physical observations and/or the results of investigations were included in 35% (18/51) studies

Which candidate predictors were considered and/or included was not always described exhaustively; systematic reviews have highlighted insufficient reporting in prediction modelling studies of which predictors were available for analysis, how and when they were selected, or the number of predictors analysed/included (Moons et al., 2015). Some studies

referred to selection of candidate predictors based on *a priori* beliefs (Bottle et al., 2013; Nolan & Thomas, 2008). Eapen et al. (2013) described selecting variables for inclusion on the basis of their clinical importance, likely availability in the EHR, and significance in statistical tests; however, it was not specifically described how many variables were considered.

In USA studies payer/insurance status was often included as a covariate; however, due to their eligibility criteria the common insurance types could be considered to be confounded by age to some extent:

- Medicare (people 65 years of age and over and younger people with disabilities or end stage renal disease)
- Medicaid (people with a low income)

Indeed, Jiang et al. (2005) compounded this by limiting patients included in their study to Medicare enrolees aged 65 compared to Medicaid enrolees aged 64 and under; thereby excluding younger, disabled patients, as well as the uninsured.

Moons et al. (2015) highlighted that systematic reviews of prediction model studies have consistently shown poor reporting and handling of missing data; and that omitting participants on the basis of missing data is not only inefficient, but can cause serious bias if the data are not missing completely at random. Many of the studies in the literature review referred to participants being excluded from analysis due to missing data (Barbagelata et al., 2000; Charneski et al., 2011; Chu & Pei, 1999; Mather et al., 2014). Over a third (35%) of patients were excluded from the study by Flink et al. (2013) on the basis they did not have a documented HbA1c within the previous year and eight per cent of the cohort was excluded due to missing clinical data in the study by Bradley et al. (2013). Whilst the likelihood of readmission, gender and LOS did not differ significantly; those that were excluded were younger and more likely to have Medicare insurance than those that were included. Eapen et al. (2013) reported that missing data was problematic due to the scale of their sample and consequently imputation was undertaken (gender as male, race as white, laboratory values as the corresponding median). Such imputation can suppress the standard

deviation and the standard error, causing significant results due to the data replacement as opposed to a genuine effect (Field, 2018).

In contrast to the rest of the studies, Rothman et al. (2013) described development of a heuristic model in which relevant variables were selected to produce an index representing patient condition; many commonly-included predictors for readmission, such as age, gender and diagnosis, were specifically excluded on the basis that the model was intended to represent on 'how' rather than 'who' the patient was. Unfortunately, failure to adequately describe the cohort makes gauging applicability of the study in other contexts particularly difficult.

2.3.4.1 Pharmaceutical variables

Perkins et al. (2013) incorporated active outpatient pharmaceuticals in their model of readmission among non-dialysis dependent chronic kidney disease patients hospitalised with heart failure.

a) Number of medicines

Bisharat et al. (2012) reported that patients with six or more chronic medications were more likely to be readmitted; however, it is not specifically described what this variable represented (i.e. what was considered to be a chronic medication, whether number of medicines prescribed on admission or discharge etc.) nor how the cut-off of six was decided upon. Gildersleeve and Cooper (2013) also included two variables reflecting the number of medicines prescribed in their predictive model for readmission which was based on routinely-recorded health care data. Haas et al. (2013) discussed being unable to incorporate pharmacy data into their study, and acknowledged it as an important component of the total cost of care, and may aid predictive models based on claims information.

b) Type of medicine(s)

Four variables in the model developed by Bollu et al. (2013) to demonstrate that COPD patients treated with arformoterol had a reduced risk of readmission compared to those

treated with short-acting beta (β)-agonists, concerned medication, specifically prescription of:

- anticholinergics,
- corticosteroids,
- antibiotics and
- β-agonists (arformoterol protective compared to nebulised short-acting β-agonists).

Cardiovascular medication was assessed as a predictor in the predictive model for readmission among CHF patients developed by Jenghua and Jedsadayanmata (2011); however, a significant association was not identified. It may be the case that those not requiring readmission due to appropriate medication of their condition readmission were balanced by those who experienced adverse events due to their medication and those who did not benefit from their prescribed medication due to non-adherence. Sales et al. (2013) included several medicines as variables in their model to evaluate the impact of an educational intervention among heart failure patients on readmission, specifically:

- statins,
- β-blockers,
- aspirin,
- ACEis,
- furosemide and
- spironolactone.

However none of these contributed significantly in univariable or multivariable analysis. Sakr et al. (2008) reported reduced heart-failure readmission risk among acute decompensated heart failure patients treated with nesiritide in addition to maximal standard therapy compare to maximal standard therapy alone, and around one-third fewer black heart failure patients prescribed isosorbide dinitrate and hydralazine in addition to standard therapy were readmitted within 30 days compared to placebo (Win et al., 2012)

2.3.5 Model development

No study included in the literature review fully met the requirements set out in the *TRIPOD Checklist* (Collins, Reitsma, Altman, & Moons, 2015).

2.3.5.1 Model specification

It has been found in systematic reviews of multivariable prediction models that the strategy used to build models is often unclear (Moons et al., 2015). The variable selection process was generally poorly defined and it was often not clear whether multivariable analysis involved an elimination process. Less than one-quarter of studies undertaken for the purpose of predicting readmission included this literature review detailed robust processes for selecting/eliminating predictors (3/13). The variable selection the criteria for inclusion in multivariable analysis in all three involved demonstration of statistical significance, or a trend towards this, in univariable analysis:

- Mather et al. (2014) progressed predictors to multivariable analysis according to whether $p<0.15$ in univariable analysis
- Singal et al. (2013) progressed predictors multivariable analysis according to univariable $p<0.2$; variables were retained in the multivariable analysis on the basis of $p<0.05$.
- Rothman et al. (2013) developed sub-models using stepwise forward logistic regression with $p<0.05$ for retention; the authors described a heuristic approach, and data pertaining to the predictors included was not presented; rather, what was presented was the performance of the resulting index as a composite predictor.

Perkins et al. (2013) described manually removing variables to achieve a model with satisfactory goodness-of-fit and parsimony whilst maximizing the area under the receiver operating characteristic curve.

2.3.5.2 Predictors

Among models developed for the purpose of predicting individuals' risk of readmission (13), predictors included in final models were categorised as described in Table 2.3:

Table 2.3: Predictors in final models included in the literature review					
Demographic	**Domestic**	**Socioeconomic**	**General health**	**Clinical condition**	**Treatment**
Age (7) Gender (6) Race/ethnicity (2)	Marital status (2) Nursing home resident (1)	Health insurance status (4) Median income (1) Number of recent address changes (1)	Comorbidity (8) Prior utilisation (7) Prescribed medication (3)	Physical observations/test results (5) Acuity of admission (3) Service assignment (2) Diagnosis (2) Severity of disease (1)	LOS (5)

Variables reflecting the patient's general health status were the most frequently included (18), followed by demographics (15) and the clinical condition treated during the index admission (12); although variables reflecting socioeconomic status were less-frequently considered as candidate predictors, possibly due to the subjective nature of measuring socioeconomic status, these variables were noted to contribute significantly to multivariable models in which they were included.

Both variables included in the model developed by Au et al. (2002) to predict readmission represented the patient's general health status (comorbidity and prior health care utilisation). Rothman et al. (2013) developed the *Rothman Index* to reflect clinical condition, comprised of 26 clinical measurements from nursing assessments, physical observations and laboratory test results. The article does not specify detail about the variables included; for the purpose of this literature review they were considered to reflect the patient's general health status and the patient's clinical condition during the index admission. Bradley et al. (2013) categorised the *Rothman Index* and adjusted for age, gender, insurance status, service assignment and primary discharge diagnosis. It was identified that patients in the

top two risk categories, representing those with the poorest condition on discharge, were significantly more likely to be readmitted. The authors advocated:

- embedding such indices into the EHR to provide a dynamic tool for gauging patient condition, and
- application of meaningful cut-points for practical application, to enable clinicians to intervene specifically for patients at risk and prevent readmission.

Tan et al. (2013) applied a cut-point of 10 to the *LACE Index* (van Walraven et al., 2010a) and demonstrated the resulting binary variable was effective in predicting readmission. The model comprised variables reflecting the patient's:

- general health status (comorbidity, prior utilisation),
- clinical condition during the index admission (acuity of admission), and
- treatment during their index admission (LOS); was an effective predictor of unplanned readmission having controlled for
- demographic factors (age, gender and ethnicity),
- factors related to the patient's clinical condition during the index admission (admission to the Intensive Care Unit), and
- hospital factors (year of admission).

The model developed by Gildersleeve and Cooper (2013), which was based upon the *LACE Index* (van Walraven et al., 2010a) and built into the EHR, comprised variables representing the patient's:

- general health status (comorbidity, prior utilisation, prescribed medication),
- clinical condition during the index admission (acuity of admission),
- treatment during their index admission (LOS),
- demographic factors (age, gender),
- domestic factors (marital status),
- socioeconomic status (insurance)

The model produced by Perkins et al. (2013) to predict readmission among patients who had been admitted for HF and also had CKD comprised 23 predictors reflecting the patient's:

- general health status (medical history, active outpatient pharmaceuticals, physical observations, laboratory tests recent health care resource utilisation) and
- clinical condition during the index admission (medical history, active outpatient pharmaceuticals, physical observations, laboratory tests).

The model produced by Singal et al. (2013) to predict readmission among patients admitted with cirrhosis included:

- socioeconomic variables (number of address changes and payer status) in addition to those reflecting the patient's
- general health status (number of admissions in previous year) and
- clinical condition during the index admission (laboratory test results).

Mather et al. (2014) achieved improved performance of the CMS medical record model's performance by the addition of variables reflecting the patient's general health status (healthcare utilisation, comorbidity) and socioeconomic status (median household income).

The model developed by Eapen et al. (2013) comprised demographic factors (age and race) and the patient's clinical condition during the index admission (laboratory test results). Haas et al. (2013) identified the *Adjusted Clinical Groups* (ACG) model had the best performance for predicting readmission in their comparison of seven models. The AGC model reflects the patient's general health status (comorbidities) and demographics (age and gender).

The decision tree model developed by Lee (2012) was found to out-perform the equivalent logistic regression model. The variables included represented the patient's:

- general health status (prior health care utilisation, comorbidity)
- clinical condition during the index admission (diagnosis, acuity of admission, service assignment)
- demographics (gender, age)
- socioeconomic factors (insurance status, region of residence)

- treatment during the index admission (accompanying treatments, surgery, LOS)

Parker et al. (2003) found that comorbidity predictors drawn from pharmacy data achieved similar performance in predicting readmission to those from the medical record, and inclusion of both resulted in a small but statistically significant improvement.

The only significant predictor in the final model developed by Jenghua and Jedsadayanmata (2011) was LOS >5 days; no significant association between cardiovascular medication and readmission was identified.

2.3.5.3 Power

Moons et al. (2015) highlighted that numerous systematic reviews have found prediction model studies frequently do not provide a rationale for the sample size. Consistent with these findings, very few studies included in this literature review described prospective calculation of the required sample size and/or statistical power:

- Dedhia et al. (2009) described that their study power was set to 0.8 with an alpha of 0.05 and a 7.5% absolute reduction in readmission rate considered meaningful. It was calculated that, based on an historical readmission rate of around 25%, approximately 230 patients would be required in each study arm (pre and post intervention).
- Weiss et al. (2007) reported that it had been determined by power analysis that a sample of 120 would be sufficient to achieve 80% power in multiple regression analyses with up to 10 predictor variables at moderate effect size; however, details of the power analysis were not described.

Although such calculations were rarely presented, several authors discussed potential inadequacy in their study's sample size/power:

- Sales et al. (2013) referred to not achieving their intended sample size; however, prospective sample size calculation is not described in the method.
- Fisher et al. (2013) listed a relatively small sample size as a limitation.
- Jasti et al. (2008) stated the small number of readmissions observed in their study may have reduced power to identify important risk factors.

- Hwang et al. (2003) stated their ability to identify other predictors was limited by insufficient statistical power.
- Parker et al. (2003) stated their sample size did not allow for inclusion of Diagnosis Reference Group or primary diagnosis in their model.
- Having identified AKI without CKD and CKD without AKI as predictors for readmission for heart failure among heart failure patients, controlling for age, gender, number of chronic conditions, payer status, diabetes, valvular heart disease, drug abuse and psychoses; Thakar et al. (2012) stated that the subgroup of patients with both AKI and CKD was relatively small and thus the study was likely inadequately powered to detect an effect had it existed.
- Mather et al. (2014) referred to limited power in relation to whether readmissions were pneumonia–related or not; although, it was reported that large parameter estimates or standard errors were not observed and that these can be diagnostic of too few events per predictor.

Conversely, Rosen et al. (2013) highlighted that their utilisation of a composite outcome measure helped to ensure adequate statistical power. It was possible to calculate the number of readmissions observed per predictor in multivariable analysis in around half of studies (47%, 24/51). The number of candidate predictors included in multivariable analysis ranged from less than one to 38 and the number of readmissions observed ranged from 11 to 262,026; between two and 6895 readmissions were observed per predictor. Peduzzi, Concato, Kemper, Holford, and Feinstein (1996) recommended at least 10 events per predictor variable; Figure 2.12 demonstrates that one-third (29%, 8/24) of the studies that presented enough detail to calculate the number of readmissions per predictor included in multivariable analysis did not meet the recommendation (Fisher et al., 2013; Flink et al., 2013; Jasti et al., 2008; Mather et al., 2014{Sales, 2013 #420; Pouw et al., 2000; Reyes Calzada et al., 2007; Torres et al., 2004)}.

The results of these studies should be interpreted with caution in light of the potential problems associated with having fewer than 10 events per predictor, including bias in the

regression coefficients, large sample variance, inaccurate confidence intervals, conservative Wald statistics under the null hypothesis, and paradoxical associations (Peduzzi et al., 1996).

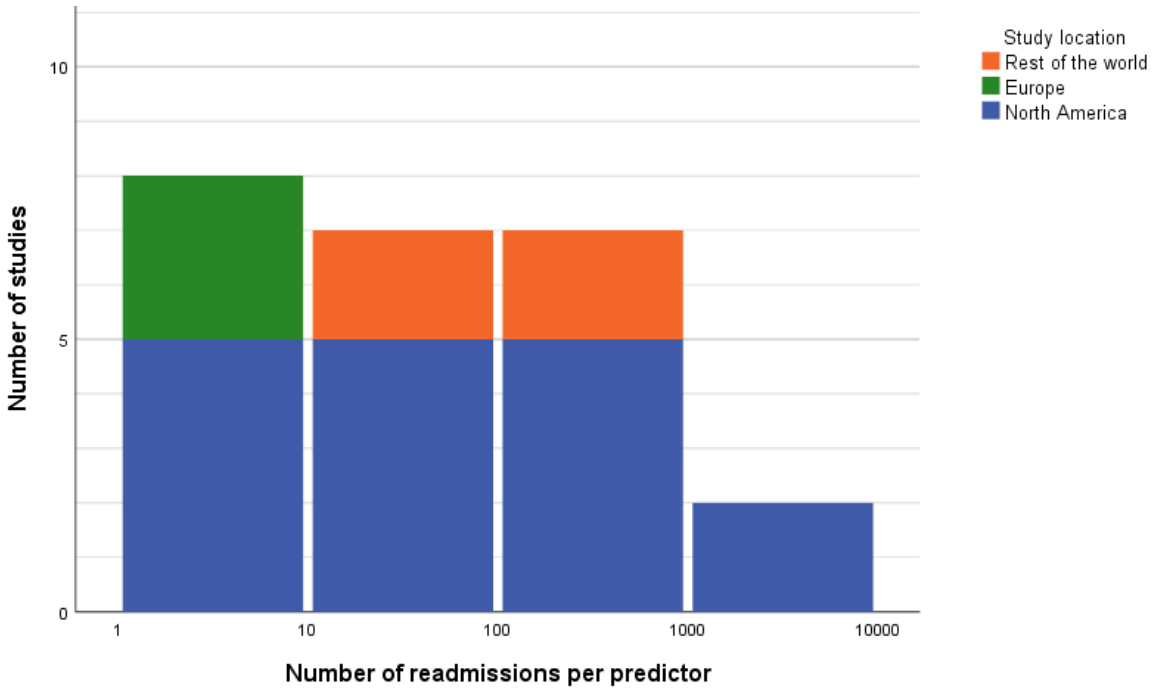

Figure 2.12: Number of readmissions per predictor in multivariable analyses of studies included in the literature review

2.3.5.4 Stage of development

Moons et al. (2015) defined categories for prediction model studies as set out in Table 2.4. The majority of studies included in the literature review did not involve validation (40); where validation was undertaken it tended to be internal (9/11). Split-sample validation was utilised in the majority of studies that involved validation (5):

- 50:50 Bradley et al. (2013); Keenan et al. (2008)
- 30:70 Eapen et al. (2013); Lee (2012)
- 25:75 Singal et al. (2013)

Gildersleeve and Cooper (2013) and Keenan et al. (2008) each utilised data from different time periods for model validation to derivation, and bootstrapping was utilised in three

studies (Mather et al., 2014; Perkins et al., 2013; Sakr et al., 2008). Rothman et al. (2013) validated their model of patient condition, which was developed using mortality data, for predicting readmission; and Haas et al. (2013) conducted external validation of existing models for the purpose of comparison.

Table 2.4: Prediction model study types defined by Moons et al. (2015)

Analysis Type	**Description**
Type 1a	Development only Development of a prediction model where predictive performance is then directly evaluated using exactly the same data (apparent performance)
Type 1b	Development and validation using resampling Development of a prediction model using the entire data set, but then using resampling (e.g., bootstrapping or cross-validation) techniques to evaluate the performance and optimism of the developed model. Resampling techniques, generally referred to as "internal validation", are recommended as a prerequisite for prediction model development, particularly if data are limited
Type 2a	Random split-sample development and validation The data are randomly split into 2 groups: one to develop the prediction model, and one to evaluate its predictive performance. This design is generally not recommended or better than type 1b, particularly in case of limited data, because it leads to lack of power during model development and validation
Type 2b	Non-random split-sample development and validation The data are non-randomly split (e.g., by location or time) into 2 groups: one to develop the prediction model and one to evaluate its predictive performance. Type 2b is a stronger design for evaluating model performance than type 2a, because allows for non-random variation between the two data sets
Type 3	Development and validation using separate data Development of a prediction model using 1 data set and an evaluation of its performance on separate data (e.g., from a different study)
Type 4	Validation only The evaluation of the predictive performance of an existing (published) prediction model on separate data

2.3.6 Model performance

Discrimination (17) and goodness-of-fit (12) were the measures of model performance that were most commonly referred to; these are each discussed in more detail below. Six studies referred to collinearity; four of these utilised Variance Inflation Factors (VIFs) to assess multicollinearity.

- Torres et al. (2004) described examining collinearity by VIF (Variance Inflation Factor) and centring age at its mean to reduce collinearity; however the result was not reported. Similarly, Stevens et al. (2014) described evaluating VIFs to detect problems with predictor collinearity and the result was not reported.
- reported identifying elevated VIFs for diabetes and human immunodeficiency virus having reviewed regression collinearity diagnostics due to concern that collinearity may be influencing estimates of the standard error; the results are not presented, however the authors describe them to be "at levels that would not normally cause concern".
- Bradley et al. (2013) reported no substantial concern of multicollinearity having calculated the VIF for their categorical version of the *Rothman Index* to be 1.52.

Rothman et al. (2013) described determining multicollinearity by Pearson correlation coefficient and disregarding the less frequently collected variable of any pair with a result greater than 0.7. Tan et al. (2013) specified that they did not adjust for CCI or ED visits to avoid collinearity as these variables were used to compute the LACE Index (van Walraven et al., 2010a). Collinear predictors in multivariable analysis account for similar variance in the outcome, making it difficult to assess the importance of individual variables' contribution. Collinearity can also result in large standard errors, resulting in predictor equations that are unstable across samples and coefficients that are not representative of the population (Field, 2018).

2.3.6.1 Goodness-of-fit

The Hosmer-Lemeshow goodness of fit test (HL) represents model calibration; predicted and observed frequencies are tested by chi-squared test for deciles of predicted probability. A non-significant result ($p>0.05$) indicates that the model's predictions are not significantly different from the observed values, confirming that it adequately fits the data. The test does not indicate the extent of variance in the outcome explained by the model, and is prone to identifying smaller differences significant in large sample sizes (Garson, 2016).

- Parker et al. (2003) reported that goodness-of-fit was problematic in both their models (HL 16.6, *p* 0.04; HL 17.3, *p* 0.03).
- Bradley et al. (2013) described their model as well calibrated on the basis of HL 1,574.96, *p* 0.68).
- Singal et al. (2013) stated there was no evidence of lack of fit for their model (*p* 0.94)
- Gildersleeve and Cooper (2013), Jurado Gamez et al. (2013), Tan et al. (2013) and Mather et al. (2014) each reported their model's HL goodness-of-fit (HL 21.6, *p* 0.006; HL 5.59; *p* 0.69; HL 13.1, df 8, *p* 0.107; and HL 5.92, *p* 0.66; respectively), however these figures were not supported by presentation of any interpretation.
- Pines et al. (2010) described assessing models goodness of fit using HL and reporting results if $p>0.05$; no results were reported.
- Jasti et al. (2008) and Reyes Calzada et al. (2007) each refer to assessing goodness-of-fit using the Hosmer-Lemeshow test; however, the results were not reported.

Haas et al. (2013) refer to assessing goodness of fit by comparing observed and predicted readmissions in the lowest and highest deciles of predicted probabilities.

Nagelkerke's R^2 is the most commonly-cited pseudo R^2 (Garson, 2016). It represents the percentage reduction in error in a logistic regression model; values range from zero to one, and the higher the magnitude of the effect size the higher the value (Field, 2018).

Gildersleeve and Cooper (2013) and Mather et al. (2014) each referred to Nagelkerke's R^2 in addition to Hosmer-Lemeshow.

- Gildersleeve and Cooper (2013) reported 14% variance was accounted for
- Mather et al. (2014) did not present a result.

Among studies which assessed goodness-of-fit and presented the results, goodness-of-fit was more often adequate than problematic (6/8 studies reported HL *p-values* >0.05); just one quarter (3/12) of studies that referred to assessing goodness-of-fit presented an interpreted result.

2.3.6.2 Discrimination

The c-statistic (area under the receiver operating characteristic curve) is a measure of a model's discriminative power; in other words, how often it categorises cases correctly. Values range from 0.5 to 1, with 0.5 no better than chance and 1 representing perfect prediction (Garson, 2016). Kansagara et al. (2011) further interpreted discriminative ability as determined by the c-statistic according to the following thresholds:

- 0.7 to 0.8 indicates modest or acceptable performance
- >0.8 indicates good performance

Table 2.5: Interpretation of c-statistics for models developed for the purpose of predicting readmission included in the literature review		
Interpretation of c-statistic according to Kansagara et al. (2011)	**C-statistic and citation**	**Study author's appraisal of c-statistic achieved**
0.5 (no better than chance)	0.59 (Eapen et al., 2013)	
	0.62 (Rothman et al., 2013)	Comparable with models designed exclusively to predict readmission
0.6	0.66 (Singal et al., 2013)	Predictive capability exceeded prior models in cirrhosis
	0.67 (Mather et al., 2014)	Reasonable discrimination
	0.691 (Parker et al., 2003)	
0.7 (modest/ acceptable)	0.70 (Tan et al., 2013)	
	0.70 (Gildersleeve & Cooper, 2013)	Compared favourably with other published models
	0.73 (Bradley et al., 2013)	Moderately discriminative
	0.743 (Perkins et al., 2013)	
	0.74 to 0.81 (Haas et al., 2013)	
0.8 (good)		

C-statistics were presented for 12 models in the literature review, ranging from 0.59 to 0.97. C-statistics presented for models developed for the purpose of predicting readmission are summarised in context of the interpretation by Kansagara et al. (2011) in Table 2.5. Studies which involved validation tended to present a c-statistic (9/11), whereas those describing development alone did not (3/40), and studies involving validation tended to report lower c-statistics than those that did not proceed beyond development; performance

is likely to be overestimated when predictive accuracy is assessed in the same data used to develop the model (Moons et al., 2015).

Eapen et al. (2013) concluded that such models should be prospectively tested against clinical gestalt to understand whether they improve risk stratification.

Haas et al. (2013) identified that the *Adjusted Clinical Group* (ACG) model had the best performance in relation to readmission in their comparison of existing models, on the basis it had the greatest c-statistic; however, it was noted that the confidence interval overlapped with that achieved for *Minnesota Tiering* (0.80-0.83 and 0.78-00.81 respectively), indicating that either may have had the best performance. This is perhaps unsurprising, given that *Minnesota Tiering* is based on a product of ACGs. The authors stated that focusing care coordination to the patients the most likely to benefit requires appropriate identification of the highest risk/utilisation patients.

2.4 Conclusion

Considering publications presenting original data about the likelihood of, and/or influence of pharmaceutical intervention on, readmission within 30 days among adult medical patients; the existing literature supports that there is potential for predicting patients' risk of readmission using data that is routinely recorded on prescriptions. Many of the variables that contributed significantly to existing models could be obtained from discharge prescriptions, yet none of those included in the literature review were developed for quantifying patients' risk of readmission on the basis of information from their prescription. Existing models tended:

- to have been developed by retrospective cohort study
- to focus on specific sub-groups such as those with a particular condition, most commonly heart failure, and/or of a particular age
- to utilise data routinely recorded during the delivery of health care
- to most often include variables representing the patient's general health status in final models; examples of such variables included prescribed medication
- to involve model derivation; the minority of studies that progressed to validation utilised a split-sample approach.

Some studies not only considered the outcome of readmission, but other clinical measures such as mortality and LOS; some also investigated the reason(s) for readmission and others incorporated time-to-readmission into their analyses. These additional analyses were useful for providing context and thereby facilitating discussion around the practical utility of predicting readmissions. Predictive model development was generally poorly defined, and the majority of studies did not present a prospective power calculation. Models tended to achieve adequate goodness-of-fit and modest discriminative performance; no obvious trends were observed in relation to study characteristics and model performance. The selection of prescription variables for evaluation as potential predictors of readmission and the intended procedures for quantifying readmission risk based on prescription variables are presented in Chapter 3.

Chapter 3 General Methods

3.1 Introduction

Having reviewed the relevant literature in order to assess the context and evidence base for the potential of predicting readmissions using routinely recorded prescription information in Chapter 2, the relevant options for evaluating prescription variables as predictors of readmission are explored in this chapter and presented alongside a description of, and justification for, the candidate predictors and the methods selected.

3.2 Study design

3.2.1 Strategy of enquiry

A quantitative approach[18] was identified as the most appropriate for identifying prescription variables associated with readmission and understanding which were the most effective predictors.

Predictive models for (re)hospitalisation have been successfully developed using routinely recorded inpatient data (Billings et al., 2012; Blunt et al., 2014; Bottle et al., 2006; Bradley et al., 2013; Silverstein et al., 2008); Gildersleeve and Cooper (2013) concluded that their model demonstrated the necessary elements could be readily collected from the electronic health record and the risk calculation automated. A wealth of data was available in the Trust's records to enable correlational[19] research to be undertaken with the goal of developing the Trust's existing systems to enable readmission risk to be determined using

[18] Involving application of deductive reasoning to test objective theories by examination of relationships between variables (Creswell, 2009)

[19] Observational research to identify relationships between naturally occurring variables (Field, 2018)(Field, 2018)

routinely recorded information. Statistical techniques were employed to determine the likelihood that any differences observed in readmission risk according to prescription variables were due to chance.

3.2.2 Methods

The study involved quantitative analysis of data obtained by structured review of existing NHS data to objectively identify statistically significant associations between prescription variables and whether adult patients were readmitted within 30 days of discharge home from the Trust's Medical Short Stay Units (MSSUs). The intention was to model the likelihood of readmission in relation to prescription variables and thereby quantify clinically relevant risk factors.

3.2.2.1 Sampling

a) Setting

The study data were drawn from all discharge prescriptions from the Trust's MSSUs over six months, between:

- 26th August 2013 and 23rd February 2014 for Calderdale Royal Hospital (Hospital A)
- 9th September 2013 and 9th March 2014 for Huddersfield Royal Infirmary (Hospital B)

The MSSUs were selected for the study based on their generalist nature which encouraged clinical heterogeneity among the sample, avoiding restriction by age or diagnosis, as well as their tendency for emergency admissions and readmissions: the majority of emergency readmissions follow an emergency admission (Sg2, 2011; Zerdevas & Dobson, 2008) and general medicine has been shown to be among the specialties with the highest readmission rates (Chambers & Clarke, 1990; Yam et al., 2010; Zerdevas & Dobson, 2008). Additionally, some of the most common clinical causes of readmission are consistent with conditions commonly treated on MSSUs, such as infections and exacerbations of long term medical conditions (Sg2, 2011). Furthermore, medical admissions are more likely to be related to pharmaceutical care issues which may be amenable to pharmacist intervention (Krska,

Hansford, Seymour, & Farquharson, 2007; Paulino, Bouvy, Gastelurrutia, Guerreiro, & Buurma, 2004).

Moons et al. (2015) highlighted that developing different models for different hospitals/settings results in localised research, which can cause health care providers difficulty in deciding which to use. Cluster sampling was utilised to minimise the risk of overfitting the model to either hospital's data: the hospitals comprised one trust, but were located in different towns with different provision for primary care; community and social services, encouraging results representative of the wider health system (see also 3.3.2.3 External validity). The Trust was the provider of community health services around Hospital A; however, community health services were provided by an independent organisation in Hospital B's locality. The Trust was liable for the financial penalty for readmissions irrespective of community or social care provision.

The study period was selected pragmatically with respect to both duration and timing. The duration was selected on the basis of allowing enough time for a planned change in delivery of a key pharmaceutical service (described in 3.2.2.2 b) Mandating pharmacist validation) to be embedded into routine practice and for equivalent baseline data to be captured. The goal of obtaining a large, representative sample with enough readmissions for robust statistical analysis was also an important consideration in determining the study period (see also 3.2.2.1 b) Sample size); such opportunistic data access has been utilised in similar studies that have had successful outcomes, for example Rothman et al. (2013).

b) Participants

The analysis was prospectively limited to:

- Patients with an NHS number
    - To enable the linkage of discharge data with readmission data, mirroring the process by which cases for financial penalty are identified.
- Adult patients (aged 18 years and over)
    - Exclusion of those less than 18 years of age is consistent with many studies of readmission risk (Friebel et al., 2018; Kansagara et al., 2011); instances of

younger people discharged from adult wards were expected to be minimal, and considered atypical of the usual function of the wards.

- Patients discharged home
    - To ensure transfers to other care providers did not inflate the denominator, and given that patients transferred elsewhere may have different underlying risk (see also 1.3 Readmission rate calculation), to foster development of a model generalisable among those discharged home. This approach was consistent with Johnson et al. (2012), Pines et al. (2010), Rothman et al. (2013) and Tan et al. (2013), who each specifically restricted their study participants to those discharged home.

Unit of analysis

It was possible for patients to be discharged from the study wards more than once during the six-month study period. Patients providing data from more than one discharge could result in clustering at patient-level among discharges; consequently there was a risk that the assumption of independence of errors may not be met, which could result in overconfidence in the precision of parameter estimates (Field, 2018). Whether or not to exclude patients' subsequent discharges was therefore carefully considered. It was acknowledged in the Department of Health's report *Emergency readmission rates: further analysis* that repeat admissions had made a significant contribution to the rise in readmission rates (Zerdevas & Dobson, 2008). As discussed in 2.3.2.4 a) Unit of analysis, readmission prediction studies do not always describe whether patients could contribute more than one observation to the analysis; however, Halfon et al. (2006) acknowledged that patients could experience multiple admissions and opted to retain each admission in their analysis on the basis that each admission had its own characteristics, as did Morris (2018), who considered each admission to represent an opportunity for preventable issues to arise. Repeat admissions were a reality of the population the study wards served, and their exclusion would result in loss of data as well as potentially producing a model which did not genuinely represent the cohort. Consequently, having acknowledged the risk of

clustering, discharge was selected as the unit of analysis, with prescription and pharmaceutical intervention variables attached at discharge level. This approach resulted in a hierarchical structure to the data, which is illustrated for five typical patients in Figure 3.1.

Sample size

A large sample was sought to maximise representativeness and precision, thereby encouraging confidence in the model's estimates. It was estimated that if patients admitted to the MSSUs, which had approximately 50 beds, had the maximum anticipated length of stay (3 days, see also 3.2.2.2 b) Length of stay) then around 3000 admissions could be anticipated during the 6 month study period. This would be broadly consistent with the median sample size among the studies included in the literature review. The Trust's readmission rate was just over 11% (Calderdale and Huddersfield NHS Foundation Trust, 2013a) and it was expected that the MSSUs would have a higher than average readmission rate given their emergency medical nature. It was therefore estimated that more than 300 readmissions could be expected, which would be enough to support up to 30 predictors in the intended predictive model development (Peduzzi et al., 1996). This was considered to be more than it would be practical to include given the intention of clinical application (Royston, Moons, Altman, & Vergouwe, 2009), thus confirming that a sufficiently large sample could be anticipated.

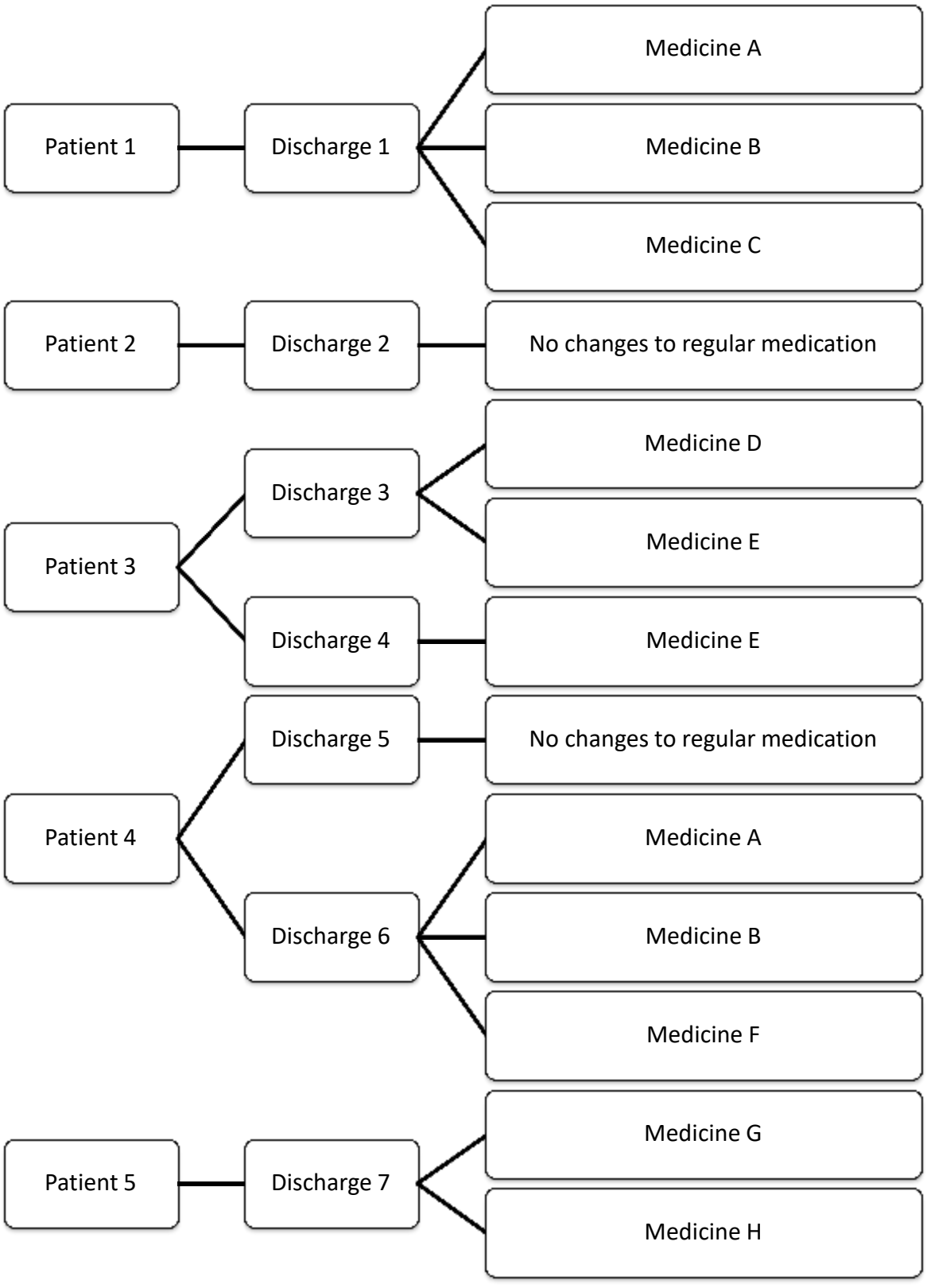

Figure 3.1: Hierarchical data structure

3.2.2.2 Selection and definition of variables

Due to the utilisation of existing data, the variables available for evaluation as predictors were those that were routinely recorded. The dependent variable was routinely monitored and reported for *PbR* (Department of Health, 2013). The independent variables that were routinely recorded were typical of UK hospital discharge prescriptions (see Appendix B), corresponding with the National Prescribing Centre (2008) minimum standard for information that should be provided to primary care by discharging hospitals.

a) Dependent variable

To ensure the results could be interpreted in the context of national policy and the Trust's goal to reduce readmissions, as well as meet the objectives of the study, the outcome (dependent) variable was readmission within 30 days as defined within the *PbR Guidance* 2013-14 (Department of Health, 2013) as:

1. Readmission within 30 days (yes/no), and
2. Number of days to readmission (0 to 30).

This is consistent with the:

- *TRIPOD* (Moons et al., 2015) recommendation that outcomes and duration of follow-up are relevant to patients and clinical decision making
- approach of many studies included in the literature review; Eapen et al. (2013) and Keenan et al. (2008) each specifically recognised that their outcome measure being aligned with public reporting was a study strength.

b) Independent variables

As stated above, the candidate predictor (independent) variables were those that were routinely recorded on discharge prescriptions which the literature review supported could reasonably be expected to relate to readmission.

Discharge variables

Despite the relatively common application of prior health care utilisation as a predictor of readmission (Au et al., 2002; Baillie et al., 2013; Billings et al., 2012; Gildersleeve &

Cooper, 2013; Halfon et al., 2006; Lee, 2012; Marcantonio et al., 1999; Mather et al., 2014; Perkins et al., 2013; Singal et al., 2013), it was highlighted in guidance about predictive risk models for UK health service commissioners that frequent prior hospitalisation may not be a practical choice of predictor for readmission due to regression to the mean[20] (Lewis, Curry, & Bardsley, 2011). Consequently, prior hospital utilisation was not considered for evaluation as a predictor of readmission in this study. It was noted, however, that (Picker et al., 2015) identified that the number of medicines prescribed at discharge was correlated with the number of ED visits in the six months prior to admission (see also Number of medicines prescribed).

Discharge site and method of discharge

The study wards were equivalent MSSUs located at each of the Trust's hospital sites. Typical of multi-hospital trusts, the medical care was led by different consultants and care provided by different teams for each unit; however, Trust-wide policies and procedures would apply and the pharmacy service was governed by the same Medicine Code (Calderdale and Huddersfield NHS Foundation Trust). There was further potential for systematic differences in the care provided during the observation period due to the differences in primary, community and social care provision around each locality as described in 3.2.2.1 a) Setting.

Whether patients were discharged via a discharge lounge was indicated on their discharge prescription. A discharge lounge is effectively a holding area to which medically stable patients are transferred whilst awaiting an aspect of their discharge, enabling their bed on the ward to be freed-up. One of the reasons patients may be discharged via a discharge lounge is to await medicines being dispensed. The Trust operated a one-stop dispensing strategy[21] and the *Medicines Code* (Calderdale and Huddersfield NHS Foundation Trust)

[20] A phenomenon in which outlying initial observations tend to precede observations closer to the average (Linden, 2013).

[21] Non-stock medicines for inpatients were dispensed so that they were suitable for issue against a discharge prescription where appropriate (Calderdale and Huddersfield NHS

stipulated that the discharge prescription would need to be sent to pharmacy, where it would be clinically validated by a pharmacist as part of the dispensing process, if any of the following applied:

- Multi-compartment compliance aids were required
- Eye preparations were required
- Reducing/increasing regimens were required
- The patient had less than 14 days' supply on the ward
- New items were prescribed which were not available as ward stock

Whether patients were discharged via a discharge lounge was therefore relevant to the analysis because patients discharged via a lounge could be more likely to require such items supplying from pharmacy on discharge.

Admission and discharge days

Services, including pharmacy, within the Trust were generally reduced at the weekends during the study period; pharmacy staff typically worked a weekend once or twice every two months. Due to the reduced availability/capacity of many services over the weekend it could be expected that, amongst other shortfalls, those admitted and/or discharged over the weekend may not benefit from clinical pharmacy services delivered routinely during the week. The *Evidence base* report of the NHS Services Seven Days a Week Forum (n.d.) stated that trusts with limited clinical pharmacy services over the weekend reported increases in missed and delayed doses, more prescription errors, lack of medicines reconciliation and delays to discharge, and that one trust had identified substantially reduced emergency duty and critical medicines call-out rates and improved rates of medicines reconciliation post-weekend having introduced a weekend clinical pharmacy service; however, these statements were not referenced. It has been demonstrated that pharmacists' recommendations to prescribers in a UK hospital were significantly less likely

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Foundation Trust).(Calderdale and Huddersfield NHS Foundation Trust). Such strategies are intended to improve efficiency and prevent unnecessary delays to discharge.

to be actioned within 24 hours over the weekend (Pontefract, Hodson, Marriott, Redwood, & Coleman, 2016). Allaudeen, Vidyarthi, Maselli, and Auerbach (2011b) hypothesised that weekend discharge may affect readmission risk on the basis that services, including pharmacy, operated with limited staffing on weekends; however, an independent association was not identified despite the study being well-powered. Dobrzanska and Newell (2006) reported that weekend discharge was a risk factor for readmission among elderly patients, although the data to support this were not presented. Blunt et al. (2014) noted high levels of readmissions were associated with discharge dates before public holidays and over the weekends; these were categorised as preference in their hierarchy of avoidable admissions; however, it has been demonstrated that hospitals with well-designed consultant working practices including weekend cover for acute medical units have significantly lower 28-day readmission rates (Bell, Lambourne, Percival, Laverty, & Ward, 2013). Although unplanned admissions would be outside the control of the Trust, day of admission was a variable of interest because it was possible that it could impact upon the quality of care delivered; similarly, day of discharge was a variable of interest on the basis that the quality of care on and following discharge may depend on the day of the week.

Length of stay

Patients were admitted to the MSSUs on the basis of their anticipated length of stay (LOS); the Trust defined a short stay as up to 72 hours. Reducing LOS is a priority for the NHS because of the need to improve efficiency and increasing demand for hospital beds: length of stay and admission rate are fundamental drivers for emergency bed use among elderly patients (Imison et al., 2012). Furthermore, it has been demonstrated that additional days in hospital are associated with increasing risk of adverse drug reactions, infections and pressure sores (Hauck & Zhao, 2011). It has, however, been suggested that complex, elderly patients may be discharged earlier than would be ideal due to increasing hospital use and pressure to reduce LOS (Cotter et al., 2012). An analysis of HES data identified that readmission rates increased as the average LOS decreased between 1998/9 to 2006/7 (Robinson, 2010). Short lengths of stay have been associated with readmissions (Bjorvatn,

2013; Dobrzanska & Newell, 2006; Lee, 2012) and medication errors among the elderly, with reduced time available for patient education suggested as a potential reason (Ziaeian, Araujo, Van Ness, & Horwitz, 2012); it is possible that short length of stay impacts upon the discharge process. However, Baker, Einstadter, Husak, and Cebul (2004) found that a shorter than expected LOS was not associated with readmission. Conversely, studies of readmission have commonly identified increasing LOS as a risk factor (Allaudeen et al., 2011b; Donzé, Aujesky, Williams, & Schnipper, 2013a; Picker et al., 2015; Shu, Lin, Hsu, & Ko, 2012; van Walraven et al., 2010a; Yam et al., 2010) which could reflect that those who have a prolonged stay tend to be more unwell, and possibly the extent to which patients' independence may be reduced by their role as a recipient of care during their time as a hospital inpatient. For example, patients who would normally manage their own medicines at home would be unlikely to continue to do so whilst staying on the MSSUs due to the wards' procedures for medicines management: this could render them 'out of practice' when they come to resume this responsibility on discharge, particularly if their prescription has been changed during their stay. The inconsistency of the direction of the relationship between LOS and readmission risk could be due to LOS reflecting both severity of illness and hospital efficiency (Goldfield, 2010), and length of stay was consequently a variable of interest in this study.

Demographic variables

Despite their common inclusion in readmission risk prediction model development, age and gender often do not contribute significantly to final models (Kansagara et al., 2011). Nonetheless, their inclusion in model development is ubiquitous and they were routinely recorded among the discharge prescription data; on this basis they were considered variables of interest in this study.

Gender

Studies have identified men as more likely than women to be readmitted (Baker et al., 2012; Chambers & Clarke, 1990; Halfon et al., 2006; Silverstein et al., 2008; van

Walraven, Wong, & Forster, 2012b; Zapatero et al., 2012; Zerdevas & Dobson, 2008). However, it has also been reported that gender is not independently predictive of readmission (Carter et al., 2018; Donzé et al., 2013a; Novotny & Anderson, 2008; Picker et al., 2015; Ruiz, Garcia, Aguirre, & Aguirre, 2008; Shu et al., 2012; Yam et al., 2010). It has been reported that women are:

- more likely to be admitted due to drug related problems (Cunningham, Dodd, Grant, McMurdo, & Richards, 1997) and/or an adverse event in the 30 days after discharge (Forster et al., 2004)
- prescribed more medicines on average, and
- more likely to have unjustified medication on their discharge prescriptions (Perren et al., 2009).

In the *Health Survey England 2013*, more women reported having taken medication in the previous week compared to men. Women were also more likely to report having taken non-steroidal anti-inflammatory drugs, and/or medication for COPD, whilst men were more likely to report having taken antiplatelet medication (Health & Social Care Information Centre, 2014a); each of these are identified as high-risk medicines in the Medicines Use Review service specification (see also 3.2.2.2 b) MUR High Risk Medicines) (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a). Women form a greater proportion of patients admitted due to adverse drug reactions compared to those admitted for other reasons (Pirmohamed et al., 2004). Given the conflicting evidence around the relationship between gender and readmission, and that the literature indicates women may be more prone to medicines-related problems which may result in readmission, gender was a variable of interest in this study.

Age

With increasing age comes increasing multi-morbidity which increases risk of admission and readmission (Vest, Gamm, Oxford, Gonzalez, & Slawson, 2010; Zerdevas & Dobson, 2008). In the *Health Survey England 2013* the number of medicines people reported taking in the previous week increased with increasing age: 50% of those 65 years of age and over

reported taking at least 3 medicines compared to over 70% of those aged 75 or over; over one third of those aged 75 and over reported taking at least six medicines. Almost all people aged 65 years of age or over that needed help with activities of daily living reported taking prescribed medication, with most taking more than three (Health & Social Care Information Centre, 2014a). Patients admitted due to ADRs have been found to be older on average than patients admitted for other reasons (Pirmohamed et al., 2004), and the prevalence of ADRs causing hospital admission is higher among elderly patients (Kongkaew, Noyce, & Ashcroft, 2008). Teymoorian, Dutcher, and Woods (2011) found almost a quarter of readmissions were attributed to ADR among patients over 80 years of age. Hospitalisations due to ADR have been found to be more likely to be preventable among elderly patients (Beijer & de Blaey, 2002); however, it has also been reported that there is no difference in the proportion of avoidable readmissions according to age (Yam et al., 2010), and that younger patient are more likely to be readmitted (Picker et al., 2015). Studies of readmission risk often focus on the elderly (Bjorvatn, 2013; Dobrzanska & Newell, 2006; Williams & Fitton, 1988; Witherington et al., 2008) or stratify by age (Zapatero et al., 2012; Zerdevas & Dobson, 2008); yet, despite elevated readmission rates among the elderly (Chambers & Clarke, 1990; Zerdevas & Dobson, 2008) it has also been reported that age is not independently predictive of readmission (Shu et al., 2012). It is probable that another characteristic related to age, such as increasing severity of illness and/or comorbidity, and/or reducing independence could account for the positive relationship that is sometimes found between readmission rate and age. Nonetheless, age was a variable of interest in this study due to the risk of medication-related problems increasing with increasing age (Beijer & de Blaey, 2002).

Address

As described in the context of variability in readmission rate calculation in the Introduction, studies vary in terms of accounting for/exclusion of those discharged to care facilities: Silverstein et al. (2008) found discharge to skilled nursing facilities to be predictive of readmission and Bjorvatn (2013) found those discharged to care had an increased risk of

readmission. Those residing in institutions were excluded from the Health Survey *England 2013* on the basis that they tend to be older and have poorer health status compared to the general population (Health & Social Care Information Centre, 2014a). However, it is arguable that those living in care should be having their care needs met to some extent, and consequently, whether patients were discharged to 24-hour care was a variable of interest in this study.

Although the proportion of people who reported having taken medication in the last week was not found to vary by region (Health & Social Care Information Centre, 2014a), geographical location has been found to be an important driver for emergency admission (Imison et al., 2012). Additionally, low socioeconomic status/deprivation is known to be associated with an increased proportion of people taking medication (Health & Social Care Information Centre, 2014a), feeling supported to manage their health (NHS Rightcare and Public Health England, 2016a), emergency admission (Imison et al., 2012), and readmission (Amarasingham et al., 2010; Mather et al., 2014; Williams & Fitton, 1988). Furthermore, patients with a low-socioeconomic status are more likely to consider difficulty adhering to medication a contributory factor to their readmission (Kangovi et al., 2012). Socioeconomic status and deprivation can be gauged according to postcode (Mather et al., 2014; Silverstein et al., 2008), and consequently postcode was a variable of interest in this study.

Prescription variables

Medication changes

Among recently discharged patients, medicine-related problems are more likely to be identified for those with changes made to their prescription whilst in hospital (Paulino et al., 2004). Forster, Murff, Peterson, Gandhi, and Bates (2005) found that all but one of 45 adverse drug events experienced by patients in the weeks following discharge from hospital in the USA related to a new medicine or altered dose, and in the UK, Witherington et al. (2008) found that prescriptions changes had been made during the index admission for the majority of elderly patients who were readmitted. Prescription changes could relate to

readmission risk for a number of reasons, particularly given the cohort typically had a short stay, including:

- Insufficient time to fully assess the clinical effect of prescription alterations during admission. For example, it is recommended that at least four weeks be allowed to determine the response to antihypertensive treatment alterations (Joint Formulary Committee, 2014); however, patients would not be expected to be on the SSUs for four weeks (see also 3.2.2.2 b) Length of stay).
    - The intended effect may not be realised e.g. further treatment adjustments may be necessary after discharge
    - Adverse effects can develop over time (Forster et al., 2005)
- Prescription changes may not be adequately communicated (Care Quality Commission, 2009; Hammad, Wright, Walton, Nunney, & Bhattacharya, 2014), actioned, and/or monitored (Coleman et al., 2005)
    - Patients may not adhere to their new prescription (Barber, Parsons, Clifford, Darracott, & Horne, 2004; Ziaeian et al., 2012)
    - Primary care providers may not implement intended changes

Whether discharge prescriptions contained changes was therefore a variable of interest in this study. The detail captured among the data included: new medicines started, medicines altered (e.g. dose, frequency, formulation), and medicines stopped.

Prescriptions that only described the changes made

When writing discharge prescriptions for patients whose length of stay was up to 24 hours, the Trust's prescribers had the option to apply a clause to the electronic discharge medication summary (EDMS) stating:

- No changes to pre-admission medications or dose of any medication, or
- No changes to pre-admission medications other than the changes identified below (Calderdale and Huddersfield NHS Foundation Trust).

It was necessary to account for such prescriptions as they were unsuitable for inclusion in many of the analyses of prescription characteristics due to the missing data, although discharge and demographic details were complete.

Potential eligibility for referral to the New Medicines Service

The New Medicines Service (NMS) is an Advanced Service under the Community Pharmacy Contractual Framework designed to improve adherence in patients prescribed new medicines, thus improving health outcomes and reducing hospital admissions. Patients eligible to receive the service were those initiated on:

- Anticoagulants
- Medicines for hypertension
- Medicines for asthma or COPD, and/or
- Medicines for type 2 diabetes (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013b).

NMS involves patients being recruited by a community pharmacist when the new medicine is initially dispensed, followed by a review to identify any problems after one to two weeks and a further follow up after another two to three weeks. Medicines started during admission were dispensed by the hospital pharmacy, necessitating a referral by secondary care in order for eligible patients to access NMS in community pharmacy post-discharge. The Trust did not have a system in place for routine referral to the NMS at the time of the study, and it is therefore expected that patients did not receive the service. The indication for medication prescribed was not reliably recorded on the discharge prescriptions, and it was therefore not possible to confirm eligibility for the service for every new prescribed item, only the potential. Nonetheless, potential eligibility for NMS was a variable of interest due to the expectation that the service could mitigate medicines-related risk of readmission.

Potential eligibility for Medicines Use Review

Medicines Use Review (MUR) is an Advanced Service within the NHS Community Pharmacy Contractual Framework. MURs involve an accredited community pharmacist conducting a

structured review of medicines use: specifically, why and how medicines should be used, identifying and addressing any problems as appropriate, and feeding back to the prescriber as necessary. Such reviews are intended to optimise medicine use and prevent avoidable admissions, and could therefore be expected to contribute to preventing readmissions. A significant proportion of MURs conducted are required to be targeted (TMURs) (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a); the target groups are described under the individual sub-headings that follow, although, it is important to note that MURs address all medicines irrespective of the target group for eligibility. It was not known whether patients:

- met eligibility criteria such as having used the same community pharmacy, which offered the MUR service, for three consecutive months
- had received an MUR in community pharmacy prior to admission, and if so,
    - had sufficient change in circumstance to warrant an MUR at an interval of less than 12 months
- had accessed an MUR during the observation period

The Trust did not have a process for referral to the service at the time of the study; however, this would not preclude patients from accessing the service during the observation period. Nonetheless, potential eligibility for MUR was a variable of interest due to the expectation that the service could mitigate medicines-related risk of readmission.

MUR High Risk Medicines

MUR high risk medicines are defined on the basis of three principles:

1. potential to cause preventable harm such as avoidable hospital admission
2. potential for harm to be caused by omission, overuse, or incorrect use
3. potential for harm to be prevented by an MUR, e.g. related to use rather than dosage (Pharmaceutical Services Negotiating Committee & NHS Employers, 2012)

MUR high risk medicines (high risk medicines, HRMs) comprise medicines from British National Formulary (BNF) sections: 2 sub-sections 2.2 (diuretics), 8.1 and 8.2 (anticoagulants), and 9 (antiplatelets), and BNF chapter 10, sub-section 1.1 (non-steroidal

anti-inflammatory drugs, NSAIDs) (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a). These medicines were identified by Pirmohamed et al. (2004) as causing the majority of ADRs resulting in hospital admissions to UK hospitals.

MUR Post-discharge Target Group

Patients may be eligible for a post-discharge MUR provided that they meet the general criteria previously set out, are prescribed more than one medicine, and their prescription has been changed during their hospital stay (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a).

MUR Respiratory Target Group

Patients may be eligible for a respiratory targeted MUR provided they meet the general criteria set out previously, and are prescribed more than one medicine, at least one of which from BNF sections:

- 3.1.1 Adrenoceptor agonists
- 3.1.2 Antimuscarinic bronchodilators
- 3.1.3 Theophylline
- 3.1.4 Compound bronchodilator preparations
- 3.2 Corticosteroids
- 3.3 Cromoglicate and related therapy, leukotriene receptor antagonists and phosphodiesterase type-4 inhibitors) (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a)

Many of these medicines are used in COPD which is associated with an elevated readmission rate (Sg2, 2011; Zerdevas & Dobson, 2008); although, many may also be used in asthma and therefore their presence on a discharge prescription does not necessarily positively identify COPD.

MUR Cardiovascular Target Group

The cardiovascular MUR target group was introduced on 1st January 2015 (after the study period) and patients would not therefore have received an MUR targeted on the basis of

cardiovascular medication. Whether patients met the criteria for a cardiovascular MUR was a variable of interest in order to explore whether the introduction of this target group may have potential to reach those at risk and prevent readmissions. Patients may be eligible for a cardiovascular targeted MUR by their community pharmacist provided they meet the general criteria set out previously, and are prescribed more than three medicines, at least one of which from BNF sections:

- 2 Cardiovascular System
- 6.1 Drugs used in diabetes
- 6.2 Thyroid and antithyroid drugs (Pharmaceutical Services Negotiating Committee, 2019)

Number of medicines prescribed

Given that prescribing of medication is the most common intervention in health care (National Institute for Health and Care Excellence, 2015), it could be expected that people with more, and/or more complex health conditions, which may put them at increased risk of complications necessitating (re)admission, would generally be prescribed more medicines; indeed, the potential for routine pharmacy data compared to diagnostic data representing comorbidity in readmission risk prediction has been demonstrated (Parker et al., 2003). It was identified in the *Health Survey for England 2013* that the majority of patients with longstanding illness reported having taken a medicine in the last week, and that those who considered their illness to limit their day to day activities were more likely to report having taken three or more medicines compared to those who did not consider their illness to be limiting (Health & Social Care Information Centre, 2014a). Increasing comorbidity has been associated with readmission (Baker, Zou, & Su, 2013; Berkowitz & Anderson, 2013; Bjorvatn, 2013; Picker et al., 2015; Shu et al., 2012; van Walraven et al., 2010a) and although less commonly considered, increasing number of medicines prescribed has also been associated with hospital readmission (Hansen et al., 2011; Picker et al., 2015) and reutilisation (Baker et al., 2013; Bolas, Brookes, Scott, & McElnay, 2004; Scullin, Hogg, Luo, Scott, & McElnay, 2012). It has been demonstrated that comorbidity and number of

medicines prescribed explain much of the same variation in readmission (Gildersleeve & Cooper, 2013), and models which have considered both have consequently tended to retain only one or the other (Baker et al., 2013; Picker et al., 2015; van Walraven et al., 2010a). Gildersleeve and Cooper (2013) interpreted the unique variance in readmission according to the number of medicines prescribed compared to comorbidity as potentially representing appropriate medication. The concurrent use of multiple medicines is termed polypharmacy. Polypharmacy is often necessary to manage long term conditions (LTCs), and has increased with increasing prevalence of multi-morbidity and an ageing population: 14% of people under 40 years of age reported having an LTC, and this increased steadily with age to 58% among those over 60 years of age (Department of Health, 2012a). Barnett et al. (2012) reported that 75% of 75-year-olds in the UK have more than one LTC, increasing to 82% among 85-year-olds. Whilst it was estimated that the number of people with one LTC would remain relatively stable over the coming 10 years from 2008, the number of people with multiple LTCs was set to increase by 50% (Department of Health, 2012a). The King's Fund defined polypharmacy as:

- appropriate when prescribing is in line with best evidence for complex or multiple conditions in circumstances where medicines use is optimised, and
- problematic when prescribing of multiple medicines inappropriately, or where the intended benefit of the medicines is not realised (Duerden, Avery, & Payne, 2013).

On one hand, effective treatment could be expected to reduce the risk of (re)admission; however, the risk of harm from medicines increases with polypharmacy (National Institute for Health and Care Excellence, 2015). Exposure to medicines increases the risk of high risk prescribing (Guthrie et al., 2011) and adverse drug reactions (ADRs). Patients who experience and/or are admitted due to ADRs are prescribed more medicines (Forster et al., 2005) (Cunningham et al., 1997). Forster et al. (2004) identified that almost a quarter of patients experienced adverse events within 30 days of discharge from a USA general medical ward. The majority of adverse events related to medicines, almost one in five resulted in readmission, and 14% of readmissions due to ADR were preventable. It is

thought that over five per cent of hospital admissions are caused by ADRs (Betteridge, Frampton, & Jardine, 2012; Pirmohamed et al., 2004). Medicines adherence has been shown to decline with increasing polypharmacy (Elliott, Barber, Clifford, Horne, & Hartley, 2008), which could result in the intended benefits of medication not being realised, increasing the risk of adverse outcomes that may result in (re)admission. Consequently, the number of medicines prescribed was an important variable of interest.

Doses per day prescribed

The number of doses per day prescribed combines the directions for use with the number of medicines prescribed, reflecting medication regimen complexity (Lipton & Bird, 1994). Patients' knowledge about their prescribed dosages decreases with increasing number of doses per day (Parkin, Henney, Quirk, & Crooks, 1976), and non-adherence increases with increasing medication regimen complexity (Mansur, Weiss, & Beloosesky, 2012). Consequently, the number of doses prescribed per day could be expected to relate to adherence and support for adherence such as the use of multi-compartment compliance aids and/or carers to prompt medication. Difficulty adhering to discharge medication was among the top three contributory issues identified by patients in a survey following readmission to a USA hospital (Kangovi et al., 2012), and failure to address problems with medication compliance during the index admission contributed to over a quarter of readmissions among elderly patients in the UK (Witherington et al., 2008). The number of doses prescribed per day was consequently a variable of interest in this study.

<u>British National Formulary (BNF) chapter of prescribed medication</u>

Medication prescribed on discharge was categorised according to BNF chapter to reflect the body system most commonly associated with each medicine, specifically:

Chapter 1. Gastro-intestinal system (GI)

Chapter 2. Cardiovascular system (CV)

Chapter 3. Respiratory system

Chapter 4. Central nervous system (CNS)

Chapter 5. Infections (antimicrobials)

Chapter 6. Endocrine system

Chapter 7. Obstetrics, gynaecology & urinary tract (GU)

Chapter 8. Malignant disease and immunosuppression

Chapter 9. Nutrition & blood

Chapter 10. Musculoskeletal & joint diseases (MSK)

Chapter 11. Eye

Chapter 12. Ear, nose & oropharynx (ENT)

Chapter 13. Skin

Chapter 15. Anaesthesia (Joint Formulary Committee, 2014)

Consistent with level one prescription reviews (Task Force on Medicines Partnership & The National Collaborative Medicines Management Services Programme, 2002) commonly undertaken in UK dispensaries (see also Pharmacist validation), the indication for medication prescribed was not reliably recorded on discharge prescriptions. The number of BNF chapters from which medication was prescribed could be expected to reflect multi-morbidity to some extent, given that each chapter relates to a different body system. As discussed in relation to the number of medicines prescribed (above), increasing multi-morbidity is commonly associated with readmission. Furthermore, some conditions are associated with an increased risk of readmission and the presence of these could be inferred by prescribed medication. For example, respiratory disease (Bjorvatn, 2013; Carter et al., 2018; Dobrzanska & Newell, 2006) could be inferred by prescription of medication from BNF chapter 3; however, it may not be so simple in the case of the more specific predictor COPD (Donzé et al., 2013b; Sg2, 2011; Zerdevas & Dobson, 2008) because many of the medicines in Chapter 3 can be used for asthma as well (see also Figure 4.20); nonetheless, (Baker et al., 2013) identified prescription of systemic corticosteroids in the prior three months as a predictor of rehospitalisation among COPD patients. Whilst some classes of medicine have contributed to predictive models for admission (Donnan, Dorward, Mutch, & Morris, 2008), few studies have reported the classes of medication specifically associated

with 30-day readmission (Allaudeen et al., 2011b; Barry, 2013). It is known that certain medicines are more likely to be associated with: prescribing errors (Lewis et al., 2009); time taken to/whether prescribers action hospital pharmacists' recommendations (Pontefract et al., 2016); discrepancies after discharge; (Coleman et al., 2005); medication-related problems/pharmaceutical care issues (Krska et al., 2001; Paulino et al., 2004); and/or hospital admissions due to their propensity to cause harm (Howard et al., 2007; Parekh et al., 2018; Pirmohamed et al., 2004). The medicines most commonly taken by respondents of the *Health Survey for England 2013* included antihypertensives and analgesics (Health & Social Care Information Centre, 2014a): it seems relevant that diuretics, which can be used as antihypertensives, and NSAIDs, which are used for analgesia, are among the medicines identified as high-risk in the MUR service specification (see also 3.2.2.2 b) MUR High Risk Medicines) (Pharmaceutical Services Negotiating Committee & NHS Employers, 2012). Prescribing of any medicine should be on the basis that the perceived benefits outweigh any expected risk. The risks and benefits may be dynamic because they can change with other patient-specific factors such as medical conditions and medication; renal, hepatic or cognitive function; or even social support. There are often a number of options for pharmacological treatment of a disease, and the medication prescribed represents a modifiable risk factor in some cases e.g. anticholinergic medication prescribed for patients who become prone to falls. Consequently, the BNF chapter of medicines prescribed was a variable of interest in this study.

Anticholinergic Cognitive Burden

Medicines with anticholinergic (antimuscarinic)[22] activity have been shown to have a cumulative association with anticholinergic adverse effects, cognitive impairment and mortality in elderly patients (Boustani, Campbell, Munger, Maidment, & Fox, 2008; Fox et al., 2011; Rudolph, Salow, Angelini, & McGlinchey, 2008; Ruxton, Woodman, & Mangoni,

[22] The blockade of acetylcholine and its action upon muscarinic receptors resulting in side effects commonly including dry eyes, dizziness, sedation, confusion, delirium, and falls

2015). Anticholinergic medication has been implicated in drug-related admissions of elderly patients (Gillespie et al., 2009); it has also been demonstrated that high anticholinergic exposure among older adults is associated with social deprivation and care home residence (Sumukadas, McMurdo, Mangoni, & Guthrie, 2014). Impairment of cognition or other functions which could ultimately result in mortality could also be expected to lead to readmission, and the anticholinergic cognitive burden of discharge prescriptions was therefore a variable of interest in this study. Boustani et al. (2008) presented the anticholinergic cognitive burden (ACB) score, which is made up of the medicines' cumulative cognitive anticholinergic negative effects. Individual medicines were assigned scores according to the perceived severity of their anticholinergic cognitive effects (1 = mild, 2 = moderate, 3 = severe). The authors recommended that older patients (65 years of age and over) who presented with cognitive symptoms, mild cognitive impairment or delirium whose prescriptions contained any medicine with an ACB score of two, or had an overall ACB score of three or more were reviewed with a view to minimising the score and the associated risk. Recent guidance for the NHS continues to promote minimising the use of anticholinergic medicines where possible (PrescQIPP, 2016; Scottish Government Model of Care Polypharmacy Working Group, 2015). The discharge prescription data did not consistently indicate whether the patients had cognitive symptoms, however, given the evidence that high anticholinergic burden can lead to poor outcomes, it was considered relevant to analyse the prescription criteria of the recommendation despite the absence of clinical context around cognitive impairment.

Pharmaceutical intervention

Pharmacist validation

Pharmacist validation of a prescription involves critical review to assess the clinical appropriateness of the medicines prescribed for the patient with consideration for the prescribed drug, dose and frequency of administration, formulation and method of administration, quantity, indication, contraindications, cautions, product license, formulary

status and cost-effectiveness, as well as confirming that the prescription meets legal requirements. The degree of scrutiny applied may vary depending on the complexity of the patient, medication regimen and discharge, whether validation is conducted with reference to the patient, prescriber and/or clinical notes, and whether medication review has been conducted recently. Four levels of medication review were defined in *Room for Review* (2002) as follows:

0 Ad-hoc Review: unstructured, opportunistic review - typically a query about a specific aspect of a prescription

1 Prescription Review: technical review of list of patient's medicines, normally without access to notes and/or patient

2 Treatment Review: with access to the clinical record but not necessarily the patient

3 Clinical Medication Review: face-to-face review of medicines and conditions with access to the full clinical record and involving the patient as a full partner.

Corresponding levels were reflected in the Trust's drug charts and it was expected that all prescriptions would receive the highest possible level of review initially, and that subsequent reviews would be carried out at the level deemed appropriate in the circumstances. Discharge prescriptions were annotated according to whether they had or had not been validated by a pharmacist, however, details of medication reviews undertaken prior to discharge were not documented on discharge prescriptions. Therefore, although it was known whether a discharge prescription was validated by a pharmacist, the extent to which the prescription had, or had not, been subject to pharmacist review during the patient's admission was not reflected in the data. Considering that the study wards had daily pharmacist cover during normal working hours it would be expected that patients who had been on the ward for more than one weekday would have had their prescription reviewed by a pharmacist, although this was unmeasured. Christensen and Lundh (2016) found insufficient evidence that medication review reduces readmissions in their Cochrane review of medication review for hospitalised inpatients. Nonetheless, pharmacist validation of the discharge prescription was a variable of interest because it has been estimated that

prescribing errors affect half of admissions (Lewis et al., 2009) and inadequate discharge prescription communication is known to contribute to preventable readmissions (Witherington et al., 2008). Pharmacist validation of discharge prescriptions has been shown to be effective in intercepting prescribing errors (Abdel-Qader, Harper, Cantrill, & Tully, 2010) which have been shown to have potential to cause harm (Perren et al., 2009), and represents a key function of the clinical pharmacy service that is intended to ensure the safe and effective use of medicines. Whether validation was conducted on the ward was also captured in routine data, which is relevant to this study because ward-level validation facilitates access to the patient, prescriber and notes required for clinical medication review, and there is evidence that problems identified during pharmacist validation of discharge prescriptions commonly requires access to ward-level resources (Upton, Taylor, Cullen, & Urban, 2013).

Mandating pharmacist validation

The system by which discharge prescriptions were submitted for validation by a pharmacist changed substantially at the mid-point of the study, and this was the change upon which the study period was based. During the first three months (phase one), pharmacist validation of discharge prescriptions was optional. The Trust's Medicines Code stipulated that:

> *Where possible an Electronic Discharge should receive a clinical check by a pharmacist. In most cases the Electronic Discharge will not need to be dispensed by the pharmacy department, as the patient will have a sufficient quantity labelled for discharge in the cabinet. The patient must have at least 14 days' supply of medication on discharge (or enough to cover if it is a short course of medication) or have a supply at home, which is sufficient to cover the course (Calderdale and Huddersfield NHS Foundation Trust, 2012b).*

As previously discussed, the Trust had a one-stop dispensing system in operation and the *Medicine Code* stipulated that discharge prescriptions would need to be sent to pharmacy, where they would be validated by a pharmacist as part of the dispensing process, if any of the following applied:

- Multi-compartment compliance aids (MCAs) were required
- Eye preparations were required
- Reducing/increasing regimens were required
- The patient had less than 14 days' supply on the ward
- New items were prescribed which were not available as ward stock (Calderdale and Huddersfield NHS Foundation Trust)

Prescriptions that required dispensing at the point of discharge would therefore tend to include last minute additions to prescribed regimens, MCAs, and prescriptions for patients who had been in hospital long enough for their own and/or one-stop dispensed supplies to fall short of the required 14 days' supply on discharge. Two nurses would assemble the patient's discharge medication on the ward if no supply was required from pharmacy, and submission for pharmacist validation would therefore be prompted by the need for medication to be dispensed on discharge.

In the latter three months of the study (phase two) pharmacist validation of discharge prescriptions was mandated during pharmacy's normal working hours, irrespective of the need for supply, as the result of the implementation of a CQUIN[23] (Commissioning for Quality and Innovation) target.

Medicines reconciliation

Medicines reconciliation is defined by the Institute for Healthcare Improvement as:

> *The process of identifying a person's current medicines and comparing them with the current list in use, recognising any discrepancies, and documenting any changes, thereby resulting in a complete list of medicines, accurately communicated (National Institute for Health and Care Excellence, 2015)*

It can be considered in two discrete stages:

[23] Commissioning for Quality and Innovation: providers are reimbursed by commissioners subject to achieving locally-agreed quality improvement targets (NHS England, 2016)

1. Documenting a complete and accurate list of a patient's current medication regimen within 24 hours of admission
2. Comparing the basic reconciliation information to the current inpatient prescription: pharmacy professionals can highlight discrepancies between the medication regimen prior to admission and that prescribed on admission, however, action to resolve discrepancies must be undertaken by a prescriber (National Prescribing Centre, 2008)

The National Institute for Health and Clinical Excellence and National Patient Safety Agency (2007) recommended pharmacists be involved in the medicines reconciliation process as soon as possible after admission to hospital. Medicines reconciliation is considered crucial on admission to hospital and on discharge back to primary care to ensure that an accurate list of medication the patient is taking is captured and communicated; prescriptions must be communicated effectively through care transitions for the benefits of medication to be realised. Ziaeian et al. (2012) reported that four out of every five patients among an elderly cohort experienced a medicines reconciliation error or a misunderstanding of medication change after discharge, with one in five experiencing both; in the UK, it has been estimated that prescribing error affects half of all hospital admissions (Lewis et al., 2009). Accurate medicines reconciliation can prevent unintentional prescription changes (Schnipper et al., 2009), thereby ensuring that medicines are prescribed with complete knowledge of what a patient is already taking. Inadequate discharge prescription communication is known to contribute to preventable readmissions (Witherington et al., 2008), and elevated readmission rates have been identified among patients with prescription discrepancies on discharge (Coleman et al., 2005). Although evidence of medicines reconciliation being effective in reducing readmissions is lacking (Schnipper et al., 2009), medicines reconciliation was a variable of interest in this study due to its efficacy in reducing discrepancies and errors which can result in readmission (Coleman et al., 2005), and medicines reconciliation status being routinely recorded on discharge prescriptions.

At the time of data collection it was standard procedure within the Trust for drug histories to be undertaken by pharmacy technicians on admission and for medicines reconciliation to subsequently be conducted by pharmacists. This was recorded on the drug chart. On discharge medicines reconciliation was recorded using a tick box on the electronic discharge prescription, documented as part of pharmacist validation of the discharge prescription.

Multi-compartment compliance aids

Multi-compartment compliance aids (MCAs) are defined by the Royal Pharmaceutical Society (2013a) as:

> *a repackaging system for solid dosage form medicines, such as tablets and capsules, where the medicines are removed from manufacturer's original packaging and repackaged into the MCA…MCA exist as both sealed or unsealed systems, and cassette (where several medicines can be in one compartment) or blister (where there is only one dose of a medication in each compartment) systems.*

The RPS encouraged development of better understanding of the evidence-base around the use of MCAs, and recommended that, given the lack of evidence to support their use, pharmacists should dispense medicines in original packs supported by appropriate pharmaceutical care in the absence of a specific need for an MCA (Royal Pharmaceutical Society, 2013a). It was identified in a Cochrane review that reminder packaging (MCAs) may represent a simple method for improving adherence for patients with selected conditions (Mahtani, Heneghan, Glasziou, & Perera, 2011), and another Cochrane review has since concluded that interventions for medication self-management were generally effective in improving adherence, however, results for studies of reminder packaging (MCAs) were mixed and further research was recommended (Ryan et al., 2014). Whilst MCAs do not represent a suitable intervention for all, they are in common use; MCAs were reported to be a recommendation of over 10% of domiciliary medication reviews conducted by pharmacists among elderly patients after discharge from hospitals in the UK (Holland et al., 2005). Used appropriately, MCAs can enable some patients who would otherwise become unable to manage their own medicines to remain engaged and maintain some independence. Coleman, Parry, Chalmers, and Min (2006) reported a reduction in

readmissions among patients who were provided an intervention designed to empower them to take an active role during care transitions and ultimately self-manage: the study did not specifically address MCAs, however, the role of MCAs in the context of maximising independence seems compatible with the findings. On the other hand, MCAs are often provided to facilitate carers to administer medication, and therefore do not always represent support for independence with medication. The *Medicine Code* stated that the discharge prescription would need to be sent to pharmacy if MCAs were required (Calderdale and Huddersfield NHS Foundation Trust). When MCAs were dispensed on discharge the pharmacist would annotate the prescription with the usual community pharmacy, and the discharge note would then be faxed to the pharmacy to support their preparation of subsequent MCAs. Dispensing of MCA(s) on discharge did not therefore represent only the dispensed device, but also enhanced medicines reconciliation activity involving community pharmacy. Individual pharmacist's interpretation of what constituted an MCA, or the need to document the patient was using one was not assessed. Furthermore, it is possible that patients who were not dispensed an MCA could have used a self-filled MCA and this would not necessarily be evident from their discharge prescription. Whether MCAs were dispensed was routinely recorded on the discharge prescription and, given the potential for an association between adherence and readmission (Yam et al., 2010), was a variable of interest in this study.

3.2.2.3 Data collection

The Health Informatics Service (THIS) provided raw data from electronic discharge summaries (EDS) within the Trust's electronic patient administration system (PASWEB) for every discharge from the MSSUs during the study period including:

- NHS number
- Patient's age
- Admission date
- Discharge date
- Discharging ward

Separate 30-day outcome data were also provided, including date of:

- Readmission
- Death

The discharge data were cross-referenced with outcome data after manual data collection had been undertaken by the practitioner researcher, which involved individual review of each electronic discharge medication summary (EDMS, a component of the EDS) using PASWEB to obtain further data including:

- Whether the discharge summary was incomplete
- Whether the patient was discharged via a discharge lounge
- Gender
- Whether the address indicated 24 hour care
- Postcode district
- Whether a clause indicating that only changes were detailed on the prescription was included
- Each prescribed item (drug, dose, frequency, status, reason, course)
- Whether the prescription had been validated by a pharmacist
    - Whether such validation had been undertaken on the ward
- Whether the medicines had been reconciled
- Whether the prescription indicated an MCA had been dispensed

3.2.2.4 Data processing

A unique identifier was allocated for each prescription entry, discharge, and patient. A cipher was created relating this to NHS number, and NHS number was then removed from the working data set to comply with information governance requirements that identifiable data remain under NHS encryption. The following additional variables were created using those described above:

- Number of times each individual was discharged from the study wards during the study period (repeat admissions)

- Whether discharge occurred during the first or second phase of the study (pharmacist validation optional or mandatory)
- Day of the week on admission
    - Whether admitted during the week or at the weekend
- Day of the week on discharge
    - Whether discharged during the week or at the weekend
- Length of stay (number of days between admission and discharge)
- Discharging hospital (Wards 2A and 2B = Hospital A, Ward 6 = Hospital B)
- Number of medicines prescribed
    - Number of medicines started, altered, unchanged and stopped
        - Whether prescribed medicines were intended to continue (intended duration longer than the observation period of 30 days)
        - Whether the discharge prescription potentially met the criteria for referral to the NMS
        - The number of medicines prescribed on admission
            - The change in the number of medicines prescribed on discharge compared to on admission
    - Number of prescribed doses per day (see below)
- BNF chapter of each medicine prescribed (see below)
    - Whether each medicine was a MUR high risk medicine
    - Anticholinergic Cognitive Burden Score for each medicine prescribed
    - Whether the discharge prescription potentially met the criteria for TMUR
        - Which type(s) of TMUR the prescription potentially met the criteria for
- Time to readmission (number of days between discharge and readmission)

The number of total and continuing doses prescribed per day was calculated for each discharge: where the frequency involved a range, the number of doses per day was considered to be the minimum that complied with the prescription instructions (e.g. once or twice a day = 1, up to four times a day when required = 0, four times a day = 4).

Prescribed items were also categorised according to BNF chapter and section according to the 2013 Prescription Cost Analysis (Health & Social Care Information Centre, 2014c); categorisation was conducted with reference to the 'reason' column and in the context of the rest of the prescription to clarify the indication as necessary. This enabled categorisation according to whether prescribed medicines potentially met the criteria for referral to community pharmacy services NMS and/or TMUR (Pharmaceutical Services Negotiating Committee & NHS Employers, 2013a, 2013b). Each item prescribed was also assigned the applicable ACB according to Aging Brain Care (2012) and Boustani et al. (2008). Variables in the resulting dataset are summarised in Figure 3.2 below, and described in Table 4.1:

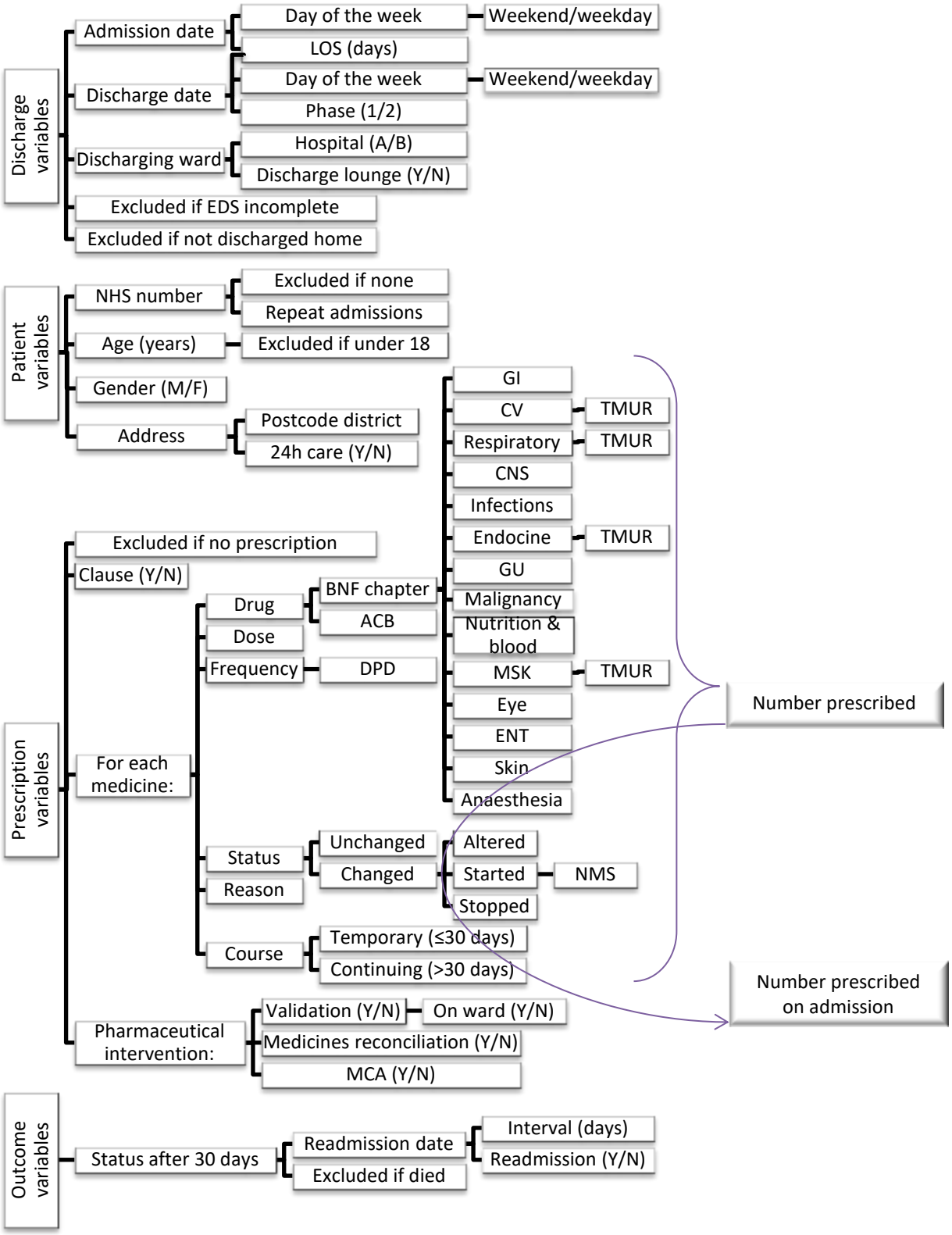

Figure 3.2: Data collection, processing and the resulting variables

3.2.2.5 Data analysis

Data analysis was undertaken using IBM SPSS Statistics Version 24, and comprised exploratory, logistic regression and survival analysis.

a) Exploratory analysis

Exploratory Data Analysis was undertaken to characterise the data (see Chapter 4), encompassing:

- Validating and gauging the quality of the data, including ensuring all entries were plausible as well as quantifying the extent of missing data
- Summarising minimum, maximum, average and distribution for numerical variables; and frequencies for categorical variables
- Investigating associations between variables by inferential statistics to inform predictor selection

Categorical variables

Frequencies are presented for categorical variables. Frequencies were analysed by the Pearson chi-squared test to determine whether variables were independent of one another; with results presented as chi-squared statistic with degrees of freedom, significance level, and with measure of association expressed as phi coefficient (χ^2_{DF}, p, φ). A phi statistic <0.3 was interpreted as representing a weak association, 0.3 to 0.7 a moderate association, and >0.7 a strong association.

Numerical variables

The minimum and maximum values are presented for numerical variables as well as the average and dispersion; histograms are presented to demonstrate the distribution of numerical variables. Mean values were compared according to categorical variable group membership by *t*-test, presented with the 95% confidence interval for the difference, *t* statistic with degrees of freedom and significance level (95% CI, t_{DF}, p); population pyramid plots are presented to demonstrate significant differences. Correlation between numerical

variables was assessed by scatterplot; when a linear relationship was identified this was quantified by Pearson's correlation coefficient (with associated significance level), presented as (r, p) and explored by linear regression to identify the extent of variation in one variable explained by the other, presented as F statistic with degrees of freedom, significance level, coefficient of determination & equation (F_{DF}, p, r^2 & equation).

Statistical significance

It was acknowledged that the large sample size would enable the detection of small, statistically significant, albeit potentially unimportant and clinically insignificant differences. Additionally, conducting multiple comparisons was expected to increase the familywise error rate[24] which would result in statistical significance being identified by chance due to the underlying margin of error: test results were considered statistically significant if the associated p-value was <0.05, corresponding to an alpha level of five per cent, which is expected to incorrectly identify one non-significant result as significant in every 20 tests; the beta level was also set at a conventional threshold of 0.2, which can be expected to fail to identify one significant result as significant in every five tests. It is possible to reduce the likelihood of type I error[25] at the expense of increasing the likelihood of type II error[26]; however, identifying significant associations was prioritised over confirming their absence in order to provide opportunity for the potential clinical significance to be assessed. Consequently, the greater risk of type I error was acknowledged and accepted.

[24] Probability of type I error in a set of tests conducted on the same data (Field, 2018)

[25] Incorrectly identifying a relationship that is not significant as significant (false positive) (Field, 2018)

[26] Incorrectly identifying a relationship that is significant as non-significant (false negative) (Field, 2018)

Missing data

Pairwise exclusion[27] was utilised in order to minimise the impact of missing data. Whilst this prevented cases with missing data from being unnecessarily excluded from analysis of variables that were not affected by missing data, it also resulted in variability in the number of cases included in analyses involving different combinations of variables, and this is evident as denominator variation throughout the exploratory analysis.

b) Logistic regression analysis

Logistic Regression was undertaken to model readmission within 30 days (see Chapter 5). The effectiveness of individual variables as predictors of readmission was explored by simple logistic regression and the collective influence of independent predictors (i.e. adjusted, controlling for the other variables in the model) was then quantified by multiple logistic regression.

Binary logistic regression

Logistic regression enables the probability of a categorical outcome to be estimated based on observed values of related variables by fitting a linear model to the data; this is achieved by logit transformation of the dependent variable. Equation 3.1 demonstrates that the probability of the outcome occurring, *P*(*Y*), is predicted based on parameter estimates (*b*s) and log-transformed predictor values (*X*s):

Equation 3.1: Logistic regression

$$P(Y) = \frac{1}{1 + e^{-(b_0 + b_1 X_{1i} + b_2 X_{2i} + \cdots + + b_n X_{ni})}}$$

(Armitage, Berry, & Matthews, 2002; Collett, 2003; Field, 2018).

[27] Elimination is limited to cases for which the necessary combination of values are not available, irrespective of whether the case has missing values for other variables (Field, 2018)

Binary logistic regression was selected as the most suitable method for predicting the likelihood of readmission within 30 days depending on a combination of categorical and continuous predictor variables from discharge prescriptions, as well as determining the effect size and relative importance of the predictor variables.

Modelling strategy

1 Screening candidate predictor variables

The potential of the candidate predictor variables to predict readmission was assessed by simple logistic regression with a relatively liberal threshold for significance ($p<0.2$). Variables identified as having potential were assessed for correlation and multicollinearity to rationalise those taken forward for the multivariable model.

2 Building the predictive model

The predictors' collective potential was assessed by multiple logistic regression. The candidate predictors were entered into the model hierarchically, with pharmaceutical variables taking priority. Predictors that did not contribute significantly ($p<0.05$) were disregarded one by one until only those contributing significantly were included; producing the most simple, yet effective (parsimonious), predictive model.

3 Optimising the predictive model

The balance between identifying patients who would be readmitted and ruling out those who would not was explored by ROC curve analysis, to identify the most effective predictive model and its optimal classification threshold (the probability above which readmission was predicted).

4 Validating the predictive model

Split-sample validation was undertaken by training the model on a random selection of cases and testing the resulting model's performance on the remaining cases. Sensitivity analysis was conducted by comparing the final model which included all discharges, with a version limited to the first discharge for each individual in order to determine whether the parameter estimates were affected by the potential clustering previously described (see 3.2.2.1 b) Unit of analysis)

Finally, diagnostic statistics were inspected to identify outliers, quantify their influence on the model, and evaluate the final model's fit.

Model specification

Whether patients were readmitted according to the 30-day readmission rule (Department of Health, 2013) (No = 0, Yes = 1) met the requirement for a meaningfully coded, mutually exclusive, dichotomous dependent variable, and prospectively selecting the candidate predictor variables as described in 3.2.2.2 b) Independent variables fulfilled the requirement that all relevant variables be included, and all irrelevant variables be excluded, insofar as possible. Utilising automated methods where possible to draw the data from existing records and conducting data validation minimised error and missing data among variables (Garson, 2016). The relationships between candidate predictor variables and readmission were explored in the Exploratory Analysis to confirm the requirement for absence of complete separation[28] was met (Field, 2018). Additionally, because including related variables in the multivariable model could violate the requirement for independent observations, resulting in increased standard errors and potentially producing parameter estimates which were not representative of the population (see also Significance of parameter estimates), it would not be correct for closely related variables to be included as predictors in the multivariable model (Field, 2018).

Peduzzi et al. (1996) recommended that at least 10 events per predictor were required to maintain the validity of logistic regression models; the maximum number of predictor variables in the multivariable analysis was therefore limited by the number of readmissions observed. Given that listwise deletion[29] applies in logistic regression analysis, the number of readmissions observed was limited by the variable with the most missing data. Which of the candidate predictor variables from each group was selected for inclusion in the multivariable model was based on:

- the extent of missing data

[28] A situation in which the outcome can be perfectly predicted by the predictor(s) (Field, 2018)

[29] Cases are eliminated from analyses if values are missing for any variable, irrespective of whether the necessary combination of values are available for a particular test (Field, 2018)

- the anticipated practicality of application in the clinical setting
    - Although dichotomising continuous variables is discouraged because of the resulting loss of detail and accuracy (Bouwmeester et al., 2012), simplicity is important in models intended for clinical application and it is considered less practical for practitioners to calculate a value than assign a binary category (Royston et al., 2009). Furthermore, Bradley et al. (2013) found a categorical version of the *Rothman Index* explained more variance as well as being more clinically useful than the continuous version. Consequently whether the loss of detail outweighed the increased simplicity achieved by dichotomising numerical variables was carefully considered when deciding which expression of such predictors (e.g. whether any HRMs were prescribed and the number of HRMs prescribed) to retain.

The rationalised variables were then assessed for correlation (strong, r>0.5) and multicollinearity (variance inflation factor, VIF >10) to ensure those included in the multivariable analysis were suitably independent of one another: a VIF greater than 10 can indicate a serious problem, and an average substantially greater than one can be indicative of bias (Field, 2018). See also 0(

Model performance).

As previously described (0 Unit of analysis) it was possible for patients to contribute more than one discharge to the analysis; individuals should not provide multiple observations at different time points in logistic regression due to the requirement for independent observations (Garson, 2016) and consequently sensitivity analysis was undertaken (as described in 3.2.2.5 b) Sensitivity analysis) to assess whether the model parameters were affected by the potential clustering.

Due to the pharmacy context for the project, the multivariable logistic regression model was specified in blocks to ensure that the contribution of pharmaceutical variables took priority over the contribution of the other variables, specifically:

Block 1 Pharmaceutical variables

Block 2 Other variables

Using this method ensured that non-pharmaceutical variables were only retained in the model if they explained variance in the outcome that was not explained by the pharmaceutical variables.

Parameter estimation

Parameter estimates are essential for calculating the probability of the outcome using the logistic regression equation; they were calculated by maximum-likelihood estimation, which seeks to maximise the log likelihood[30] (Field, 2018). Parameter estimates are presented with their standard error (SE) and 95% confidence interval for the final logistic regression model as well as the associated validation and sensitivity analysis models.

Assessing the model

Significance of parameter estimates

The significance of the contribution of the parameter estimates to the overall fit of a logistic regression model is determined by the significance of the corresponding Wald statistic. Wald can be underestimated when parameter estimates and standard errors are large, which can result in variables that contribute significantly to the model being incorrectly disregarded (Field, 2018). Consequently, the associated parameter estimates and standard errors were consulted for each non-significant variable discarded. As recommended by Petrie and Sabin (2009), a relatively liberal significance threshold was applied for the screening (simple logistic regression) process to ensure that variables with apparently weaker independent relationships with readmission were not prematurely disregarded. The effect of this is demonstrated by Amarasingham et al. (2010): gender contributed significantly to the multivariable model having been retained despite making a conventionally insignificant contribution in the simple logistic regression model. Similarly, insurance status and number

[30] The odds that the observed outcome may be predicted from the observed values of the predictor variables

of ambulatory medications did not contribute significantly in the univariable analysis undertaken by Gildersleeve and Cooper (2013), but did so in the final model. The level of $p<0.2$ applied in this study was consistent with Amarasingham et al. (2010), Singal et al. (2013) and Forster et al. (2005). All variables with $p<0.2$ in relation to readmission in simple logistic regression analysis proceeded to multiple logistic regression analysis. Backward elimination was then utilised in the multivariable analysis; specifically, the variable contributing least significantly was disregarded and the analysis re-run until all of variables included were contributing significantly at the conventional significance level of $p<0.05$.

Effect size

Odds ratio

The odds of an outcome occurring is the probability that it occurs divided by the probability that it does not. Odds ratios (ORs), which are the exponential of the associated parameter estimate, indicate the change in odds resulting from a unit change in the associated predictor (Field, 2018), for example: the effect of an additional year of age, or male compared to female gender on readmission risk. The further ORs are from one the greater effect size they indicate, with values less than one representing a protective effect. Odds ratios are presented with their 95% CIs (which should not cross one for a significant effect to be inferred) for the final multiple logistic regression model, as well as the associated validation and sensitivity analysis models.

Accuracy

Classification tables represent model effect size based on predictive success; specifically, the percentage of cases that are correctly classified (accuracy, or discrimination). Accuracy accounts for whether predictions are correct, but not how close predictions are. Careful interpretation is required because accuracy can depend on the underlying event rate, for example: a model predicting that no patients would be readmitted in a cohort for which the readmission rate was 11% would achieve 89% accuracy without correctly identifying any

patients at risk. Nonetheless, classification tables enable calculation of sensitivity and specificity, and are useful for gauging model performance. They are presented for the final multiple logistic regression model as well as the associated validation and sensitivity analysis models.

Receiver operating characteristic (ROC) curve analysis

Receiver operating characteristic curves graphically represent the classification capability of a model across classification threshold configurations demonstrating its discriminative capability. Sensitivity is plotted on the *y*-axis, and 1-specificity is plotted on the *x*-axis, with a diagonal reference line (0.5) representing a result equivalent to chance: points closest to the top left-hand corner and furthest from the reference line have the most favourable combined sensitivity and specificity. The greater the area under the curve (AUC, c-statistic), the better the model's discriminative capability (see also 2.3.6.2 Discrimination)

As with classification tables, ROC curve analysis accounts for whether predictions are correct, but not how close they are. ROC curve analysis was applied in two ways:

1. To identify the most effective model for predicting readmission
2. To optimise the classification threshold for the probability of readmission

In practice the most suitable classification threshold would depend on the context in which the model would be applied, as it is necessary to balance the importance of identifying those who would be readmitted against the consequence of identifying too many patients for intervention. Health systems should select a suitable threshold based on their target for reduction, and the anticipated cost and effectiveness of intervention. For example, the Trust was working towards a target of reducing readmissions by one-third (Calderdale and Huddersfield NHS Foundation Trust, 2012a). Implementing an intervention effective in preventing 50% of readmissions would necessitate selection of a threshold that identified two-thirds of the patients that would be readmitted for intervention in order to achieve the desired 33% reduction. In order for implementation of intervention to be cost-effective the cost of providing it to the patients identified by the model would need to be less than or equal to:

- the cost of the readmissions which would be prevented and/or
- any financial reward of meeting the reduction target, and/or
- any budget for preventing readmissions based on improvements to other consequences of readmission than financial cost, e.g. perceived quality of care or patient experience

The more expensive the intervention, the greater priority would need to be attributed to the model's specificity in order to prevent costly intervention from being delivered for patients who would not require it. The priority attributed to sensitivity is not limited to expense, but also the potential consequence of the outcome, for example it would generally be justifiable to regard sensitivity as holding greater importance in a model identifying those for effective intervention to prevent mortality, than for intervention to improve an outcome solely related to satisfaction or efficiency. ROC curves demonstrate that greater specificity comes at the expense of poorer sensitivity, resulting in fewer patients who may benefit from intervention being identified.

Goodness of fit

- *Likelihood ratio*

Multiplying the log likelihood by minus two produces a statistic that has a chi-square distribution (deviance, -2LL). The difference between the deviance of a baseline model[31] and the deviance of the fitted model(s)[32] is the likelihood ratio, which demonstrates the improvement achieved by including the predictor(s) (Field, 2018). The conventional significance level of $p<0.05$ was applied for determining the significance of differences in model fit throughout the multiple logistic regression model building process. Deviance is

[31] Based on frequency of the outcome alone i.e. all cases predicted to have the most frequently occurring outcome

[32] Includes the predictors

presented for the multiple logistic regression models (as -2LL X^2_{df}, p) to enable comparison of versions.

- *Pseudo R^2*

As previously described in 2.3.6.1 , Pseudo R^2 measures express the percentage reduction in error in a logistic regression model; values range from zero to one, and the higher the magnitude of the effect size the higher the value (Field, 2018). Nagelkerke's (R^2_N) was selected for this study as it is the most commonly cited pseudo R^2 (Garson, 2016); it is presented throughout the multiple logistic regression modelling process as a gauge of goodness of fit.

- *Hosmer-Lemeshow test*

As described in 2.3.6.1 , the Hosmer-Lemeshow goodness of fit test (HL) represents model calibration; predicted and observed frequencies are tested by chi-squared test for deciles of predicted probability. A non-significant result ($p>0.05$) indicates that the model's predictions are not significantly different from the observed values, confirming that it adequately fits the data. The test does not indicate the extent of variance in the outcome explained by the model, and is prone to identifying smaller differences significant in large sample sizes (Garson, 2016). HL (X^2_{df}, p) is presented to evaluate the calibration of the final model.

Box-Tidwell transformation

Logistic regression requires a linear relationship between continuous independent variables and the log odds of the dependent variable (linearity of the logit). If this assumption is not met then the resulting model may underestimate the relationship between the predictors and readmission. Linearity of the logit was tested by Box-Tidwell transformation, in which a non-significant result confirms a linear relationship. Specifically, an interaction term for each predictor multiplied by its natural logarithm (Ln) was added to the final logistic regression model; the significance of the associated parameter estimates is presented to provide assurance the assumption was met (Field, 2018; Garson, 2016).

Internal validation

There is evidence that model performance is similar among studies which utilise split-sample cross-validation and those that utilise external validation (Kansagara et al., 2011), the purpose of which is to test the model's performance in a different sample than that from which it was derived to gauge generalisability within that population; an advantage of cross-validation is that it makes efficient use of available resources because it does not require separate data collection be undertaken. The model was cross-validated by splitting the data randomly into training and validation subsets approximating 80% and 20% respectively. The predictors from the final model were then used to produce the validation model in the training subset, and the probability of readmission among the validation subset was predicted using the resulting parameter estimates. Finally, the parameter estimates and predictive capability of the final and validation models were compared for similarity to gauge the suitability of the model for application to the Trust's MSSU patients in general (Field, 2018). External validation was outside the scope of the study, however, it would be required to determine the validity of applying the model to other wards or trusts.

Sensitivity analysis

As previously described in 3.2.2.1 b) Unit of analysis, there was a risk that the assumption of independence of errors may not be met due to the potential for repeat admissions involving the same patient(s); this could result in overconfidence in the precision of parameter estimates (Field, 2018). Consequently, sensitivity analysis was undertaken to explore whether any potential clustering affected the predictive model. The final model was re-specified to produce the sensitivity analysis subset, which was limited to the first discharge observed for each patient (primary observations). Subsequent discharges were excluded, and the resulting model was compared with the final model to confirm whether repeat admissions had affected the parameter estimates or the model's predictive capability.

Diagnostic statistics

Diagnostic statistics were examined to identify points which deviated significantly from the main trend of the data (outliers), to quantify their influence on the model, and evaluate the final model's fit.

Residuals

Residuals are a type of distance measure. Distance reflects the error of prediction for a given observation in terms of the distance of the predicted value to the regression line; in other words, the difference between the observed and predicted value. Residual analysis has three main purposes: to identify outliers, patterns of error, and heteroscedasticity (inconsistent variability in the outcome across predictor values). Standardised residuals are the raw residuals expressed in standard deviation (SD) units (mean 0, SD 1), with zero representing perfect prediction, negative residuals representing overprediction, and positive residuals representing underprediction. Standardised residuals greater than:

- ±3.29 (outliers) correspond to alpha level 0.001 - any may be a cause for concern
- ±2.58 correspond to alpha level 0.01 - more than 1% indicate a higher than expected level of error
- ±1.96 correspond to alpha level 0.05 - more than 5% indicate the model may be a poor representation of the data (Field, 2018; Garson, 2016).

The standardised residuals were plotted against the observed outcome, the predicted probability, and the order of data collection to visually represent the associated error in terms of discrimination, accuracy, and data collection effects (Garson, 2016). The means of the predictor variables for outliers (cases with a standardised residual less of three or more) were inspected by *t*-test to identify whether any particular characteristics in the predictor variables were associated with outliers in order to detect any sub-group(s) in which the model performed poorly.

Influence statistics

Influence reflects the effect of omitting an observation on the model's parameter estimates and predicted probability. Cook's distance is a measure of the influence of a case on the model; values greater than one may be a cause for concern (Field, 2018). Cook's distance was inspected to identify influential cases.

c) Survival analysis

Survival Analysis was undertaken to model the time to readmission (see Chapter 6). Readmission behaviour of groups was compared by Kaplan-Meier Survival Analysis and the influence of predictors on the time to readmission was quantified by Cox Proportional Hazards Regression.

Definitions

In the context of survival analysis:

- the hazard is the event of interest (i.e. readmission) occurring, and
- survival is the absence of the hazard.

The survival and hazard functions reflect the probability of their respective outcomes having occurred at a given time and the respective cumulative functions reflect accumulation over time. The hazard rate is the instantaneous probability that the event of interest will occur at any given time during follow up (given survival through prior time intervals) (Collett, 2015).

Variables

Status variable

The event, or status, variable was whether patients were readmitted according to the 30-day readmission rule (Department of Health, 2013). Cases for which readmission was not

observed were right-censored[33]; there were no left-censored[34] cases. Patients who were not readmitted but died within 30 days of discharge were excluded from the study.

Time variable

The time to readmission, which was expressed on a discrete scale to one days' accuracy, reflected the time that elapsed between discharge and subsequent readmission or censorship within 30 days.

Independent variables

The covariates were those identified as predictors of readmission by logistic regression in Chapter 5.

Kaplan-Meier Survival Analysis

Kaplan-Meier survival analysis (KMSA) (Kaplan & Meier, 1958) is a non-parametric[35], descriptive procedure for characterising survival; which in this study survival represented not being readmitted. KMSA involves grouping cases into intervals insofar as the accuracy the data enables, so that each interval is occupied by at least one observation: specifically 30 intervals of one day in this study. The survival function is estimated at each interval, and is assumed to be constant in between. The result can be presented graphically, with the x-axis representing time and the y-axis representing cumulative survival i.e. the number of patients that had not been readmitted. Corresponding estimates of the survival distribution can be plotted on the same axis to compare different factor levels[36], and the survival function of the groups can be compared for equality by significance tests such as the logrank test (Garson, 2012).

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[33] Duration was known only to exceed the observation period

[34] Unknown duration between exposure to risk, i.e. discharge, and outcome (Collett, 2015)

[35] Not relying on the assumption that the sampling distribution takes a particular form (typically a normal distribution) (Field, 2018)

[36] Group membership for categorical predictor variables, e.g. younger compared to older patients

Model specification

The independent variables were both continuous. Consequently, for KMSA they were transformed into binary factors according to optimum categorisation thresholds identified by ROC curve analysis as previously described (see Receiver operating characteristic (ROC) curve analysis); they were subsequently further divided into ordinal factors with multiple similarly-sized levels to further explore readmission behaviour according to their values.

Statistics

Mean times to readmission are presented with their 95% confidence interval (CI). The conventional significance threshold of $p<0.05$ was applied for the logrank test for equality of survival functions, presented as: X^2_{DF}, p.

Assumptions

The event of interest (readmission) should be dependent only on time; cases that enter the study at different points in absolute time should behave similarly. There should be no systematic differences between censored and uncensored cases.

Logrank: censoring must be unrelated to prognosis, and survival probability must be consistent throughout the study period.

There was no reason to expect that any of these assumptions were not met.

Cox Proportional Hazards Regression

Cox Proportional Hazards Regression (CPHR) (Cox, 1972) is a predictive modelling technique suitable for investigating the effect of covariates on survival. CPHR estimates the extent to which each predictor increases or decreases the time to the event of interest occurring, enabling the mean to be estimated based on values of the predictor variables. CPHR is a semiparametric model: non-parametric in relation to time (represented as rank order of occurrence of events with ties handled by Breslow's approximation (Breslow, 1974,

cited by Garson (2013) in SPSS), and parametric[37] in relation to covariates (Armitage et al., 2002). The dependent variable in CPHR is the hazard rate (i.e. the readmission rate), which is assumed to have a linear relationship with time; covariates are multiplicative in relation to the hazard rate. The survival curve produced by CPHR is representative of a hypothetical case which has mean values for the predictor variables (Garson, 2013). An individual's hazard at a given time can be estimated using Equation 3.2:

Equation 3.2: Cox proportional hazards regression

$$h_i(t) = exp(b_1X_{1i} + b_2X_{2i} + \cdots + b_nX_{ni})h_0(t)$$

Where hi(t) represents an individual's hazard at time t, b represents a regression coefficient, X represents the corresponding predictor variable value, and $h_0(t)$ represents the baseline hazard function (Collett, 2015).

Model specification

The model was specified in blocks which mirrored the specification of the final logistic regression model. Consequently, the contribution of variation in the pharmaceutical variable (number of medicines prescribed) to the Cox regression model was prioritised over the contribution of variation in age, consistent with the logistic regression model presented in Chapter 5.

Statistics

As for logistic regression, the statistical significance of individual parameters' contribution to the model was confirmed by the significance of their associated Wald statistic (see Significance of parameter estimates). The exponent of a predictor's CPHR coefficient is the hazard ratio (HR), which is interpreted in the same way as the odds ratio in logistic regression (see Odds ratio): HRs greater than one indicate the covariate increases the odds of the event occurring, resulting in a decreased interval to the event of interest, whilst HRs

[37] Relying on the assumption that the sampling distribution takes a particular form (typically a normal distribution) (Field, 2018)

less than one indicate a protective effect. Hazard ratios are presented with their SE and 95% CI.

Assumptions

In order for the assumption of proportional hazards to be met the hazard ratio must be constant across time. This was assessed visually using the Kaplan-Meir plots presented in 6.3.1.2

3.3 Rigour

3.3.1 Reliability

Consistency was ensured by structured data collection, systematic data processing and analysis, and interpretation being undertaken by the same researcher. Automation was utilised wherever possible to minimise human error i.e. data that could be extracted directly from PASWEB was provided by THIS rather than being transcribed in the manual data collection. Data entry was systematically validated e.g. by confirming that all values recorded for each field were plausible.

Unfortunately, the address data collected were not ultimately suitable for analysis due to potential inaccuracy resulting from an information governance safeguard intended to prevent confidential patient information being inadvertently posted to a previous address. This meant that the address displayed on the EDMS represented the patient's address at the time of data collection, which was not necessarily their address at the time of discharge; 24 hour care and postcode district data were consequently disregarded, and the intended evaluation of socioeconomic factors was not possible.

3.3.2 Validity

Denscombe (2014) summarised the advice of Platt (1981) and Scott (1980) that documentary data require evaluation in relation to four criteria. These are set out in the context of this study below:

1 Authenticity

Authenticity was guaranteed as the data were extracted directly from the Trust's patient administration system.

2 Representativeness

The data were a genuine representation of the written prescription information provided by secondary care to the patient and primary care on discharge.

3 Meaning

Some aspects of the discharge data required interpretation which the researcher's role as a practitioner enabled e.g. deciphering shorthand prescription directions, as well as detecting apparent inconsistencies in the interpretation of medicines reconciliation status and recognising the limitations of the data, i.e. medicines reconciliation and MCAs being recorded in the discharge data as part of pharmacist validation and consequently not representing independent variables (described in 4.2.4 Pharmaceutical intervention).

4 Credibility

The data were an authentic and genuine representation of prescription information provided on discharge; however, the prescriptions were not assessed for accuracy and some inaccuracy was to be expected given the volume of discharges and prescribed items and known hospital prescribing error, post-discharge discrepancy, and medical coding inaccuracy rates (Blunt et al., 2014; Coleman et al., 2005; Lewis et al., 2009).

3.3.2.1 Construct validity

Variables were defined on the basis of the literature review (see 3.2.2.2 Selection and definition of variables) to ensure inclusion of relevant, and exclusion of irrelevant, variables (Garson, 2016). The outcome data provided were the basis for gauging performance and payment (or penalty) and the independent variable data were extracted from discharge prescriptions retrospectively. The data reflected the information provided by the Trust to the patient and primary care at the point of discharge and was taken at face value. This has

important implications for interpretation of the results; the data represent what was recorded on discharge prescriptions produced for the purpose of delivering health care, and not any direct observation undertaken for the purpose of research.

3.3.2.2 Internal validity

Utilisation of existing data ensured that it was genuinely representative of real-world practice. The impact of missing data was minimised by the utilisation of pairwise deletion in the exploratory analyses (see also 3.2.2.5 a) Missing data).

Patients who were not readmitted and died within the observation period were excluded from the analysis on the basis that they were not at risk of readmission after they had died.

The pharmacy team were aware that the study was being undertaken and it is probable that this raised the profile of readmission and prompted reflection around the potential role of the pharmacy team. There is no reason to expect that the pharmacy team's awareness of the study had any effect on the outcome as the effectiveness of pharmaceutical intervention in reducing the risk of readmission was not known.

It is possible that changes in services outside the scope of the study took place, and that these could influence the outcome of interest. For example, it is known that there was intermittent cover of a readmission virtual ward for some patients for 30 days after discharge; however, it is not known which patients received this service, or precisely when which elements were in operation. Similarly, it is not known what admission avoidance schemes were offered in primary care, what their eligibility criteria were, or whether these were offered throughout the full study period. Such schemes are unlikely to have been offered consistently given that primary and social care services were delivered by different providers for the different localities. The Trust was actively working towards a goal of reducing readmissions throughout the study period (Calderdale and Huddersfield NHS Foundation Trust, 2013b) as well as other goals including improving medics' communication with patients, and improving patient information on discharge (Calderdale and Huddersfield NHS Foundation Trust, 2013a) and it is possible that work undertaken towards these goals could have influenced the readmission rate, although no such effect has been published.

3.3.2.3 External validity

Generalisability was ensured in terms of:

- The dependent variable being defined by the national 30-day readmission rule definition for readmission (see also 3.2.2.2 a) Dependent variable), and
- The independent variables by utilising routinely recorded information in line with national standards for discharge prescriptions (see also 3.2.2.2 Selection and definition of variables)

Split-sample validation was undertaken to test the predictive model's performance on a sample other than that from which it was derived (see Internal validation). The generalisability of the model depends on:

- Whether those discharged during the study period were representative of those discharged year-round.
    - Winter pressure is an accepted phenomenon within the NHS (The Health Foundation, 2018); Blunt et al. (2014) explained fluctuations in monthly readmission rates over several years as increases over winter. A study of readmission among elderly patients in West Yorkshire previously identified an increased number of readmissions between January and April (Dobrzanska & Newell, 2006). However, it has also been reported that seasonal variation in readmission is minimal (Jencks, Williams, & Coleman, 2009) and it was noted that the number of readmissions reported by the Trust was relatively high at times during the spring/summer period between 2010-12 (Calderdale and Huddersfield NHS Foundation Trust, 2013a).
    - Potential for seasonal variation in MSSUs' case mix, admission and readmission rates, and how these compare with other wards and trusts was outside the scope of this study, but could be quantified by further investigation.
- Whether other health systems have similar wards to the Trust's MSSUs, with consideration for the population served, conditions treated, threshold for admission,

approach to treatment, anticipated/average length of stay, discharge procedures, and primary care/community and social services.

- The above would require assessing by the health system considering adopting the model to gauge the appropriateness of its application to the intended cohort. In terms of population served:
    - Greater Huddersfield Clinical Commissioning Group (CCG) has been identified as having LTC prevalence and unplanned admissions for Ambulatory Care Sensitive Conditions[38] (ACSCs) generally in line with the national average, with the exception of slightly higher than average prevalence of COPD (NHS Rightcare and Public Health England, 2016b).
    - Calderdale CCG has been identified as having LTC prevalence generally in line with the national average, with the exception of a slightly lower than average prevalence of COPD; however, patients experience more unplanned admissions for ACSCs compared to the national average (NHS Rightcare and Public Health England, 2016a).
- Although outside the scope of this study, the model's performance in other wards and trusts could be assessed by external validation to confirm its portability.

3.4 Ethics

A summary research protocol was presented to the Trust's Medicines Management Committee on 23rd January 2014, who confirmed their full support.

[38] Conditions where effective community care can help to prevent the need for hospital admission

The research protocol was reviewed by University of Huddersfield School of Applied Sciences Ethics Committee on 15th April 2014, and approval was confirmed on 22nd April 2014.

NHS Research Ethics Committee approval was sought via the Integrated Research Application System (IRAS) on 27th May 2014, and following a meeting with National Research Ethics Service Committee Yorkshire & the Humber - Leeds West on 11th July 2014, approval was confirmed on 17th July 2014.

NHS Management approval was granted by the Trust's Research & Development department on 17th July 2014.

The project required approval of the Confidentiality Advisory Group (CAG) under Section 251 of the Health Act ("National Health Service Act," 2006) in addition to ethical review under the Health Service (Control of Patient Information) Regulations ("The Health Service (Control of Patient Information) Regulations," 2002) because it required access to NHS patient data without their explicit consent to use their data for research purposes. Approval was also sought from the Health Research Authority via IRAS on 27th May 2014, and following review by the CAG, conditional approval was confirmed on 24th June 2014. Clarification was provided to meet the specific conditions set out, and final approval was granted on 19th November 2014.

3.5 Conclusion

This chapter has explored, described and justified the selection of methods for evaluating prescription variables as predictors of readmission: correlational analysis of existing prescription data. In Chapter 4 the data are characterised to describe the cohort, assess the quality of the data, and identify relationships between prescription variables in order to determine which were suitable for taking forward for evaluation as candidate predictors of readmission, thus ensuring the validity of the main analyses that follow in Chapter 5 and Chapter 6.

Chapter 4 Exploratory Analysis

4.1 Introduction

Having described the selection of methods and variables, as well as data collection and processing in Chapter 3, the exploratory data analysis presented in this chapter was undertaken to characterise the data and explore the candidate predictor variables' relationship to one another. The intention of conducting exploratory data analysis prior to the main data analyses was to assess the quality of the data and describe the cohort, to ensure the validity of the main analyses and consider the potential generalisability of the findings. The study objective addressed in this chapter is:

Objective 1 To identify prescription variables that may be associated with readmission (candidate predictor variables).

Each variable is presented sequentially and analysed in the context of the preceding variables; descriptive statistics for each variable are followed by inferential statistics for associations with the variables presented previously. The purpose was to identify any excessive correlation/collinearity or unexpected characteristics of, or association between, discharge prescriptions variables in order to ensure the variables progressed to the main analyses were appropriate as candidate predictors for readmission (see also 3.2.2.5 a) Exploratory analysis). The variables are summarised in Table 4.1:

Table 4.1: Variables selected for evaluation in the exploratory analysis			
Type	**Group**	**Variable**	**Measure**
Categorical	Discharge	Discharging hospital	Hospital A/Hospital B
		Discharged via a discharge lounge	Yes/No
		Day of admission	Monday, Tuesday, Wednesday, Thursday, Friday = Week day/Saturday, Sunday = Weekend
		Day of discharge	
		Study phase	One/Two
	Demographic	Gender	Male/Female
	Prescription	Clause included	Yes/No
		Prescribed GI medicine(s)	Yes/No
		Prescribed CV medicine(s)	Yes/No
		Prescribed respiratory medicine(s)	Yes/No
		Prescribed CNS medicine(s)	Yes/No
		Prescribed antimicrobial medicine(s)	Yes/No
		Prescribed endocrine medicine(s)	Yes/No
		Prescribed GU medicine(s)	Yes/No
		Prescribed medicine(s) for malignant disease & immunosuppression	Yes/No
		Prescribed medicine(s) for nutrition & blood	Yes/No
		Prescribed MSK medicine(s)	Yes/No
		Prescribed eye medicine(s)	Yes/No
		Prescribed ENT medicine(s)	Yes/No
		Prescribed skin medicine(s)	Yes/No
		Prescribed anaesthetic medicine(s)	Yes/No
		Prescribed MUR high risk medicines	Yes/No
		Prescribed medicine(s) meeting criteria for respiratory MUR	Yes/No
		Prescribed medicine(s) meeting criteria for cardiovascular MUR	Yes/No
		Met criteria for ACB review	Yes/No
		Prescription contained changes	Yes/No

Table 4.1: Variables selected for evaluation in the exploratory analysis			
Type	**Group**	**Variable**	**Measure**
		New medicine(s) had been started	Yes/No
		Prescribed temporary medicine(s)	Yes/No
		Potentially met criteria for referral to NMS	Yes/No
		Medicine(s) had been stopped	Yes/No
		Met criteria for post-discharge MUR	Yes/No
		Potentially met criteria for targeted MUR	Yes/No
		Prescribed more medicines compared to on admission	Yes/No
	Pharmaceutical intervention	Prescription validated by a pharmacist	Yes/No
		Validation conducted on the ward	Yes/No
		Medicines reconciled	Yes/No
		Dispensed MCA	Yes/No
	Outcome	Readmitted within 30 days	Yes/No
Numerical	Discharge	Length of stay	Days
	Demographic	Age	Years
	Prescription	Medicines prescribed	Count
		Doses per day prescribed	Count
		GI medicines prescribed	Count
		CV medicine prescribed	Count
		Respiratory medicines prescribed	Count
		CNS medicines prescribed	Count
		Antimicrobial medicines prescribed	Count
		Endocrine medicines prescribed	Count
		GU medicines prescribed	Count
		Medicines for malignant disease & immunosuppression prescribed	Count
		Medicines for nutrition & blood prescribed	Count
		MSK medicines prescribed	Count
		Eye medicines prescribed	Count
		ENT medicines prescribed	Count
		Skin medicines prescribed	Count
		Anaesthetic medicines prescribed	Count
		High risk medicines prescribed	Count
		ACB	Score

Table 4.1: Variables selected for evaluation in the exploratory analysis			
Type	**Group**	**Variable**	**Measure**
		Prescription changes	Count
		New medicines started	Count
		Temporary medicines (number)	Count
		Medicines stopped (number)	Count
		Difference in medicines prescribed compared to admission	Count
		Medicines on admission	Count
	Outcome	Time to readmission	Days

4.2 Results

4.2.1 Summary

Discharges from the study wards during the study period and corresponding readmissions in the context of the inclusion and exclusion criteria are described in Figure 4.1. The key demographics of the cohort are summarised in Table 4.2 in the context of the hospital from which the patient was discharged from and whether they were readmitted or not. Categorical variables are summarised in Table 4.3 and numerical variables are summarised in Table 4.4. Statistically significant relationships between categorical variables are summarised in Table 4.5 and statistically significant relationships involving numerical variables are summarised in Table 4.6 and Table 4.7.

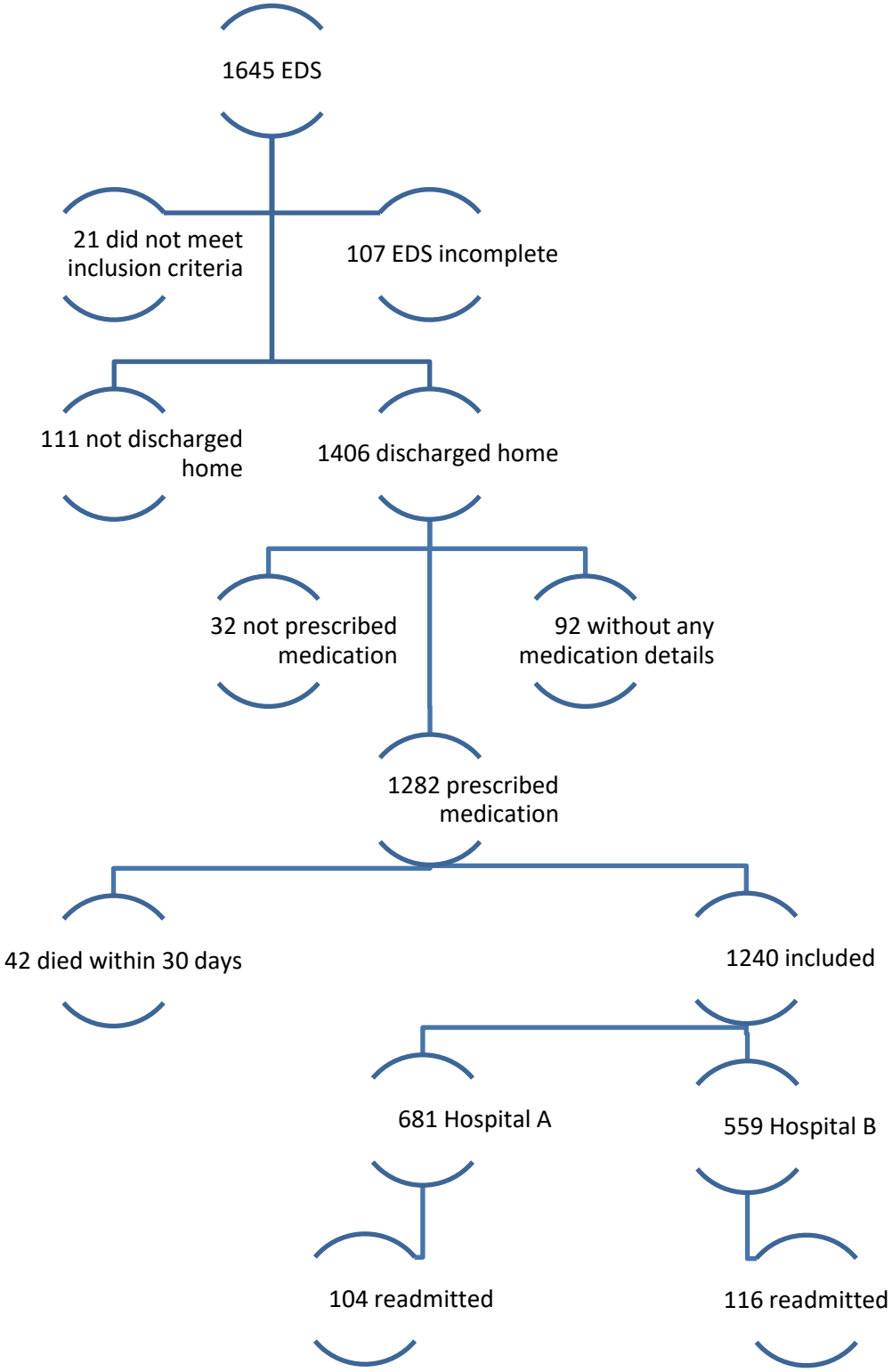


Figure 4.1: Discharges in the context of the inclusion and exclusion criteria

Table 4.2: Summary of demographic variables according to site and outcome									
Variables	**All**			**Readmitted**			**Not readmitted**		
	N (%)			**N (%)**			**N (%)**		
	1240 (100.0)			220 (17.7)			1020 (82.3)		
Hospital									
A	681 (54.9)			104 (15.3)			577 (81.8)		
B	559 (45.1)			116 (20.8)*			443 (79.2)		
Gender									
Female	671 (54.1)			112 (16.7)			559 (83.3)		
Hospital A	*369 (55.0)*			*54 (14.6)*			*315 (85.4)*		
Hospital B	*302 (45.0)*			*58 (19.2)*			*244 (80.8)*		
Male	569 (45.9)			108 (19.0)			461 (81.0)		
Hospital A	*312 (54.8)*			*50 (16.0)*			*262 (84.0)*		
Hospital B	*257 (45.2)*			*58 (22.3)*			*199 (77.4)*		
	Mean (SD)	**Median (IQR)**	**Range**	**Mean (SD)**	**Median (IQR)**	**Range**	**Mean (SD)**	**Median (IQR)**	**Range**
Age (years)	68.5 (19.2)	74.0 (27.0)	18 to 100	72.2 (17.4)	77.0 (20.0)	18 to 100	67.6 (19.4)	73.0 (29.0)	18 to 100
Hospital A	*67.9 (19.3)*	*73.0 (26.0)*	*18 to 100*	*72.0 (16.8)*	*75.5 (19.5)*	*18 to 93*	*67.1 (19.6)*	*72.0 (28.0)*	*18 to 100*
Hospital B	*69.3 (19.0)*	*75.0 (28.0)*	*18 to 100*	*73.4 (18.0)*	*78.0 (21.0)*	*21 to 100*	*68.2 (19.1)*	*74.0 (29.0)*	*18 to 98*

* $p<0.05$

Table 4.3: Frequency for categorical variables			
Variables	**Categories**	**N (%)**	**Cases**
Discharging hospital	Hospital A Hospital B	681 (54.9) 559 (45.1)	1240
Discharged via lounge	No Yes	1065 (85.8) 175 (14.1)	1240
Day of admission	Weekday Monday to Friday Weekend: Saturday and Sunday	925 (74.6) 315 (25.4)	1240
Day of discharge	Weekday: Monday to Friday Weekend: Saturday and Sunday	984 (79.4) 256 (20.6)	1240
Gender	Female Male	671 (54.1) 569 (45.9)	1240
Clause applied to prescription	No Yes	1117 (90.1) 123 (9.9)	1240

Table 4.3: Frequency for categorical variables			
Variables	**Categories**	**N (%)**	**Cases**
Prescribed medication from BNF chapter:			
4 – CNS		874 (75.3)	1160
2 – CV		818 (70.7)	1157
1 – GI		765 (66.6)	1148
6 – Endocrine System		595 (51.9)	1147
9 – Nutrition and blood		566 (49.6)	1141
5 – Infections (antimicrobials)		560 (47.9)	1169
3 – Respiratory System	Yes	435 (38.5)	1129
10 – MSK		233 (20.6)	1129
13 – Skin		118 (10.6)	1117
7 – GU		95 (8.5)	1119
11 – Eye		79 (7.1)	1120
12 – ENT		69 (6.2)	1120
8 – Malignant disease and immunosuppression		39 (3.5)	1116
15 – Anaesthesia		20 (1.8)	1116
Prescribed MUR high risk medicine	Yes	676 (58.8)	1149
	No	473 (41.2)	
Met targeted respiratory MUR criteria	No	747 (66.4)	1125
	Yes	378 (33.6)	
Met targeted cardiovascular MUR criteria	Yes	638 (56.1)	1137
	No	499 (43.9)	

Table 4.3: Frequency for categorical variables			
Variables	**Categories**	**N (%)**	**Cases**
Suitable for ACB review	No Yes	905 (81.1) 211 (18.9)	1116
Changes made to prescription	Yes No	1131 (91.2) 109 (8.8)	1240
Met targeted post-discharge MUR criteria	Yes No	1063 (89.0) 132 (11.0)	1195
Met targeted MUR criteria	Yes No	1127 (94.5) 66 (5.5)	1193
New medicines prescribed	Yes No	1034 (83.4) 206 (16.6)	1240
Prescribed temporary course	Yes No	668 (53.9) 572 (46.1)	1240
Potentially eligible for referral to NMS	No Yes	1061 (85.6) 172 (13.9)	1233
Medicines stopped	No Yes	835 (67.3) 405 (32.7)	1240
Change in number of medicines prescribed during admission	Increase No change Decrease	764 (68.5) 217 (19.5) 134 (12.0)	1115
Discharge prescription validated by a pharmacist	Yes No	781 (63.0) 459 (37.0)	1240

Table 4.3: Frequency for categorical variables			
Variables	**Categories**	**N (%)**	**Cases**
Discharge prescription validated on ward	Yes No	45 (5.8) 736 (94.2)	781
Discharge phase	One Two	631 (50.9) 609 (49.1)	1240
Medicines reconciled by pharmacist on discharge	Yes Unknown No	735 (90.6) 52 (6.4) 24 (3.0)	811
Using a multi-compartment compliance aid	Yes No	222 (27.9) 574 (72.1)	796
Readmitted within 30 days	Yes No	220 (17.7) 1020 (82.2)	1240

Table 4.4: Averages and ranges for numerical variables				
Variables	**Mean (SD)**	**Median (IQR)**	**Range**	**Cases**
Length of stay (days)	4.36 (4.18)	3.0 (3.75)	0 to 39	1240
Age (years)	68.5 (19.2)	74.0 (27.0)	18 to 100	1240
Number of medicines prescribed	9.05 (4.80)	9.00 (7.00)	1 to 27	1116
Number of doses per day prescribed	13.2 (7.70)	12.0 (10.0)	0 to 42	1059
Number of BNF chapters medicines prescribed from	4.48 (1.87)	4.00 (3.00)	1 to 10	1116

Table 4.4: Averages and ranges for numerical variables				
Variables	**Mean (SD)**	**Median (IQR)**	**Range**	**Cases**
Number of medicines from BNF chapters:				
1 – GI	1.03 (1.01)	1.00 (2.00)	0 to 6	
2 – CV	2.23 (2.23)	2.00 (4.00)	0 to 11	
3 – Respiratory System	1.07 (1.69)	0.00 (2.00)	0 to 9	
4 – CNS	1.84 (1.74)	1.00 (3.00)	0 to 11	
5 – Infections (antimicrobials)	0.59 (0.723)	0.00 (1.00)	0 to 4	
6 – Endocrine System	0.81 (1.02)	1.00 (1.00)	0 to 6	
7 – GU	0.09 (0.293)	0.00 (0.00)	0 to 2	1116
8 – Malignant disease and immunosuppression	0.04 (0.234)	0.00 (0.00)	0 to 2	
9 – Nutrition and blood	0.80 (1.07)	0.00 (1.00)	0 to 8	
10 – MSK	0.23 (0.501)	0.00 (0.00)	0 to 3	
11 – Eye	0.08 (0.338)	0.00 (0.00)	0 to 3	
12 – ENT	0.07 (0.292)	0.00 (0.00)	0 to 3	
13 – Skin	0.16 (0.563)	0.00 (0.00)	0 to 6	
15 – Anaesthesia	0.02 (0.133)	0.00 (0.00)	0 to 1	
Number of high risk medicines	0.91 (0.975)	1.00 (1.00)	0 to 5	1116
ACB score	1.79 (2.07)	1.00 (3.00)	0 to 15	1116
Number of changes made to prescription	3.00 (2.26)	3.00 (3.00)	0 to 13	1239
Number of new medicines started	2.03 (1.74)	2.00 (2.00)	0 to 13	1240
Number of medicines prescribed temporarily	0.923 (1.20)	1.00 (1.00)	0 to 16	1240
Number of medicines stopped	0.59 (1.08)	0.00 (1.00)	0 to 7	1239
Change in number of medicines prescribed	1.45 (2.08)	1.00 (3.00)	-7 to 13	1115

Table 4.4: Averages and ranges for numerical variables				
Variables	**Mean (SD)**	**Median (IQR)**	**Range**	**Cases**
Number of medicines prescribed on admission	7.61 (4.82)	7.00 (7.00)	0 to 26	1115
Time to readmission (days)	12.8 (8.77)	11.5 (15.0)	1 to 30	220

Table 4.5: Statistically significant chi-squared test results			
Variables		**Proportion (%)**	**Test statistic & significance**
Discharged via lounge Discharged from ward	Admitted at the weekend	58/175 (33.1) 257/1065 (24.1)	χ^2_1=6.44, p=0.011, φ=0.072
Hospital B Hospital A	Discharged at the weekend	136/559 (24.3) 120/681 (17.6)	χ^2_1=8.43, p=0.004, φ=0.082
Weekday admission Weekend admission		217/925 (23.5) 39/315 (12.4)	χ^2_1=17.6, p<0.001, φ=0.119
Discharged at the weekend Discharged during the week	Clause applied to prescription	36/256 (14.1) 87/984 (8.8)	*χ21=6.20, p=0.013, φ=0.071*
Women Men	Prescription potentially eligible for referral to NMS	110/668 (16.5) 62/565 (11.0)	*X21=7.70, p=0.006, φ=0.079*
Discharged via lounge Discharged from ward	Prescription validated	141/175 (80.6) 640/1065 (60.1)	χ^2_1=27.0, p<0.001, φ=0.148
Discharged during the week Discharged at the weekend		659/984 (67.0) 122/256 (47.7)	χ^2_1=32.5, p<0.001, φ=0.162
No clause applied to prescription Clause applied to prescription		714/1117 (63.9) 67/123 (54.5)	χ^2_1=4.24, p=0.039, φ=0.059
Prescribed cardiovascular medication Not prescribed cardiovascular medication		551/818 (67.4) 190/339 (56.0)	χ^2_1=13.3, p<0.001, φ=0.107
Prescribed respiratory medication Not prescribed respiratory medication		301/435 (69.2) 422/694 (60.8)	χ^2_1=8.17, p=0.004, φ=0.085

Table 4.5: Statistically significant chi-squared test results			
Variables		**Proportion (%)**	**Test statistic & significance**
Prescribed central nervous system medication Not prescribed central nervous system medication		585/874 (66.9) 158/286 (55.2)	χ^2_1=12.8, p<0.001, φ=0.105
Prescribed medication for infection Not prescribed medication for infection		375/560 (67.0) 367/609 (60.3)	χ^2_1=5.65, p=0.017, φ=0.070
Prescribed endocrine system medication Not prescribed endocrine system medication		398/595 (66.9) 337/552 (61.1)	χ^2_1=4.24, p=0.039, φ=0.061
Prescribed GU medication Not prescribed GU medication		72/95 (75.8) 644/1025 (62.9)	χ^2_1=6.28, p=0.012, φ=0.075
Prescribed anaesthetic medication Not prescribed anaesthetic medication		17/20 (85.0) 697/1096 (63.6)	χ^2_1=3.91, p=0.048, φ=0.059
Prescribed high risk medicines Not Prescribed high risk medicine		455/676 (67.3) 282/473 (59.6)	χ^2_1=7.15, p=0.007, φ=0.079
Patients over 64 and suitable for ACB review Patients over 64 and not suitable for ACB review		148/205 (72.2) 367/573 (64.0)	χ^2_1=4.48, p=0.034, φ=0.076
Prescribed temporary medication Not prescribed any temporary medication		514/769 (66.8) 200/347 (57.6)	χ^2_1=8.79, p=0.003, φ=0.089
Phase two Phase one		520/609 (85.4) 261/631 (41.4)	χ^2_1=258, p<0.001, φ=0.456
Phase two: Discharged via discharge lounge Discharged from ward		 114/121 (94.2) 406/488 (83.2)	χ^2_1=9.43, p=0.002, φ=0.124

Table 4.5: Statistically significant chi-squared test results			
Variables		**Proportion (%)**	**Test statistic & significance**
Phase two: Admitted at the weekend Admitted during the week		 146/162 (90.1) 374/447 (83.7)	χ^2_1=3.97, p=0.046, φ=0.081
Phase one: No clause applied to prescription Clause applied to prescription		 249/577 (43.2) 12/54 (22.2)	χ^2_1=8.92, p=0.003, φ=0.119
Phase one Phase two	Dispensed multi-compartment compliance aid	108/272 (39.7) 114/524 (21.8)	χ^2_1=28.7, p<0.001, φ=0.171
No clause applied to prescription Clause applied to prescription		58/574 (10.1) 9/222 (4.1)	χ^2_1=7.60, p=0.006, φ=0.098
Prescribed MUR high risk medication Not prescribed MUR high risk medication		170/466 (36.5) 49/286 (17.1)	χ^2_1=32.1, p<0.001, φ=0.207
Not prescribed temporary medication Prescribed temporary medication		109/346 (31.5) 113/450 (25.1)	χ^2_1=3.97, p=0.042, φ=0.071
Hospital B Hospital A	Readmitted	116/559 (20.8) 104/681 (15.3)	χ^2_1=6.32, p=0.012, φ=0.071
Prescribed GI medication Not prescribed GI medication		165/765 (21.6) 44/383 (11.5)	χ^2_1=17.4, p<0.001, φ=0.123
Prescribed CV medication Not prescribed CV medication		169/818 (20.7) 41/339 (12.1)	χ^2_1=11.8, p=0.001, φ=0.101
Prescribed antimicrobial medication Not prescribed antimicrobial medication		113/560 (20.2) 94/609 (14.3)	χ^2_1=4.51, p=0.034, φ=0.062

Table 4.5: Statistically significant chi-squared test results			
Variables		**Proportion (%)**	**Test statistic & significance**
Prescribed endocrine system medication Not prescribed endocrine system medication		125/595 (21.0) 79/552 (14.3)	χ^2_1=8.78, p=0.003, φ=0.088
Prescribed medication for nutrition and blood Not prescribed medication for nutrition and blood		119/566 (21.0) 85/575 (14.8)	χ^2_1=7.57, p=0.006, φ=0.081
Prescribed ENT medication Not prescribed ENT medication		20/69 (29.0) 180/1051 (17.1)	χ^2_1=6.21, p=0.013, φ=0.074
Prescribed MCA Not prescribed MCA		54/222 (24.3) 92/574 (16.0)	χ^2_1=7.36, p=0.007, φ=0.096

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Hospital B Hospital A	LOS (days)	4.74 (4.25) 4.04 (4.09)	95% CI for the difference 0.228 to 1.16, t_{1170}=2.92, p=0.004
Weekday discharge Weekend discharge		4.53 (4.41) 3.68 (3.00)	95% CI for the difference 0.392 to 1.31, t_{576}=3.64, p<0.001
Older patients (aged 74 and older) Younger patients (aged 73 and under)		4.77 (4.33) 3.92 (3.97)	95% CI for the difference 0.390 to 1.31, t_{1240}=3.62, p<0.001
Clause not applied to prescription Clause applied to prescription		4.69 (4.25) 1.33 (1.15)	95% CI for the difference 3.03 to 3.68 days, t_{614}=20.4, p<0.001

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Prescribed high risk medicine Not prescribed high risk medicine		4.97 (4.40) 4.10 (3.92)	95% CI for the difference 0.387 to 1.36 days, t_{1080}=3.53, p<0.001
Prescription potentially eligible for referral to NMS Prescription did not meet NMS criteria		5.48 (4.67) 4.16 (4.05)	95% CI for the difference 0.584 to 2.07 days, t_{215}=3.52, p=0.001
Validated by a pharmacist Not validated by a pharmacist		4.69 (4.58) 3.78 (3.30)	95% CI for the difference 0.470 to 1.35 days, t_{1190}=4.05, p<0.001
Readmitted Not readmitted		5.12 (5.32) 4.19 (3.87)	95% CI for the difference 0.181 to 1.67 days, t_{271}=2.45, p=0.015
Discharged via lounge Discharged from ward	Age (years)	72.6 (16.5) 67.8 (19.5)	95% CI for the difference 2.09 to 7.54, t_{260}=3.48, p=0.001
Clause not applied to prescription Clause applied to prescription		69.1 (18.9) 63.1 (20.5)	95% CI for the difference 2.20 to 9.84 years, t_{146}=3.12, p=0.002
Prescribed high risk medicine Not prescribed high risk medicine		74.1 (15.5) 61.9 (21.2)	95% CI for the difference 9.96 to 14.4 years, t_{812}=10.7, p<0.001
Patients over 64 and not suitable for ACB review Patients over 64 suitable for ACB review		80.8 (8.03) 79.4 (7.80)	95% CI for the difference 0.201 to 2.71 years, t_{395}=2.28, p=0.023

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Validated by a pharmacist Not validated by a pharmacist		70.0 (18.6) 66.0 (19.8)	95% CI for the difference 1.71 to 6.18 years, t_{912}=3.46, p=0.001
Phase one: Validated by a pharmacist Not validated by a pharmacist		 72.0 (18.3) 66.3 (20.1)	 95% CI for the difference 2.67 to 8.71 years, t_{590}=3.70, p<0.001
MCA Non-MCA		79.2 (12.6) 66.5 (19.2)	95% CI for the difference 10.3 to 14.9 years, t_{488}=10.8, p<0.001
Readmitted Not readmitted		72.7 (17.4) 67.6 (19.4)	95%CI for the difference 2.53 to 7.74 years, t_{346}=3.88, p<0.001
Discharged via discharge lounge Discharged from the ward	Medicines (number)	10.2 (4.80) 8.88 (4.78)	95% CI for the difference 0.466 to 2.11 medicines, t_{205}=3.09, p=0.002
Women Men		9.36 (4.76) 8.70 (4.84)	95% CI for the difference 0.092 to 1.22 medicines, t_{1090}=2.28, p=0.023
Older patients (74 years and over) Younger patients (73 years and under)		9.43 (4.28) 8.63 (5.30)	95% CI for the difference 0.228 to 1.37 medicines, t_{1010}=2.75, p=0.006
Prescribed MUR high risk medicine Not prescribed MUR high risk medicine		10.7 (4.64) 6.82 (4.07)	95% CI for the difference 3.35 to 4.38 medicines, t_{1080}=14.8, p<0.001

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Patients over 64 and suitable for ACB review Patients over 64 and not suitable for ACB review		12.7 (4.57) 8.51 (3.90)	95% CI for the difference 3.49 to 4.89 medicines, t_{336}=11.7, p<0.001
Prescription potentially eligible for referral to NMS Prescription did not meet NMS criteria		10.2 (4.48) 8.85 (4.82)	95% CI for the difference 0.622 to 2.16 medicines, t_{222}=3.57, p<0.001
Validated by a pharmacist Not validated by a pharmacist		9.61 (4.67) 8.07 (4.89)	95% CI for the difference 0.944 to 2.12 medicines, t_{800}=5.11, p<0.001
Phase one: Validated by a pharmacist Not validated by a pharmacist		 10.1 (4.22) 7.96 (4.70)	 95% CI for the difference 1.36 to 2.82 medicines, t_{559}=5.62, p<0.001
MCA Non-MCA		11.4 (4.63) 9.00 (4.56)	95% CI for the difference 1.66 to 3.13 medicines, t_{390}=6.37, p<0.001
Readmitted Not readmitted		10.8 (5.34) 8.67 (4.60)	95% CI for the difference 1.31 to 2.91 medicines, t_{267}=5.19, p<0.001
Hospital B Hospital A	High risk medicines (number)	1.05 (1.05) 0.80 (0.889)	95% CI for the difference 0.134 to 0.365 high risk medicines, t_{997}=4.23, p<0.001
ACB review Not ACB review		1.45 (1.10) 0.99 (0.948)	95% CI for the difference 0.291 to 0.630 high risk medicines, t_{339}=5.35, p<0.001
Potentially eligible for NMS Not eligible for NMS		1.28 (1.05) 0.84 (0.942)	95% CI for the difference 0.267 to 0.616 high risk medicines, t_{201}=4.98, p<0.001

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Readmitted Not readmitted		1.10 (0.982) 0.87 (0.969)	95% CI for the difference 0.082 to 0.383 high risk medicines, t_{290}=3.04, p=0.003
Women over 64 years of age Men over 64 years of age	ACB (score)	1.97 (2.05) 1.59 (1.85)	95% CI for the difference 0.094 to 0.655, t_{744}=2.62, p=0.009
Prescribed high risk medicines Not prescribed high risk medicines	Changes (number)	3.30 (2.38) 2.79 (2.14)	95% CI for the difference 0.249 to 0.776 changes, t_{1080}=3.81, p<0.001
Patients over 64 and suitable for ACB review Patients over 64 and not suitable for ACB review		3.80 (2.57) 3.05 (2.17)	95% CI for the difference 0.326 to 1.11 changes, t_{338}=3.59, p<0.001
Older patients (74 years and over) Younger patients (73 years and under)		3.14 (2.23) 2.85 (2.29)	95% CI for the difference 0.038 to 0.541 changes, t_{1230}=2.25, p=0.024
Validated by a pharmacist Not validated by a pharmacist		3.26 (2.28) 2.56 (2.15)	95% CI for the difference 0.437 to 0.945 changes, t_{1010}=5.33, p<0.001
Hospital B Hospital A	Medicines started (number)	2.18 (1.86) 1.91 (1.63)	95% CI for the difference 0.072 to 0.465 medicines started, t_{1120}=2.68, p=0.008
Patients over 64 and suitable for ACB review Patients over 64 and not suitable for ACB review		2.31 (1.93) 1.9 (1.61)	95% CI for the difference 0.109 to 0.700 medicines started, t_{331}=2.69, p=0.007

Table 4.6: Statistically significant *t*-test results			
Variables		**Mean (SD)**	**Test statistics**
Validated by a pharmacist Not validated by a pharmacist		2.20 (1.76) 1.74 (1.66)	95% CI for the difference 0.272 to 0.665 new medicines, t_{1010}=4.69, p<0.001
Non-MCA MCA		2.34 (1.81) 1.86 (1.62)	95% CI for the difference 0.211 to 0.732 new medicines, t_{445}=3.56, p<0.001
Hospital B Hospital A	Temporary medicines (number)	1.06 (1.41) 0.81 (0.982)	95% CI for the difference 0.117 to 0.393 temporary medicines, t_{965}=3.61, p<0.001
Discharged during the week Discharged at the weekend	Medicines stopped (number)	0.63 (1.11) 0.44 (0.935)	95% CI for the difference 0.059 to 0.328 medicines stopped, t_{462}=2.83, p=0.005
Hospital A Hospital B		0.71 (1.22) 0.45 (0.860)	95% CI for the difference 0.140 to 0.373 medicines stopped, t_{1210}=4.32, p<0.001
MCA Non-MCA		0.79 (1.20) 0.57 (1.09)	95% CI for the difference 0.044 to 0.407 stopped medicines, t_{370}=2.45, p=0.015

Table 4.7: Statistically significant linear regression results		
Variables	**Equation**	**Test statistics**
Number of medicines & doses per day prescribed on discharge	Doses per day = 0.325 + 1.43(medicines)	$F_{1,1060}$=4510, p<0.001, r^2=0.810

Table 4.7: Statistically significant linear regression results		
Variables	**Equation**	**Test statistics**
Number of medicines & number of BNF chapters prescribed from	BNF chapters = 1.62+0.316(medicines)	$F_{1,1110}$ =2140, p<0.001, r^2=0.658
Number of medicines prescribed on admission & discharge	Medicines prescribed at discharge = 2.19+0.903(medicines prescribed on admission)	$F_{1,1110}$=5120, p<0.001, r^2=0.821

4.2.2 Discharge and demographic variables

4.2.2.1 Discharge site and method

Just over half of discharges included in the study were from Hospital A and the remainder were from Hospital B. In the majority of cases patients were discharged directly from the ward, although around one in seven were discharged via a discharge lounge.

4.2.2.2 Admission and discharge days

The average number of admissions was six (6.1, SD 2.8, range 1 to 16) per day and 40 (SD 16, range 2 to 57) per week. The most common day for admission was Thursday (16.0%, 199/1240), and the least common was Wednesday (12.3%, 152/1240). Figure 4.2 shows how admissions were distributed through the week:

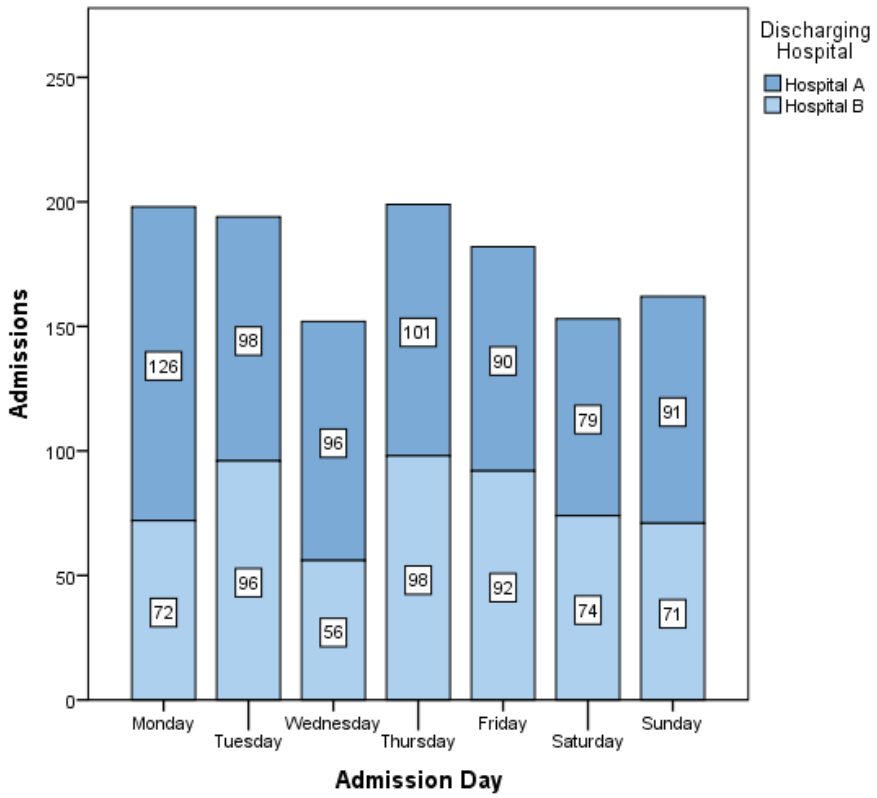


Figure 4.2: Admissions according to day of the week

One quarter of admissions occurred over the weekend. Patients who were admitted at the weekend were marginally more likely to be discharged via a discharge lounge than patients admitted during the week.

The average number of discharges was close to seven per day (6.7, SD 2.7, range 1 to 15), and 47 per week (SD 8.3, range 31 to 67). The most common day for discharge was Tuesday (17.6%, 218/1240) and the least common was Sunday (9.0%, 111/1240). Figure 4.3 shows how discharges were distributed through the week:

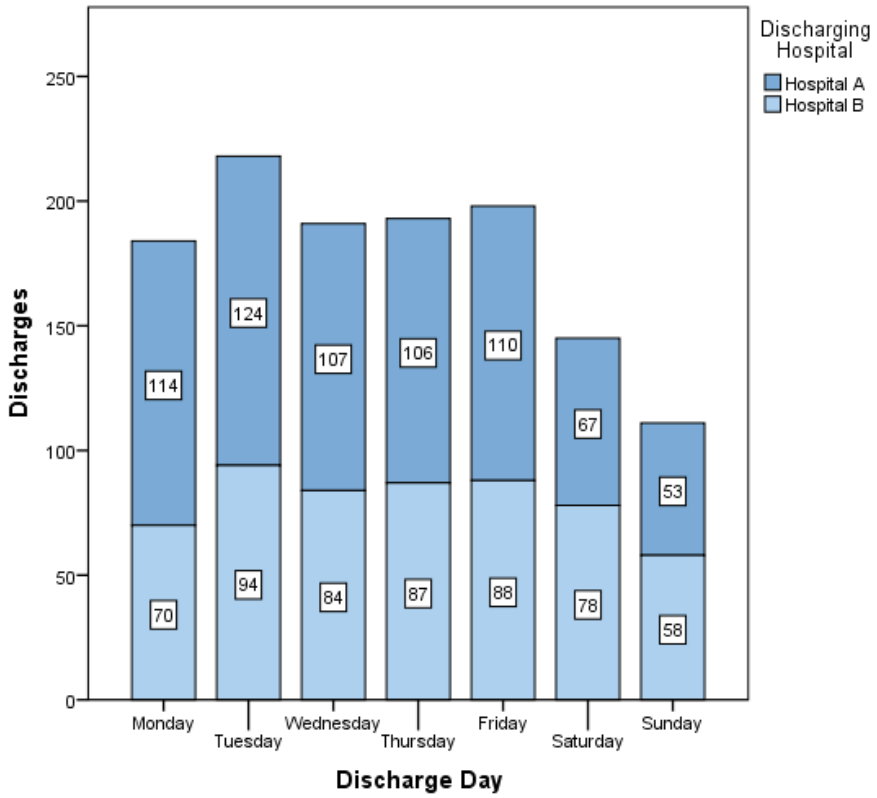


Figure 4.3: Discharges according to day of the week

One-fifth of discharges occurred over the weekend, and Hospital B processed a slightly greater proportion of discharges over the weekend than Hospital A. Patients admitted during the week were slightly more likely to be discharged at the weekend than those admitted at the weekend.

4.2.2.3 Length of stay (LOS)

The mean length of stay was just over four days, with almost half (44.4%, 551/1240) of patients staying on a short stay unit longer than the Trust's anticipated timeframe of three days and one in eight remaining over one week. The positive skew in Figure 4.5 confirms that, consistent with the anticipated LOS inferred by admission to an MSSU, LOS tended to be short (see also 3.2.2.2aiii):

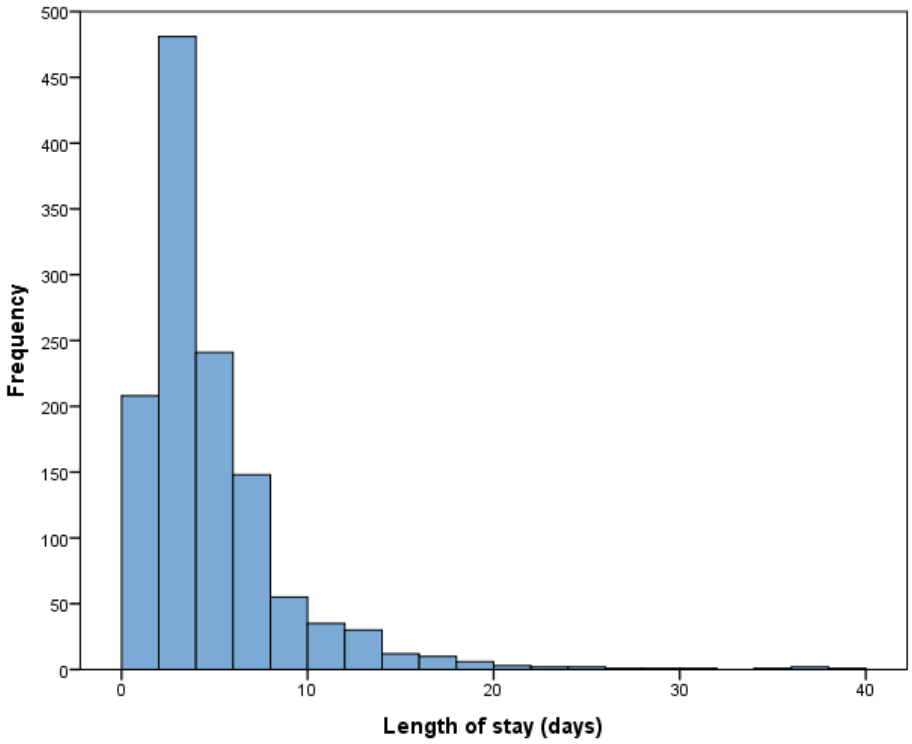


Figure 4.4: Length of stay (LOS)

A statistically significant difference was observed when comparing sites: those discharged from Hospital B had a significantly longer average LOS than those discharged from Hospital A. Figure 4.5 shows that a greater proportion of patients discharged from Hospital A had a LOS of 2 or 3 days compared to patients discharged from Hospital B, although both sites had patients with a much longer LOS than the average:

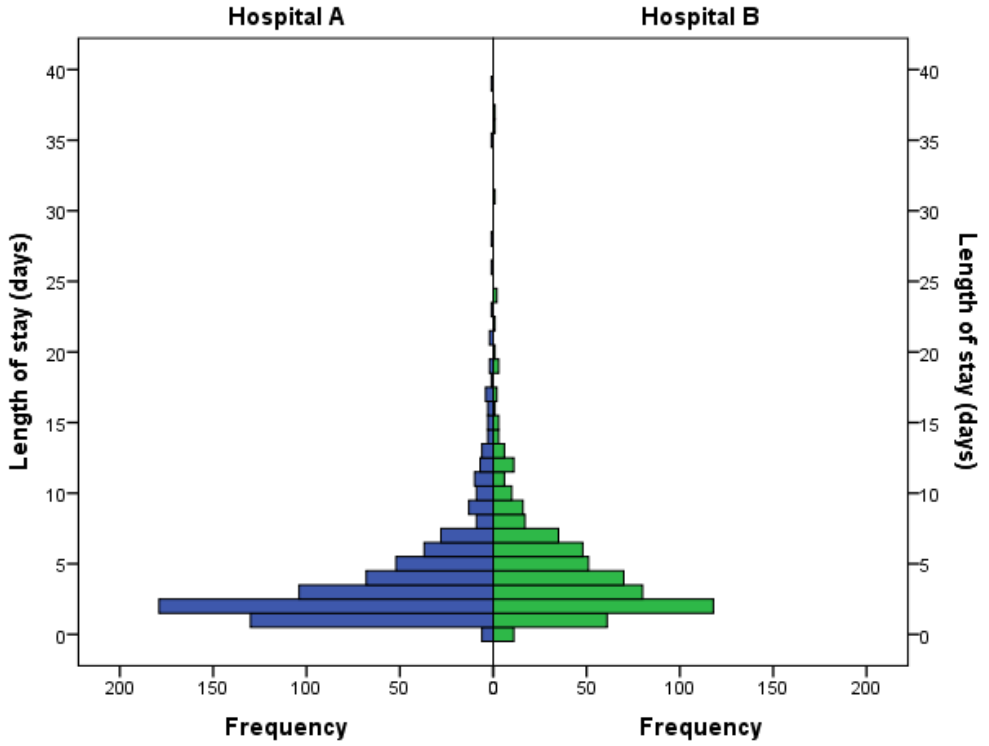


Figure 4.5: LOS according to hospital site

Figure 4.6 demonstrates that patients discharged at the weekend tended to have a shorter LOS than patients discharged during the week:

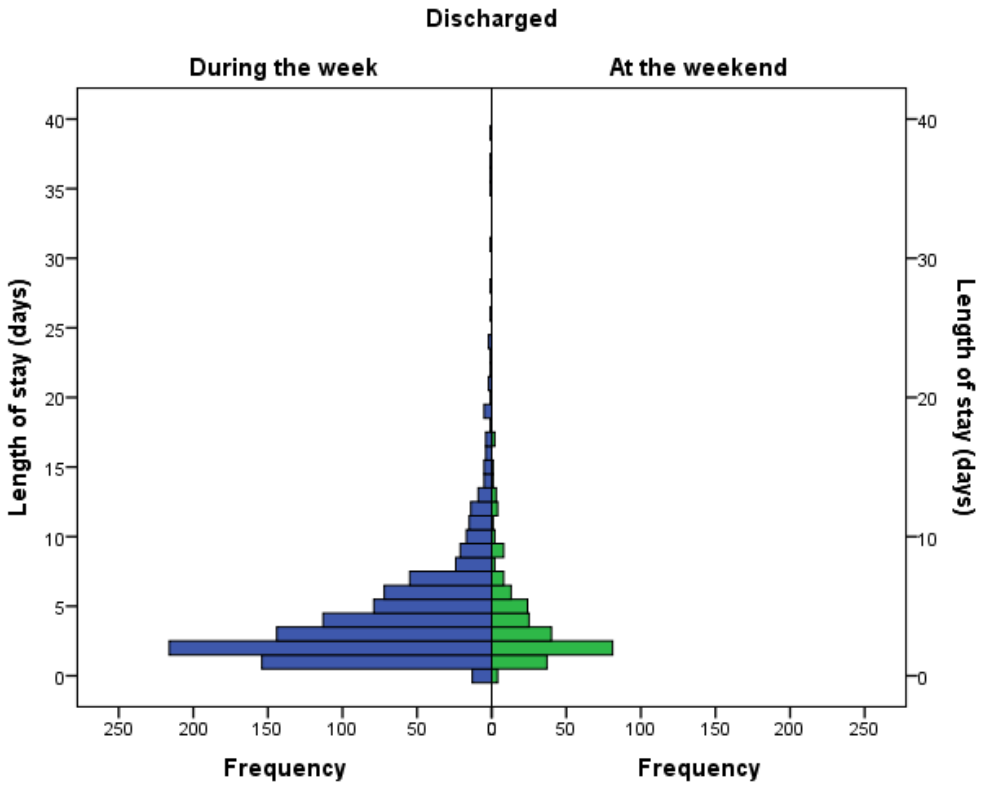


Figure 4.6: LOS according to whether discharged during the week or at the weekend

4.2.2.4 Repeat admissions

The 1240 discharge prescriptions belonged to 1160 patients. Repeat admissions comprised less than seven per cent of discharges (80/1240) with 70 patients presenting twice, and five patients presenting three times during the six month study period.

4.2.2.5 Gender and age

Just over half of patients were female, and patients' ages ranged from 18 to 100. Almost half (616/1240) of patients were between 70 and 90 years of age. Figure 4.7 demonstrates that the cohort included reasonable representation across the age range, with a negative skew reflecting that patients tended to be older:

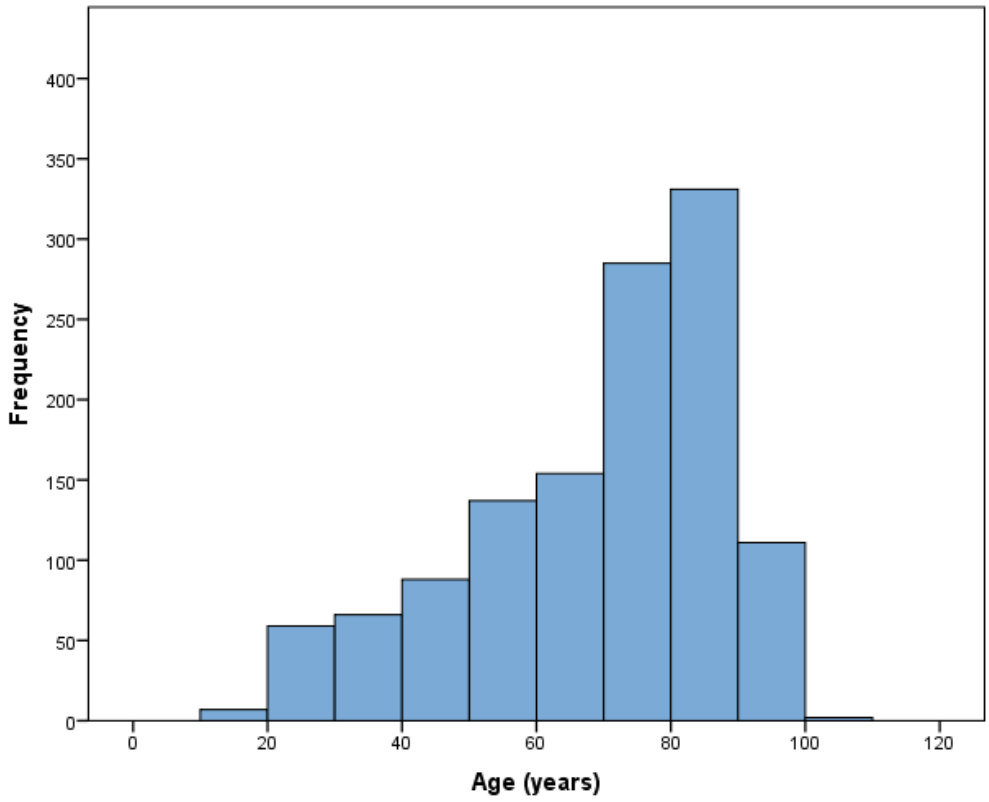


Figure 4.7: Age of patients discharged

Patients discharged via a discharge lounge were significantly older on average than those discharged directly from the ward; Figure 4.8 demonstrates that whilst the age of patients discharged directly from the ward spanned the full range, it was unusual for patients under around 40 years of age to be discharged via a discharge lounge:

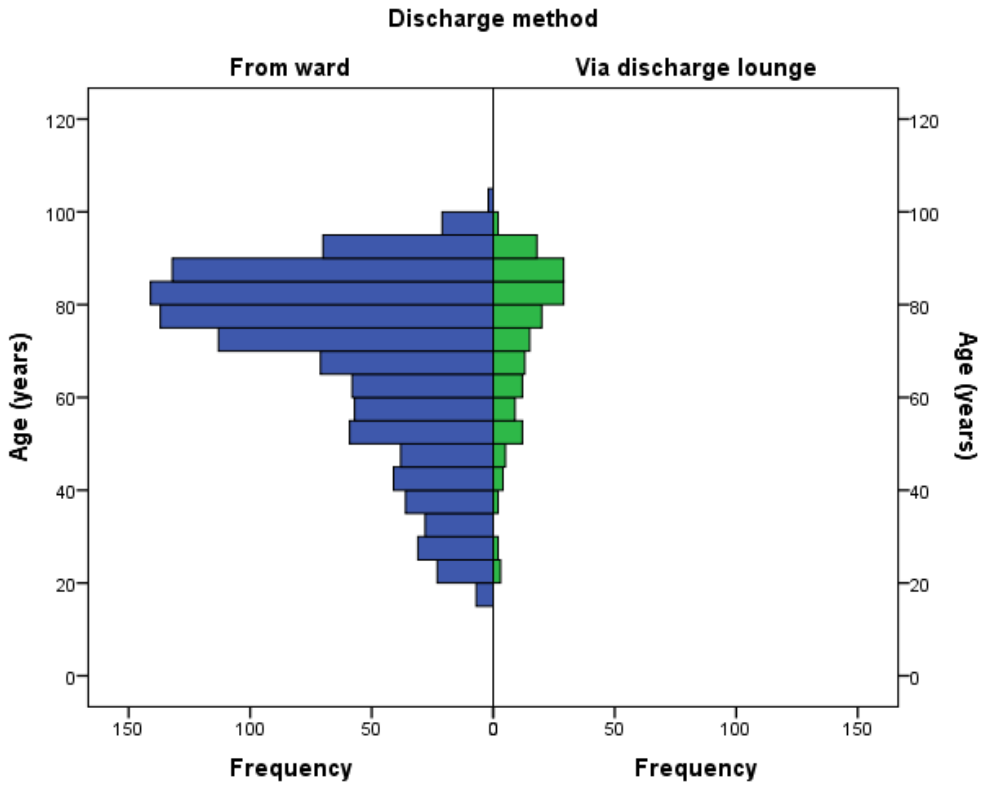


Figure 4.8: Age of patients according to discharge method

The relationship between age and LOS was not linear. Splitting the cohort in half according to age (51.4%, 637/1240; 74 years of age and over, older) confirmed that older patients had a significantly longer average LOS compared to younger patients (73 years of age and under). Figure 4.9 demonstrates that a greater proportion of older patients having stays exceeding one week compared to younger patients accounted for much of the difference:

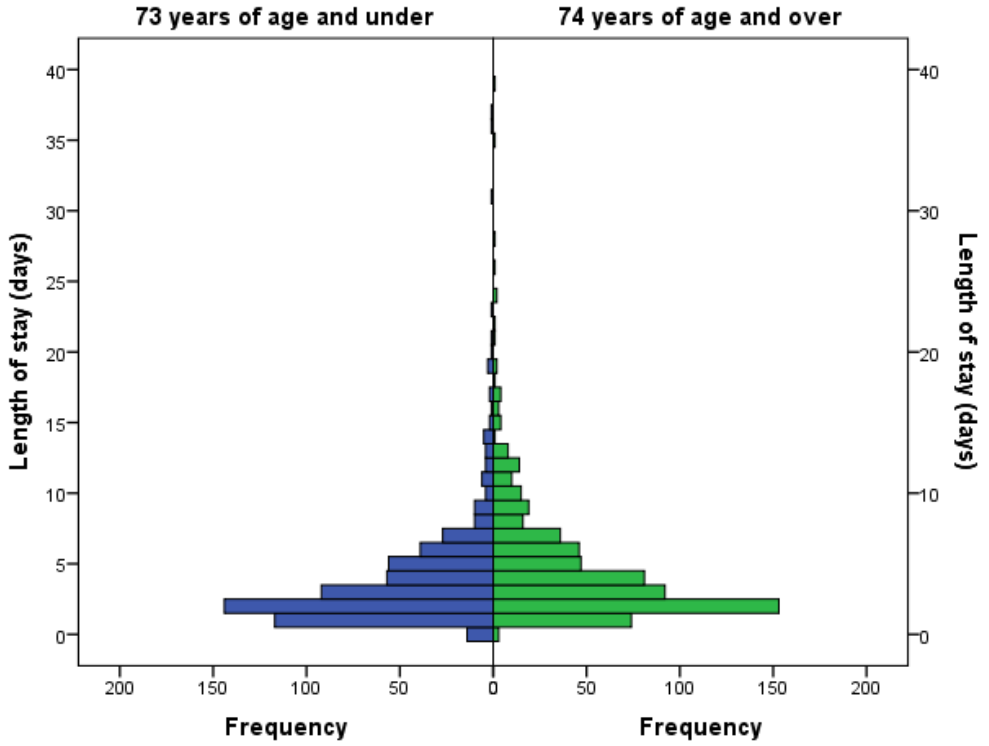


Figure 4.9: LOS for younger patients compared to older patients

4.2.3 Prescription variables

4.2.3.1 Prescriptions that only detailed changes

Around one in ten discharge prescriptions contained a clause stating "no changes to pre-admission medications or dose of any medication" (6) or "no changes to pre-admission medications other than the changes identified below" (117), rendering those prescriptions unsuitable for inclusion in many of the analyses of prescription factors because the medicines prescribed were not itemised on the discharge prescription. The discharge and patient characteristics of these prescriptions are characterised below, in order to identify any systematic differences between them and those which contained full prescription information.

- Clauses were included on prescriptions more often for discharges at the weekend than discharges during the week. The average LOS was significantly shorter for

patients who had a clause applied to their prescription compared to patients who did not, as shown in Figure 4.10 below.

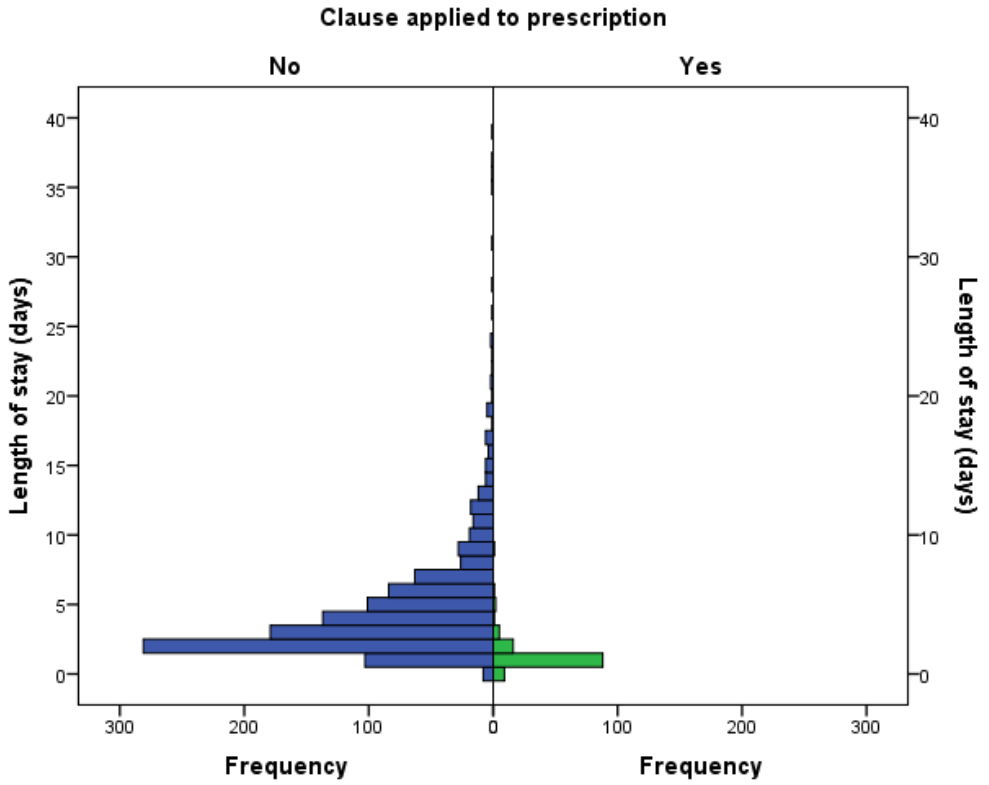


Figure 4.10: LOS according to whether clause applied to prescription

The LOS for patients whose prescriptions contained these clauses ranged from zero to nine days, with one-fifth (21.1%, 26/123) of discharge prescriptions that contained a clause belonging to patients whose LOS was more than one day.

Patients who had a clause applied to their prescription were younger on average than those whose did not. Figure 4.11 demonstrates that the number of patients who had a clause applied to their prescription was fairly consistent across the age range; however, this represented a substantially smaller proportion of older patients' prescriptions:

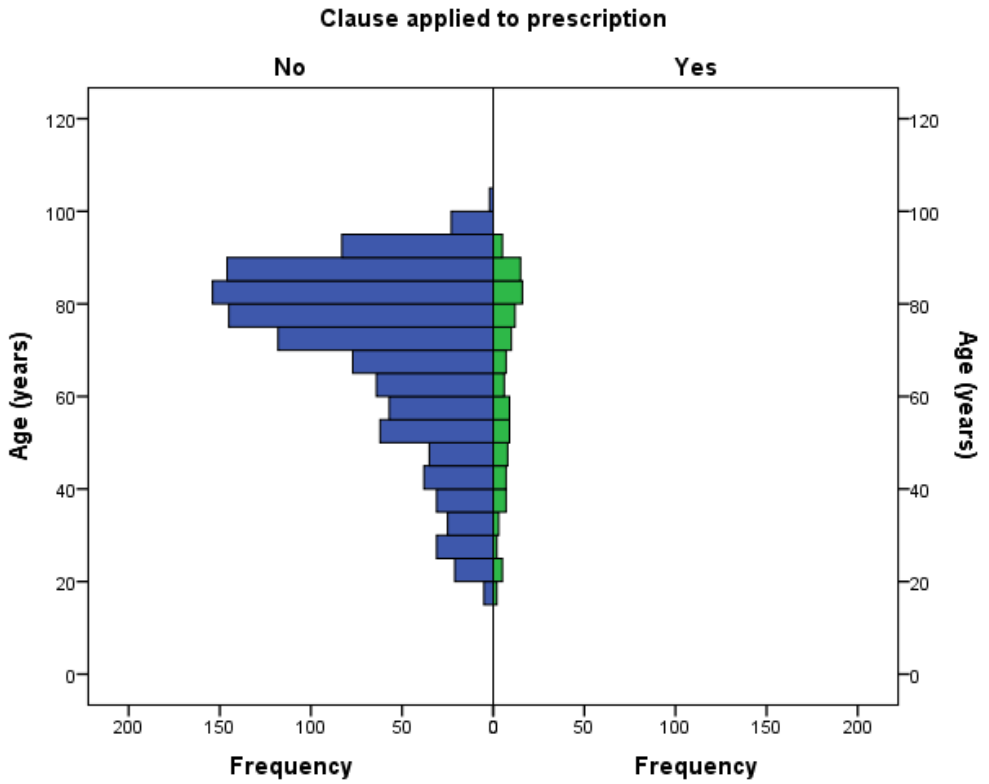


Figure 4.11: Age according to whether clause applied to prescription

One further discharge prescription contained an entry indicating that the patient was involved in a clinical trial without specifying the number or nature of the trial medicine(s) prescribed, rendering it unsuitable for inclusion in analyses of prescription factors which follow.

4.2.3.2 Number of medicines prescribed

Figure 4.12 shows that the number of medicines prescribed had a slightly positively skewed distribution:

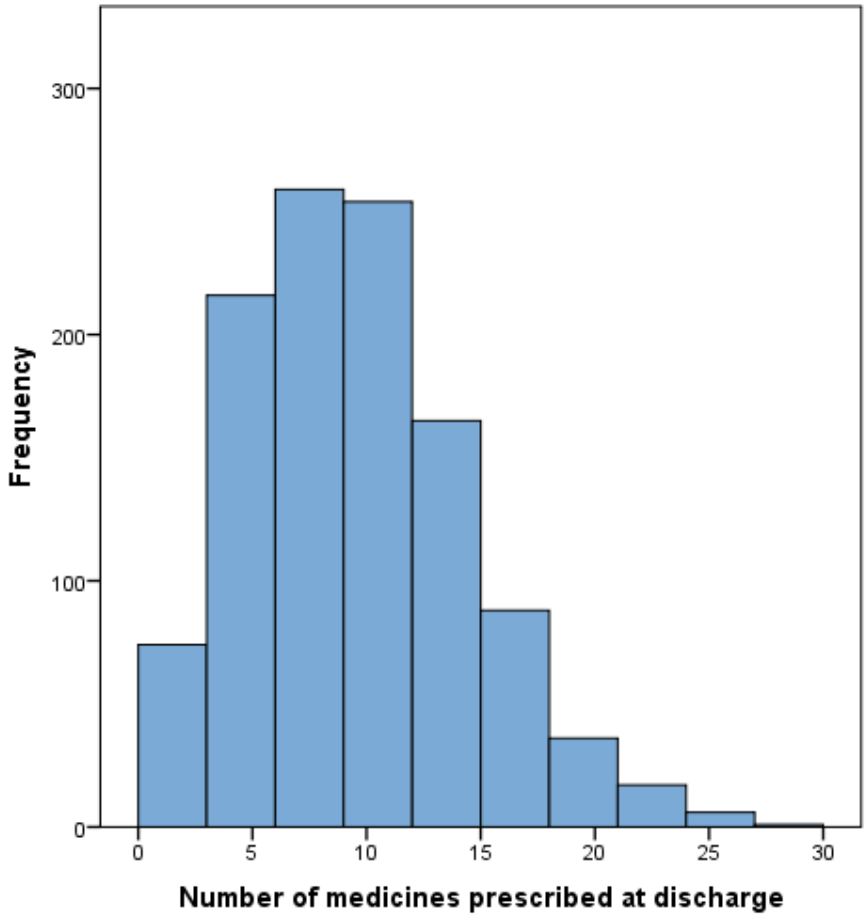


Figure 4.12: Number of medicines prescribed at discharge

Patients discharged via a discharge lounge were prescribed significantly more medicines on average than those who were discharged directly from the ward, as demonstrated in Figure 4.13:

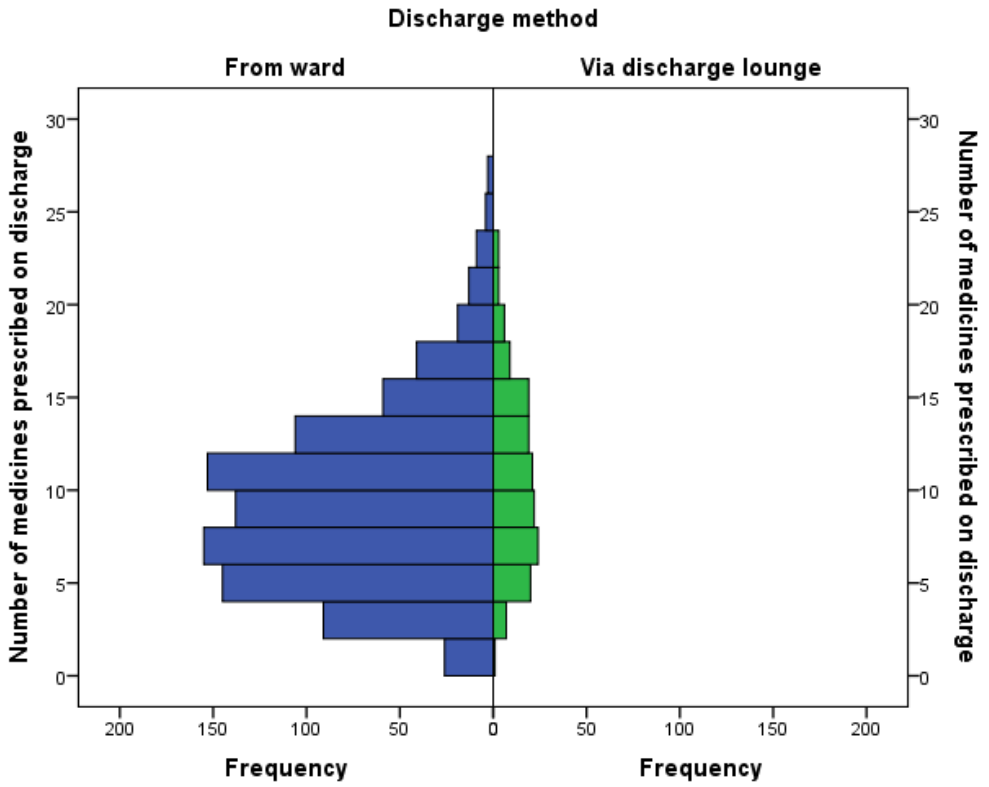


Figure 4.13: Number of medicines prescribed at discharge according to discharge method

Women were prescribed significantly more medicines at discharge on average compared to men, as demonstrated in Figure 4.14:

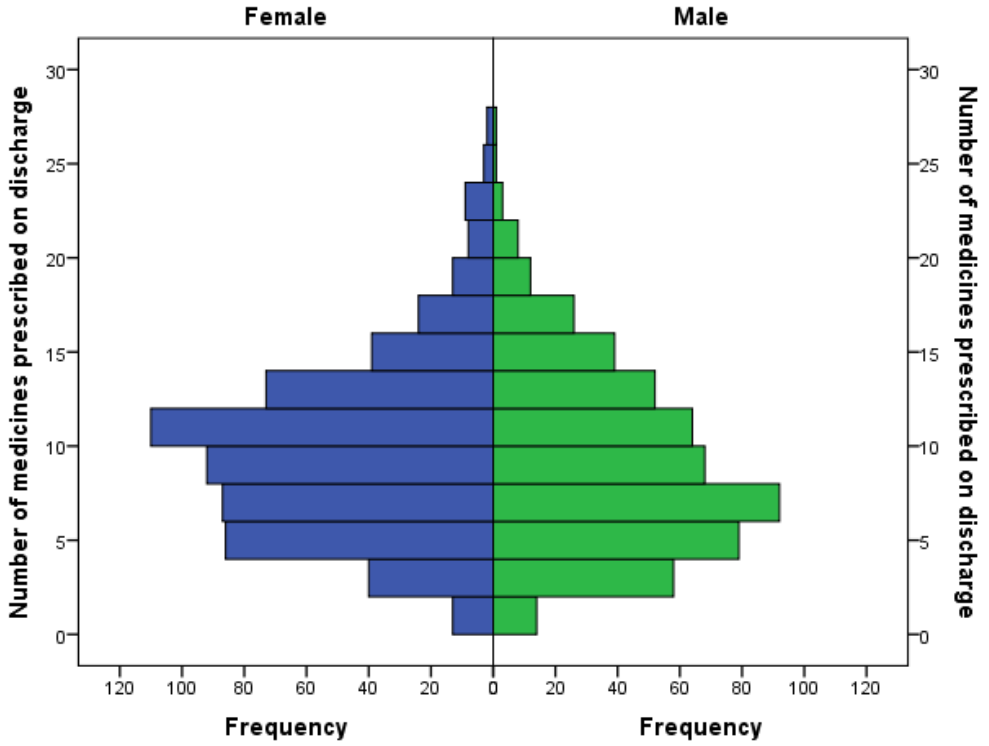


Figure 4.14: Number of medicines prescribed for women compared to men

As previously described, older patients had a longer average LOS, although the relationship between the variables was not linear. There was not a linear relationship between LOS or age with the number of medicines prescribed at discharge either, indicating that no obvious collinearity existed between these variables. Older patients were, however, prescribed a significantly greater number of medicines on average compared to younger patients, as shown below in Figure 4.15:

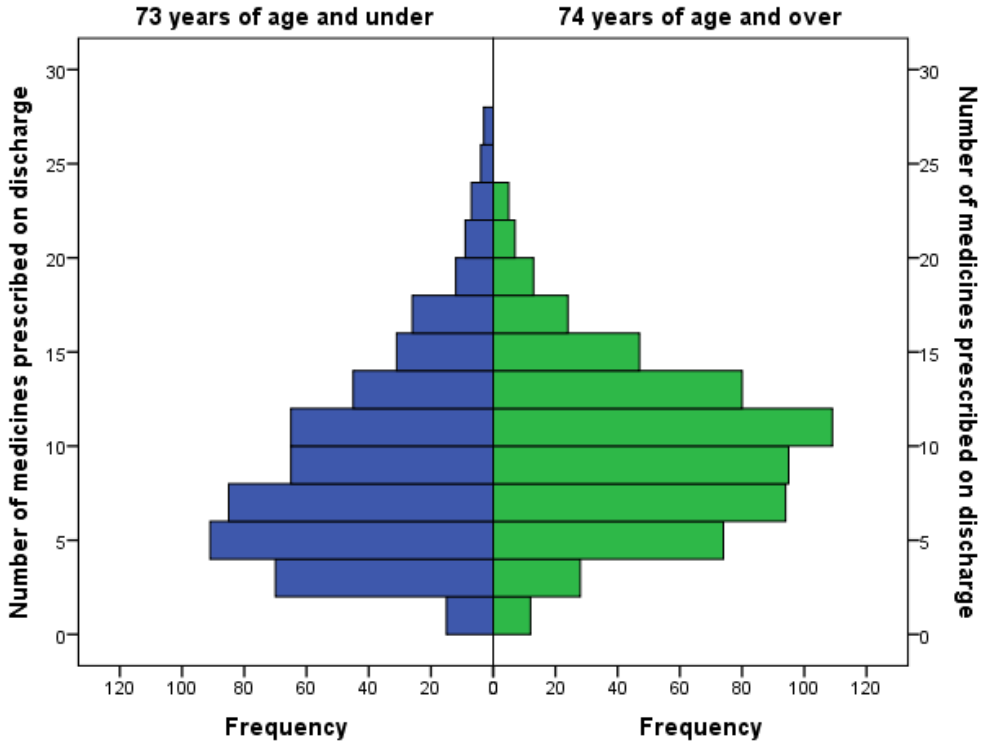


Figure 4.15: Number of medicines prescribed for younger patients compared to older patients

4.2.3.3 Number of doses prescribed per day (DPD)

In addition to the 124 prescriptions unsuitable for analysis due to missing data as described above, the directions for use did not contain enough detail for the number of prescribed doses per day to be calculated for a further 57 prescriptions; it was possible to calculate the number of doses per day prescribed for 85.4% of discharge prescriptions. Figure 4.16 shows that DPD had a very similar distribution to the number of medicines prescribed at discharge (see also Figure 4.12):

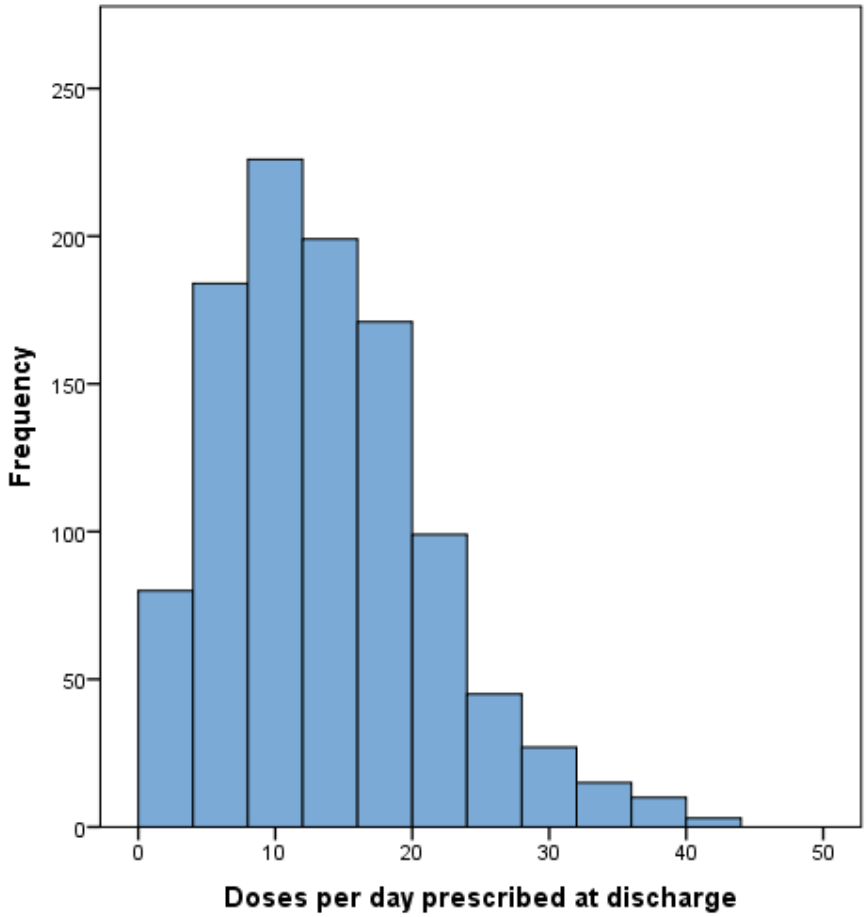


Figure 4.16: Number of doses per day on discharge prescriptions

There was a strong relationship between the number of doses per day and the number of medicines prescribed at discharge (r=0.900, p<0.001), with variation in the number of medicines prescribed accounting for 81.0% of the variation in the number of doses per day and each additional medicine prescribed equating to an increase of 1.4 doses per day. Figure 4.17 demonstrates the linear relationship between the number of medicines and doses per day prescribed at discharge:

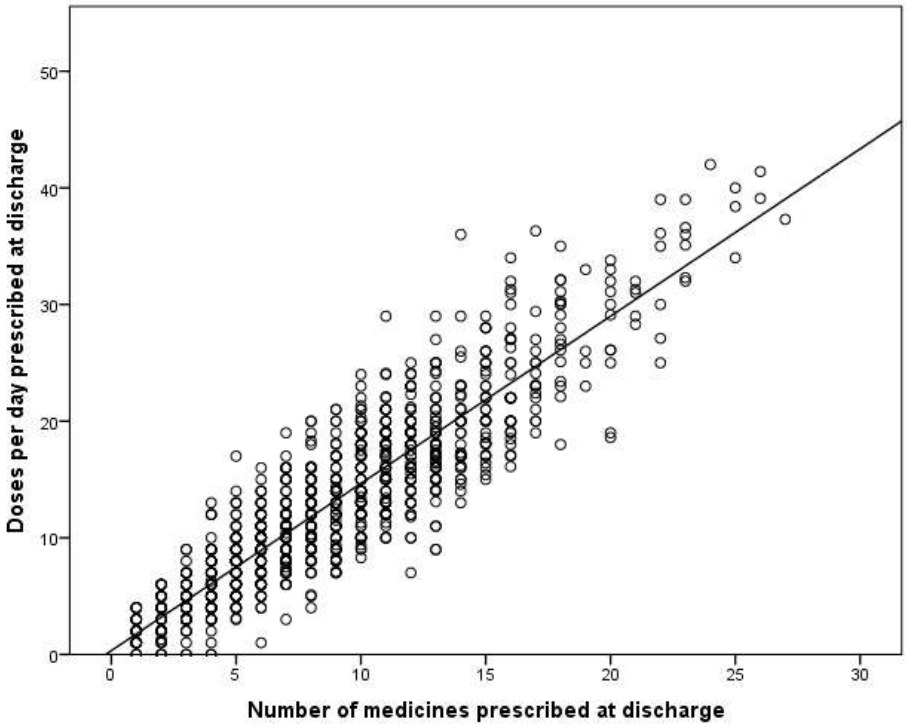


Figure 4.17: Number of doses per day and medicines prescribed at discharge

To avoid potential issues of collinearity due to the strong relationship between the number of medicines and the number of doses per day prescribed at discharge, analyses of DPD in the context of the other variables were not conducted in addition to the analyses involving the number of medicines.

4.2.3.4 BNF chapters of prescribed medication

A total of 10103 medicines prescribed over 1116 discharges for 993 individuals were included. The prescribed items are summarised according to BNF chapter in Figure 4.18:

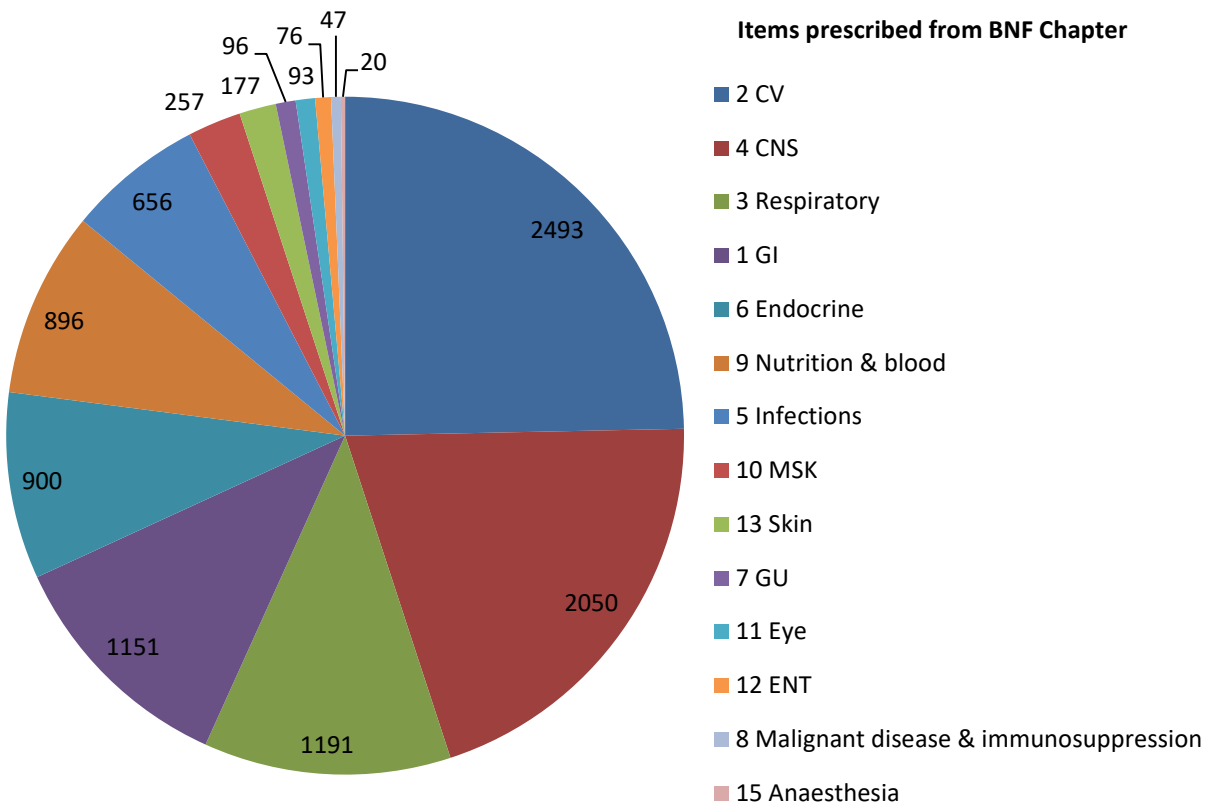


Figure 4.18: Frequency for prescription of medicines from each BNF chapter

The proportion of medicines prescribed from each BNF chapter was broadly consistent with published national figures for prescriptions dispensed in the community (Health & Social Care Information Centre, 2013b), although it appears that more respiratory medicines were prescribed among the cohort than the national figure, as shown in Figure 4.19:

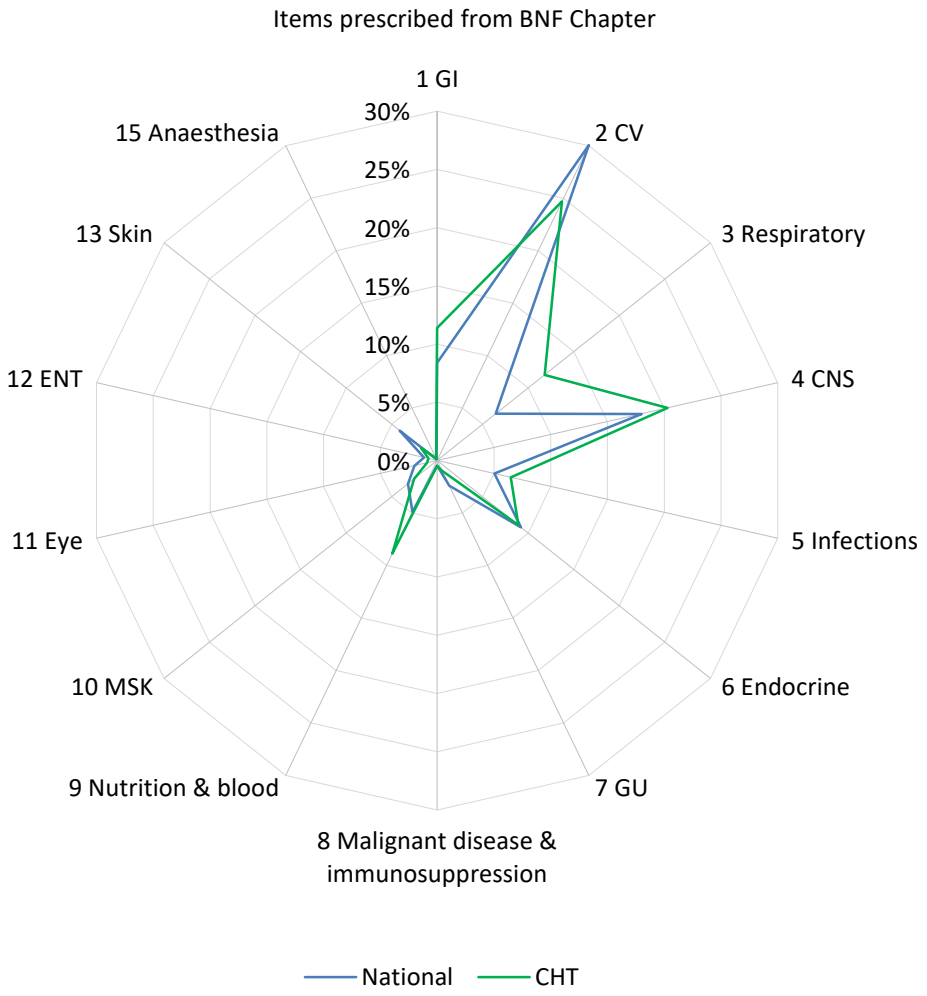


Figure 4.19: Proportion of prescriptions according to BNF chapter

Medicines prescribed from the four BNF chapters that featured most prominently accounted for over two-thirds of all prescribed items (68.1%), specifically the cardiovascular (CV, 24.7%), central nervous (CNS, 20.3%), respiratory (11.8%), and gastro-intestinal (GI, 11.4%) system chapters. The number of discharges involving medication from the most prevalent BNF chapters was as follows:

- Three-quarters of prescriptions included medicine from the CNS chapter
- Over two-thirds of prescriptions included medicine from the CV chapter
- Two-thirds of prescriptions included medicine from the GI chapter

Around half of discharge prescriptions analysed included both CNS and GI medicines (53.1%), around half included both CNS and CV medicines (52.0%), and 48.4% included

both CV and GI medicines. Over one-third of prescriptions (38.7%) included GI, CV and CNS medicines, whilst only 57 (5.1%) did not contain medicines from any of these BNF chapters.

When the BNF chapters were considered in terms of the whether discharge prescriptions contained any medication from each chapter rather than the number of items prescribed from each chapter, medication for the respiratory system contributed a much smaller portion and the positions of CV and CNS medicines were reversed. This is because patients prescribed respiratory or cardiovascular medicines tended to be prescribed more medicines from the same chapter concurrently, reflecting that treatment guidelines for chronic medical conditions within these chapters involved a stepwise approach to prescribing, with additional medicines from within the chapter being prescribed when optimising the use and dosage of the prior step does not achieve the desired outcome. Examples of stepwise prescribing guidelines for medical conditions typically treated on the MSSUs are presented below in Figure 4.20:

BNF chapter	Condition	Therapeutic class of drug
2 Cardiovascular	Heart failure	ACE inhibitor & beta blocker + spironolactone + digoxin
	Hypertension (over 55 years of age)	Calcium-channel blocker + ACE inhibitor + thiazide-related diuretic + beta-blocker
3 Respiratory	Asthma	Short-acting $beta_2$ agonist + inhaled corticosteroid + leukotriene receptor antagonist + long-acting $beta_2$ agonist
	COPD (FEV_1 ≥50%)	Short-acting $beta_2$ agonist + long-acting $beta_2$ agonist + inhaled corticosteroid + long-acting muscarinic antagonist

(Joint Formulary Committee, 2014)

Figure 4.20: Stepwise prescribing guideline examples

All prescriptions for medication from BNF chapter 15 (Anaesthetics) were specifically for midazolam injection, and the prescriptions also included other anticipatory medication[39]. Figure 4.21 demonstrates the distribution for the number of BNF chapters from which medicines were prescribed:

[39] Medicine(s) used to manage symptoms commonly experienced during the end of life

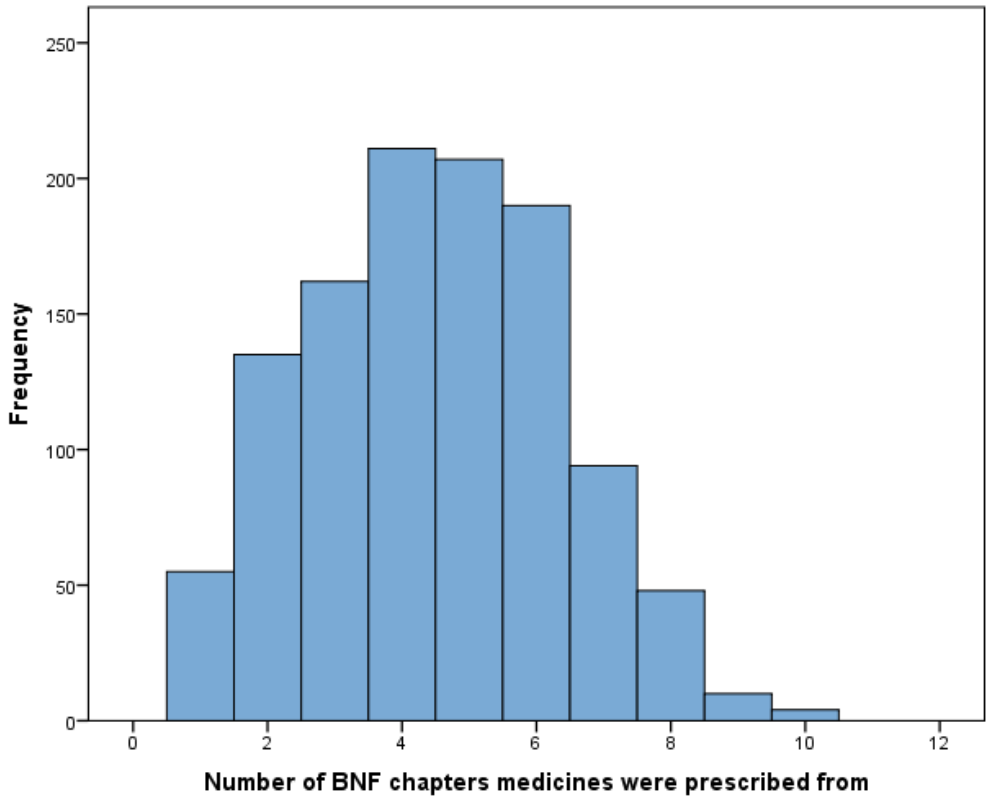


Figure 4.21: Number of BNF chapters from which medicines were prescribed

The number of medicines prescribed was strongly correlated with the number of BNF chapters medicines were prescribed from (r=0.811, p<0.001). Figure 4.22 below confirms that this relationship was linear and linear regression demonstrated that 65.8% of variation in the number BNF chapters that medicines were prescribed from was explained by variation in the number of medicines prescribed, with medicines being prescribed from 4.5 BNF chapters on average corresponding to 9.1 medicines being prescribed on average.

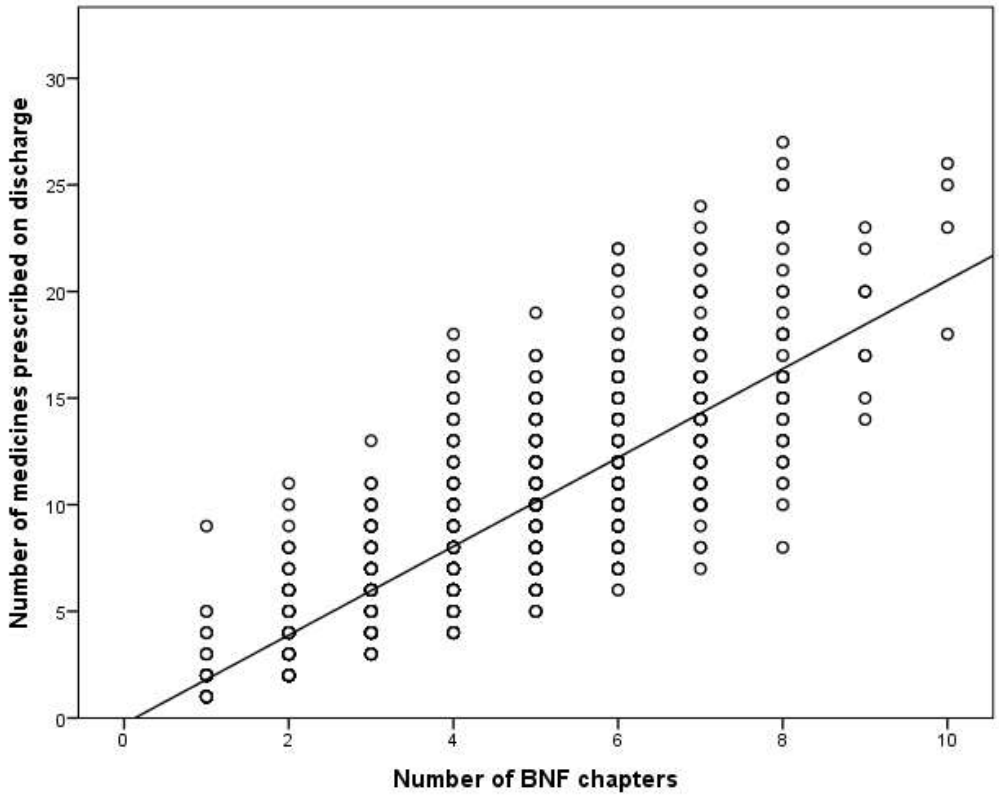


Figure 4.22: Number of medicines prescribed and number of BNF chapters concerned

To avoid potential issues of collinearity, analyses of the number of BNF chapters medicines were prescribed from were not conducted for subsequent variables in addition to number of medicines prescribed due to the strong association between the number of BNF chapters from which medicines were prescribed and the number of medicines prescribed.

4.2.3.5 Potential eligibility for Medicines Use Review (MUR)

a) MUR High Risk Medicines (HRMs)

Around one in 10 (10.0%) medicines prescribed were high risk medicines according to the MUR national target group criteria (see 3.2.2.2 b) MUR High Risk Medicines). The number of high risk medicines on discharge prescriptions is shown in Figure 4.23:

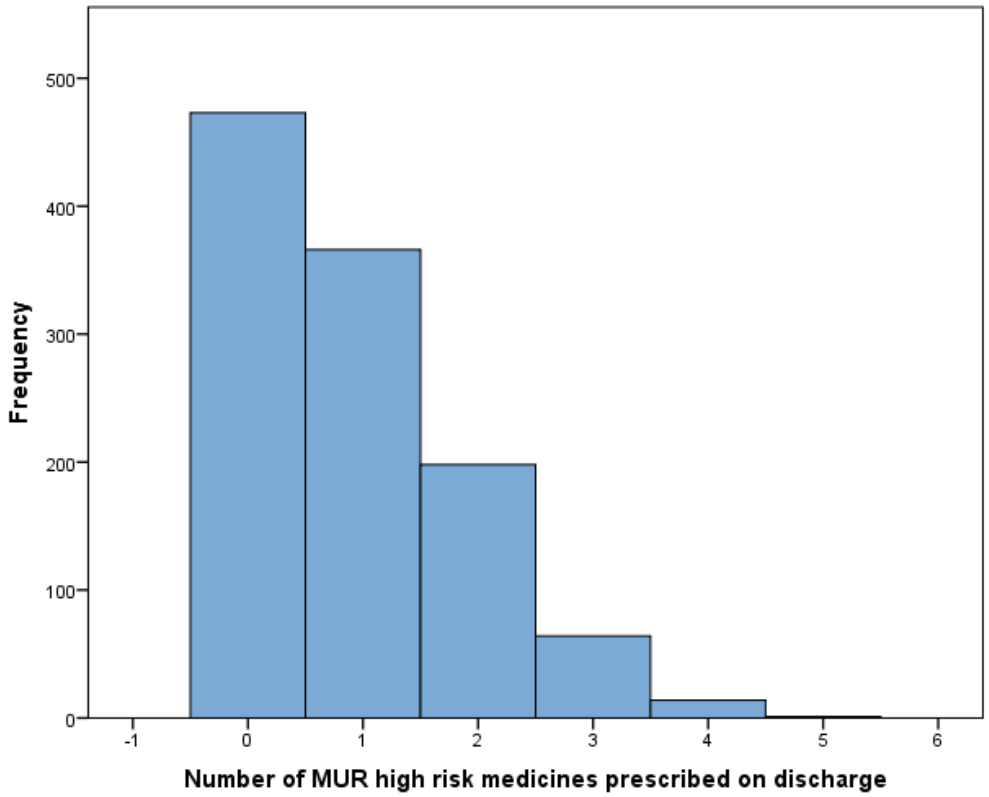


Figure 4.23: Number of high risk medicines (HRMs) prescribed on discharge

Patients discharged from Hospital B were prescribed significantly more high risk medicines than patients from than Hospital A. Patients prescribed high risk medicine(s) had a significantly longer average LOS and were significantly older compared to patients who were not prescribed any high risk medicine, as described in Figure 4.24 and Figure 4.25:

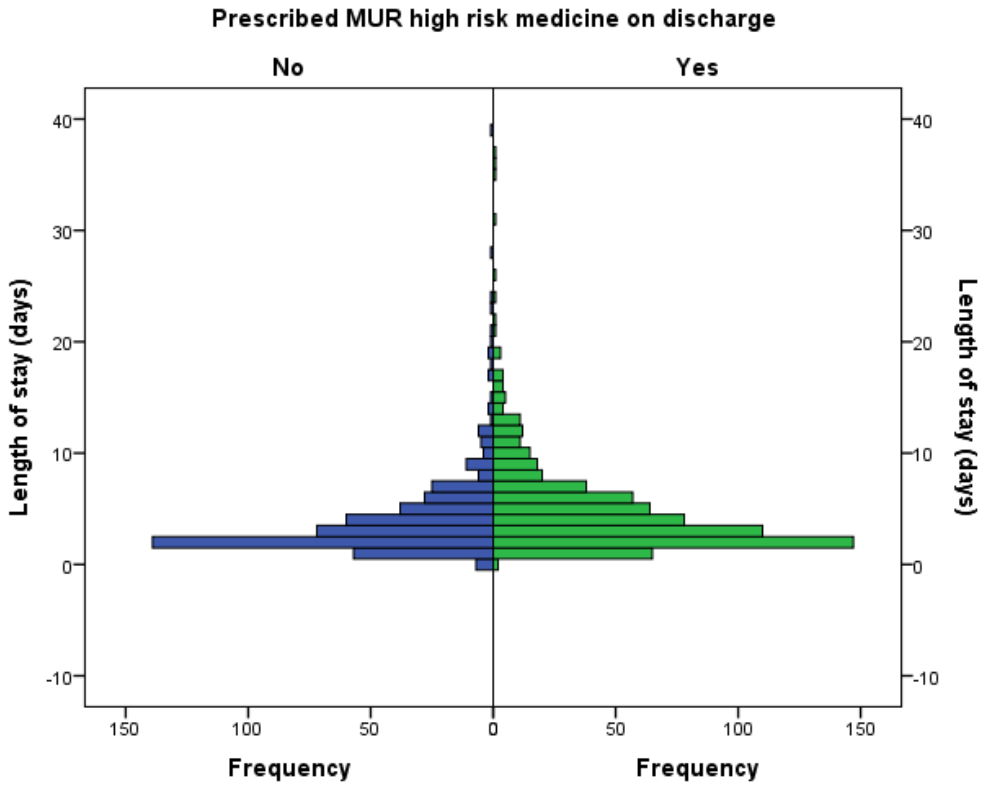


Figure 4.24: LOS according to whether prescribed high risk medication

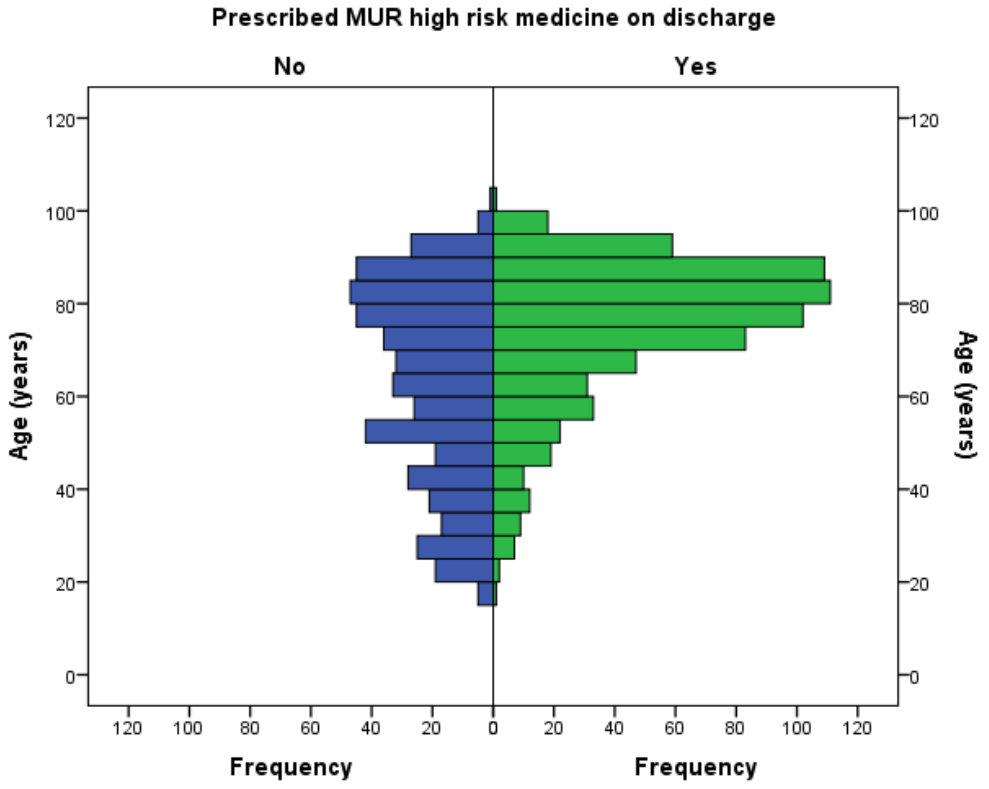


Figure 4.25: Age according to whether prescribed high risk medication

The relationship between the number of high risk medicines prescribed and the number of medicines prescribed altogether was not linear; patients prescribed high risk medication were prescribed more medicines on average than patients who were not prescribed any high risk medication, as shown in Figure 4.26:

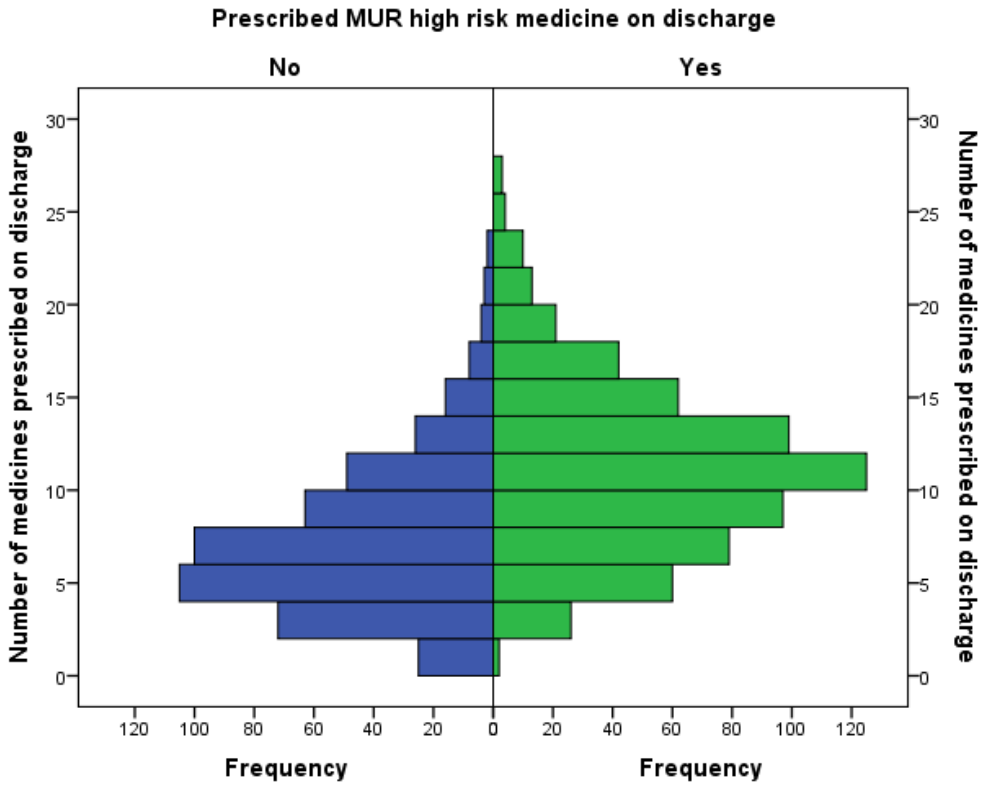


Figure 4.26: Number of medicines according to whether prescribed high risk medication

Due to the majority of high risk medicines being from BNF chapter 2 (Cardiovascular system, CV), the vast majority of discharge prescriptions that contained a high risk medicine contained a CV medicine (95.4%, 637/668), and vice versa (79.4%, 637/802).

b) Respiratory MUR Target Group

The majority of discharge prescriptions that contained a medicine from BNF chapter 3 (Respiratory system) met the respiratory MUR target group criteria (87.7%, 378/431), constituting one-third of all discharge prescriptions.

c) Cardiovascular MUR Target Group

Over half of the discharge prescriptions would have been eligible for a targeted cardiovascular MUR. Whether patients were prescribed any medicine from BNF chapter 2 (Cardiovascular system) accounted for 76.2% (481/631) of those that would have been eligible for a targeted cardiovascular MUR.

4.2.3.6 Anticholinergic Cognitive Burden

The anticholinergic cognitive burden score for discharge prescriptions was most commonly zero (31.6%, 353/1116); Figure 4.27 shows ACB score was positively skewed:

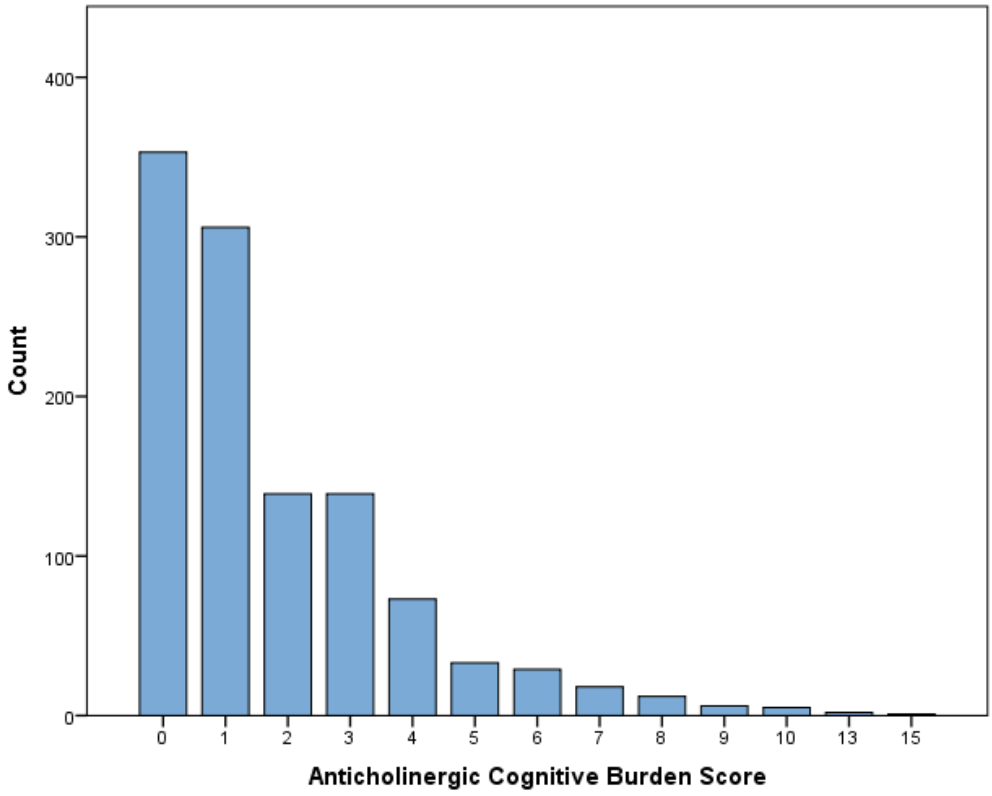


Figure 4.27: Anticholinergic Cognitive Burden (ACB) Score on discharge

Patients 65 years of age and over constituted two-thirds (65.6%, 813/1240) of the cohort, yet less than one-fifth of discharge prescriptions were identified as suitable for ACB review (patient 65 years of age or over prescribed medication with ACB score >2, (Boustani et al., 2008)).

Figure 4.28 demonstrates the very small, although statistically significant, difference in the average age of patients whose prescriptions were suitable for ACB review, compared to those 65 years of age and over whose prescriptions were not (patients suitable for ACB review were one year younger, on average):

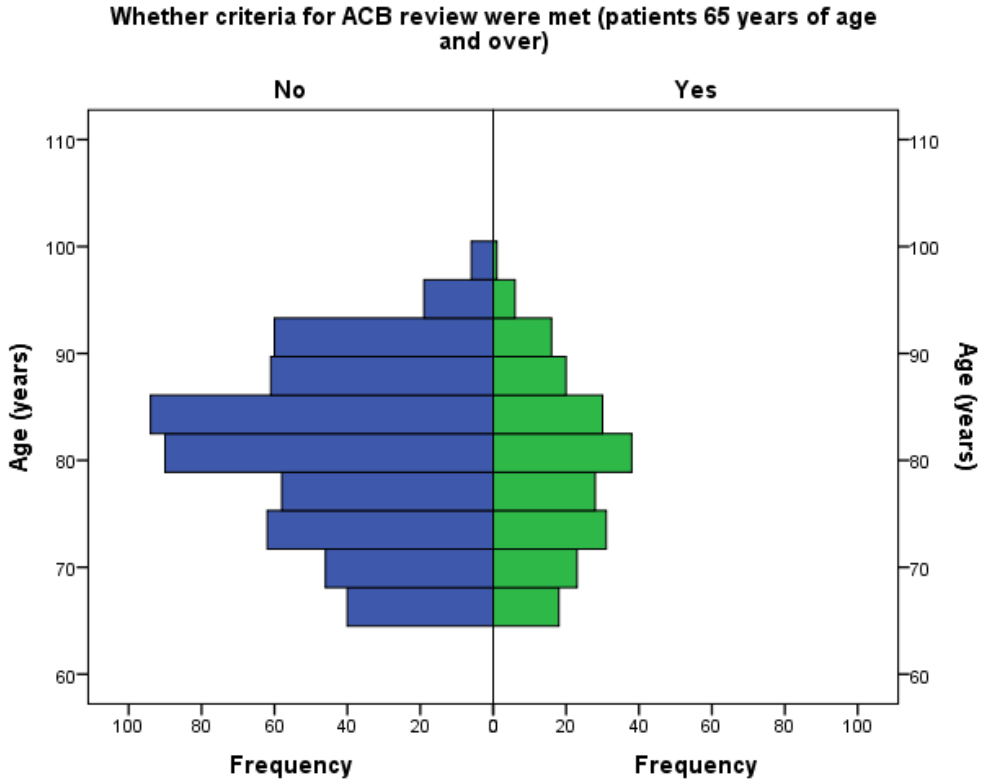


Figure 4.28: Age for patients aged 65 years and over according to whether prescription was suitable for ACB review

The mean number of medicines prescribed at discharge was greater for prescriptions that were suitable for ACB review compared to prescriptions for patients 65 years of age and over that were not suitable for ACB review, as shown in Figure 4.29:

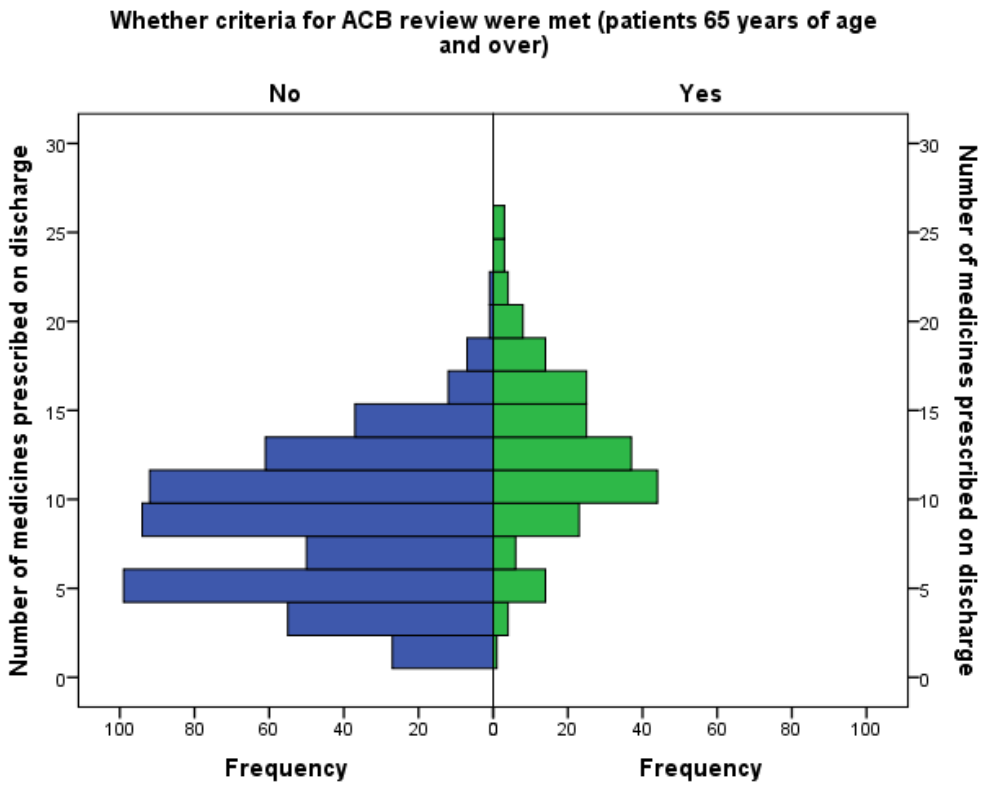


Figure 4.29: Number of medicines prescribed at discharge according to whether prescription suitable for ACB review for patients aged 65 years and over

Prescriptions that were suitable for ACB review contained more high risk medicines on average than prescriptions for patients 65 years of age and over that were not suitable for ACB review, as shown in Figure 4.30:

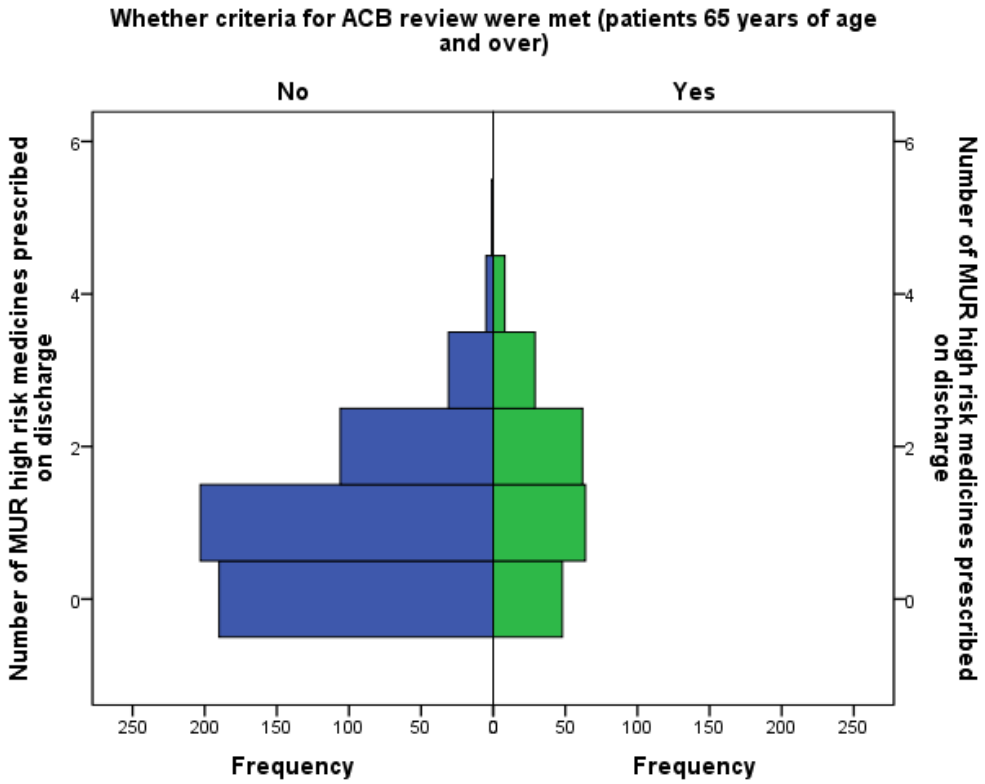


Figure 4.30: Number of high risk medicines prescribed for patients 65 years of age and over according to whether the discharge prescription was suitable for ACB review

Figure 4.31 demonstrates that among those 65 years of age and over, women had greater anticholinergic burden compared to men:

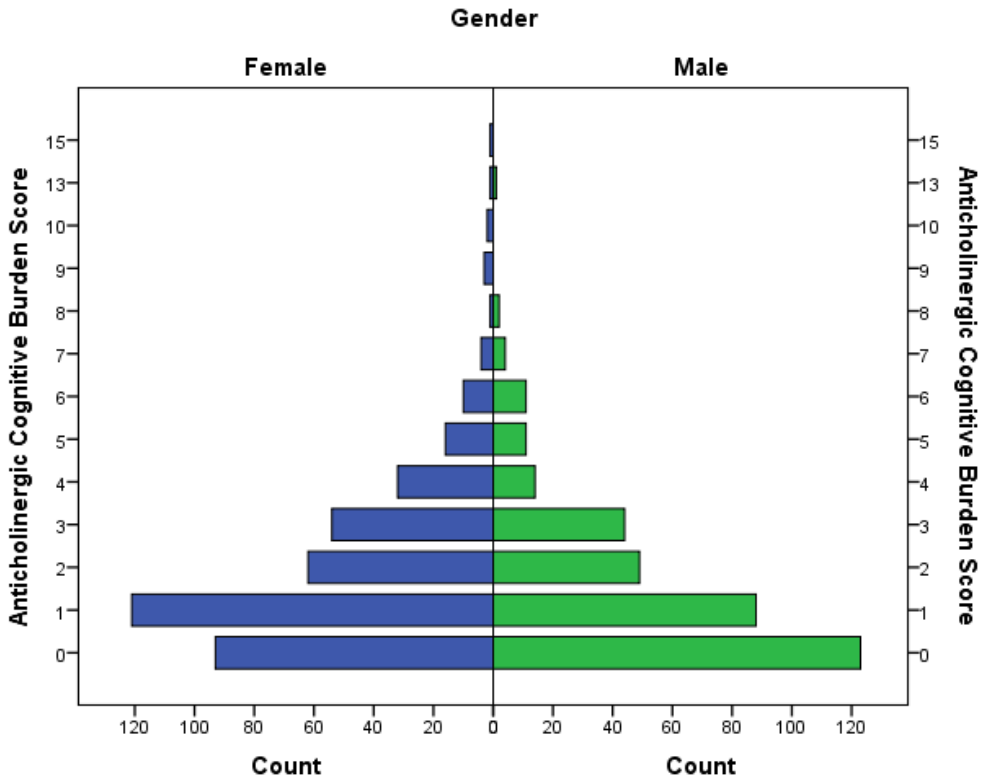


Figure 4.31: ACB among patients 65 years of age and over according to gender

4.2.3.7 Medication changes

The vast majority of discharge prescriptions included changes to the patient's medication regimen, therefore the likelihood of any change being made to prescriptions according to the other variables was not assessed. The number of changes could not be calculated for one discharge prescription because it indicated that all medication prescribed prior to the admission had been stopped without detailing the previous prescription. Figure 4.32 below shows that the distribution for number of changes on discharge prescriptions was positively skewed:

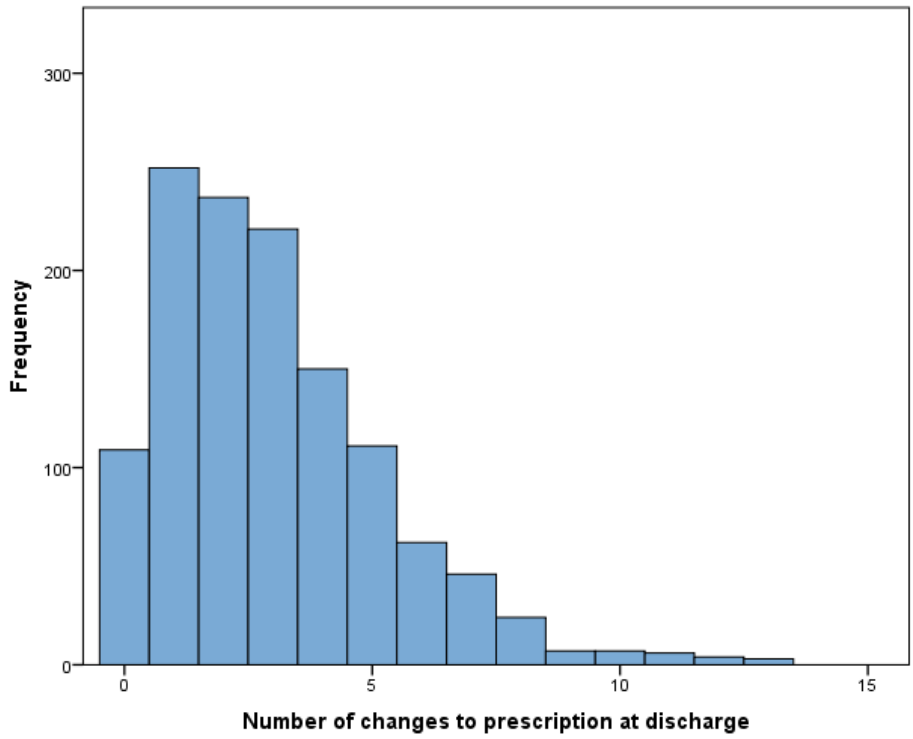


Figure 4.32: Number of changes made to prescriptions at discharge

Prescriptions that included high risk medicines contained significantly more changes on average than prescriptions without any high risk medicines. Prescriptions which were suitable for ACB review also contained significantly more changes than prescriptions for patients 65 years of age and over that were not suitable for ACB review. These relationships are demonstrated in Figure 4.33 and Figure 4.34 respectively:

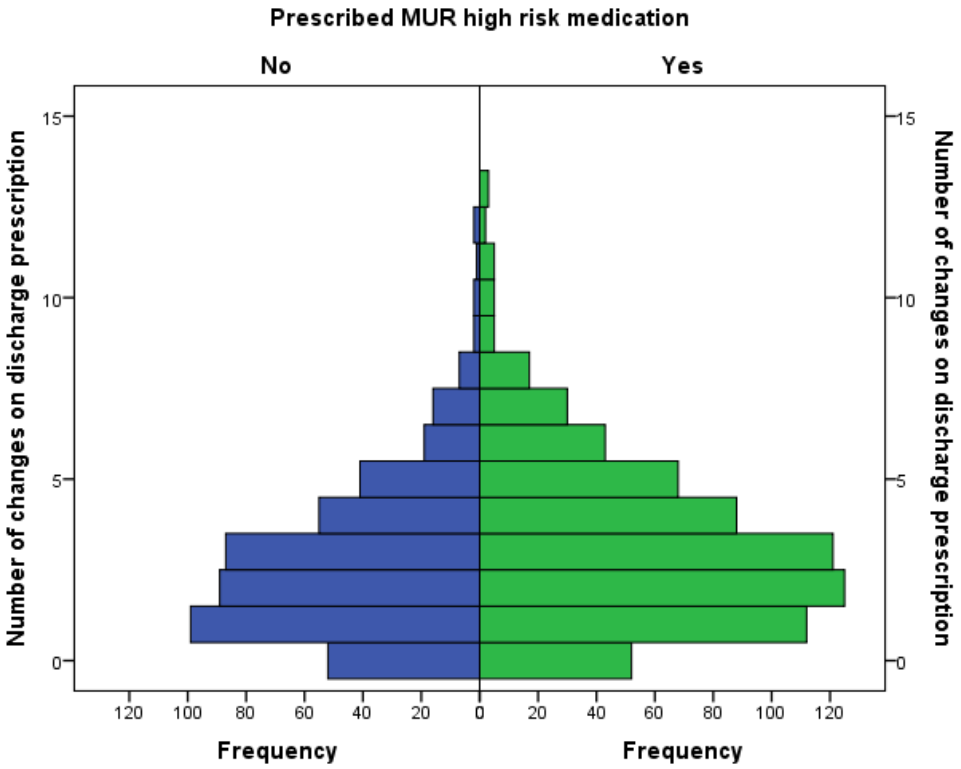


Figure 4.33: Number of changes according to whether prescribed HRM

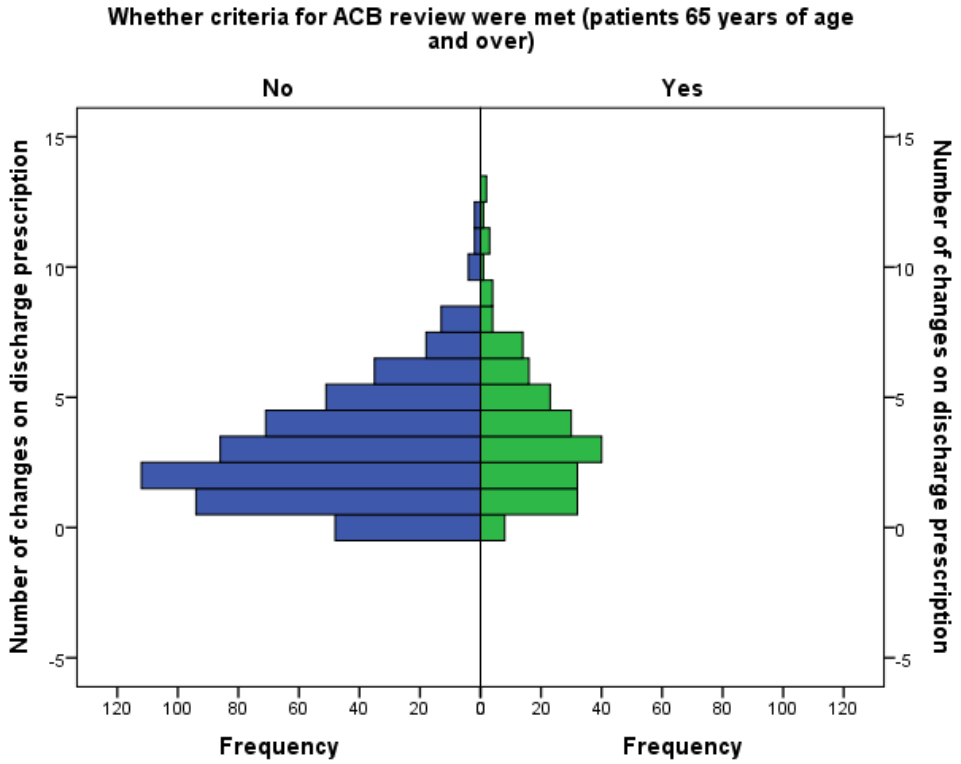


Figure 4.34: Number of changes on discharge prescriptions for patients aged 65 years and over according to whether the prescription was suitable for ACB review

Although older patients' prescriptions contained more changes on average compared to younger patients (see Figure 4.35), the relationships between the number of changes on prescriptions and age, length of stay and number of medicines prescribed were not linear.

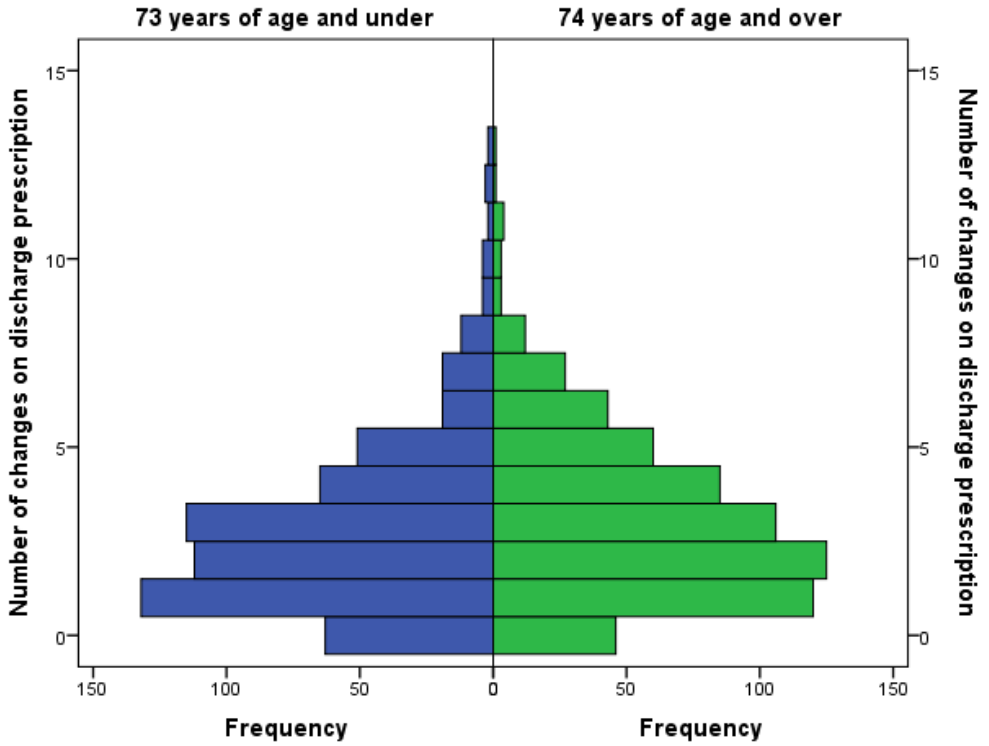


Figure 4.35: Number of changes on discharge prescriptions of younger patients compared to older patients

a) Medicines Use Review Post-discharge Target Group

Provided that patients met the general MUR eligibility criteria set out previously, the vast majority of discharge prescriptions would have met the target group criteria for a post-discharge MUR because they contained two or more current medicines and changes had been made to the prescription since admission.

b) Medicines Use Review Target Groups

The vast majority of discharge prescriptions met the criteria in place for a targeted MUR at the time of discharge (high risk medicine, respiratory or post-discharge).

c) New medicines started

The vast majority of discharge prescriptions contained a new medicine. Figure 4.36 demonstrates that the positively skewed distribution for the number of new medicines prescribed was very similar to that for the number of changes (see also Figure 4.32):

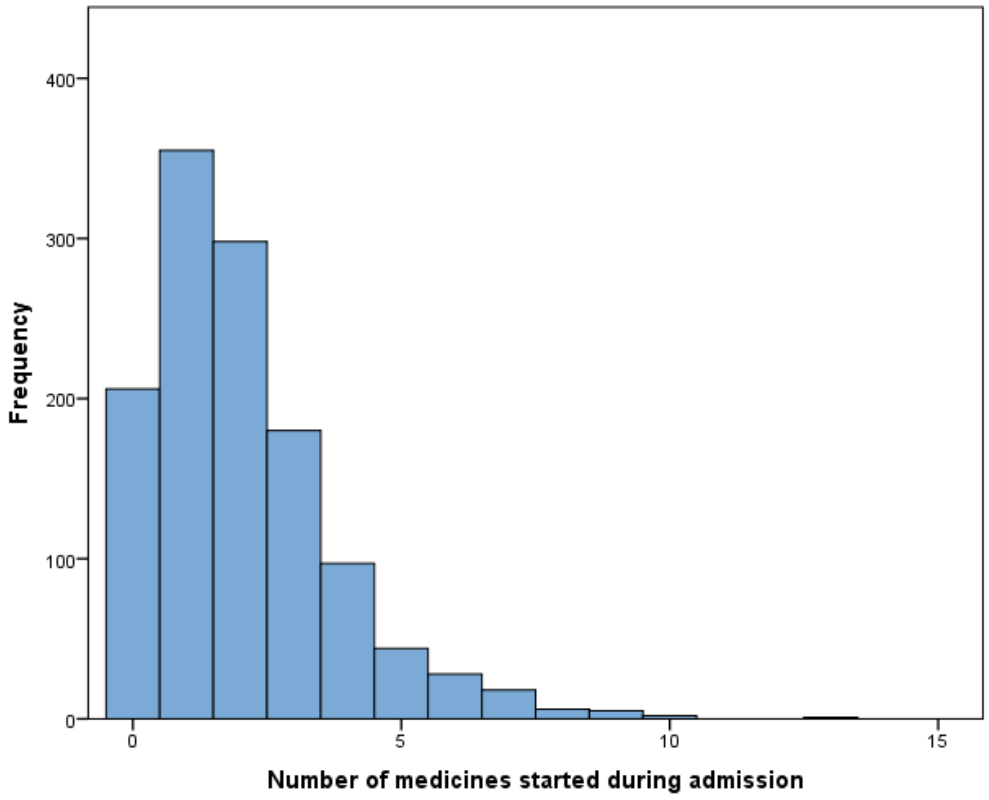


Figure 4.36: Number of new medicines prescribed on discharge

The relationship between the number of changes and the number of new medicines prescribed was not linear; however, the associations between the number of new medicines and other variables generally reflected the relationships presented above for the number of changes, with the following exceptions:

- A significant association was not identified between the number of new medicines and whether any high risk medicines were prescribed
- Patients discharged from Hospital B were prescribed more new medicines compared to Hospital A

Having established the close association between the number of new medicines and the number of changes on discharge prescriptions, analyses involving the number of new

medicines were not conducted in addition to analyses involving the number of changes for subsequent variables.

d) Courses of medication

Almost one-sixth (15.6%) of medicines prescribed on discharge were temporary courses of treatment intended to last 30 days or less. The majority of prescriptions included medicines prescribed temporarily at discharge, with some not containing any medication intended to continue on an ongoing basis (beyond 30 days). It was unusual for prescriptions to include more than five temporary medicines, and more than 10 appeared anomalous. Figure 4.37 shows the positively skewed distribution for the number of medicines prescribed temporarily on discharge:

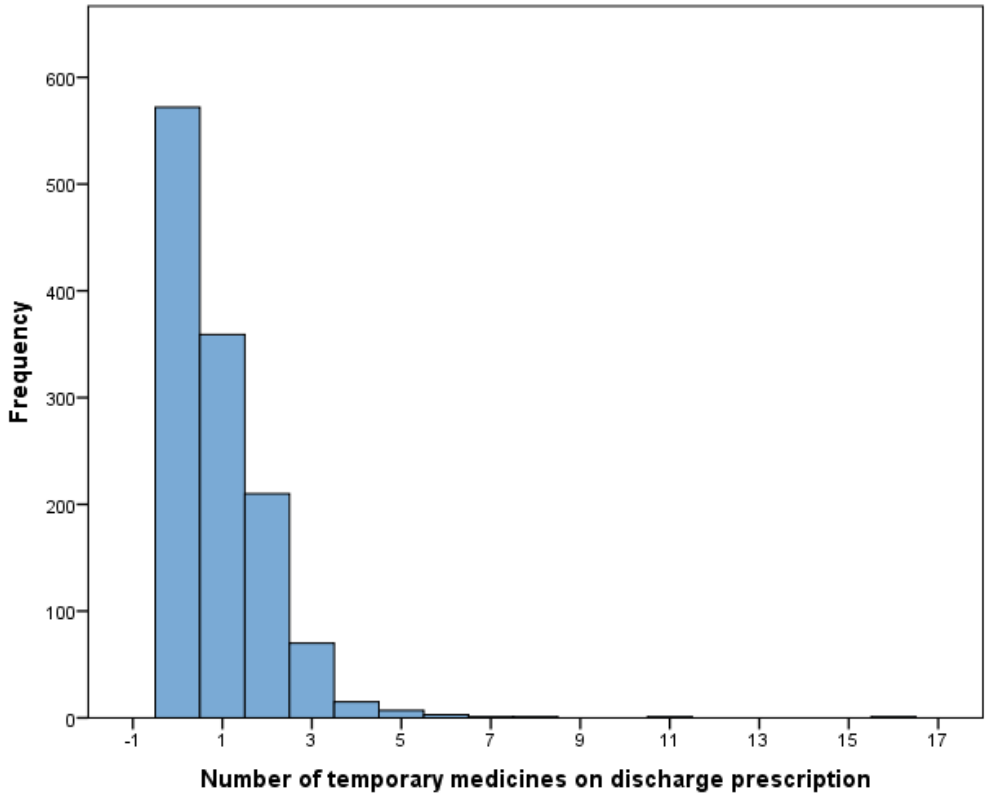


Figure 4.37: Number of medicines prescribed temporarily on discharge

Discharge prescriptions from Hospital B contained significantly more temporary medicines compared to discharge prescriptions from Hospital A.

A large proportion of temporary prescriptions were from BNF chapters concerning infection and pain; almost half were from BNF Chapter 5 - Infections (antimicrobials, 38.6%, 611/1581). Seven per cent of (45/656) prescriptions from BNF chapter 5 were intended to continue, and over half (22/38) of prescriptions including continuing antimicrobials were for patients who were also prescribed medicines from BNF Chapter 3 – Respiratory (respiratory patients); more than twice as many respiratory patients were prescribed continuing antimicrobials (22/422) compared to those not prescribed respiratory medication (16/694). Medicines from BNF Chapter 4 – Central Nervous System were the next most likely to be prescribed temporarily, constituting almost one-fifth of the total (18.0%, 285/1579).

e) Potential eligibility for referral to the New Medicines Service (NMS)

One in seven discharge prescriptions were potentially eligible for referral to NMS. Patients whose prescriptions were potentially eligible for referral to NMS had a significantly longer average LOS compared to patients whose prescriptions were not, as shown in Figure 4.38.

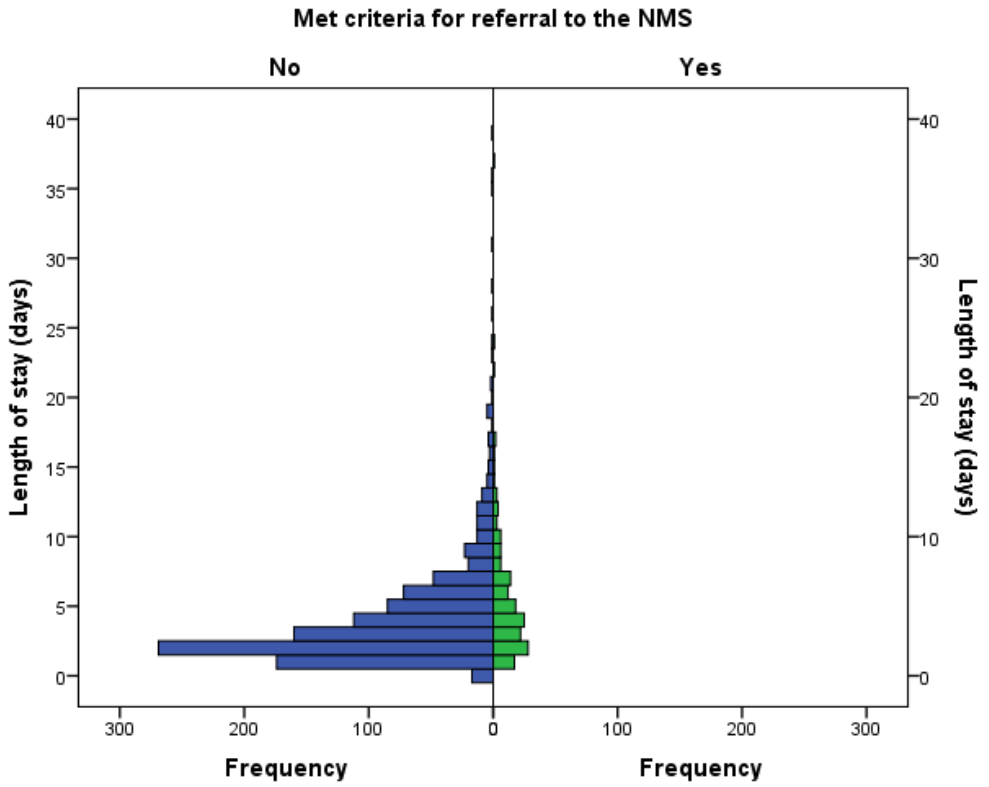


Figure 4.38: LOS according to whether potentially eligible for referral to the New Medicines Service (NMS)

Female patients' prescriptions were slightly more likely to be potentially eligible for referral to the NMS than males'; prescriptions that were potentially eligible for referral to the NMS contained more medicines on average compared to those that were not, as shown in Figure 4.39:

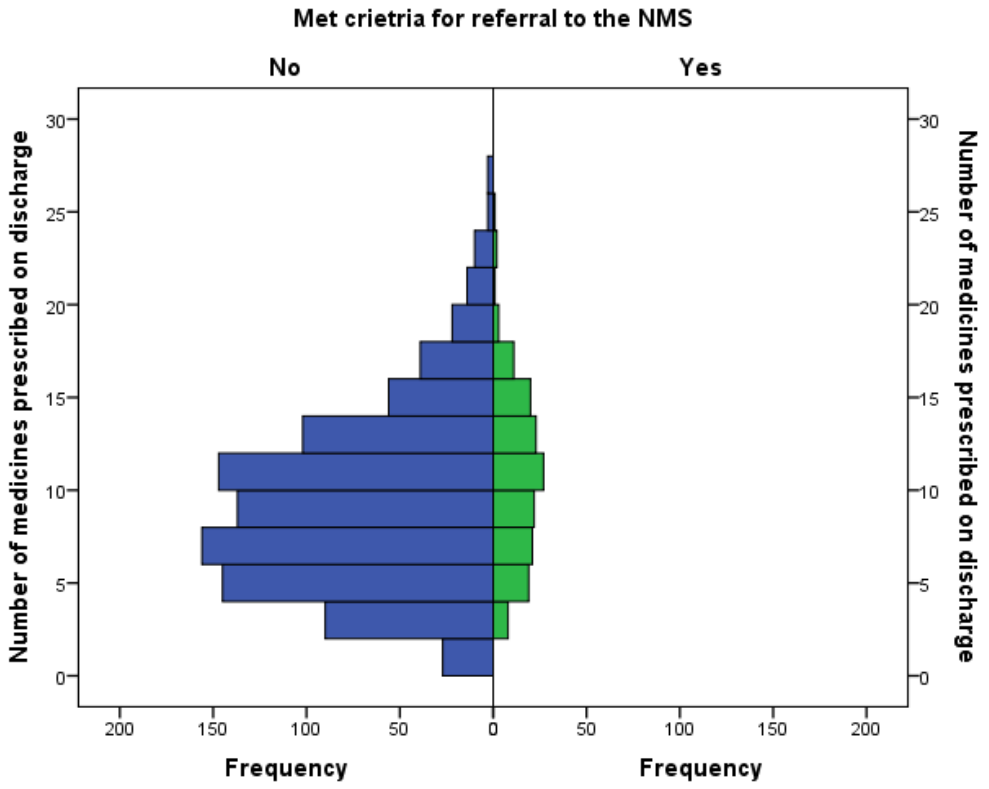


Figure 4.39: Number of medicines prescribed according to whether potentially eligible for referral to NMS

Prescriptions that were potentially eligible for referral to NMS also contained more high risk medicines than prescriptions that did not, as shown in Figure 4.40:

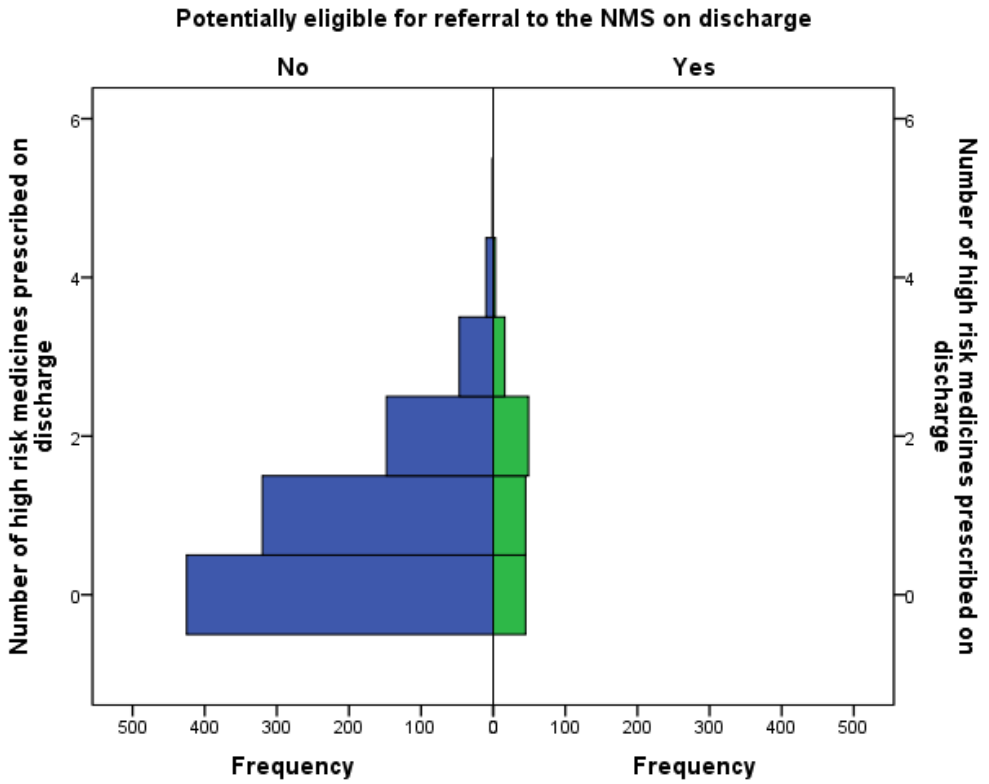


Figure 4.40: Number of high risk medicines prescribed according to whether potentially eligible for referral to NMS

f) Medicines stopped

Medication had been stopped according to one-third of discharge prescriptions. The number of medicines stopped could not be calculated for one prescription as it indicated that all medication prescribed prior to admission had been stopped, without documenting the previous prescription.

Patients who were discharged during the week had more medicines stopped on average compared to patients who were discharged at the weekend as shown in Figure 4.41 below; and, reflecting that fewer patients were discharged from Hospital A at the weekend, prescriptions from Hospital A had more stopped medicines on average compared to Hospital B, as shown in Figure 4.42:

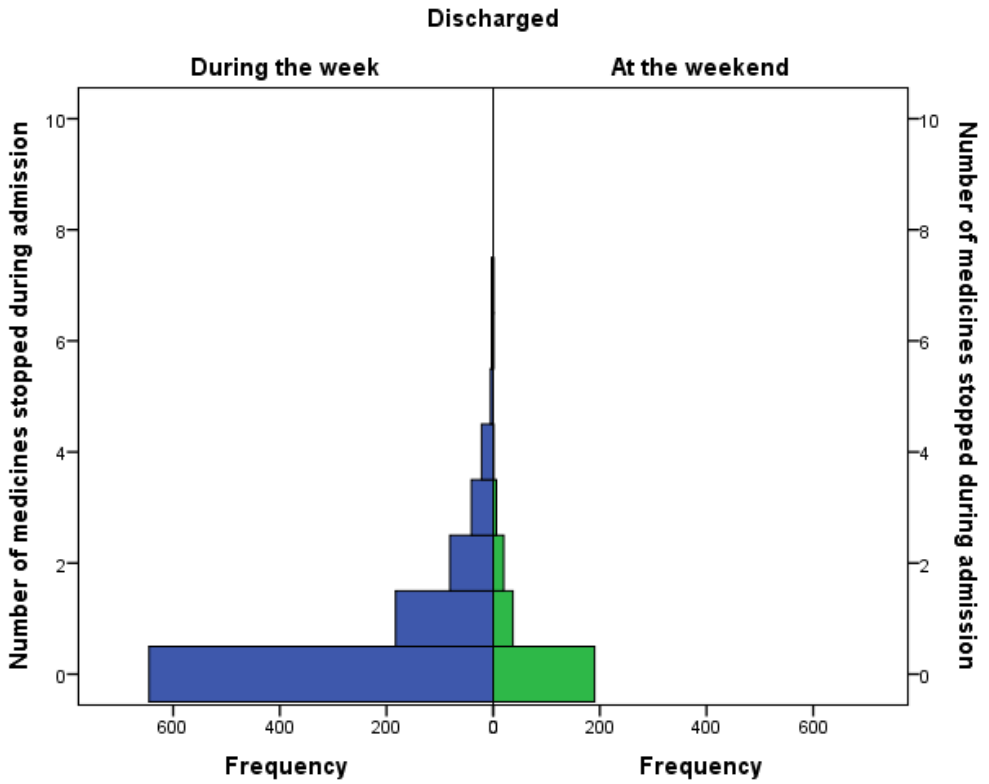


Figure 4.41: Number of medicines stopped during admission according to whether discharged during the week or at the weekend

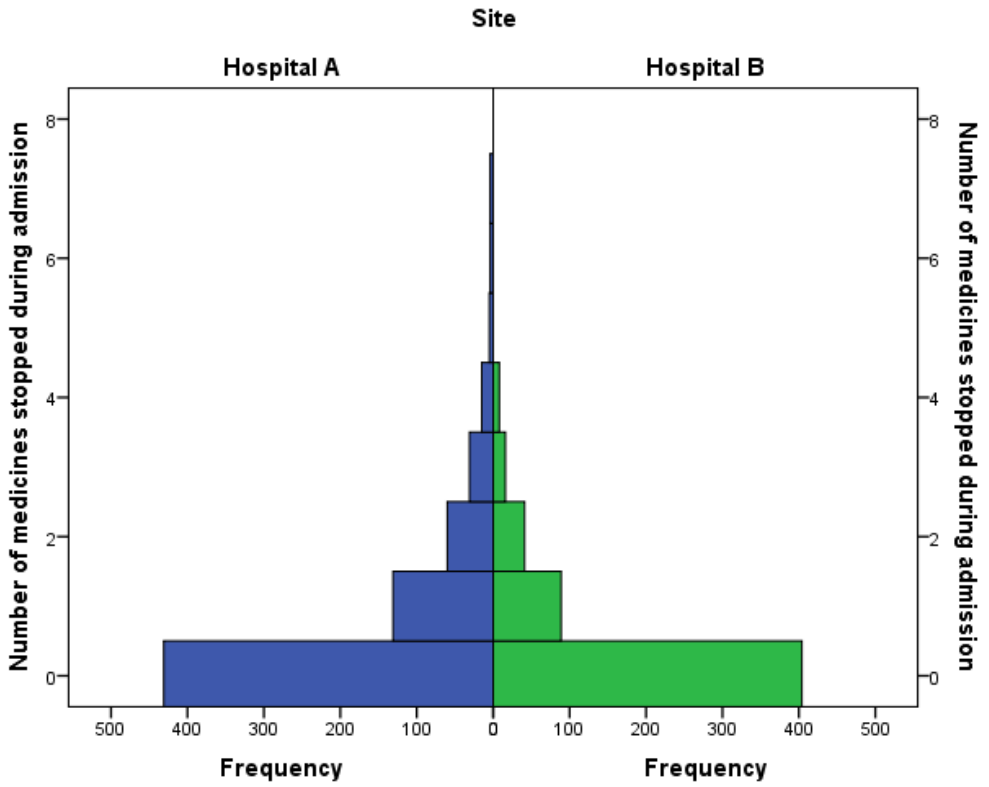


Figure 4.42: Number of medicines stopped during admission according to hospital site

g) Change in the number of medicines prescribed

Over two-thirds of patients were prescribed more medicines at discharge than on admission, compared to just 12.0% of patients who were prescribed fewer medicines at discharge than on admission; one in five prescriptions contained the same amount of medicines at discharge as on admission. The change in number of medicines prescribed from admission to discharge is demonstrated in Figure 4.43:

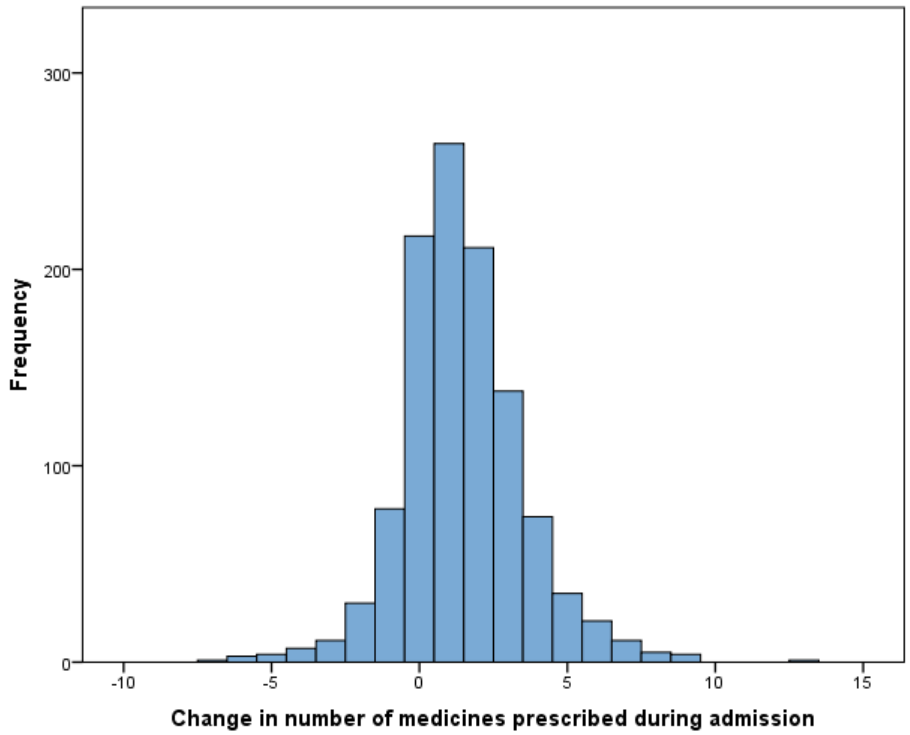


Figure 4.43: Change in number of medicines prescribed during admission

A strong relationship between the number of medicines prescribed on admission and discharge (r=0.906, p<0.001) was identified (demonstrated in Figure 4.44), with variation in the number of medicines prescribed on admission accounting for 82.1% of the variation in the number of medicines prescribed at discharge and 7.6 medicines on average being prescribed on admission corresponding to 9.1 medicines on average being prescribed on discharge. Analyses of the number of medicines prescribed on admission in relation to the other variables were not conducted in addition to the analyses involving the number of medicines prescribed on discharge because of the strong relationship between the number of medicines prescribed on admission and discharge.

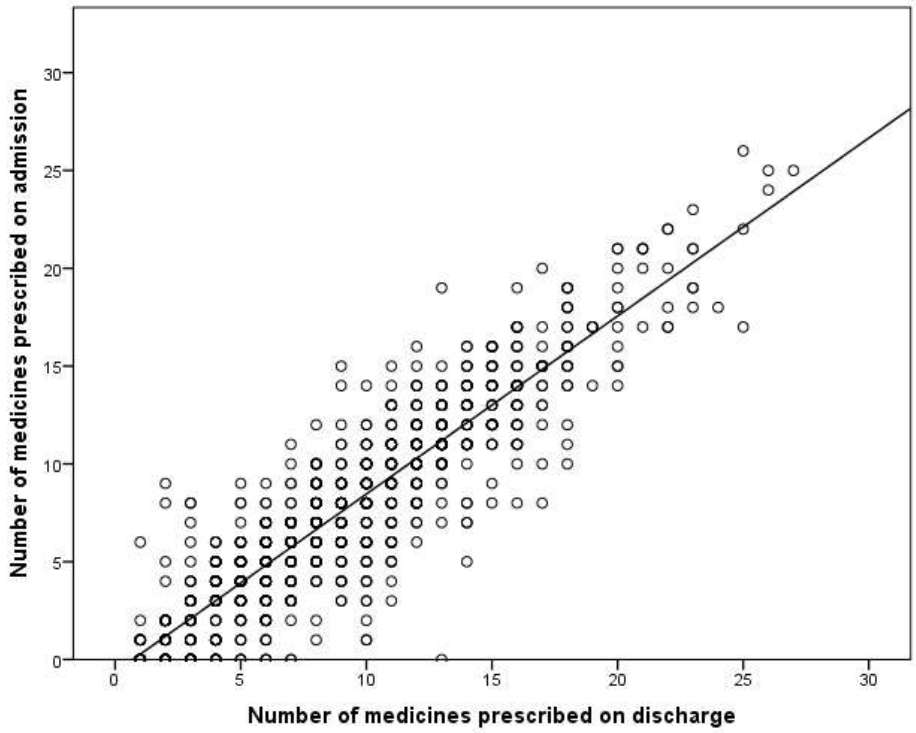


Figure 4.44: Number of medicines prescribed on admission and discharge

4.2.4 Pharmaceutical intervention

4.2.4.1 Pharmacist validation of discharge prescriptions

Almost two-thirds of discharge prescriptions were validated by a pharmacist, of which the vast minority were documented as validated on the ward. This proportion was surprisingly low considering that the clinical pharmacy team were on the wards daily. However, it was possible for pharmacists to validate discharge prescriptions at ward level without specifying as such, which could explain why so few discharge prescriptions were documented as validated at ward level; there was evidence of pharmacist involvement in 14.8% discharge prescriptions which were not documented as validated at the point of discharge. Consequently, whether prescriptions were validated on the ward or not was not included in any further analyses, as it could not be assured that the information had been captured accurately.

Patients discharged via a discharge lounge were slightly more likely to have their prescription validated than those discharged directly from the ward, as were those

discharged during the week rather than at the weekend. Figure 4.45 and Figure 4.46 below demonstrate that patients whose discharge prescriptions were validated were older and had a longer LOS, on average, compared to patients whose prescriptions were not validated.

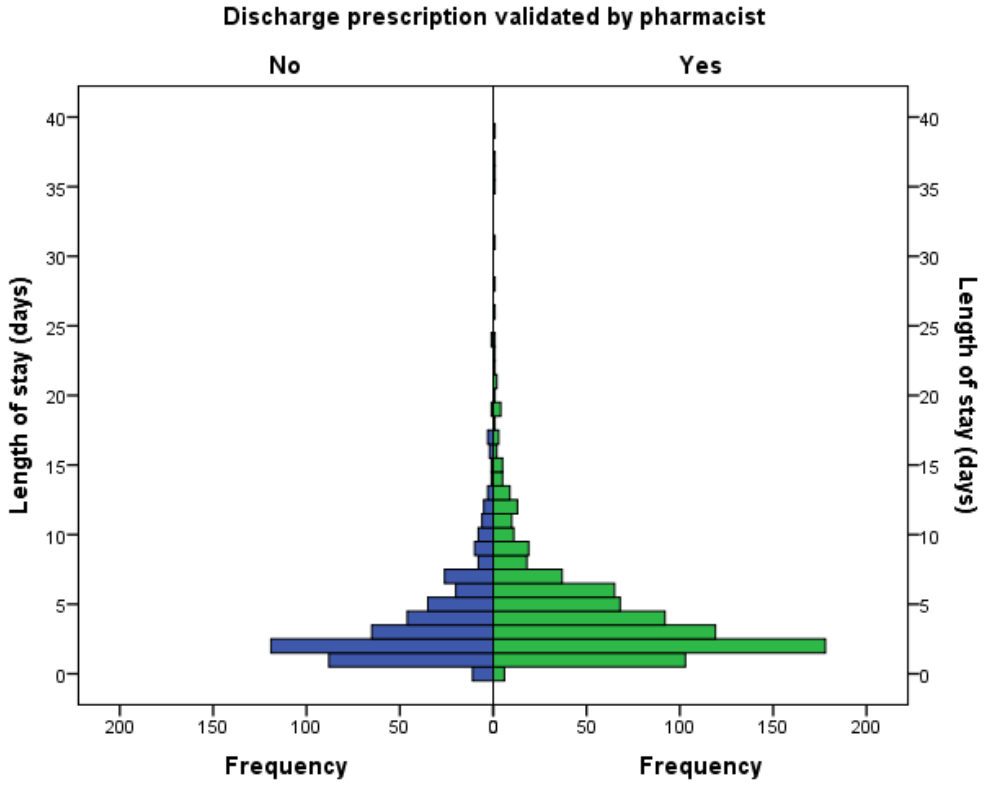


Figure 4.45: LOS according to whether discharge prescription was validated

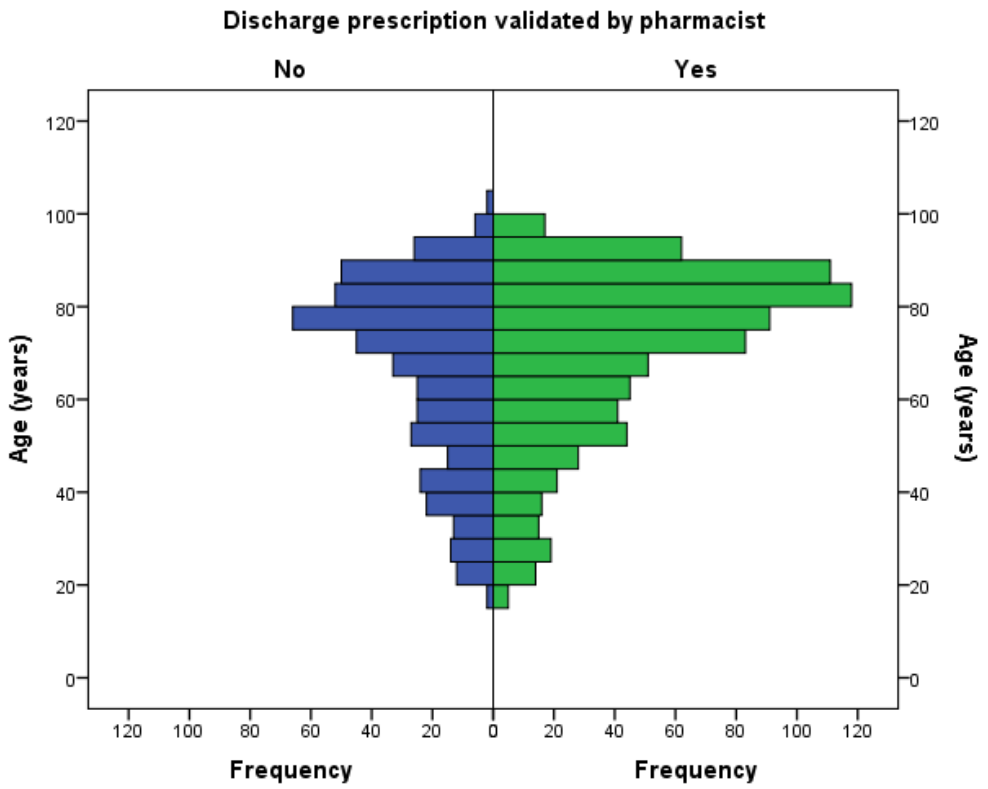


Figure 4.46: Age according to whether discharge prescription was validated

Prescriptions that contained a clause were marginally less likely to be validated than those that did not, and discharge prescriptions that were validated contained more medicines on average than discharge prescriptions that were not, as shown in Figure 4.47:

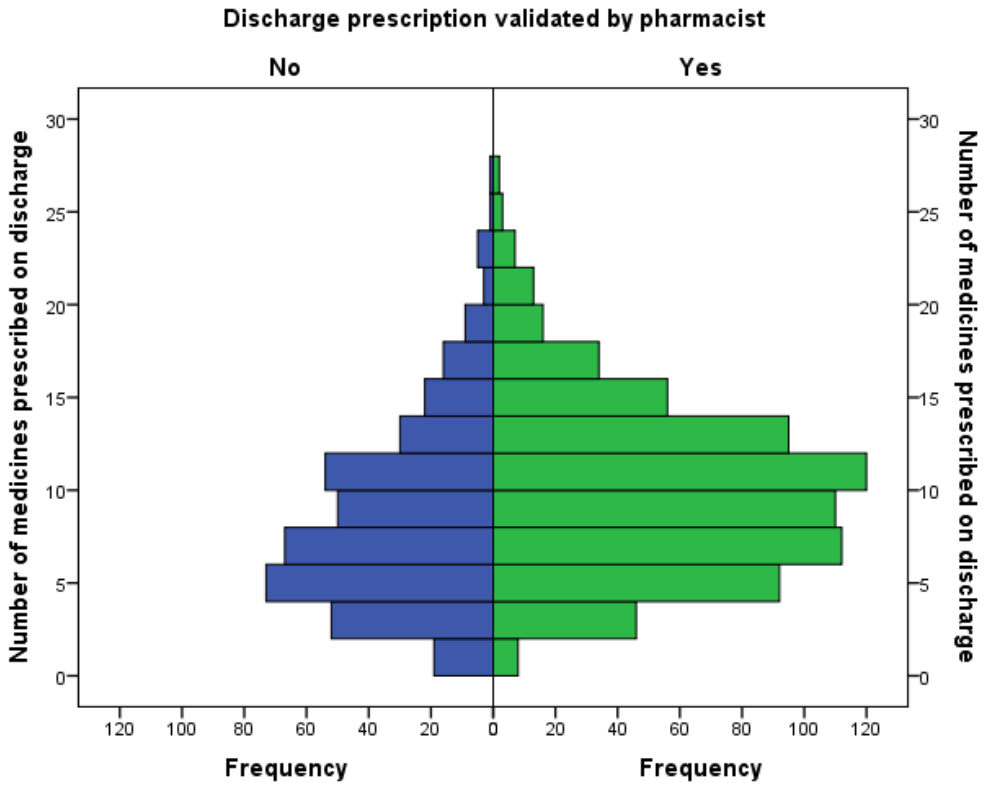


Figure 4.47: Number of medicines prescribed according to whether discharge prescription was validated

Prescriptions that contained medication from the following BNF chapters were more likely to be validated compared to prescriptions that did not contain any medication from that chapter:

Chapter 2. CV

Chapter 3. Respiratory

Chapter 4. CNS

Chapter 5. Infections

Chapter 6. Endocrine

Chapter 7. GU

Chapter 15. Anaesthesia

A marginally greater proportion of prescriptions that contained high risk medicines were validated compared to prescriptions that did not contain high risk medicines, and prescriptions which were suitable for ACB review were slightly more likely to be validated

than prescriptions for patients 65 years of age and over that were not suitable for ACB review. Discharge prescriptions that were validated contained more changes on average than discharge prescriptions that were not validated, as show in Figure 4.48:

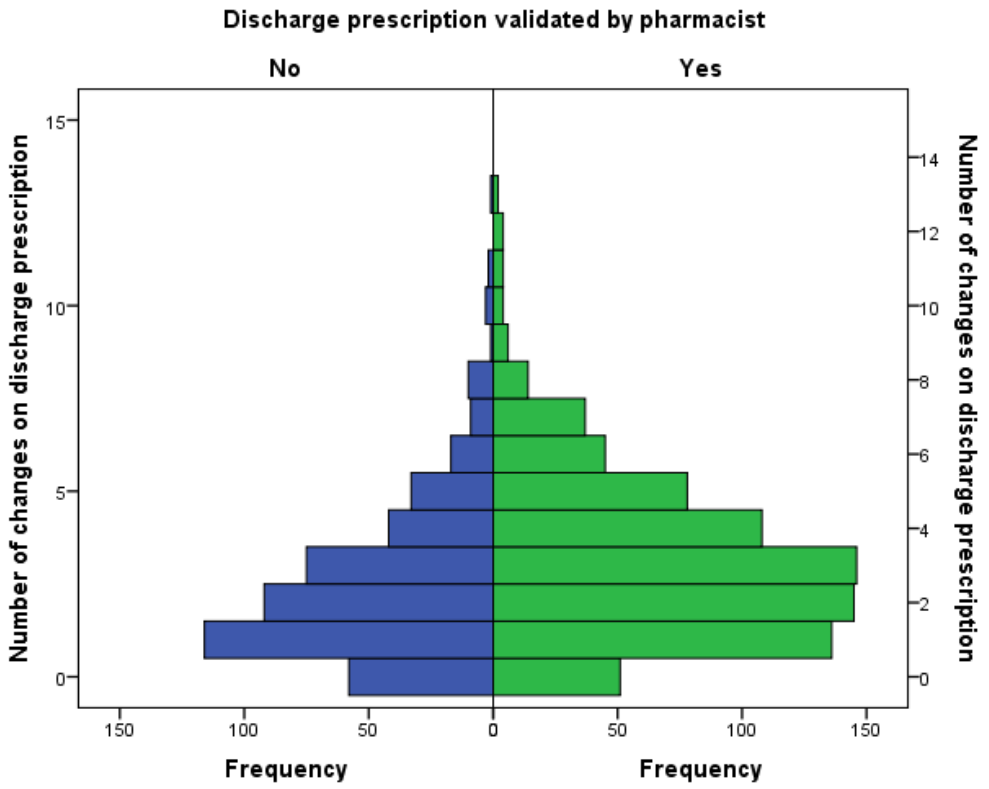


Figure 4.48: Number of changes on discharge prescription according to whether validated

Validated prescriptions contained more new medicines on average compared to prescriptions which were not validated, as shown in Figure 4.49:

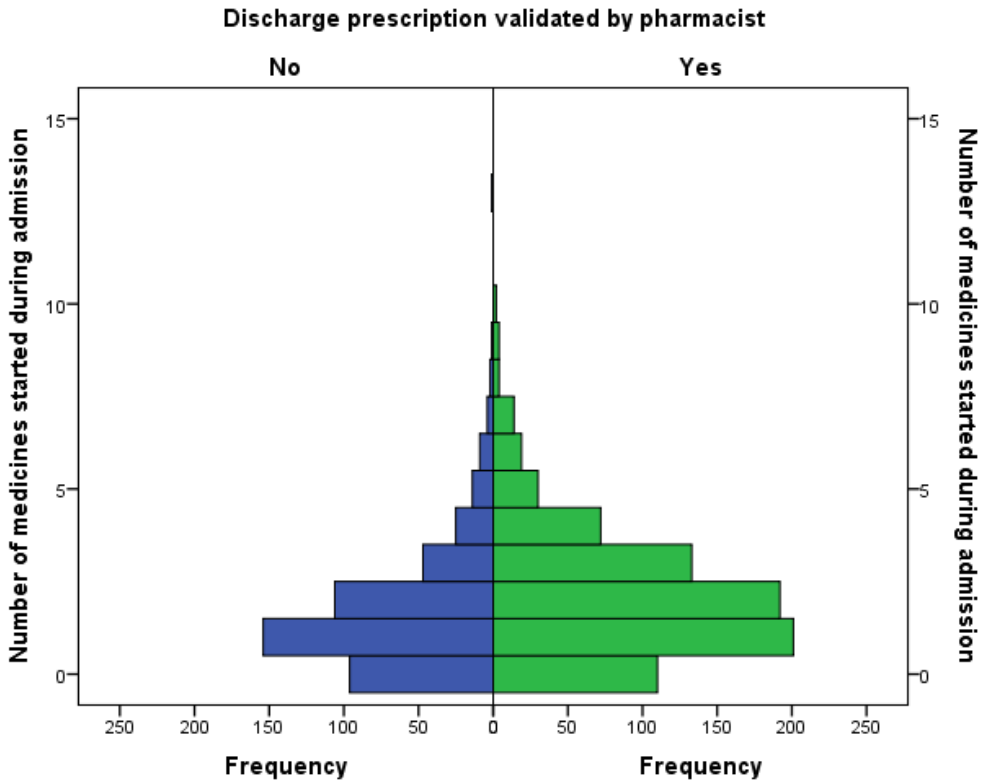


Figure 4.49: Number of new medicines prescribed according to whether discharge prescription was validated

Similarly, prescriptions that contained temporary medication were more likely to be validated compared to prescriptions that did not contain any temporary courses of medication.

The majority of prescriptions that appeared suitable for a targeted MUR or for referral for NMS were validated (63.6%, 742/1167); and the vast majority of prescriptions that were validated were potentially eligible for TMUR or NMS (95%, 742/781.

a) Mandating pharmacist validation

The characteristics of discharges, patients and prescriptions discharged were compared according to which phase of the study discharge occurred in order to identify any systematic differences and clarify whether differences were related to the change in process for pharmacist validation of discharge prescriptions between the phases.

Around half of discharges occurred in each phase. Patients in phase two of the study were significantly more likely to be discharged via a discharge lounge than patients in phase one (19.9%, 121/609 compared to 8.6%, 54/631, $\chi^2_1=32.7$, $p<0.001$, $\varphi=0.162$). Mandating pharmacist validation during normal working hours achieved a significant increase of moderate magnitude in the proportion of discharge prescriptions validated, and this effect was consistent when comparing sites. Patients who were discharged via a discharge lounge were significantly more likely to have their discharge prescription validated in the second phase of the study but not the first, and patients who were admitted at the weekend had a marginally greater chance of having their discharge prescription validated than those admitted during the week in the second phase of the study but not the first. Patients whose prescriptions were validated were significantly older on average than patients whose prescriptions were not validated in the first phase of the study but not the second, as shown in Figure 4.50:

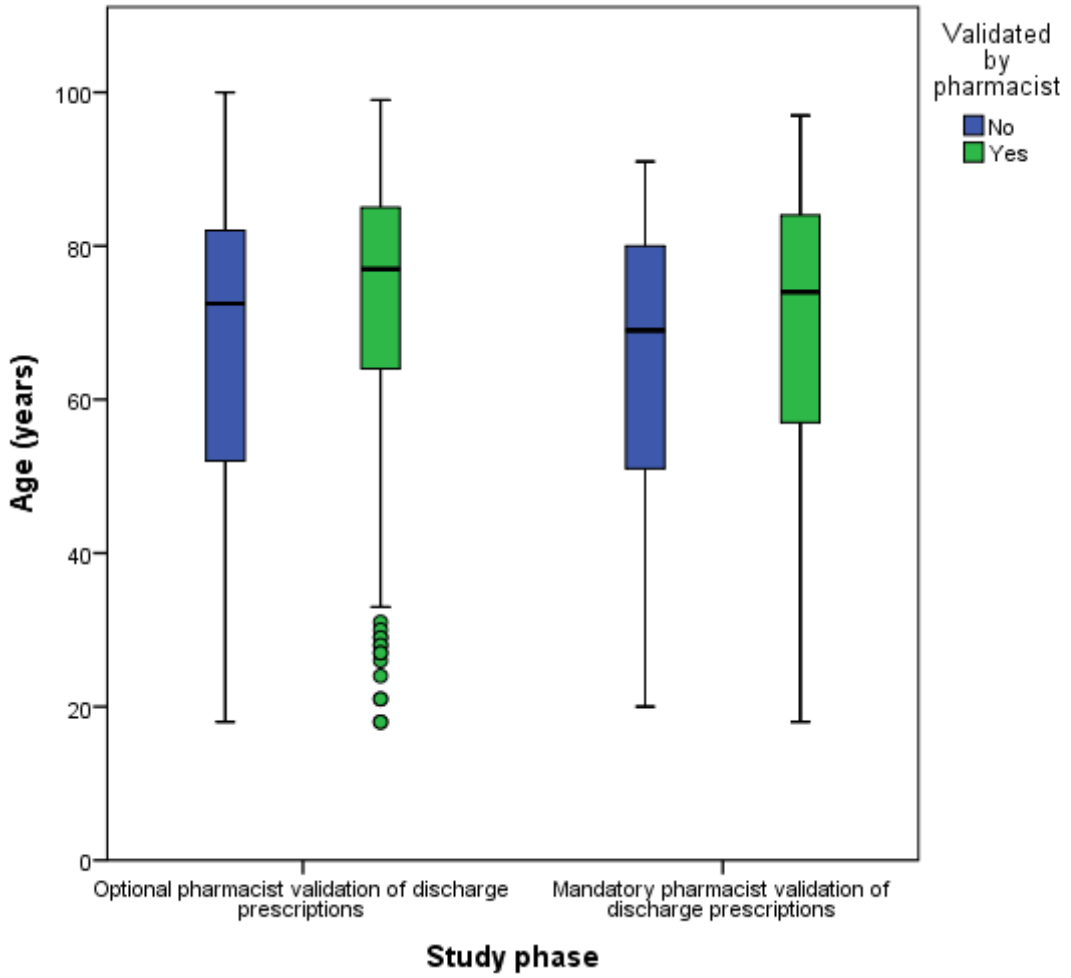


Figure 4.50: Age according to study phase and whether prescription was validated by a pharmacist

Prescriptions that were validated also contained more medicines than prescriptions that were not validated in the first phase of the study; this was not observed in the second phase, as shown in Figure 4.51.

Pharmacists validated significantly fewer prescriptions that had a clause applied to them, and consequently limited detail, than prescriptions without a clause applied during the first phase of the study; the proportion of prescriptions containing clauses validated by pharmacists was much greater in the second phase, bringing it on par with the proportion containing clauses that were not validated.

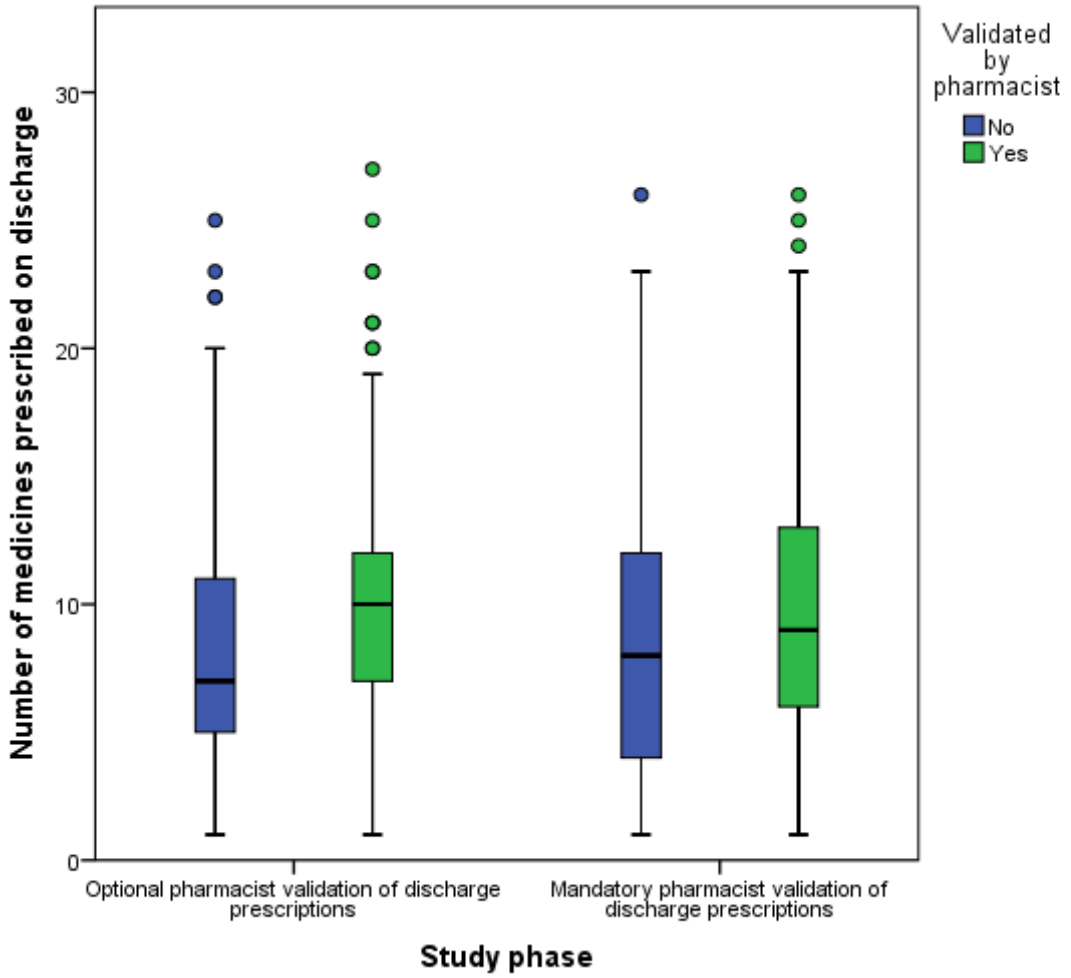


Figure 4.51: Number of medicines prescribed according to study phase and whether discharge prescription was validated

4.2.4.2 Medicines reconciliation

The medicines were recorded as reconciled on discharge by pharmacy for more than half of discharge prescriptions. Some of these also had "no changes…" clauses applied, indicating that the discharge prescription may not represent a complete, reconciled list of medicines. Very few discharge prescriptions were recorded as not reconciled, and the medicines reconciliation status was recorded as unknown or not recorded for one-third to half of discharge prescriptions. Excluding the prescriptions for which medicines reconciliation status was not recorded, the vast majority were recorded as reconciled.

Mandating pharmacist validation of discharge prescriptions increased the number of prescriptions with a medicines reconciliation status (488/609 compared to 271/631);

however, the number declared not reconciled was similar in both phases (14/609 and 10/631). Of all discharge prescriptions with a known medicines reconciliation status, the vast majority (90.6%, 688/759) were both reconciled and validated. Only 47 were not validated and reconciled, and 20 were validated and not reconciled, and four were not validated and not reconciled. A tendency to declare medicines reconciliation status for prescriptions that were reconciled and not to declare otherwise was evident, with the process for recording medicines reconciliation status resulting in a clear dependency between whether medicines reconciliation status was recorded and whether the discharge prescription was validated. Consequently, it was not appropriate to consider medicines reconciliation an independent variable; not only due to the amount of missing data, but also because the data were not missing at random. Medicines reconciliation status was therefore not analysed in addition to prescription validation in subsequent analyses.

4.2.4.3 Multi-compartment compliance aids (MCA)

Whether a multi-compartment compliance aid (MCA) was dispensed was annotated by pharmacists during validation of the discharge prescription. Consequently, validated prescriptions that did not indicate the patient was using an MCA were considered non-MCA (574). It was not known whether an MCA was in use for the 444 discharge prescriptions that were not validated by a pharmacist. Fifteen discharge prescriptions that were not validated indicated that an MCA was required, and 207 validated prescriptions indicated an MCA was required; the majority (86.0%) of MCA prescriptions were also documented as reconciled. Ten (4.5%) MCA prescriptions specified that the MCA was new. Although there was no significant difference in the number of MCAs dispensed in each phase, a significantly larger proportion of prescriptions in the first phase of the study indicated an MCA was required compared to the second phase. Patients who were dispensed an MCA were older on average compared to patients whose prescriptions did not indicate they were using an MCA, as described in Figure 4.52:

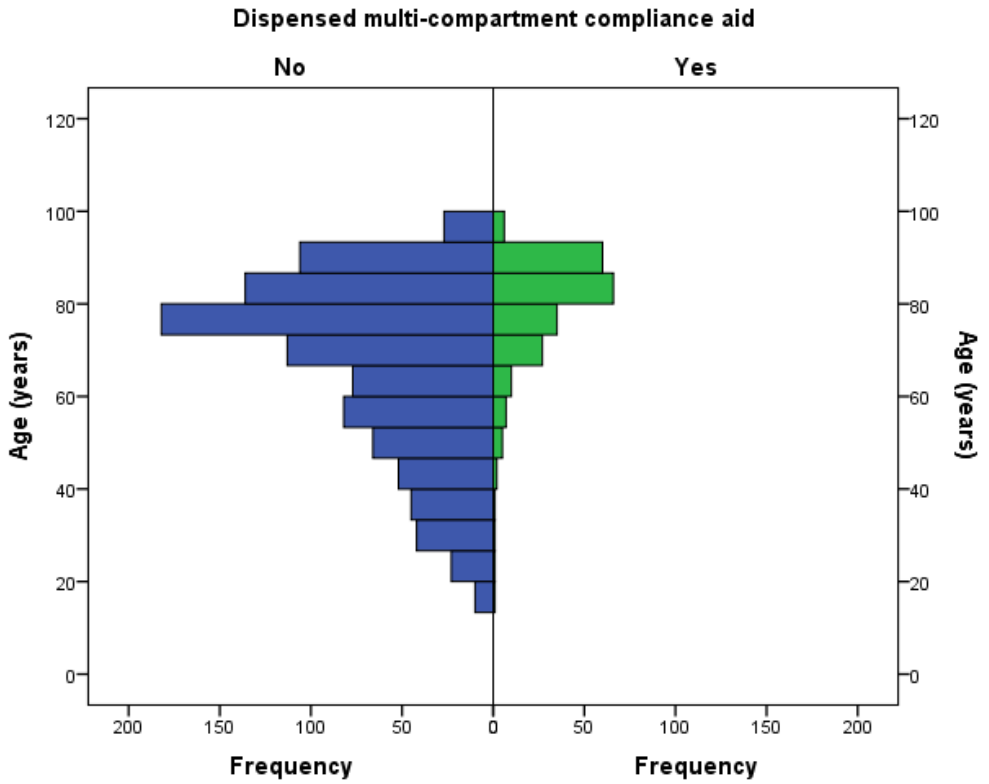


Figure 4.52: Age according to whether prescribed a multi-compartment compliance aid (MCA)

MCA prescriptions were less likely to contain a clause compared to non-MCA prescriptions. The number of medicines prescribed was not indicated for nine MCA prescriptions due to the use of these clauses. MCA prescriptions contained more medicines on average than non-MCA prescriptions, as described in Figure 4.53:

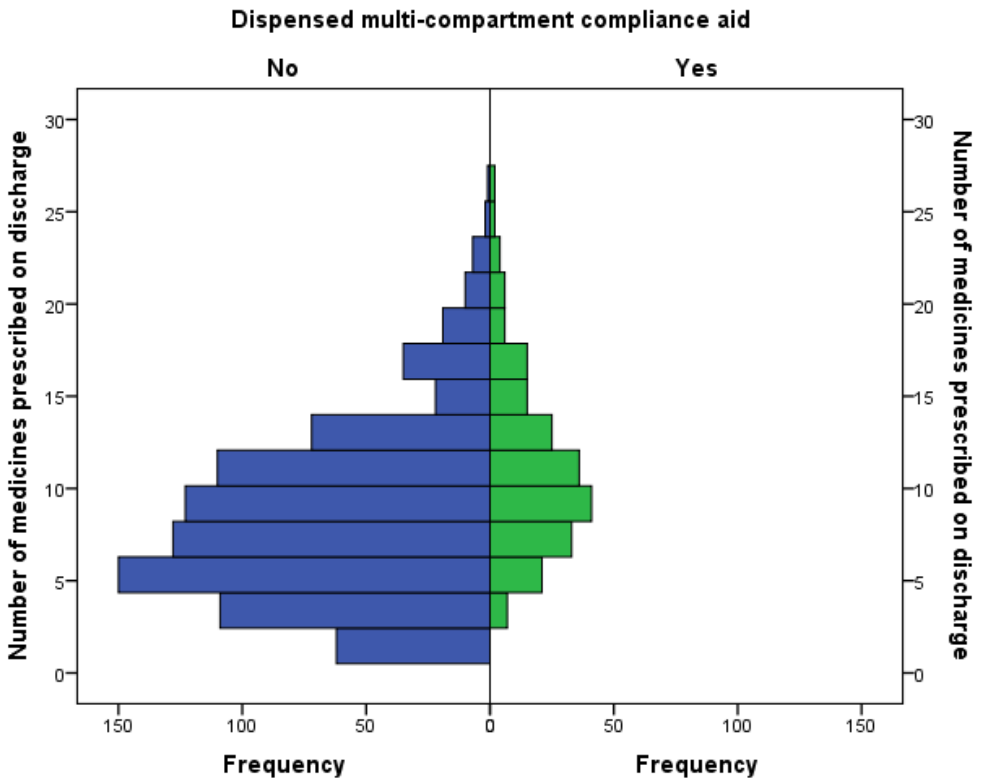


Figure 4.53: Number of medicines prescribed according to whether prescribed an MCA

Prescriptions containing MUR high risk medication were more likely to indicate an MCA was required than prescriptions which did not. The mean number of new medicines prescribed was less for MCA prescriptions compared to non-MCA prescriptions, as shown in Figure 4.54.

Although fewer prescriptions including temporary medication involved MCAs than those not including any temporary medication, the addition of temporary courses of medication at discharge remained relatively common, affecting more than half of MCA prescriptions (50.9%). The mean number of medicines stopped during admission was fewer for MCA prescriptions compared to non-MCA prescriptions.

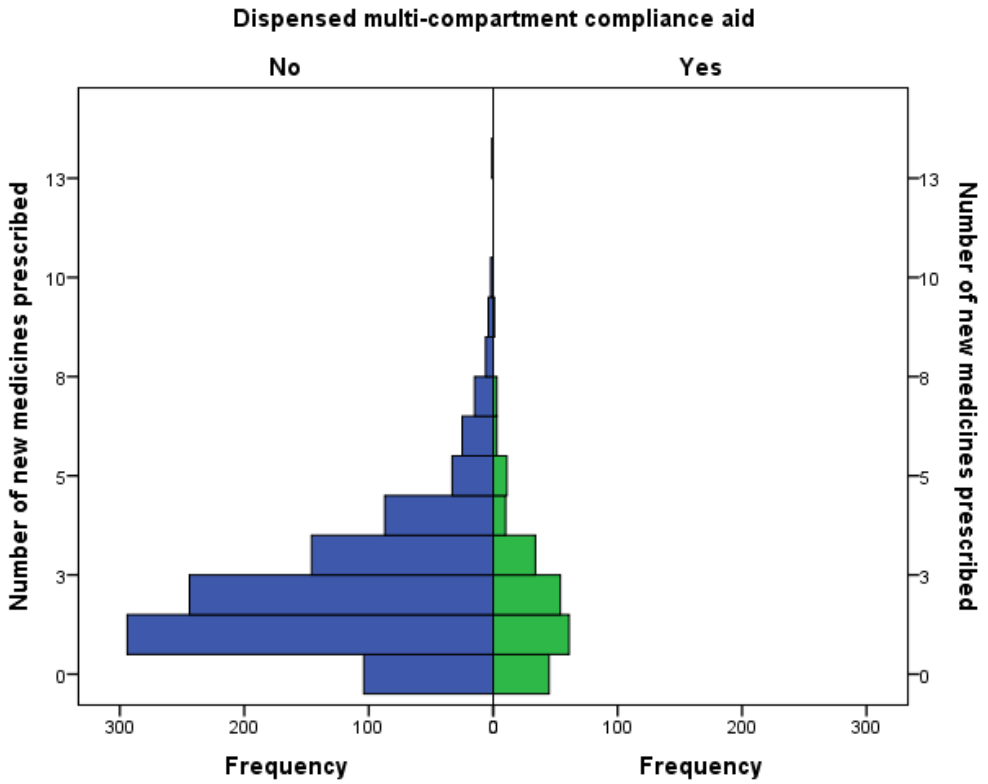


Figure 4.54: Number of new medicines prescribed according to whether prescribed an MCA

4.2.5 Outcome

4.2.5.1 Readmission within 30 days

Almost one in five discharges resulted in readmission within 30 days, equivalent to more than one discharge from the Trust's MSSUs resulting in readmission per day (36.6 readmissions per month). The number of readmissions observed was two-thirds of the number anticipated (220/330, see 3.2.2.1 b) Sample size).

A weak, albeit significant, difference in the proportion of patients experiencing readmission was observed when comparing sites, with Hospital B having a higher readmission rate than Hospital A. Patients who were readmitted had a longer average LOS than those who were not, as shown in Figure 4.55:

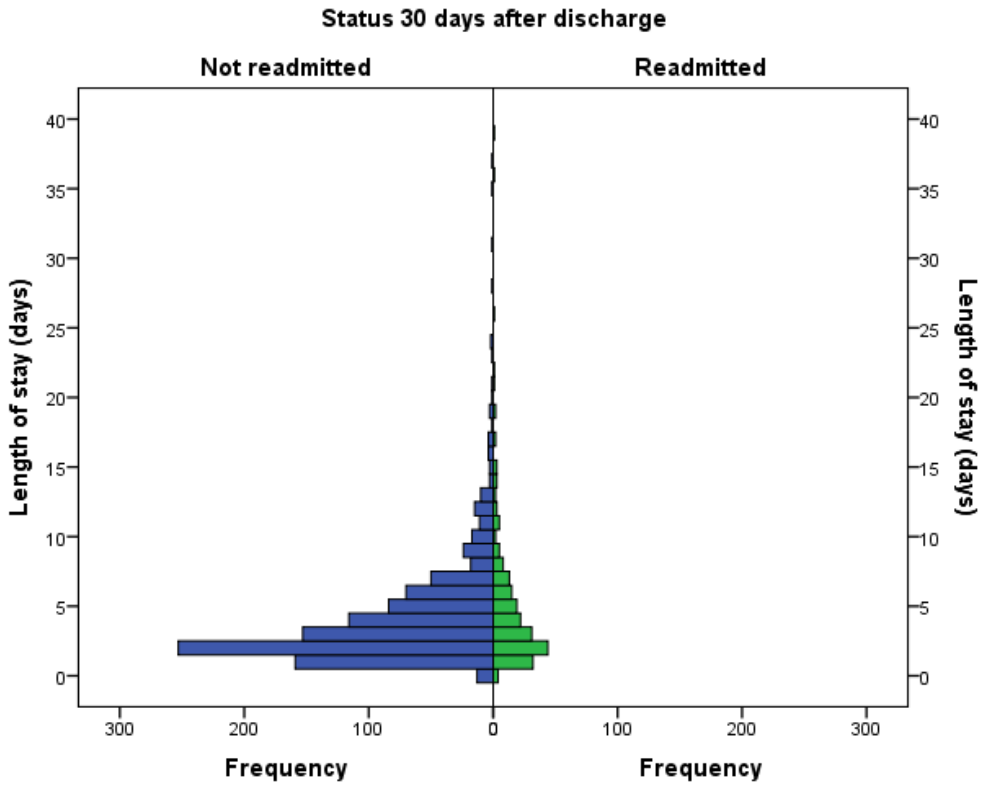


Figure 4.55: LOS according to whether readmitted

Patients who were readmitted were older on average than those who were not, as shown in Figure 4.56:

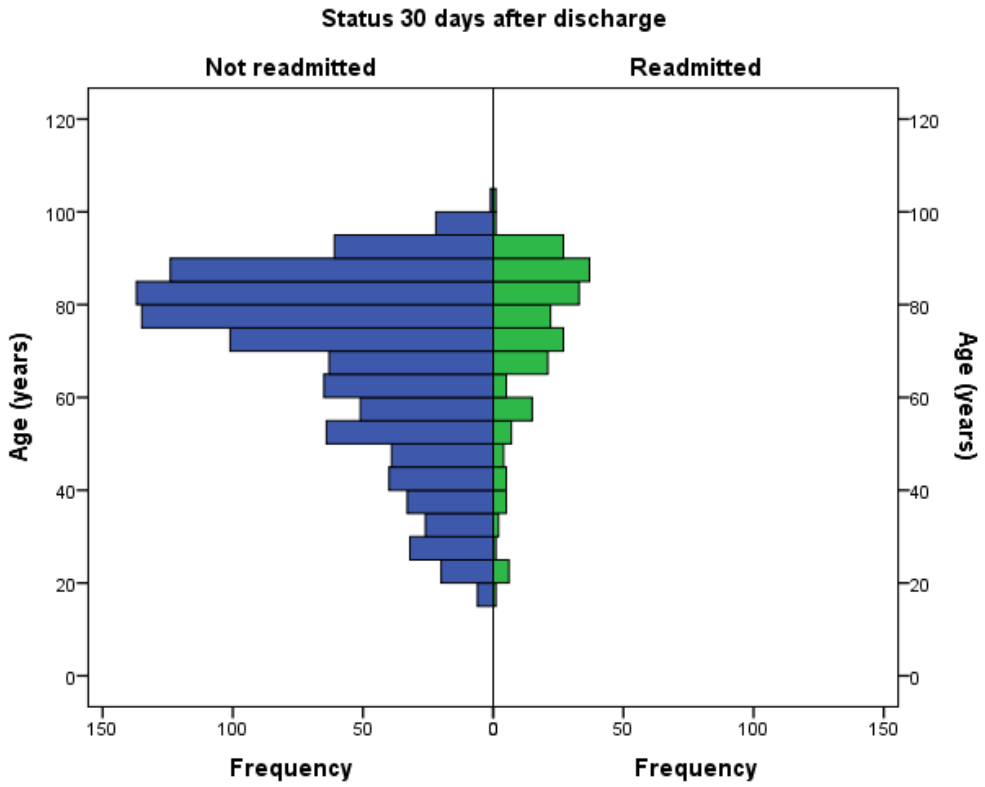


Figure 4.56: Age according to whether readmitted

Patients who were readmitted were prescribed more medicines on average than those who were not, as shown in Figure 4.57:

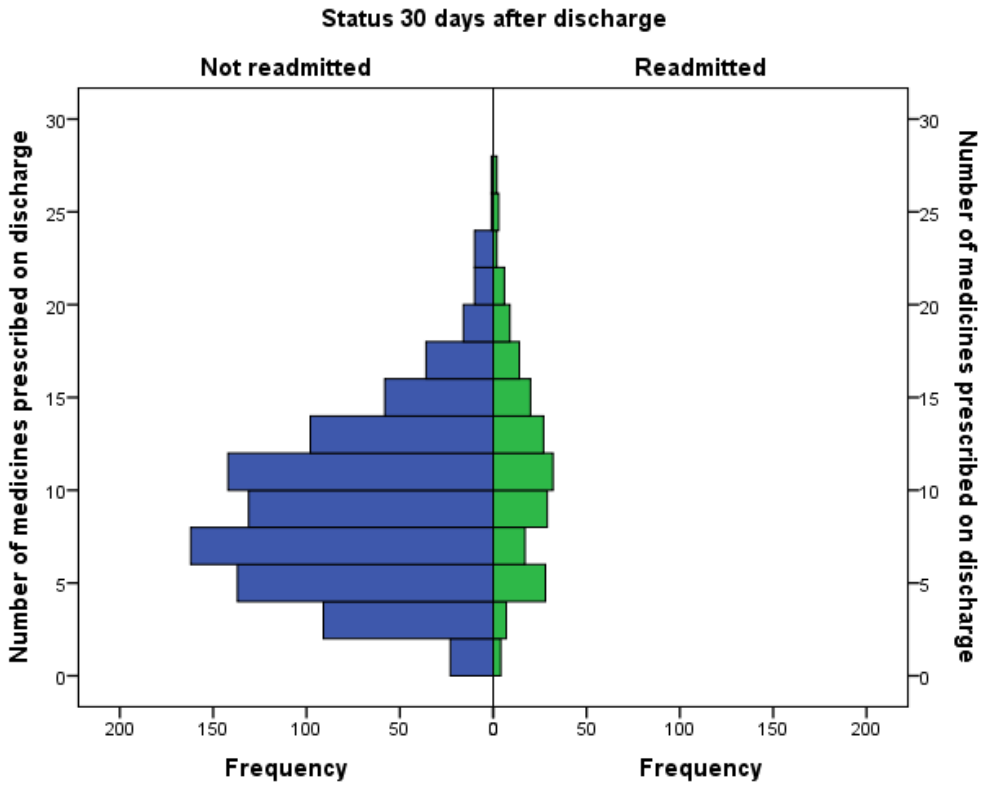


Figure 4.57: Number of medicines prescribed on discharge according to whether readmitted

A weak, yet statistically significant, relationship was identified between prescriptions that contained medication from the following BNF chapters and likelihood of readmission:

Chapter 1. GI

Chapter 2. CV

Chapter 5. Infections

Chapter 6. Endocrine system

Chapter 9. Nutrition and blood

Chapter 12. ENT

Patients who were readmitted were prescribed more high risk medicines at discharge on average compared to those who were not. There was a weak, although statistically significant, association between MCA prescriptions and readmission compared with non-MCA prescriptions.

4.2.5.2 Time to readmission

Figure 4.58 illustrates the distribution of readmission across the observation period:

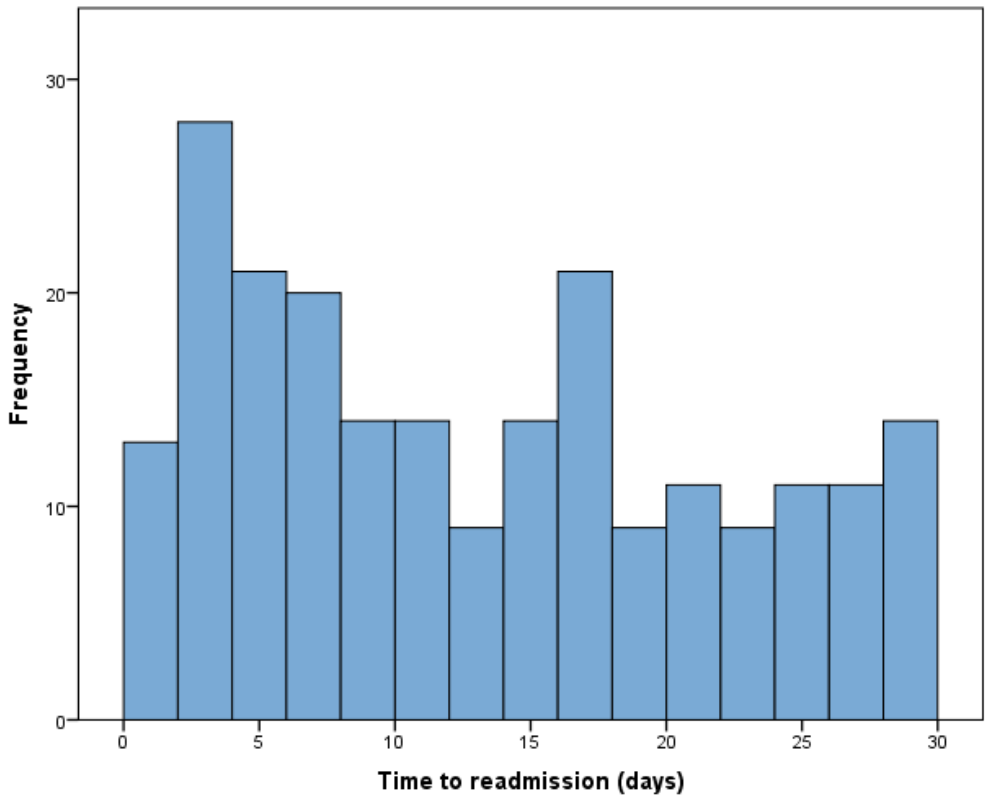


Figure 4.58: Time to readmission

Over one-third (37.3%) of readmissions occurred within the first week after discharge; another fifth (20.0%) within the second week. More readmissions (24.5%) occurred in the third week than the second, and the least readmissions occurred after three weeks (18.2%). More specifically, the most readmissions occurred during the first two days after discharge (13.6%), followed by a steady decline in readmissions until a secondary peak at two weeks. There were as many readmissions on the 16th day as the 1st following discharge (13), after which readmission numbers returned to approximately the level they had declined to before the secondary peak.

4.3 Discussion

Although smaller than anticipated, the sample size achieved was comparable with the median of studies included in the literature review and was sufficient for the intended analyses (see also 2.3.2.3 and 4.3.3).

As discussed in 3.2.2.1 b) Unit of analysis, the hierarchical data structure meant that patient-level clustering was possible. Repeat admissions comprised substantially less of the cohort than was the case for Singal et al. (2013). The vast majority of patients in this study contributed a single admission, and it was expected that any clustering would be relatively minor; nonetheless, the effect on the predictive model was assessed by sensitivity analysis, as described in 3.2.2.5 b) Sensitivity analysis, to ensure the assumption of independence of errors was met.

4.3.1 Demographics

There being fewer men than women in the cohort was consistent with more than half of the studies included in the literature review that were undertaken for the purpose of predicting readmission. Considering the study was prospectively limited to those prescribed medication on discharge, and that it is known that more women than men take medication (Health & Social Care Information Centre, 2014a), there being more women than men in the cohort could be due to more women being prescribed medication (rather than there being more women discharged from the wards overall). Women's prescriptions being more likely to qualify for NMS reflected that women tended to be prescribed more medicines, and prescriptions that were potentially eligible for referral to the NMS contained more medicines on average compared to those that were not. Women being prescribed more medicines than men was consistent with the results reported by Perren et al. (2009). In common with Sumukadas et al. (2014), among those 65 years of age and over, women had a greater anticholinergic burden compared to men, reflecting that women were prescribed more medicines in general and ACB increased with increasing polypharmacy.

The difference in average age among over 65s according to whether the prescription was suitable for ACB review was considered unlikely to be of any real clinical significance; although, it is possible that it represents prescribing practices to minimise patients' ACB as the benefits of anticholinergic medication become less likely to outweigh the increasing risks with advancing age were in line with recommendations.

The average age among patients on the MSSUs was older compared to studies included in the literature review that were undertaken for the purpose of predicting readmission and did not specifically involve elderly cohorts; over half of patients in this study were in their 70s and 80s. The cohort was however, younger in comparison to the average age among studies that did specifically involve elderly cohorts.

4.3.2 Prescriptions

A limitation of the study was that, although the indications for prescribed medicines could often be inferred, they were not known; however, polypharmacy can be expected to represent multi-morbidity to some extent. Significant correlations between the number of medicines prescribed on admission and discharge, and the number of medicines prescribed on discharge and the number of BNF chapters medicines were prescribed from were confirmed. It is possible that the number of medicines prescribed on admission is a reasonable proxy for the number of BNF chapters medicines were prescribed from, and that the number of BNF chapters medicines were prescribed from represented comorbidity (see also 3.2.2.2 b) Number of medicines prescribed). Further work would be necessary to validate whether it is the case that the number of medicines prescribed is a reasonable proxy for the number of BNF chapters medicines are prescribed from and whether the number of BNF chapters medicines are prescribed from accurately reflects comorbidity.

Exploratory analysis confirmed it was unlikely to be appropriate to include both CV and HRMs as candidate predictors in the multivariable model because most HRMs were from BNF chapter 2 (CV). Similarly, anticholinergics and high risk medicines had warfarin,

furosemide and dipyridamole in common, and NMS-qualifying medicines and high risk medicines had BNF chapter 2 subsections 2.1, 8.2, and 9 in common. Prescriptions which were potentially eligible for ACB review, referral to NMS, and/or contained high risk medicines all contained more medicines on average, demonstrating that the prescription of additional items carries increasing risk of exposure. It is a limitation of the study that it was not known whether patients accessed MUR services prior to admission or during the observation period, although it is known that a referral system was not in place. MUR high risk medicines are defined on the basis of their potential to cause harm such as avoidable hospital admission by omission, overuse, or incorrect use, preventable by structured review with a pharmacist; given that CV medicines are commonly-used and prone to error, that most HRMs were CV medicines, they represent a promising target for pharmaceutical intervention intended to prevent readmission.

All prescriptions from BNF chapter 15 were for midazolam, which was prescribed in conjunction with other anticipatory medication; it is probable that patients prescribed these medicines had different underlying risk of readmission than the rest of the cohort due to being discharged home for palliative care, and may choose to remain out of hospital on deterioration rather than be readmitted. Additionally, discharge prescriptions for these patients were more likely to be validated by a pharmacist due to the inclusion of controlled drugs. Similarly, CNS medication included controlled drugs, which could explain why prescriptions for CNS medication were more likely to be validated. CNS medicines also include analgesics and the large proportion of CNS medicines prescribed probably reflected the common addition of analgesia on discharge from the MSSUs. The number of analgesics prescribed on discharge seemed inflated by routine formulary switches of compound preparations such as co-codamol to the individual components i.e. paracetamol and codeine, as well as genuine additions. The number of medicines prescribed on discharge could also be considered inflated by temporary courses of medication such as antimicrobials and/or analgesics. The large proportion of temporary medicines being from the BNF chapter concerning infection represented courses of

antimicrobials typically prescribed for chest and urinary tract infections treated on the MSSUs. Acute prescriptions such as these can relate to short-term conditions such as an isolated urinary-tract infection, or acute exacerbations of long term conditions such as an infective exacerbation of COPD. In either case these additional courses would contribute an additional burden to regular medication regimens during the patient's recovery period, when they (or their carer) resume responsibility for administration of their medicines, having generally had their medication administered by staff during their inpatient stay. It has been shown that adherence reduces with increasing polypharmacy (Elliott et al., 2008); furthermore exposure to additional medicines increases the risk of experiencing ADRs.

The mean number of medicines prescribed on discharge was very similar to that reported by Forster et al. (2005), and the majority of discharge prescriptions containing a new medicine and the number for which medicines had been discontinued was consistent with European figures (Paulino et al., 2004), likely representing adjustment of treatment according to the presenting complaint. Prescriptions tending to contain more medicines on discharge than admission is consistent with the findings of Betteridge et al. (2012), who concluded that polypharmacy is made worse by admission to hospital, and is indicative that hospitalisation could be an influential factor in polypharmacy; although, as previously discussed, additions often comprised temporary courses and in these cases the duration of the additional medication regimen burden would be limited to the observation period and thus the long-term impact of prescription changes made in hospital would be less.

The strong relationship between the number of medicines and the number of doses per day prescribed was to be expected, given that doses per day combined the number of medicines prescribed with their directions for use; similarly, the interaction between the number of medicines prescribed on admission and discharge combined the number of medicines prescribed on discharge with the changes made to the prescription during admission. Many of the associations identified by exploratory analysis were unsurprising.

For example, prescriptions that included high risk medication were more likely to involve MCAs, and prescriptions for both high-risk medicines and MCAs tended to involve older patients who were prescribed more medicines. Polypharmacy increases with age, and being prescribed numerous regular medicines is a common reason for using an MCA, so the relationship between MCAs and high risk medicine was probably due to the likelihood of a high risk medicine being prescribed increasing with the number of items prescribed, as opposed to there being an independent relationship between high risk medicines and MCAs. Ultimately, each of these characteristics (older age; being prescribed more medicines, more high risk medicines, or dispensed an MCA) was associated with readmission. Prescriptions suitable for ACB review containing more high risk medicines than prescriptions that were not suitable among patients 65 years and older, once again, reflected that patients who were prescribed high risk medicines tended to be older and were prescribed more medicines, and that suitability for ACB review was associated with larger prescriptions as well as selective for older patients. This is consistent with the findings of Sumukadas et al. (2014): greater anticholinergic cognitive burden was associated with increasing polypharmacy because additional prescribed items each have the potential to contribute anticholinergic properties to the prescribed regimen. The proportion of prescriptions suitable for ACB review being relatively modest highlights that these could represent a relatively manageable target for the pharmacy team.

Although linear relationships between increasing age, length of stay and number of medicines prescribed were not identified, several variables were associated with increased average age, length of stay and number of medicines prescribed, for example prescriptions:

- that contained high-risk medication, and/or
- for an MCA, and/or
- that were validated by a pharmacist, and/or
- that did not contain a clause (number of medicines N/A)

These could each represent increased complexity and/or dependence on community services after discharge, which would require time to coordinate after a patient is deemed medically fit for discharge. Conversely, those discharged at the weekend tending to have a shorter LOS could reflect that less complex patients were more likely to be suitable for discharge at the weekend.

4.3.3 Readmission

The observed readmission rate was similar to other studies among general medical patients (Bradley et al., 2013). Observing fewer readmissions than anticipated was not a cause for concern as the 220 readmissions observed would support more predictor variables than it was expected would be practical to include in the predictive model given the intention for clinical application (22, Peduzzi et al. (1996) recommended 10 events per predictor).

The observed time to readmission was consistent with studies in the literature review (Bisharat et al., 2012; Singal et al., 2013). The most readmissions occurring within a week of discharge is consistent with published national trends (Sg2, 2011; Zerdevas & Dobson, 2008) and the increase in readmissions at 2 weeks could be related to two-week outpatient appointments: miscoded as described by Blunt et al. (2014), or in which problems requiring readmission were identified as described by Morris (2018); two weeks also coincides with the Trust's policy to provide at least 14 days medication on discharge.

Patients who were readmitted were also older, prescribed more medicines (consistent with the findings of Gildersleeve and Cooper (2013)), and had a longer average length of stay compared to those who were not; Tan et al. (2013) referred to the current understanding of burden and complexity of chronic disease in an ageing population being

consistent with their findings that patients with a *LACE*[40] score of ten or more were older, on average, than those with a score below ten. Indeed older patients may be more likely to have multi-morbidity requiring more medicines, less likely to be independent, and require longer stays in hospital.

4.3.4 Pharmaceutical intervention

Pharmaceutical intervention variables were the most prone to missing data; this was probably due to their method of population relying on discharge prescription validation. Moons et al. (2015) set out that even in prediction modelling studies concerning a particular intervention there may be variation in co-interventions, and that in nonrandomised studies there can be serious concern that treatment choice may be influenced by other predictors. The authors stated that although treatment can be considered a predictor, the effect of treatment being influenced by other predictors in the model cannot be easily judged.

4.3.4.1 Prescription validation

Pharmacist involvement being evident in prescriptions that were not documented as validated was likely due to the prescription being submitted for validation and:

a) the pharmacist identifying issues and returning the prescription to the prescriber for amendments, but the prescription not being re-submitted for approval
b) being validated but subsequently altered without being re-submitted for approval

It therefore expected that these prescriptions probably reflected some degree of pharmacist input despite not being documented as approved by a pharmacist; although, the extent of this would depend on whether the pharmacist's recommendations were actioned, and/or whether any alteration(s) that had invalidated a pharmacist's prior approval were relevant to the validation. Considering that the study wards had daily

[40] Length of stay, acuity of admission, comorbidity, Emergency Department attendances (van Walraven et al., 2010a)

pharmacist cover it could be expected that patients who had been on the ward for more than one day would have had their prescription reviewed by a pharmacist, and this would not be not evident from the discharge data; consequently, whether discharge prescriptions were documented as validated cannot accurately reflect the full extent of pharmacist validation of prescriptions during admissions/around discharge.

Prescriptions containing a clause being less likely to be validated by a pharmacist could reflect that pharmacists encouraged the full prescription to be documented on the discharge prescription, or that discharge prescriptions that only listed changes were less likely to require pharmacist input at discharge.

Patients discharged during the week being more likely to have their discharge prescription validated by a pharmacist reflected the routine availability of pharmacy services. Validated prescriptions tending to include more changes and new medicines demonstrated the influence of pharmacy's supply function on pharmacist validation.

The vast majority of prescriptions suitable for targeted MUR or NMS being validated demonstrates that pharmacists were well-placed to refer patients for this service, although it is known that at the time of the study no such process was in place.

Patients discharged via a discharge lounge being more likely to have their discharge prescription validated likely reflected that these patients were prescribed more medicines on average and more likely to require an MCA, and so were likely sent to the discharge lounge to await supplies being dispensed. Considered in the context of the concurrent increase in pharmacist validation of discharge prescriptions, the increased number of discharges through the discharge lounge(s) in the second phase of phase of the study reflected mandating validation of discharge prescriptions; patients would have had to wait for validation to be conducted irrespective of whether or not any medicines required dispensing. However, mandatory pharmacist validation coinciding with increasing winter pressures may also have been an important factor, as it could be expected that discharge lounge through-put would increase in order to free-up beds for admissions to the wards.

In summary, mandating pharmacist validation of discharge prescriptions in normal working hours significantly increased the proportion of prescriptions validated, and delivery was more equitable after its introduction; however, as resources were not increased pharmacists' efforts will inevitably have been spread more thinly. Pal, Babbott, and Wilkinson (2013) highlighted that pharmacist prioritisation in their study seemed appropriate; similarly, this study's data indicate that discharge prescription validation was probably targeted appropriately to older patients who had been in hospital longer and were prescribed more medicines, with more changes, prior to mandating it. Although prescription validation provides opportunities to ensure medicines optimisation, validating a prescription does not automatically result in improved quality; it must be considered what value was added by increasing the proportion of discharge prescriptions belonging to younger patients, which were more likely to include clauses and/or contain fewer items, and whether this was worth the expense of the time that could otherwise have been spent validating more complex prescriptions.

4.3.4.2 Medicines reconciliation

Neither the Discharge Medication nor Medicine Reconciliation sections of the Trust's *Medicines Code* (Calderdale and Huddersfield NHS Foundation Trust) clarified what confirming the medicines reconciled at discharge meant. It is therefore probable that different pharmacists had different interpretations; some of the discharge prescriptions recorded as reconciled probably represented a reconciled list, some that the process of medicines reconciliation had been conducted at discharge, and others that the medicines reconciliation process had been completed since admission. This ambiguity is not limited to the pharmacy team declaring the medicines reconciled, there are also implications for the interpretation of medicines reconciliation information by the multidisciplinary team on the ward and in primary care.

The large amount of prescriptions with an unknown medicines reconciliation status was a consequence of medicines reconciliation status being a field on the discharge note that was only accessible by the pharmacy team, and only usually accessed as part of

validation of the discharge prescription. Consequently, there was a strong association between pharmacist validation of discharge prescriptions and medicines reconciliation. This was further compounded by the Trust's performance being gauged by a CQUIN target for medicines reconciliation, for which the denominator excluded those with no reported value; the focus was on ensuring that those prescriptions which were validated were recorded as such, and not the converse.

Discharge prescriptions recorded as reconciled only represent those declared by pharmacy. This variable did not account for cases in which:

- other health care professionals, such as nurses or doctors could have completed medicines reconciliation
- pharmacy staff had previously conducted the first stage of medicines reconciliation and a prescriber since had resolved any discrepancies, but pharmacy not yet completed the declaration
- medicines reconciliation had not been conducted, however, the prescription did not contain any discrepancies to resolve
- It is recognised that how discharge prescriptions are processed in primary care can influence whether the intended benefits of medicines reconciliation are realised; it was not uncommon for discharge notes to be processed by administrative members of staff rather than medical or pharmacy professionals in primary care at the time the data were collected (Care Quality Commission, 2009); this would be outside the hospital's control and it is probable that it could pose a barrier to effective medicines reconciliation translating back into primary care.

4.3.4.3 Compliance aids

Increasing the proportion of discharge prescriptions validated by a pharmacist did not result in significantly more MCAs being identified/documented, which is consistent with MCA prescriptions requiring validation irrespective of study phase due to the need for supply, particularly when changes had been made.

Although less commonly than for those not dispensed an MCA, temporary medicines were prescribed along with a quarter of MCAs. There is additional potential for confusion when temporary courses are prescribed in addition to an MCA, because often such courses are dispensed separately and the patient (or their carer), who normally relies on an MCA, has to manage the additional medicine separately. Patients using MCAs and being more likely to be readmitted is consistent with the association between MCAs and readmission with older age, being prescribed more medicines, and having a longer length of stay.

4.3.5 Operational factors

Predictably, many of the strongest associations identified reflected operational factors. The only chi-squared test associated with a difference of moderate magnitude related to the proportion of discharge prescriptions validated by a pharmacist before and after pharmacist validation of discharge prescriptions was mandated in normal working hours. This provides evidence that mandating pharmacist validation of discharge prescriptions achieved the intended effect of increasing the proportion validated, although the extent of any benefits of this is not known. The difference in proportion of discharge prescriptions validated by a pharmacist for MCA and non-MCA prescriptions was of low-moderate magnitude, confirming a predictable dependency between the systems for prescribing an MCA and pharmacist validation of discharge prescriptions. Similarly, the incompatibility of prescriptions which only detailed the changes made during admission with dispensing MCAs explains why MCA prescriptions were less likely to contain a clause than non-MCA prescriptions, and the decreased LOS associated with prescriptions that contained such a clause reflected that it was intended their use would be restricted to inpatient stays of one day or less. Given the range and maximum LOS for a prescription including a clause far exceeded this, the process for ensuring their appropriate application was not robust. The consequence of the missing prescription data on those that only detailed the changes made (i.e. the inclusion of a clause) was that younger

patients with shorter average LOS and a greater tendency to be discharged at the weekend were potentially underrepresented in some of the exploratory analyses of prescription factors, compared to the analysis of discharge and patient factors.

The average LOS was consistent with the expected LOS for admission to an MSSU; it was also similar to that observed by Gildersleeve and Cooper (2013). Patients admitted during the week being more likely to be discharged at the weekend could be anticipated considering the predetermined, typical short stay inferred by admission to the MSSU and/or the average LOS. It is thought that the one discharge processed via a discharge lounge over the weekend represented a data artefact and this service was not in fact available at the weekend.

The variation between weekday compared to weekend discharges, and hospitals, in the amount of medicines stopped could be due to variation in a number of clinical or administrative practices, such as the tendency to account for medication stopped during the hospital stay as well as documenting the current prescription on discharge (prescriber or pharmacist), and the quality of prescribing in primary care (i.e. potentially inappropriate prescribing being corrected in hospital).

Patients discharged from Hospital B being prescribed more temporary courses of medication on discharge seems contrary to Hospital B having a longer average LOS, as it could be expected short courses of medication may be more likely to be completed in during the longer hospital stay; it is possible that this could reflect different working practices at different sites, for example a tendency to request the patient's General Practitioner (GP) reviews medication prescribed after a set period, even for medicines generally intended to continue. This could arise from the ward doctor, nurse or pharmacist. Similarly, Hospital B having a longer average LOS and discharging more patients at the weekend compared to Hospital A is not in line with the general trend for patients discharged at the weekend to have a shorter LOS. The significant difference in the proportion of discharges processed by each hospital at the weekend could indicate variability in factors such as:

- the patients' degree of dependence on community care as discussed in 3.2.2.2 b) (Admission and discharge days) and the accessibility/availability of such community services to support those discharged at the weekend, and
- the proactivity of the ward to ensure necessary arrangements were made in anticipation of discharge

Sunday being the least common day for discharge likely reflected the extent to which services were available on Sundays, particularly considering that this trend was not observed in admissions (for which the timing would be unplanned).

The difference between hospitals in average LOS could reflect variability in the complexity of the patients, working practices of the wards, or community care provision.

4.3.6 Variables not progressed as candidate predictors

Although comparing hospital sites was useful for identifying potential differences in patient characteristics and working practices, hospital site was not generalisable beyond the study wards and its inclusion in the predictive model would therefore limit the model's generalisability. Consequently, it was not taken forward for evaluation as a candidate predictor variable. Other variables that were not taken forward for evaluation as predictors of readmission were:

- Whether discharged via a discharge lounge
    - not independent of weekend discharge and represented an operational variable which was potentially not relevant outside of the Trust
- Repeat admissions
    - accounted for in sensitivity analysis
- Whether the discharge prescription contained a clause
    - accounted for as missing data on other variables e.g. number of medicines prescribed
- Whether/number of continuing medicines prescribed

    - highly correlated with number of medicines overall; temporary medicines taken forward due to relevance during observation period
- Number of anaesthetic medicines prescribed
    - the maximum was one and the same information was therefore captured by the categorical variable
- Whether the discharge prescription contained any changes
    - patients who did not have any changes made to their prescription were poorly represented, and those who did have changes made could be differentiated between by the number of changes made
- Eligibility for targeted MUR
    - patients who were not eligible for TMUR were poorly represented. The most relevant TMUR, post-discharge, was taken forward.
- Study phase
    - represented an operational variable which was not necessarily relevant outside of the Trust and therefore was not a generalisable predictor
- Whether pharmacist validation was conducted at ward level
    - due suspected underrepresentation
- Medicines reconciliation
    - due to missing data and dependence on pharmacist validation (data not missing completely at random, MCAR)
- Multi-compartment compliance aids
    - due to missing data and dependence on pharmacist validation (data not MCAR)

4.3.7 Candidate predictor variables

Forty-five related variables were taken forward with caution for evaluation to identify the best predictor(s) for readmission. They were considered to comprise 16 groups:

Table 4.8: Groups for related variables taken forward with caution for logistic regression analysis	
Group	**Variables**
1	1. Number of medicines prescribed (on discharge) 2. Number of doses per day 3. Number of BNF chapters medication prescribed from 4. Number of medicines prescribed on admission
2	5. Whether prescribed GI medication 6. Number of GI medicines prescribed
3	7. Whether prescribed CV medication 8. Number of CV medicines prescribed 9. Whether prescribed HRMs 10. Number of HRMs prescribed
4	11. Whether prescribed respiratory medication 12. Number of respiratory medicines prescribed
5	13. Whether prescribed CNS medication 14. Number of CNS medicines prescribed
6	15. Whether prescribed antimicrobial medication 16. Number of antimicrobial medicines prescribed
7	17. Whether prescribed endocrine medication 18. Number of endocrine medicines prescribed
8	19. Whether prescribed GU medication 20. Number of GU medicines prescribed
9	21. Whether medication for malignant disease and immunosuppression 22. Number of medicines for antimicrobial medicines for malignant disease and immunosuppression prescribed
10	23. Whether prescribed medication for nutrition and blood 24. Number of medicines for nutrition and blood prescribed

Table 4.8: Groups for related variables taken forward with caution for logistic regression analysis	
Group	**Variables**
11	25. Whether prescribed MSK medication 26. Number of MSK medicines prescribed 9. Whether prescribed HRMs 10. Number of HRMs prescribed
12	27. Whether prescribed eye medication 28. Number of eye medicines prescribed
13	29. Whether prescribed ENT medication 30. Number of ENT medicines prescribed
14	31. Whether prescribed skin medication 32. Number of skin medicines prescribed
15	33. Anticholinergic cognitive burden 34. Whether suitable for ACB review
16	35. Number of prescription changes 36. Whether met criteria for post-discharge MUR 37. Whether any new medicines had been started 38. Number of new medicines 39. Whether potentially eligible for NMS 40. Whether prescribed any temporary medication 41. Number of temporary medicines prescribed 42. Whether any medicines had been stopped 43. Number of medicines stopped 44. Whether prescribed more medication on discharge than on admission 45. Difference in number of medicines prescribed on discharge compared to admission

Additionally, the following seven variables were taken forward for evaluation as predictors of readmission:

46. Whether admitted during the week or at the weekend
47. Whether discharged during the week or at the weekend
48. Length of stay (LOS) (days)
49. Gender
50. Patient's age (years)
51. Whether prescribed anaesthetic medication
52. Pharmacist validation

4.4 Conclusion

The work presented in this chapter confirms that:

> Routinely recorded information from prescriptions contains variables which may be suitable as predictors for estimating the risk of readmission within 30 days of discharge home from an adult medical short stay unit in the UK.

The quality of the data was appraised, potential predictors identified and the cohort described to ensure the validity of the main analyses and inform the potential generalisability of the findings. In Chapter 5 the predictive capability of the candidate predictor variables is explored by simple logistic regression, the selection rationalised, and then evaluated by multivariable logistic regression with the goal of producing an effective, parsimonious[41] model for predicting readmission based on routinely-recorded prescription information.

[41] The most simple, yet effective (Field, 2018)

Chapter 5 Logistic Regression Analysis

5.1 Introduction

As set out in Chapter 1, readmission is an undesirable outcome for which hospital trusts are financially penalised (Department of Health, 2012b). It was identified in the Exploratory Analysis that almost one in five patients were readmitted within 30 days; an untargeted approach to reduce readmissions would involve needless preventative intervention for 81.8% of patients. Targeting intervention to patients at risk of readmission would conserve limited resources, and to facilitate this it is necessary to effectively predict which patients would be readmitted. Having explored the candidate predictor variables in relation to one another and the outcome in Chapter 4, the development of the logistic regression model for estimating readmission risk using prescription information is presented in this chapter. The study objectives addressed are:

Objective 2 To quantify the influence of each of the candidate predictor variables on the risk of readmission;

Objective 3 To quantify the adjusted influence, or collective contribution, of candidate predictor variables to the risk of readmission; and

Objective 4 To develop and validate a predictive model for readmission using prescription information.

5.2 Results

5.2.1 Simple logistic regression

Individual candidate predictor variables' relationship with readmission was assessed by simple logistic regression. The results of the simple regression analyses are shown below in Table 5.1:

Table 5.1: Simple logistic regression analysis

	Candidate Predictor Variable	*p*-value	N
1	Admitted at the weekend (yes)	0.225	315/1240
2	Discharged at the weekend (yes)	0.174	256/1240
3	Length of stay (days)	0.004	1240
4	Gender (female)	0.293	671/1240
5	Age (years)	<0.001	1240
6	Medicines prescribed on discharge (count)	<0.001	1116
7	Doses per day prescribed (count)	<0.001	1059
8	BNF chapters medicines were prescribed from (count)	<0.001	1116
9	Prescribed GI medication (yes)	<0.001	765/1148
10	GI medicines prescribed (count)	0.002	1116
11	Prescribed CV medication (yes)	0.001	818/1157
12	CV medicines prescribed (count)	0.002	1116
13	Prescribed respiratory medication (yes)	0.253	435/1129
14	Respiratory medicines prescribed (count)	0.032	1116
15	Prescribed CNS medication (yes)	0.500	874/1160
16	CNS medicines prescribed (count)	0.115	1116
17	Prescribed antimicrobial medication (yes)	0.034	560/1169
18	Antimicrobial medicines prescribed (count)	0.028	1116
19	Prescribed endocrine system medication (yes)	0.003	595/1147
20	Endocrine system medicines prescribed (count)	0.007	1116
21	Prescribed GU medication (yes)	0.162	95/1119
22	GU medicines prescribed (count)	0.125	1116
23	Prescribed malignant disease & immunosuppressant medication (yes)	0.401	39/1116

Table 5.1: Simple logistic regression analysis			
	Candidate Predictor Variable	***p*-value**	**N**
24	Malignant disease & immunosuppressant medicines prescribed (count)	0.422	1116
25	Prescribed nutrition & blood medication (yes)	0.006	566/1141
26	Nutrition & blood medicines prescribed (count)	0.001	1116
27	Prescribed MSK medication (yes)	0.112	233/1129
28	MSK medicines prescribed (count)	0.123	1116
29	Prescribed eye medication (yes)	0.379	79/1120
30	Eye medicines prescribed (count)	0.221	1116
31	Prescribed ENT medication (yes)	0.014	69/1120
32	ENT medicines prescribed (count)	0.015	1116
33	Prescribed skin medication (yes)	0.138	118/1117
34	Skin medicines prescribed (count)	0.386	1116
35	Prescribed anaesthetic medication (yes)	0.408	20/1116
36	Prescribed HRM(s) (yes)	0.001	676/1149
37	HRMs prescribed (count)	0.002	1116
38	ACB score	0.005	1116
39	Suitable for ACB review (yes)	0.016	211/1174
40	Changes to prescription (count)	0.305	1239
41	Prescribed new medicine(s) (yes)	0.089	1034/1240
42	New medicines prescribed (count)	0.698	1240
43	Prescribed temporary medicine (yes)	0.031	668/1240
44	Temporary medicines prescribed (count)	0.034	1240
45	Potentially eligible for referral to NMS (yes)	0.739	172/1233
46	Stopped medicine(s) (yes)	0.415	405/1240
47	Medicines stopped (count)	0.730	1239
48	Prescribed more medicines compared to admission (yes)	0.182	764/1115
49	Change in number of medicines prescribed compared to admission (count)	0.863	1115
50	Medicines prescribed on admission (count)	<0.001	1115
51	Potentially eligible for post-discharge MUR (yes)	0.169	1063/1195
52	Prescription validated by a pharmacist (yes)	0.495	781/1240

The candidate predictors were initially rationalised by disregarding those with little potential as predictors of readmission ($p>0.2$).

Two-thirds of the candidate predictor variables evaluated by simple logistic regression analysis had potential as predictors of readmission ($p<0.2$). These are summarised in the context of the number of readmissions and cases observed in Table 5.2:

Table 5.2: Variables identified as having potential as predictors for readmission

	Candidate Predictor Variable	Readmission	Cases
1	Discharged at the weekend (yes/no)	220	1240
2	Length of stay (days)	220	1240
3	Age (years)	220	1240
4	Medicines prescribed on discharge (count)	200	1116
5	Doses per day prescribed (count)	188	1059
6	BNF chapters medicines were prescribed from (count)	200	1116
7	Prescribed GI medication (yes/no)	209	1148
8	GI medicines prescribed (count)	200	1116
9	Prescribed CV medication (yes/no)	210	1157
10	CV medicines prescribed (count)	200	1116
11	Respiratory medicines prescribed (count)	200	1116
12	CNS medicines prescribed (count)	200	1116
13	Prescribed antimicrobial medication (yes/no)	207	1169
14	Antimicrobial medicines prescribed (count)	200	1116
15	Prescribed endocrine system medication (yes/no)	204	1147
16	Endocrine system medicines prescribed (count)	200	1116
17	Prescribed GU medication (yes/no)	200	1119
18	GU medicines prescribed (count)	200	1116
19	Prescribed nutrition & blood medication (yes/no)	204	1141
20	Nutrition & blood medicines prescribed (count)	200	1116
21	Prescribed MSK medication (yes/no)	202	1129
22	MSK medicines prescribed (count)	200	1116
23	Prescribed ENT medication (yes/no)	200	1120
24	ENT medicines prescribed (count)	200	1116
25	Prescribed skin medication (yes/no)	200	1117
26	Prescribed HRM(s) (yes/no)	208	1149
27	HRMs prescribed (count)	200	1116
28	ACB score	200	1116

Table 5.2: Variables identified as having potential as predictors for readmission			
	Candidate Predictor Variable	**Readmission**	**Cases**
29	Suitable for ACB review (yes/no)	210	1174
30	Whether new medicine(s) had been prescribed (yes/no)	220	1240
31	Prescribed temporary medicine (yes/no)	220	1240
32	Temporary medicines prescribed (count)	220	1240
33	Prescribed more medicines compared to admission (yes/no)	200	1115
34	Medicines prescribed on admission (count)	200	1115
35	Potentially eligible for post-discharge MUR (yes/no)	215	1195

Candidate predictor variables were rationalised not only in terms of the amount of missing data and their relationship with readmission, but also how unique any association identified was; as described in 4.3.6 and 4.3.7 , many of the variables with $p<0.2$ for readmission in simple logistic regression analysis were closely related to each another. Some variables expressed the same information, albeit in differing degrees of detail. Specifically, whether and how many:

- Medicines were prescribed from each BNF chapter
- High risk medicines were prescribed
- Temporary medicines were prescribed

Of these, the *p*-value supported retaining the categorical expression; whether:

- GI medicines were prescribed
- CV medicines were prescribed
- Endocrine medicines were prescribed
- MSK medicines were prescribed
- ENT medicines were prescribed
- HRMs medicines were prescribed
- Temporary medicines were prescribed

Although the *p*-values were slightly higher for the dichotomous equivalent variables, the difference was not considered to be substantial enough to warrant disregarding them for the sake of retaining the detail in the numerical equivalent variable; number of:

- Antimicrobial medicines prescribed
- GU medicines prescribed
- Nutrition and blood medicines prescribed

Additionally, the equivalent numerical variables tended to have more missing data (often the discharge prescriptions contained enough data to determine whether any of a type of medication was prescribed but not necessarily calculate the total). Consequently, whether any of these medicines were prescribed was taken forward and the numerical equivalent variables were disregarded.

Some variables involved subcategories of one another, specifically:

- Temporary prescriptions involved a new medicine
- Prescriptions that were larger on discharge than admission involved new medicines
- All HRMs constituted CV medicines or MSK medicines
- Prescriptions suitable for ACB review involved patients 65 years of age and over with an ACB of 3 or more (or prescribed an item scoring 2)
- Prescriptions potentially eligible for post-discharge MUR involved two or more medicines

Of these, whether new medicines were prescribed was disregarded due to its mutual exclusivity with whether temporary medicines were prescribed and whether the prescription contained more medicines on discharge compared to admission. ACB score was taken forward in favour of suitability for ACB review as age was represented in a separate variable. The remaining variables were taken forward with caution for assessment of correlation and multicollinearity.

The number of medicines prescribed on discharge was a factor in the number of:

- Medicines prescribed on admission
- Temporary medicines prescribed
- Doses per day prescribed
- BNF chapters medicines were prescribed from

Consequently, it would only be appropriate to include one of these in the final logistic regression model. The *p*-values were equal. The number of temporary medicines prescribed was already represented as whether any temporary medicines were prescribed and was consequently disregarded. Doses prescribed per day was the least favourable to take forward due to having the most missing data as well as involving a manual calculation; the number of BNF chapters from which medicines were prescribed also involved a manual assessment/calculation, as did the number of medicines prescribed on admission. These variables were consequently disregarded and the number of medicines prescribed (on discharge) was taken forward for the multivariable analysis.

5.2.1.1 Correlation and Multicollinearity

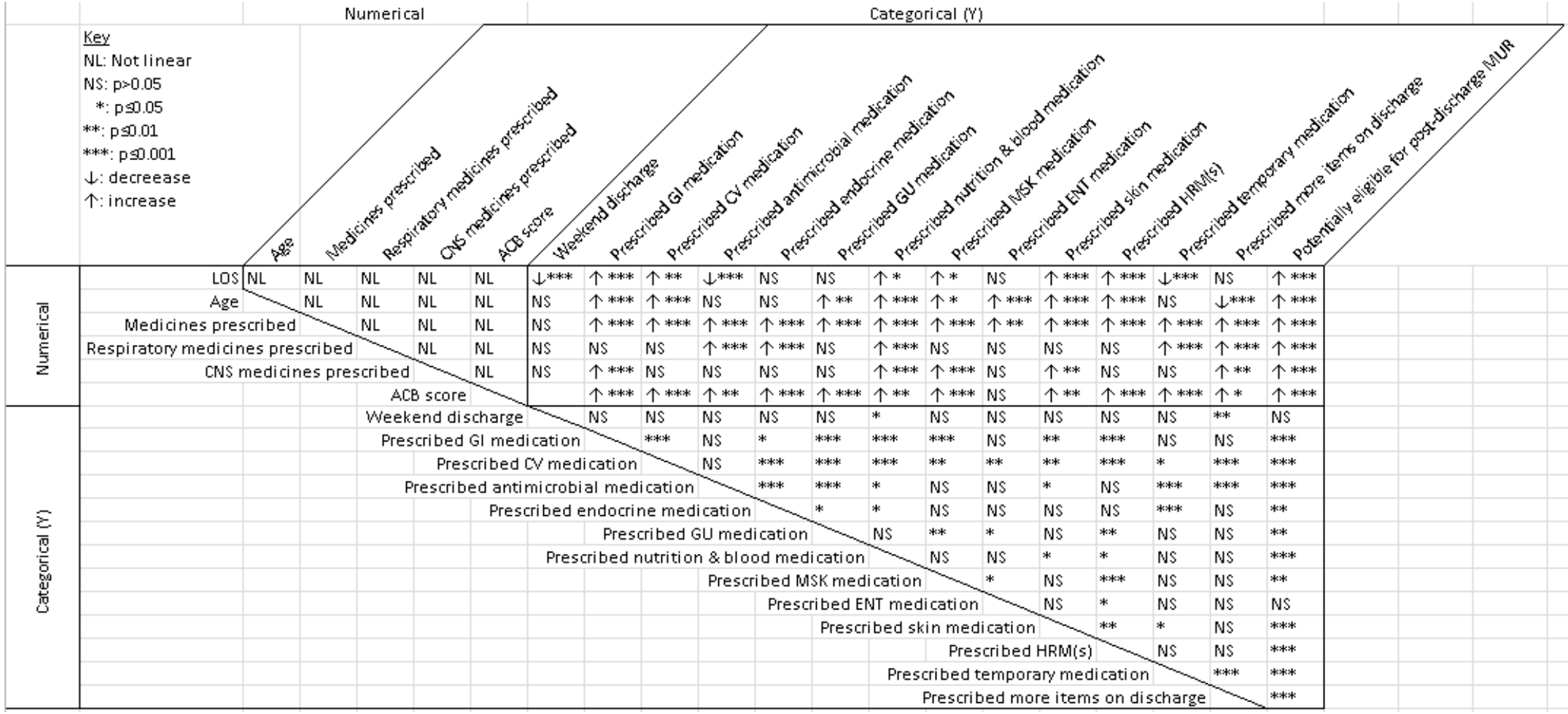
The variables taken forward for assessment of correlation and multicollinearity to ensure they were suitably independent for inclusion in the multiple logistic regression model were:

1. Discharged at the weekend (yes/no)
2. Length of stay (days)
3. Age (years)
4. Medicines prescribed on discharge (count)
5. Prescribed GI medication (yes/no)
6. Prescribed CV medication (yes/no)
7. Respiratory medicines prescribed (count)
8. CNS medicines prescribed (count)
9. Prescribed antimicrobial medication (yes/no
10. Prescribed endocrine system medication (yes/no)
11. Prescribed GU medication (yes/no)
12. Prescribed nutrition & blood medication (yes/no)
13. Prescribed MSK medication (yes/no)
14. Prescribed ENT medication (yes/no)

15. Prescribed skin medication (yes/no)
16. Prescribed HRM(s) (yes/no)
17. ACB score
18. Prescribed temporary medication (yes/no)
19. Prescribed more medicines compared to on admission (yes/no)
20. Potentially eligible for post-discharge MUR (yes/no)

Relationships between these variables identified in the Exploratory Analysis are summarised in Table 5.3. None of the numerical variables had a linear relationship with one another. No substantive multicollinearity (variance inflation factor, VIF >10) was identified: VIFs observed ranged from 1.03 to 6.03, and the average was 1.81. Consequently, all were taken forward for multivariable analysis.

Table 5.3: Relationships between the candidate predictor variables selected for multiple regression analysis



		Numerical					Categorical (Y)													
	Key NL: Not linear NS: p>0.05 *: p≤0.05 **: p≤0.01 ***: p≤0.001 ↓: decreease ↑: increase	Age	Medicines prescribed	Respiratory medicines prescribed	CNS medicines prescribed	ACB score	Weekend discharge	Prescribed GI medication	Prescribed CV medication	Prescribed antimicrobial medication	Prescribed endocrine medication	Prescribed GU medication	Prescribed nutrition & blood medication	Prescribed MSK medication	Prescribed ENT medication	Prescribed skin medication	Prescribed HRM(s)	Prescribed temporary medication	Prescribed more items on discharge	Potentially eligible for post-discharge MUR
Numerical	LOS	NL	NL	NL	NL	NL	↓***	↑ ***	↑ **	↓***	NS	NS	↑ *	↑ *	NS	↑ ***	↑ ***	↓***	NS	↑ ***
	Age		NL	NL	NL	NL	NS	↑ ***	↑ ***	NS	NS	↑ **	↑ ***	↑ *	↑ ***	↑ ***	↑ ***	NS	↓***	↑ ***
	Medicines prescribed			NL	NL	NL	NS	↑ ***	↑ ***	↑ ***	↑ ***	↑ ***	↑ ***	↑ ***	↑ **	↑ ***	↑ ***	↑ ***	↑ ***	↑ ***
	Respiratory medicines prescribed				NL	NL	NS	NS	NS	↑ ***	↑ ***	NS	↑ ***	NS	NS	NS	NS	↑ ***	↑ ***	↑ ***
	CNS medicines prescribed					NL	NS	↑ ***	NS	NS	NS	NS	↑ ***	↑ ***	NS	↑ **	NS	NS	↑ **	↑ ***
	ACB score							↑ ***	↑ ***	↑ **	↑ ***	↑ ***	↑ **	↑ ***	NS	↑ **	↑ ***	↑ ***	↑ *	↑ ***
Categorical (Y)	Weekend discharge							NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	**	NS
	Prescribed GI medication								***	NS	*	***	***	***	NS	**	***	NS	NS	***
	Prescribed CV medication									NS	***	***	***	**	**	**	***	*	***	***
	Prescribed antimicrobial medication										***	***	*	NS	NS	*	NS	***	***	***
	Prescribed endocrine medication											*	*	NS	NS	NS	NS	***	NS	**
	Prescribed GU medication												NS	**	*	NS	**	NS	NS	**
	Prescribed nutrition & blood medication													NS	NS	*	*	NS	NS	***
	Prescribed MSK medication														*	NS	***	NS	NS	**
	Prescribed ENT medication															NS	*	NS	NS	NS
	Prescribed skin medication																**	*	NS	***
	Prescribed HRM(s)																	NS	NS	***
	Prescribed temporary medication																		***	***
	Prescribed more items on discharge																			***

5.2.2 Multiple logistic regression

Pharmaceutical variables were entered as the first block:

1. Medicines prescribed (count)
2. Prescribed GI medication (yes/no)
3. Prescribed CV medication (yes/no)
4. Respiratory medicines prescribed (count)
5. CNS medicines prescribed (count)
6. Prescribed antimicrobial medication (yes/no)
7. Prescribed endocrine system medication (yes/no)
8. Prescribed GU medication (yes/no)
9. Prescribed nutrition & blood medication (yes/no)
10. Prescribed MSK medication (yes/no)
11. Prescribed ENT medication (yes/no)
12. Prescribed skin medication (yes/no)
13. Prescribed HRM(s) (yes/no)
14. ACB score
15. Prescribed temporary medication (yes/no)
16. Prescribed more medicines compared to on admission (yes/no)
17. Potentially eligible for post-discharge MUR (yes/no)

Non-pharmaceutical variables were entered afterwards, in the second block:

1. Discharged at the weekend (yes/no)
2. Length of stay (days)
3. Age (years)

At each stage, the variable contributing least significantly to the model was disregarded as described in 3.2.2.5 b) Significance of parameter estimates, and the analysis re-run, until all variables included were contributing significantly ($p<0.05$). Of the 20 variables

initially included in the first multiple regression model, 18 were removed in order of significance to produce a parsimonious model. The resulting is presented in **Table** 5.4:

Table 5.4: The multiple logistic regression model	
Model version:	**1.19**
Variables	***p*-value**
Age (years)	0.001
Number of medicines prescribed (count)	<0.001
Constant	<0.001
-2LL X^2_{DF} (*p*-value)	42.2_2 (<0.001)
Nagelkerke R^2	0.061
Observed: readmissions/cases (%)	200/1116 (17.9)
Predicted: correctly classified (%)	916/1116 (82.1)

Both of the variables included (number of medicines prescribed and patient's age) in version 19 (Model 1.19) contributed significantly, and the model had a significant association with the outcome. The inclusion of the pharmaceutical variable(s) significantly improved model fit; at the default classification threshold of $P(Y)$=0.5 in Model 1.19:

- the inclusion of the pharmaceutical variable in Block 1 (number of medicines prescribed) yielded X^2_1=30.5, p<0.001, and
- the addition of age in Block 2 yielded X^2_2=42.2, p<0.001.
- The difference between the blocks was significant at X^2_1=11.7, p=0.001, confirming that they each made a significant contribution and it was correct to include both.

However, no improvement in classification was achieved by including the predictor variables; the model's baseline prediction that no cases would be readmitted resulted in 82.1% accuracy, although the clinical utility of this is non-existent as no patients who would be readmitted would be identified.

It is desirable to identify patients at risk of readmission as early as possible in order to maximise the time available for intervention to reduce their readmission risk

(Amarasingham et al., 2010; Baillie et al., 2013; Bradley et al., 2013; Eapen et al., 2013; Gildersleeve & Cooper, 2013; Kansagara et al., 2011; Rothman et al., 2013; Silverstein et al., 2008; Singal et al., 2013). Consequently, Model 1.19 was re-specified to produce an alternative model which would enable identification of patients likely to be readmitted at the point of admission, specifically: the number of medicines prescribed on the discharge prescription was replaced by the number of medicines prescribed on admission. The outcome is shown in Table 5.5:

Table 5.5: Alternative multiple logistic regression model

Model version:	**2.1**
Variables	***p*-value**
Age (years)	0.003
Number of medicines prescribed on admission (count)	<0.001
Constant	<0.001
-2LL X^2_{DF} (*p*-value)	39.2_2 (<0.001)
Nagelkerke R^2	0.057
Observed: readmissions/cases (%)	200/1115 (17.9)
Predicted: correctly classified (%)	915/1115 (82.1)

The observed reduction in accuracy, effect size and goodness of fit was negligible compared to Model 1.19. Both Model 1.19 and Model 2.1 were taken forward for ROC curve analysis to determine which had the best potential for balancing sensitivity and specificity.

5.2.2.1 Discrimination

a) Comparing models

Figure 5.1 compares the discriminative capability of Model 1.19 and Model 2.1 by ROC curve analysis, which were both found to be significant at $p<0.001$:

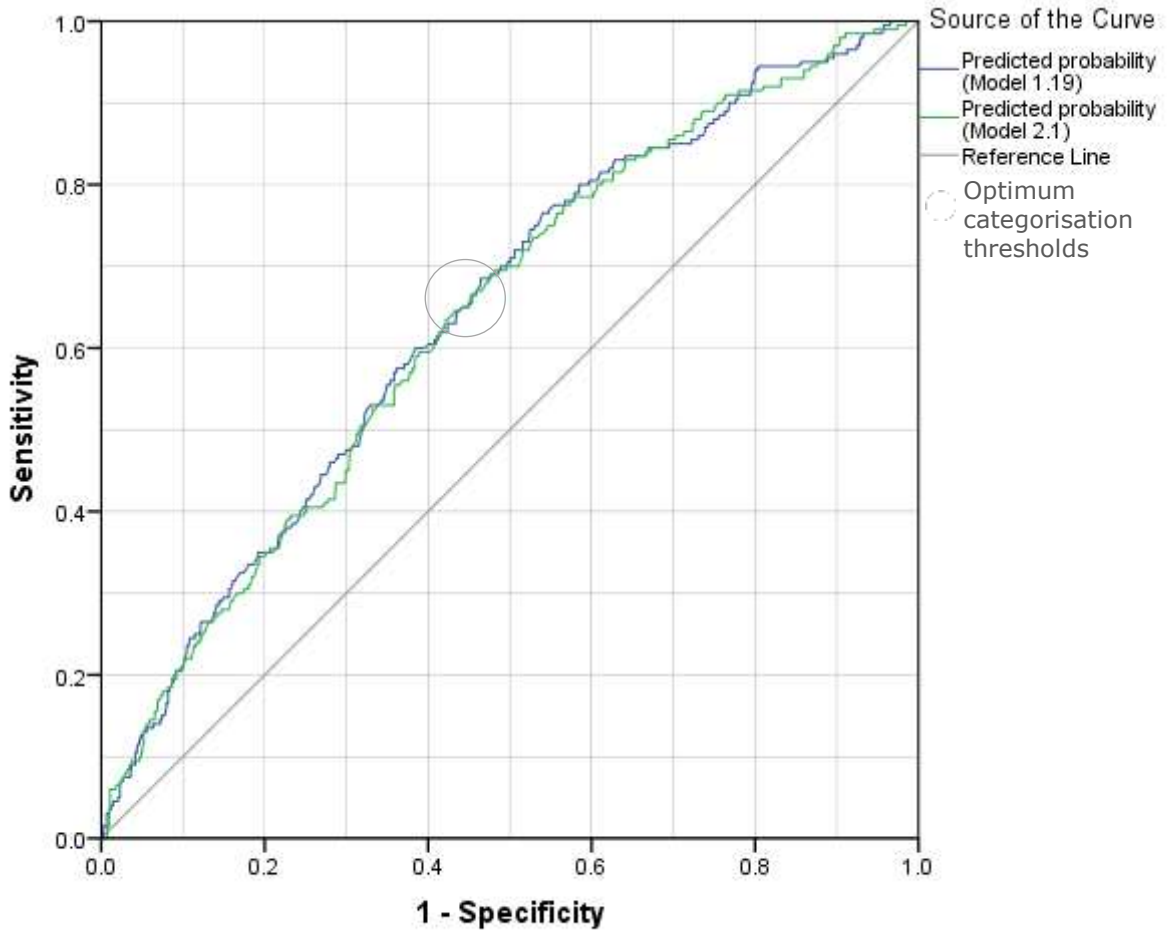


Figure 5.1: ROC curve for Model 1.19 and Model 2.1

The AUC for Model 1.19 was marginally greater than for Model 2.1 (0.642 and 0.637 respectively); however, the confidence intervals overlapped (0.601 to 0.684 and 0.596 to 0.679 respectively) indicating that either model could have had the true highest value. Essentially, there was no difference between the models' discriminative capability.

5.2.2.2 The final multiple logistic regression model

Model 2.1 was taken forward on the basis that differences between the fit and predictive performance of Models 1.19 and 2.1 was marginal, and furthermore Model 2.1 had the practical advantage of being suitable for application on admission rather than discharge. The model parameters for the final model are shown in Table 5.6 below:

Table 5.6: The final multiple logistic regression model (Model 2.1)				
Variable	***b* [SE]**	**95% CI for Odds Ratio**		
		Lower	**Odds Ratio**	**Upper**
Medicines prescribed on admission (count)	0.077 [0.016]	1.05	1.08	1.12
Years of age	0.015 [0.005]	1.01	1.02	1.03
Constant	-3.21 [0.377]		0.040	
R^2_N = 0.057. -2LL X^2_2 = 39.2, p<0.001				

Controlling for increasing age, each additional medicine prescribed on admission increased the odds of readmission by eight per cent, and controlling for increasing number of medicines prescribed on admission, each additional year of age increased the odds of readmission by two per cent. Equation 5.1 demonstrates the application of the parameter estimates to predict an individual's likelihood of readmission according to Model 2.1:

Equation 5.1: Calculating probability of readmission according to Model 2.1

$$Probability\ of\ readmission = \frac{1}{1 + e^{-(-3.21 + 0.077 medicines + 0.015 age)}}$$

Medicines = number of medicines prescribed on admission

Age = years of age

Table 5.7 demonstrates probability of readmission calculated according to Model 2.1 as a percentage across deciles of age and quintiles of number of medicines prescribed on admission:

Table 5.7: Percentage probability of readmission according to Model 2.1							
Age (years)	**Number of medicines prescribed on admission**						
	0	**1**	**5**	**10**	**15**	**20**	**25**
20	5%	6%	7%	11%	15%	20%	27%
30	6%	6%	9%	12%	17%	23%	30%
40	7%	7%	10%	14%	19%	26%	34%
50	8%	8%	11%	16%	21%	28%	37%
60	9%	10%	13%	18%	24%	32%	40%
70	10%	11%	14%	20%	27%	35%	44%
80	12%	13%	16%	22%	30%	38%	48%
90	13%	14%	19%	25%	33%	42%	52%
100	15%	16%	21%	28%	36%	46%	55%
Risk group	**Low** Below average readmission rate (≤18%)		**Medium** Between the average and twice the average readmission rate		**High** Twice the average readmission rate and above (≥36%)		

a) Calibration

Homer-Lemeshow's goodness-of-fit test was not significant (X^2_{df} 6.11_8, p=0.635), indicating that Model 2.1's predictions were not significantly different from the observed values across probability deciles, and confirming adequate fit of the model's estimates to the data.

b) Optimising the classification threshold

The probability of readmission ($P(Y)$) predicted by Model 2.1 ranged from 0.050 to 0.428; the default classification threshold of 0.5 did not yield any positive predictions because $P(Y)$ did not cross 0.5. $P(Y)$ ranged from 0.058 to 0.379 for those who were readmitted, compared to 0.050 to 0.428 for those who were not readmitted, confirming that the calculated probabilities were not well-differentiated according to the outcome; consequently, selecting the classification threshold would require a compromise between

correctly identifying those who would be readmitted, and ruling out those who would not.

The points with the most favourable combined sensitivity and specificity, highlighted in Figure 5.1, lay between sensitivity 0.6 and 0.7, and specificity 0.5 and 0.6. Predicted probability for readmission for points in this section ranged from 0.170 to 0.185. Classification thresholds of $P(Y)$=0.203, identified as having sensitivity 0.5; $P(Y)$=0.150, identified as having sensitivity 0.8; and $P(Y)$=0.118, identified as having sensitivity 0.9, were also evaluated for comparison. Table 5.8 demonstrates the performance of Model 2.1 at the selected classification thresholds as well as the default $P(Y)$=0.5 (options):

Table 5.8: Predictive performance of Model 2.1 according to classification threshold

Option	$P(Y)$	Sensitivity	Specificity	Accuracy (%)
A	0.500	0	1	82.1
B	0.203	0.500	0.684	65.1
C	0.185	0.605	0.592	59.5
D	0.170	0.700	0.504	53.9
E	0.150	0.805	0.384	49.5
F	0.118	0.900	0.246	36.3

Option A was disregarded because it did not have any practical applicability; it did not distinguish between patients who would and would not be readmitted, and thus would not enable intervention to be targeted.

Option B correctly identified one in two (50.0%, 100/200) patients who would be readmitted. Patients who would be readmitted constituted just over one-quarter (25.7%, 100/389) of those flagged for intervention. Over two-thirds (68.4%, 626/915) of patients who would not be readmitted were correctly ruled out.

Option C correctly identified three out of every 5 (60.5%, 121/200) patients who would be readmitted. Patients who would be readmitted constituted just less than one-quarter (24.5%, 121/494) of those flagged for intervention. Three out of every five (59.2%, 542/915) patients who would not be readmitted were correctly identified; this classification threshold demonstrated the best balance between positive and negative predictive performance.

Option D correctly identified two out of three (70.0%, 140/200) of the patients who would be readmitted. Patients who would be readmitted constituted close to one-quarter (23.6%, 140/594) of those flagged for intervention. One in two patients (50.4%, 461/915) who would not be readmitted were correctly ruled out.

Option E correctly identified four out of five (80.5%, 161/200) of patients who would be readmitted. Patients who would be readmitted constituted between one quarter and one fifth (22.2%, 161/725) of patients flagged for intervention. Two out of every five (38.4%, 351/915) patients who would not be readmitted were correctly ruled out.

Option F correctly identified the vast majority (90.0%, 180/200) of the patients who would be readmitted. Patients who would be readmitted constituted close to one-fifth (20.7%, 180/870) of those flagged for intervention. One of every four (24.6%, 225/915) patients who would not be readmitted were correctly ruled out.

Figure 5.2 demonstrates the performance of Model 2.1 according to classification threshold option:

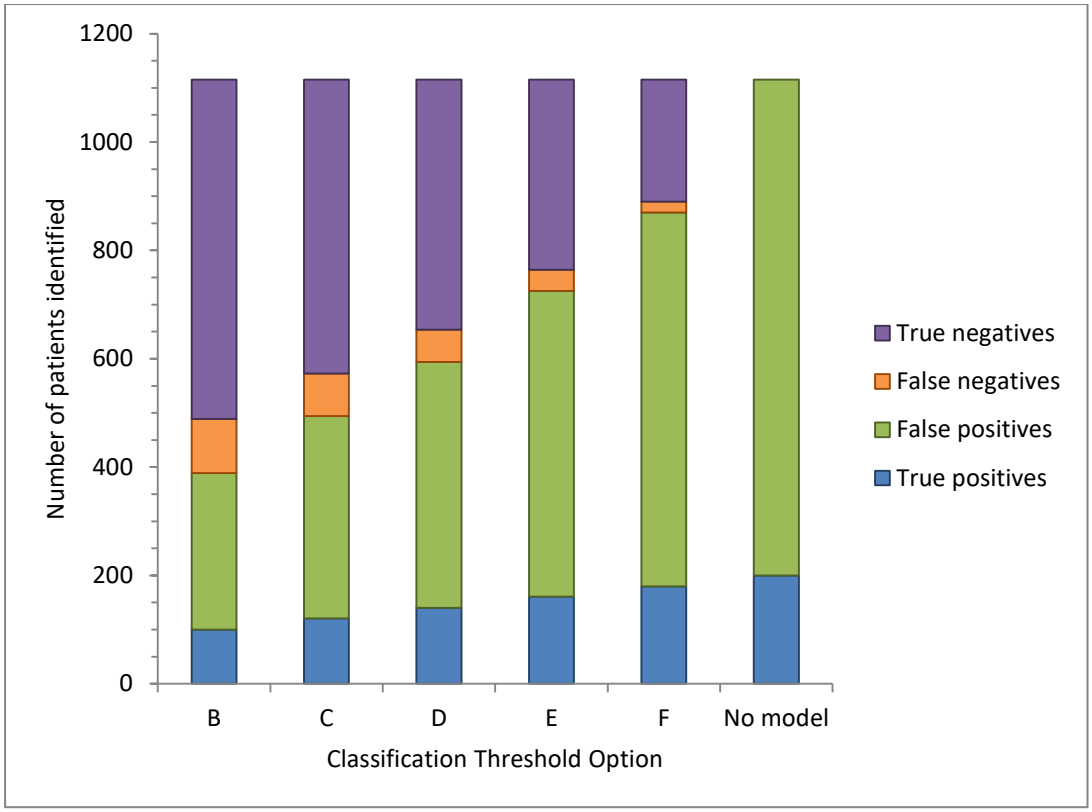


Figure 5.2: Predictive performance of Model 2.1 according to classification threshold option

Option D (*P*(*Y*) 0.170) was selected as a suitable classification threshold for Model 2.1 to take forward for residual analysis. The predictive performance of Model 2.1 with classification threshold D (Model 2.1D) is summarised in Table 5.9:

c) Accuracy

Table 5.9: Classification table for Model 2.1D

		Predicted		
		Not readmitted	**Readmitted**	**% correct**
Observed	**Not readmitted**	461	454	50.4
	Readmitted	60	140	70.0
	% correct	88.5	23.6	53.9

d) Generalisability

Model 2.1 was rerun on a random 80% selection of the data. The resulting training data subset contained 81.3% (906/1115) of all discharges with a readmission rate of 18.2% (165/906). Table 5.10 demonstrates the training model's (Model 2.1X) parameters, which were similar to the final model (Model 2.1):

Table 5.10: Validation training model (Model 2.1X)				
Variable	***b* [SE]**	**95% CI for Odds Ratio**		
		Lower	**Odds Ratio**	**Upper**
Medicines prescribed on admission (count)	0.079 [0.018]	1.05	1.08	1.12
Years of age	0.014 [0.005]	1.00	1.01	1.03
Constant	-3.14 [0.413]		0.043	
R^2_N=0.056. -2LL X^2_2 = 31.7, p<0.001				

The corresponding validation data subset contained 18.7% (209/1115) of all discharges. The readmission rate was 16.7% (35/209). Table 5.11 demonstrates that at classification threshold D ($P(Y)$=0.170) the model's (Model 2.1XD) performance was very similar for the training and validation data subsets, as well as Model 2.1D:

Table 5.11: Classification table for Model 2.1XD				
		Predicted		
		Not readmitted	**Readmitted**	**% correct**
Observed	**Not readmitted**			
	Training	356	385	48.0
	Validation	87	87	50.0
	Readmitted			
	Training	46	119	72.1
	Validation	11	24	68.6
	Overall %			
	Training	88.6	23.6	52.4
	Validation	88.8	21.6	53.1

e) Assumptions

Linearity of the logit

The Box-Tidwell transformation test result was not significant for either variable (LnAge p=0.139, LnMedicines p=0.321).

Independence of errors

Model 2.1 was re-specified to include the primary observation for each individual (the sensitivity analysis subset). In the final model 57 patients contributed data from two discharges and three patients contributed three; consequently, the sensitivity analysis subset included 1052 discharges. The readmission rate was 16.3% (172/1052) and the parameter estimates of the resulting model (Model 2.1S) are presented in Table 5.12:

Table 5.12: Sensitivity analysis model (Model 2.1S)

Variable	*b* [SE]	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
Medicines prescribed on admission (count)	0.077 [0.018]	1.04	1.08	1.12
Years of age	0.016 [0.005]	1.01	1.02	1.03
Constant	-3.40 [0.408]		0.033	
R^2_N= 0.057.-2LL X^2_2 = 35.9, p<0.001				

Table 5.13 below demonstrates the model's performance at classification threshold D ($P(Y)$=0.170, Model 2.1SD):

Table 5.13: Classification table for Model 2.1SD				
		Predicted		
		Not readmitted	Readmitted	% correct
Observed	Not readmitted	523	357	59.4
	Readmitted	70	102	59.3
	% correct	88.2	22.2	59.4

f) Diagnostic Statistics

Standardised residuals

Standardised residual values for Model 2.1, which ranged from -0.864 to 4.02, are summarised in Table 5.14 , Figure 5.3, Figure 5.4, and Figure 5.5:

Table 5.14: Standardised residuals for Model 2.1	
Value	N (%)
±1.96	110 (9.9)
±2.58	28 (2.5)
±3.29	8 (0.7)

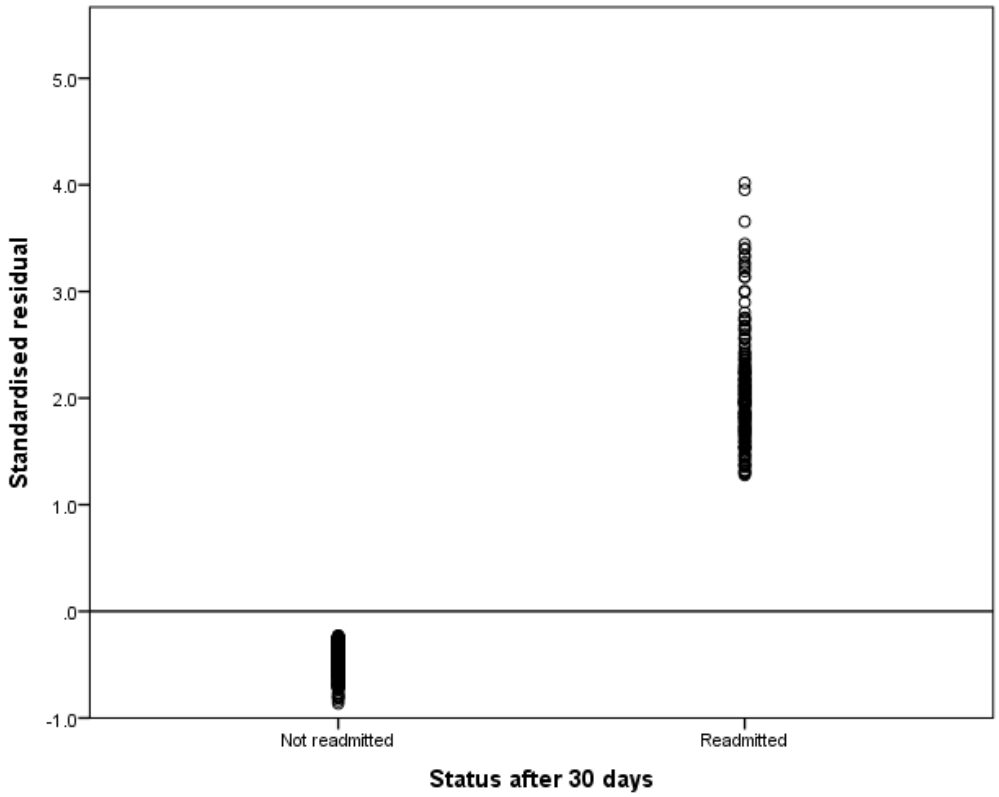


Figure 5.3: Standardised residuals according to outcome

Figure 5.4 demonstrates that the model 2.1D's predictions were not well-differentiated. The vertical line at x=0.17 represents the classification threshold, with points to the left representing cases predicted not to be readmitted and points to the right representing cases predicted to be readmitted. The horizontal line at y=0 represents perfect prediction. All 110 cases with residual ±1.96 involved underprediction; specifically, underestimating the probability of readmission for patients who would be readmitted.

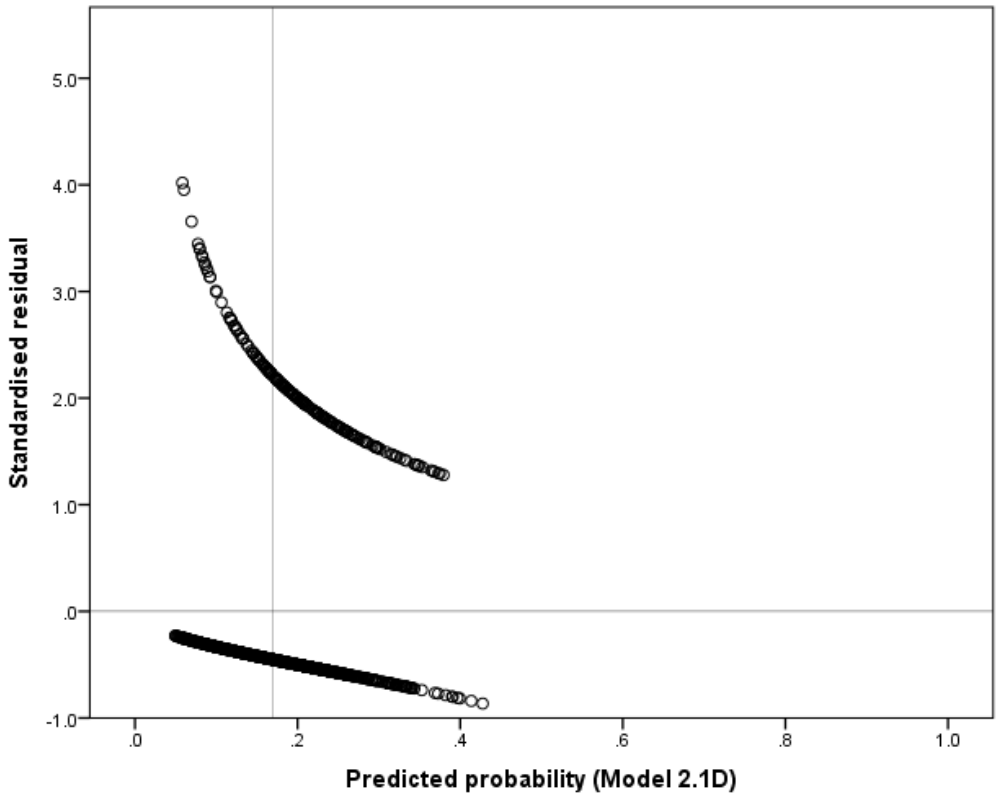


Figure 5.4: Standardised residuals according to predicted probability

Finally, Figure 5.5 below shows the distribution of residuals according to the order discharges in the study:

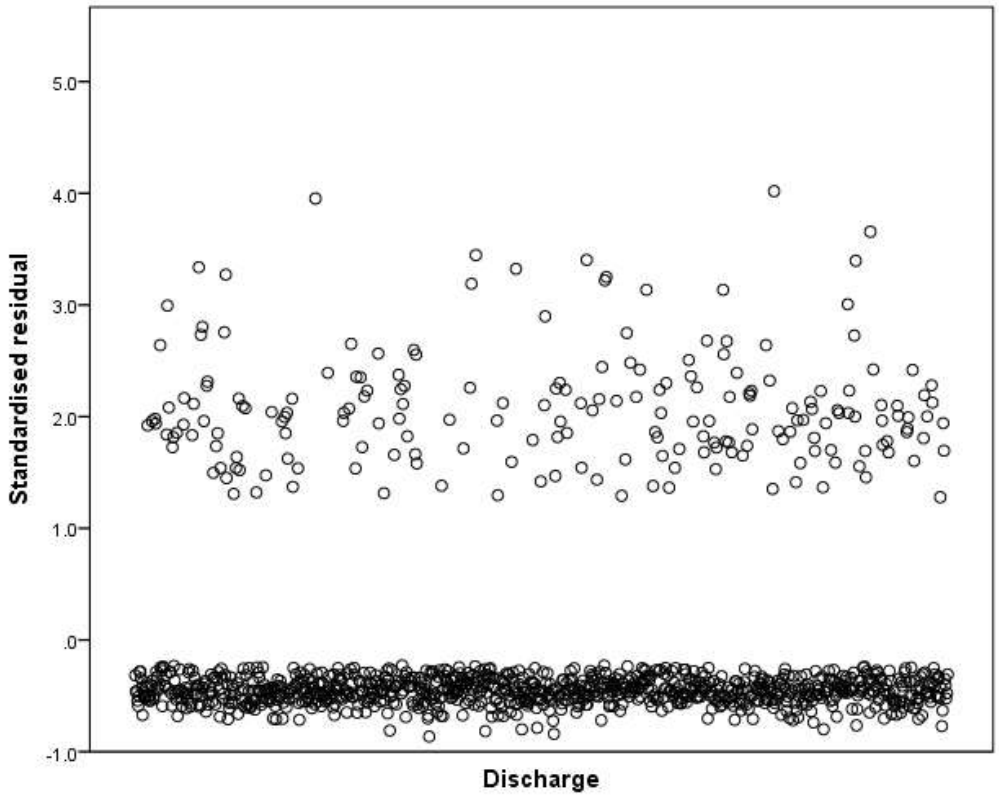


Figure 5.5: Standardised residuals according to order of discharge

The outcome for all cases with standardised residual greater ±1.96 was readmission; less than half (45%, 90/200) of patients who were readmitted had a standardised residual less than ±1.96. Outliers (cases with standardised residual ≥3.29) were significantly younger and were prescribed fewer medicines on admission on average compared to the rest of the cohort (35.3, SD 12.1 compared to 69.3, SD 18.7 years of age, 95%CI for the difference 23.9 to 44.2 years, $t_{7.25}$=7.90, p<0.001; prescribed 2.0, SD 2.20 compared to 7.7, SD 4.81 medicines, 95%CI for the difference 3.80 to 7.50, $t_{7.49}$=7.12, p<0.001).

Cook's distance

All Cook's distance values were within ±1.

5.3 Discussion

Predictors of readmission were identified from potential predictors on the basis of the Literature Review, General Methods and Exploratory Analysis. Fifty-two candidate predictors were rationalised to 35 on the basis of a relatively liberal significance threshold in simple logistic regression analysis, and these were further rationalised to 20 on the basis of their expected independence from one another; multicollinearity was not a problem among the variables taken forward to multiple logistic regression analysis.

Although an association between malignancy and readmission has often been reported (Bjorvatn, 2013; Donzé et al., 2013a; Lee, 2012; Mather et al., 2014; Picker et al., 2015; Shu et al., 2012), prescription of medication for malignant disease and immunosuppression was not identified as predictive of readmission in this analysis; admissions for cancer treatment are excluded from the 30-day readmission rule as it is accepted that readmission may be necessary and appropriate in this context (Department of Health, 2013).

Pharmaceutical variables were prioritised for retention in the multivariable analysis due the pharmacy context of the project. Increasing number of medicines prescribed and increasing age were each independently associated with increased risk of readmission. Age was included in the final model for over half of studies included in the literature review that were undertaken for the purpose of predicting readmission risk (7/13) (Bradley et al., 2013; Eapen et al., 2013; Gildersleeve & Cooper, 2013; Haas et al., 2013; Lee, 2012; Mather et al., 2014; Tan et al., 2013); only one specifically referred to including the number of medicines prescribed (Gildersleeve & Cooper, 2013). Several included variables involving number of comorbidities (4) (Au et al., 2002; Gildersleeve & Cooper, 2013; Lee, 2012; Tan et al., 2013), which could be reflected by the number of medicines prescribed to some extent (previously discussed in section 4.3.2). A number of variables that demonstrated a significant association with readmission in univariable analysis did not contribute significantly in the multivariable model, confirming that the variables' association with

readmission was explained by their relationship with the patient's age and/or the number of medicines prescribed. Specifically:

1. Length of stay (days)
2. Prescribed GI medication (yes/no)
3. Prescribed CV medication (yes/no)
4. Respiratory medicines prescribed (count)
5. Prescribed antimicrobial medication (yes/no
6. Prescribed endocrine system medication (yes/no)
7. Prescribed nutrition & blood medication (yes/no)
8. Prescribed ENT medication (yes/no)
9. Prescribed HRM(s) (yes/no)
10. ACB score
11. Prescribed temporary medication (yes/no)

GI, CV, respiratory, endocrine, high risk, and temporary medicines were included on discharge prescriptions more often than not; therefore the association of these on prescriptions for patients who were readmitted could be reasonably explained by the number of medicines prescribed overall; similarly, ACB score increased with increasing number of medicines prescribed.

Two multivariable models were developed: one suitable for application on discharge and the other suitable for application on admission. Differences between the two models in fit and predictive performance were marginal; the practical advantage of being suitable for application on admission rather than discharge, and consequently having the potential to enable earlier identification of, and intervention for, patients who would be readmitted was the basis on which the second model was progressed in preference to the first (see also 3.2.2.5 b) Model specification).

Manual calculation using the model's parameter estimates could prove onerous for clinicians to apply in the clinical setting; however, the calculation could be automated within existing systems provided that the routine recording the number of medicines prescribed on

admission was facilitated (such functionality is already in place for age). Alternatively, the chart produced to demonstrate the probability of readmission calculated according to the final model as a percentage across deciles of age and quintiles of number of medicines prescribed on admission (Table 5.7) would simplify manual application by practitioners in the clinical setting. Several studies undertaken for the purpose of predicting readmission in the literature review referred to automating calculation for point-of-care application (Eapen et al., 2013; Gildersleeve & Cooper, 2013; Singal et al., 2013; Tan et al., 2013); Bradley et al. (2013) referred to the need for a tool that did not require data collection outside of regular clinical processes and which produced output that could be easily interpreted by clinicians, referred to capturing existing data from electronic documentation without manual review, and Rothman et al. (2013) referred to avoiding risking miscalculation on clinical staff.

The thresholds for risk groups and the classification threshold were selected for demonstration purposes; it is acknowledged that alternative configurations could be considered more suitable depending on the circumstances, and in practice such thresholds would be configured to reflect the preference(s) of wards/Trusts concerned.

The effect size of the model was very small. Although statistically significant, the model explained only a portion of variation in the outcome; effect size could be improved upon by re-specifying the model with more and/or better predictors (Garson, 2016). Considering that this study included all of the reliable information on the Trusts electronic discharge prescriptions, more and/or better predictors are unlikely to be available on discharge prescriptions and consequently such re-specification would be beyond the scope of this study. Nonetheless, the final model improved upon the accuracy of indiscriminate intervention by 36% (accuracy 53.9% compared to 17.9%). Much of the improvement was achieved by correctly ruling out patients who would not readmitted, yet the model also correctly identified the majority of patients who would be readmitted (70.0%). The model's accuracy was similar to that achieved by Bradley et al. (2013) with the classification threshold set to distinguish low-risk patients (RI 80 and above) from medium and high risk

patients (RI up to 80; sensitivity 0.70 compared to 0.64, specificity 0.54 compared to 0.52, positive predictive value 0.24 compared to 0.21 and negative predictive value 0.89 compared to 0.88 respectively). The model's discriminative capability appeared only slightly better than that achieved by intern physicians in predicting readmissions among an elderly general medical cohort in the USA (c-statistics 0.64 and 0.59, respectively) (Allaudeen, Schnipper, Orav, Wachter, & Vidyarthi, 2011a), indicating that appropriate application of clinical intuition could be similarly effective in readmission prediction; however, it should be borne in mind that the c-statistic is not intended to compare samples from different populations. As per the recommendation of Eapen et al. (2013) that models be tested against clinical gestalt, further research would be required to explore this prospect.

Performance was very similar for the training and validation data subsets, as well as the final model overall, indicating the model is generalisable among patients discharged from the Trust's MSSUs. As described in 3.3.2.3 (External validity), external validation would be required to gauge the generalisability of the model if adoption outside of the Trust's MSSUs were to be considered. The parameter estimates and accuracy of the sensitivity analysis model was also similar to the final model, confirming that although there was the potential for clustering due to the hierarchical data structure, it had not substantially affected the final model. It was confirmed by Box-Tidwell transformation test that the assumption of linearity of the logit had been met for each variable, indicating that the relationship between the predictors and readmission was not likely to have been underestimated (Field, 2018; Garson, 2016). Cook's distance values indicated no cause for concern with respect to cases having undue influence on the model. There were, however, more cases for which the model fitted poorly than would be expected to occur by chance. The model was better at identifying patients who would not be readmitted than patients who would; however, there was considerable error and dispersion associated with prediction of either outcome and the absence of residuals crossing zero (representing perfect prediction) indicated that the model was relatively weak. Cases associated with the greatest error involved readmission among patients who were much younger and prescribed fewer medicines on average; typically

unusual candidates for readmission. Error was randomly distributed throughout data collection, indicating that data collection effects are unlikely.

5.4 Conclusion

The work presented in this chapter confirms:

Conclusion 1: The likelihood of readmission within 30 days of discharge home from an NHS medical short stay unit can be estimated using routinely recorded prescription information; however, the accuracy of the resulting predictions is relatively poor and may not outperform those based on clinical intuition.

Conclusion 2: Likelihood of readmission within 30 days of discharge home from an NHS medical short stay unit increases with increasing age and polypharmacy.

Risk of readmission increased with increasing polypharmacy (number of medicines prescribed) and increasing age. Each of the independent variables in the final model contributed significantly, and the model had a significant relationship with the dependent variable. The effect size was very small; nonetheless, the final model improved upon the accuracy of indiscriminate intervention to prevent readmission. Much of the improvement would be attributable to the model's ability to correctly rule out patients who would not be readmitted, conserving preventative efforts for those more likely to require it.

Time to readmission will be investigated in Chapter 6 in order to inform the timing of potential intervention intended to prevent readmissions.

Chapter 6 Survival Analysis

6.1 Introduction

Having presented the development of the logistic regression model for predicting readmission risk using prescription information in Chapter 5, survival analysis was undertaken to explore time to readmission in relation to the predictor variables and inform the timing of potential preventative efforts. The study objectives addressed are:

Objective 5 To characterise readmission behaviour depending on predictors of readmission from prescriptions, and

Objective 6 To quantify the influence of predictors of readmission from prescriptions on the time to readmission.

Survival, or time-to-event, analysis models the amount of time taken for an event of interest to take place in relation to independent predictor variables (covariates). The time to readmission and its variation according to the value of the predictor variables identified in the final logistic regression model developed in Chapter 5, specifically years of age and number of medicines prescribed on admission, is described in this chapter. Readmission behaviour among groups was explored by Kaplan-Meier survival analysis (KMSA) and the effect of the covariates on the time to readmission was studied by Cox Proportional Hazards Regression (CPHR) (Armitage et al., 2002; Collett, 2015).

6.3 Results

As previously presented in Chapter 5 Logistic Regression Analysis, readmission was the outcome for 200/1115 (17.9%) of cases included in the final model. The 1115 cases involved 1052 individuals, who contributed 30023 days of observation in total. The values for the predictor variables ranged from 0 to 26 medicines prescribed on admission (mean 7.6, SD 4.8) and 18 to 100 years of age (mean 69.1, SD 18.9). Patients were most likely to be readmitted within a week of discharge, with over one-third (36.5%, 73/200) of all patients who would be readmitted being readmitted during the first week; over half (57.0%, 114/200) of those who would be readmitted were readmitted within two weeks.

6.3.1 Kaplan-Meier Analysis

6.3.1.1 Dichotomising covariates

The ROC curve presented in Figure 6.1 below demonstrates the relationship between specificity and sensitivity for readmission of the covariates number of medicines prescribed and years of age. The points with the greatest combined sensitivity and specificity were located at the points annotated by circles on Figure 6.1 above, approximating sensitivity 0.650 and specificity 0.475 for age, and sensitivity 0.575 and specificity 0.600 for number of medicines prescribed. The coordinates of the curves for the identified points are presented in relation to the associated value for the covariates in Table 6.1.

Table 6.1: Sensitivity and specificity of the covariates for readmission			
Variable		**Sensitivity**	**Specificity**
Age (years)	71.5	0.660	0.468
	72.5	0.650	0.483
	73.5	0.630	0.496
Medicines prescribed (number)	7.5	0.540	0.632
	8.5	0.615	0.556

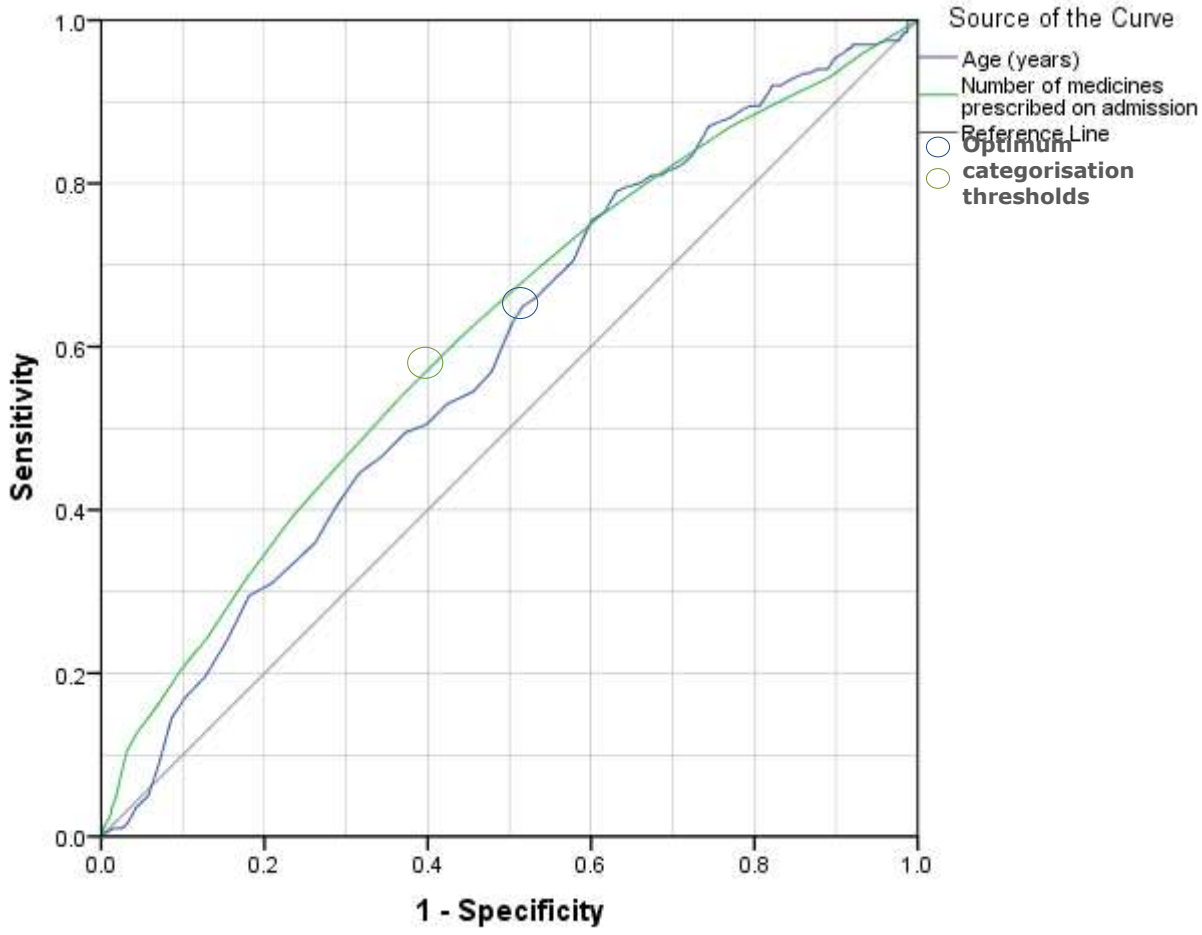


Figure 6.1: ROC curve for number of medicines prescribed and years of age as predictors of readmission

The points identified as having the greatest combined sensitivity and specificity were:

- 72 years of age, and
- 8 medicines prescribed

The covariates were therefore split at these points to create binary factors for the purpose of comparison by Kaplan-Meier analysis, with patients:

- 71 years of age and under representing younger patients (45.8%, 568/1240)
- 72 years of age and older representing older patients (54.2%, 672/1240)
- prescribed 7 or less medicines representing patients prescribed fewer medicines (52.6%, 586/1115)
- prescribed 8 or more medicines representing those prescribed more medicines (47.4%, 529/1115).

6.3.1.2 Kaplan-Meier Procedure

a) Number of medicines prescribed

A significant difference was identified in readmission behaviour when comparing those prescribed fewer and more medicines (logrank $X^2_1=18.9$, $p<0.001$). Figure 6.2 below demonstrates that the readmission rate was consistently greater for patients prescribed more medicines compared to those prescribed fewer, and was greater initially than in the subsequent period for both groups. The amount of time before the readmission rate decreased appeared to be slightly longer for those prescribed more medicines compared to those prescribed fewer, and the difference also appeared to be less substantial for those prescribed more medicines compared to those prescribed fewer.

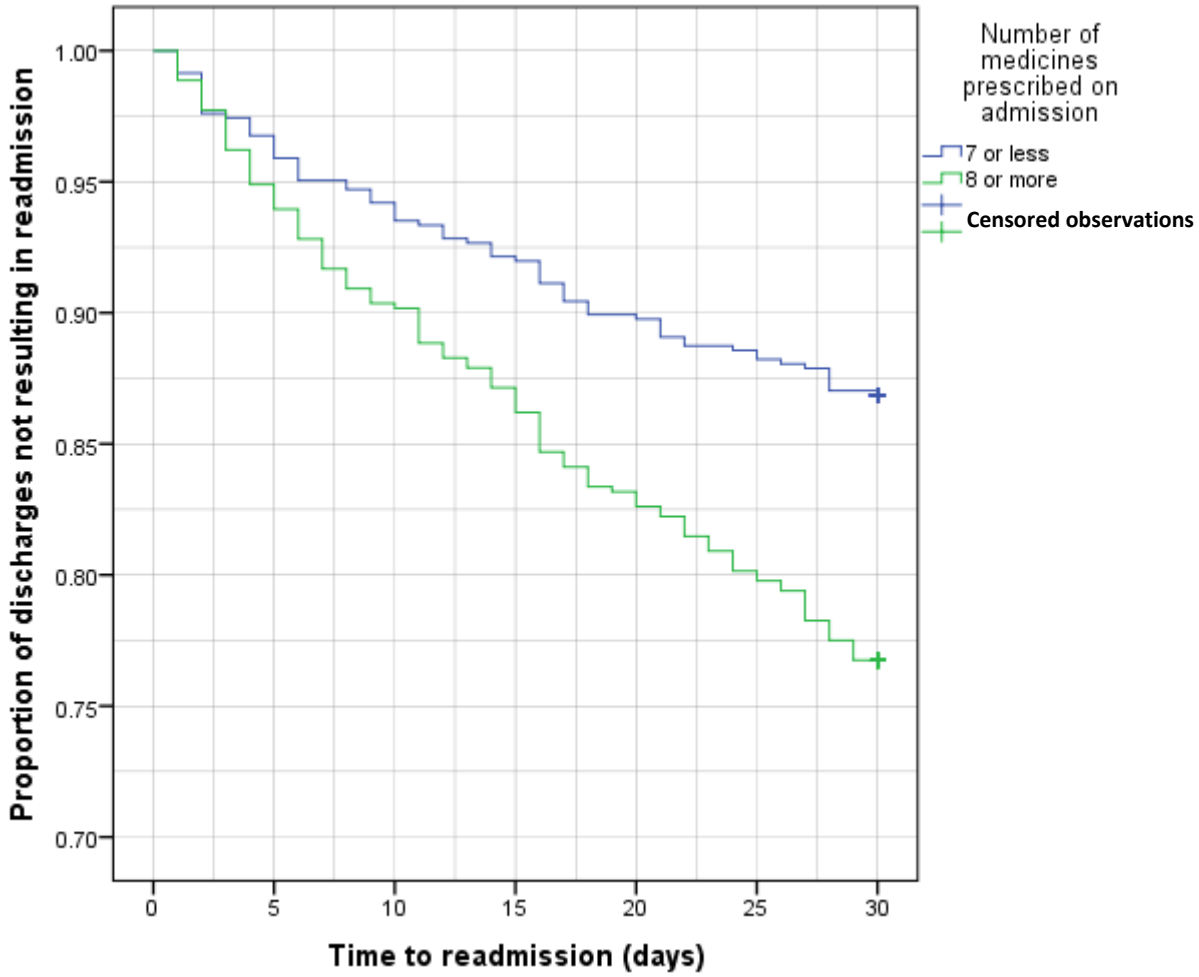


Figure 6.2: Survival plot for readmission behaviour of patients prescribed fewer compared to more medicines

The mean survival time for patients prescribed fewer medicines was longer than for those prescribed more (27.7 and 26.1 days respectively). The mean difference was 1.6 days; however, the confidence intervals indicated that the true difference could have been as little as 0.31 days or as great as 2.8 days. At 30 days, around 10% more patients prescribed more medicines had been readmitted compared to those prescribed fewer (23.3%, 123/529 and 13.1%, 77/586 respectively). The relevant statistics are summarised in Table 6.2:

Table 6.2: Readmission behaviour according to whether prescribed fewer or more medicines					
		Readmission (days)			
			Mean		
Medicines	**Discharges**	**Within 30 (%)**	**Lower 95% CI**		**Upper 95% CI**
7 or less	529	123 (23.3)	27.1	27.7	28.2
8 or more	586	77 (13.1)	25.4	26.1	26.8
Logrank X^2_1=18.9, p<0.001					

The continuous covariate number of medicines prescribed was categorised to create a multi-level ordinal factor variable, with each level representing approximately one-quarter of the cohort:

- those prescribed 3 or fewer medicines (21.1%, 235/1115)
- those prescribed between 4 and 6 medicines (23.8%, 265/1115),
- those prescribed between 7 and 10 medicines (29.1%, 324/1115),
- those prescribed 11 or more medicines (26.1%, 291/1115).

The proportion of discharges that resulted in readmission increased with increasing number of medicines prescribed; those prescribed the most medicines (11 or more) had the highest readmission rate observed for any group (26.8%, 78/291). Patients prescribed 11 or more medicines were more than twice as likely to be readmitted than patients prescribed three or less medicines (26.8%, 78/291 and 11.1%, 26/235 respectively). A significant difference was identified in the groups' readmission behaviour (logrank X^2_3=26.2, p<0.001). Figure 6.3 demonstrates that the readmission rate for patients prescribed the most medicines was consistently greater than for those prescribed fewer:

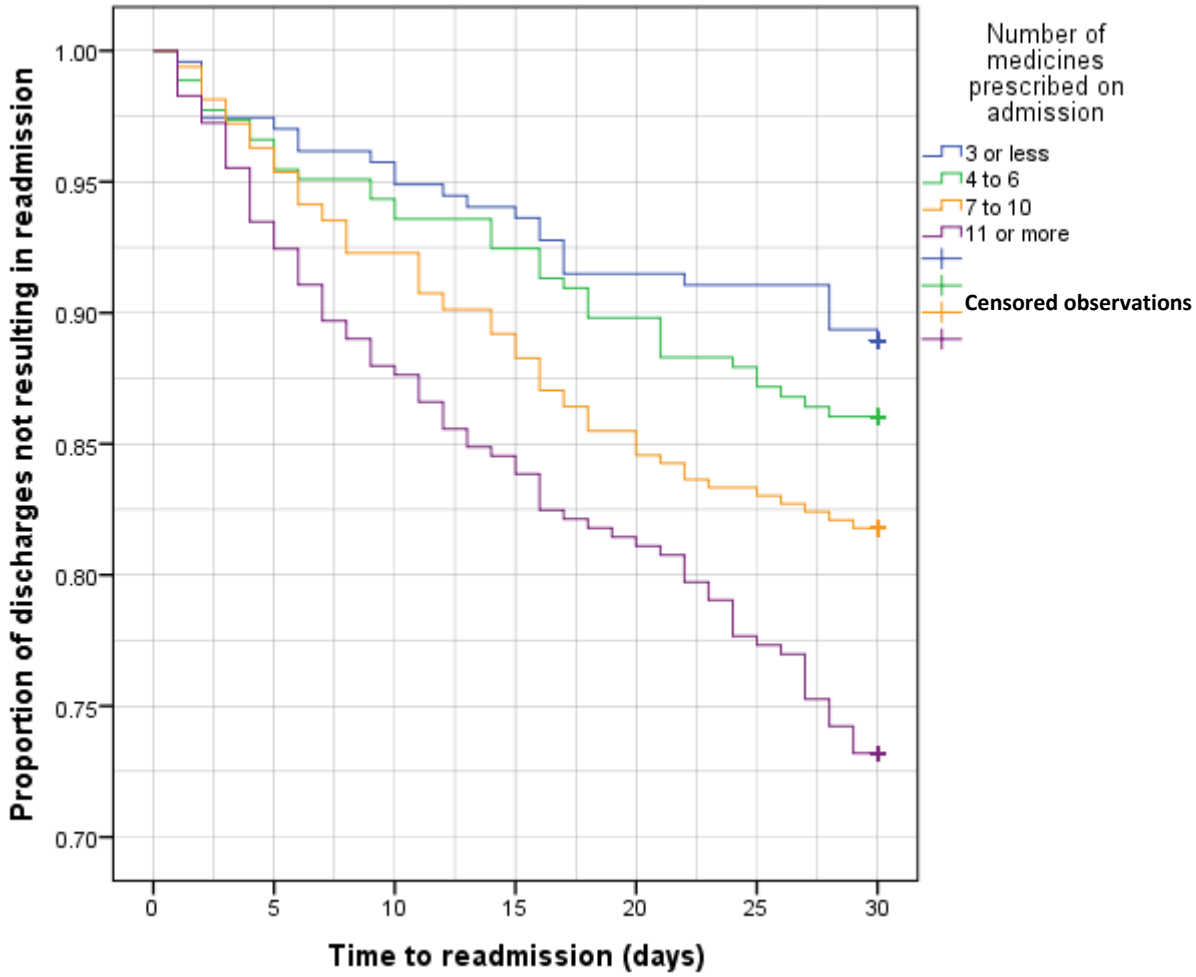


Figure 6.3: Survival plot for readmission behaviour according to number of medicines prescribed

Readmission behaviour was very similar between all of the groups for the first three days, and the middle two groups (between 4 and 10 medicines) remained very similar throughout the first week. Figure 6.4 below shows that almost as many patients prescribed the most medicines (11 or more) were readmitted during the last week as the first; this was the only group to have more readmissions in the last week than the third, and that among the other three groups, more patients were readmitted in the third week than the second:

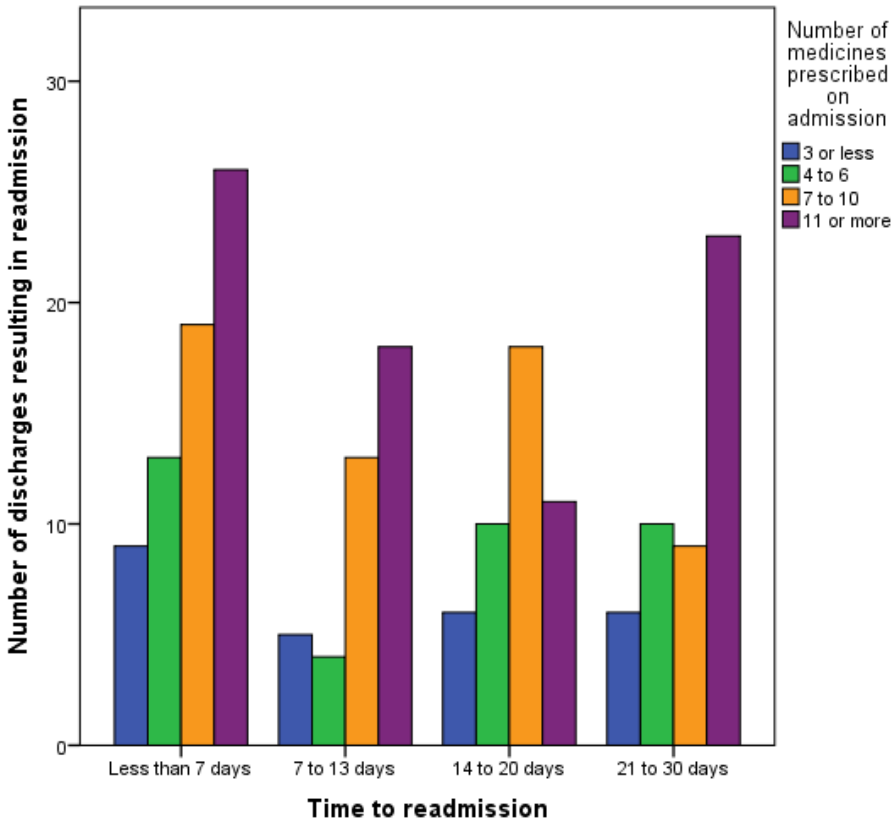


Figure 6.4: Time to readmission according to number of medicines prescribed

Although the confidence intervals for the groups' mean time to readmission overlapped with adjacent categories, there was no overlap between the two groups prescribed the fewest medicines (prescribed up to 6 medicines) and the group prescribed the most (prescribed 11 or more medicines), confirming a significant difference between these. The mean difference in time to readmission between those prescribed the fewest and those prescribed the most medicines was 2.6 days, and 2.1 days between those prescribed the second-fewest and the most medicines. The confidence intervals indicated the difference was at least 0.287 days between the second smallest and the largest group, and 0.825 days between the smallest and largest group. Table 6.3 below contains a summary of the relevant statistics:

Table 6.3: Readmission behaviour according to number of medicines prescribed					
		Readmission (days)			
			Mean		
Medicines	**Discharges**	**Within 30 (%)**	**Lower 95% CI**		**Upper 95% CI**
3 or less	235	26 (11.1)	27.3	28.1	28.9
4 to 6	265	37 (14.0)	26.8	27.6	28.4
7 to 10	324	59 (18.2)	25.9	26.8	27.6
11 or more	291	78 (26.8)	24.5	25.5	26.5
Logrank X^2_3=26.2, p<0.001					

b) Age

A similar trend in readmission behaviour was identified according to age as for the number of medicines prescribed, which is unsurprising given that the number of medicines prescribed tends to increase with increasing age. Although a significant difference was observed, it was associated with less certainty than the difference observed for number of medicines prescribed (logrank X^2_1=8.85, p=0.003). Figure 6.5 demonstrates that the readmission rate for older patients was consistently greater than for younger patients. The readmission rate was greater initially for both groups, however, it appeared there was a longer interval before the rate reduced for older patients compared to younger patients and the rate also appeared to reduce to a lesser extent for older patients than for younger patients.

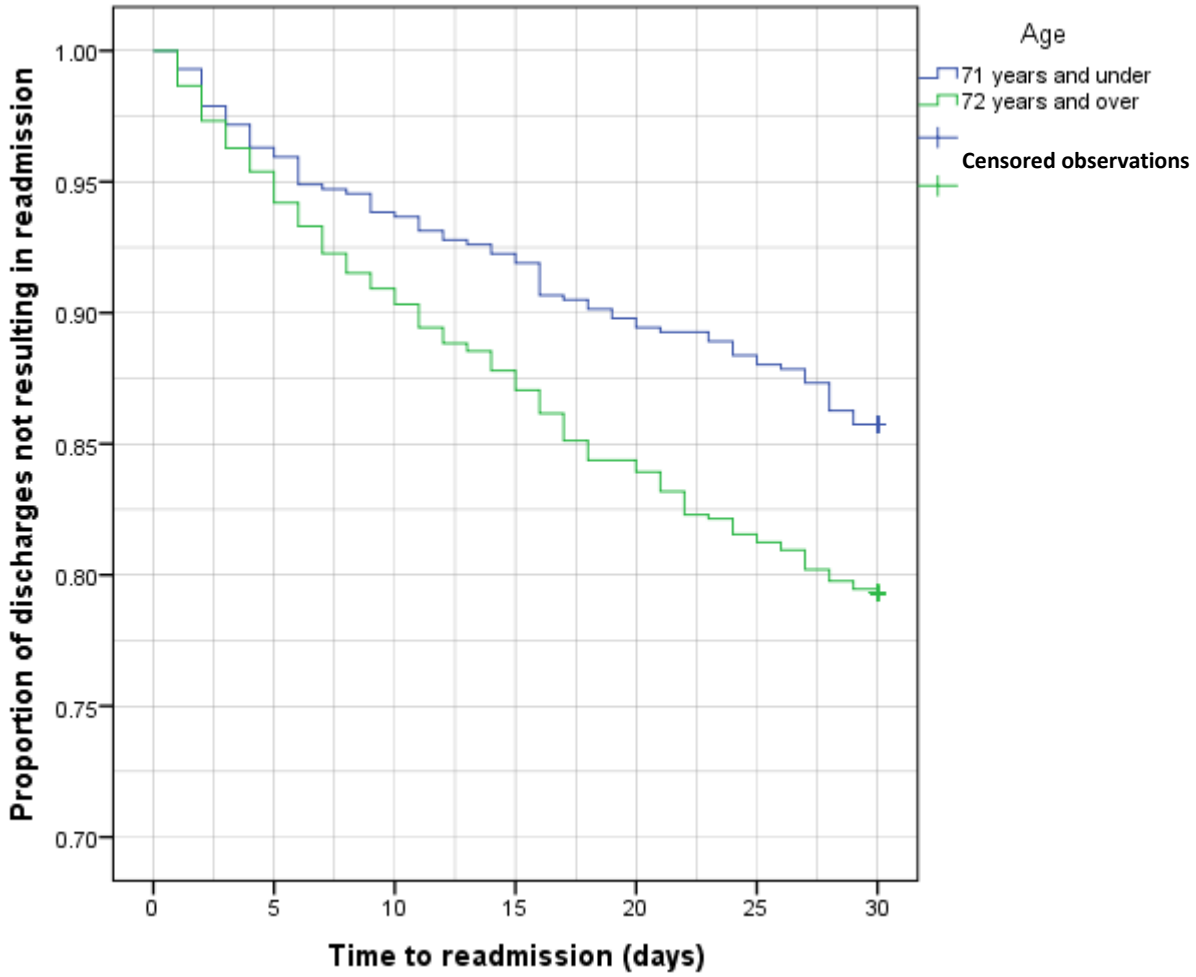


Figure 6.5: Survival plot for readmission behaviour of younger compared to older patients

At 30 days almost seven per cent more of the older patients had been readmitted than younger patients (20.7%, 139/672 compared to 14.3%, 81/568 respectively), and the mean survival time was greater for younger patients compared to older patients (28.5 and 27.2 days respectively). The mean difference was 1.3 days; however, the confidence intervals indicated that the true difference could have been as little as 0.10 days, or as much as 2.4 days. A summary of the relevant statistics is presented in Table 6.4:

Table 6.4: Readmission behaviour for younger and older patients					
		Readmission (days)			
			Mean		
Age	Discharges	Within 30 (%)	Lower 95% CI		Upper 95% CI
71 years and under	568	81 (14.3)	27.1	27.6	28.2
72 years and over	672	139 (20.7)	25.8	26.4	27.0
Logrank X^2_1=8.85, p=0.003					

The continuous covariate age was categorised to produce an ordinal multi-level factor variable for which each level comprised approximately one-third of the cohort. The groups were considered to represent:

- younger patients (64 years of age and under, 34.4%, 427/1240)
- older patients (65 to 80 years of age, 32.3%, 400/1240), and
- elderly patients (81 years of age and over, 33.3%, 413/1240).

The proportion of patients readmitted within 30 days increased with increasing age, with elderly patients being more than twice as likely to be readmitted compared to the youngest group (23.0%, 95/413 and 11.9%, 51/427 respectively). The difference observed in the groups' readmission behaviour was statistically significant (logrank X^2_2=17.9, p<0.001). Figure 6.6 below demonstrates that the readmission rate was consistently greater for elderly patients than it was for the other groups. Younger and older patients expressed very similar readmission behaviour initially; however, the readmission rate decreased substantially for younger patients within a week, and whilst the readmission rate for older patients also decreased within a few days of younger patients, this was to a lesser extent than for younger patients.

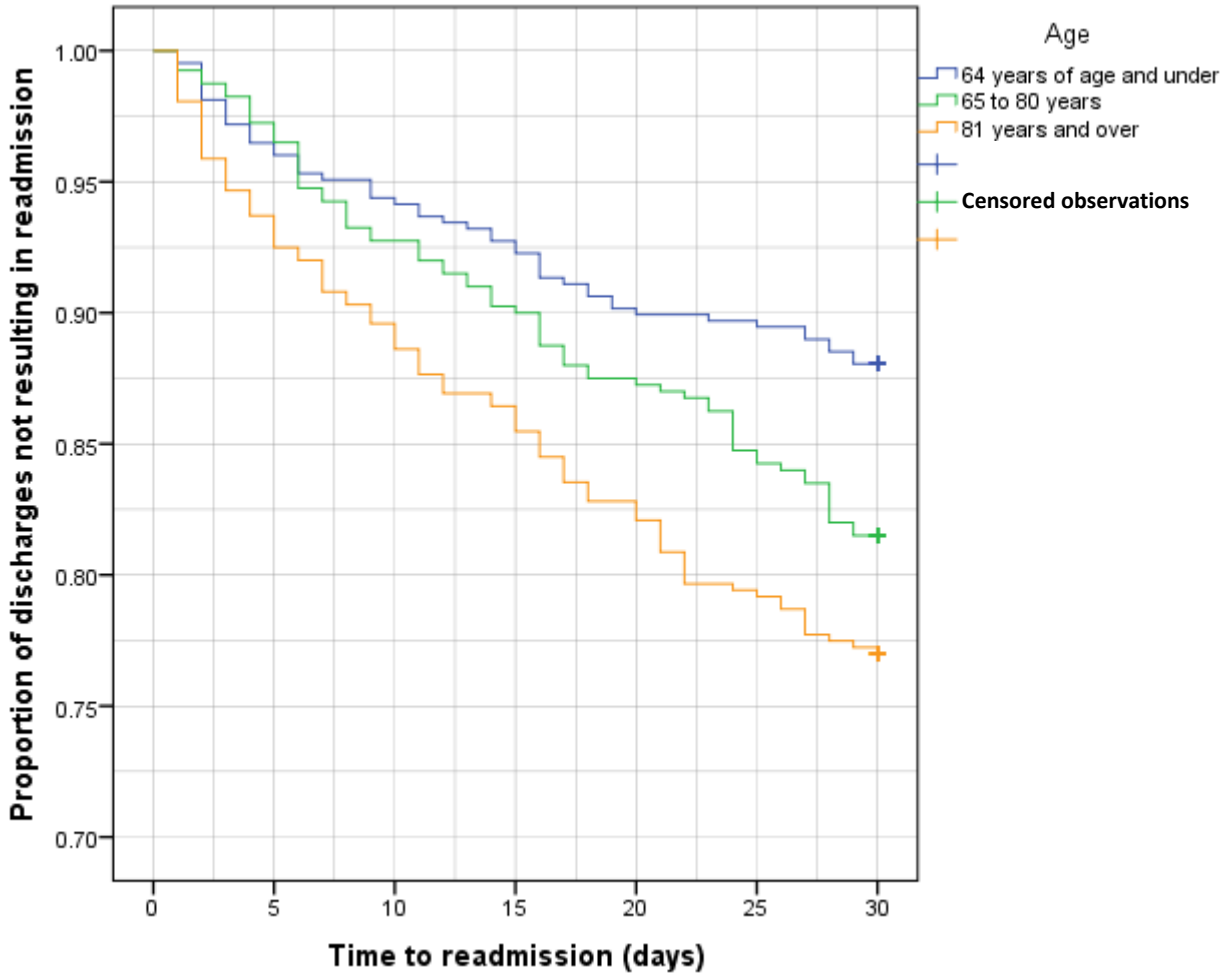


Figure 6.6: Survival plot for readmission behaviour according to age

Although the general trend was for the most readmissions to occur during the first week, more of the older patients were readmitted between day 21 and day 30 than in the first week. It was noted, however, that this interval was 2 days longer than the others, and once this was accounted for the rate was not substantially higher in the last week than the first. Figure 6.7 demonstrates time to readmission according to age group:

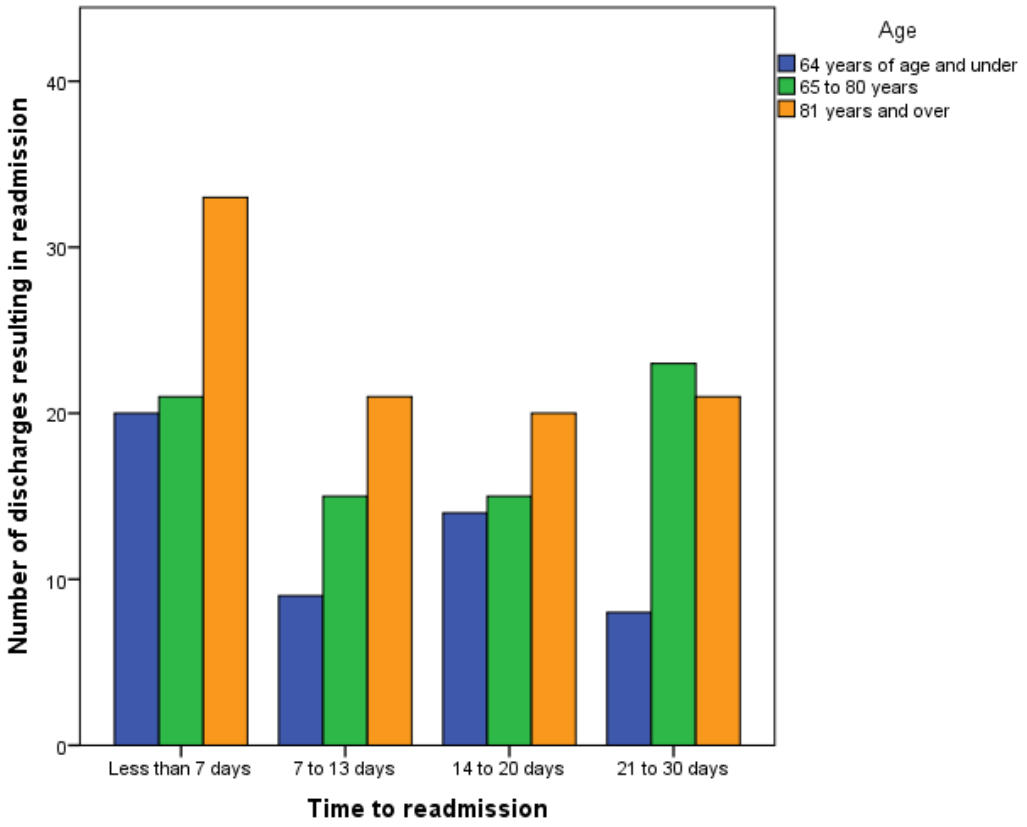


Figure 6.7: Time to readmission according to age

Although the confidence intervals for the age ranges overlapped with adjacent categories, the confidence intervals indicated there was a significant difference of at least 0.5 days between younger and elderly patients. The relevant statistics are summarised in Table 6.5:

Table 6.5: Readmission behaviour according to age					
		Readmission (days)			
			Mean		
Age	**Discharges**	**Within 30 (%)**	**Lower 95% CI**		**Upper 95% CI**
64 years and under	427	51 (11.9)	27.2	27.8	28.5
65 to 80 years	400	74 (18.5)	26.4	27.1	27.8
81 years and over	413	95 (23.0)	25.0	25.9	26.7
Logrank X^2_2=17.9, p<0.001					

6.3.2 Cox Proportional Hazards Regression

The Kaplan-Meier survival curves demonstrate that increasing values of the predictor variables resulted in relatively proportional increases in the hazard function, indicating the assumption of proportional hazards was likely met. Cox regression analysis was undertaken to obtain estimates of the effect of predictor variables on the time to readmission.

6.3.2.1 Deviance

Block 1 X^2_1: 29.5, p<0.001 (change from previous block 27.5, p<0.001)

Block 2 X^2_2: 36.2, p<0.001 (change from previous step 10.4, p=0.001)

The change in deviance between the baseline model and subsequent blocks confirmed that each of the predictor variables contributed significantly to predicting the time to readmission.

6.3.2.2 Parameter coefficients & hazard ratios

Both predictors had a hazard ratio for readmission greater than one, confirming that increasing number of medicines prescribed and age each had a positive association with

the outcome and therefore decreased the time to readmission. Each additional medicine prescribed was associated with a seven per cent decrease in the time to readmission, and each additional year of age was associated with a one per cent decrease. Table 6.6 details the regression coefficients and hazard ratios for the CPHR model, and the calculation for estimating the probability of readmission at a given time according to the CPHR model is presented in Equation 6.1:

Table 6.6: Cox regression coefficients and hazard ratios

Variable	*b* [SE]	95% CI for Hazard Ratio		
		Lower	Hazard Ratio	Upper
Medicines prescribed (on admission, count)	0.066 [0.014]	1.04	1.07	1.10
Age (years)	0.014 [0.004]	1.01	1.01	1.02
-2LL X^2_2 = 36.2, p<0.001				

Equation 6.1: Calculating the time to readmission

$$P(readmission\ at\ given\ time) = exp(0.066medicines + 0.014age)h_0(t)$$

Figure 6.8 demonstrates the readmission behaviour for patients of mean age (69.1 years) and prescribed the average number of medicines prescribed (7.61 medicines):

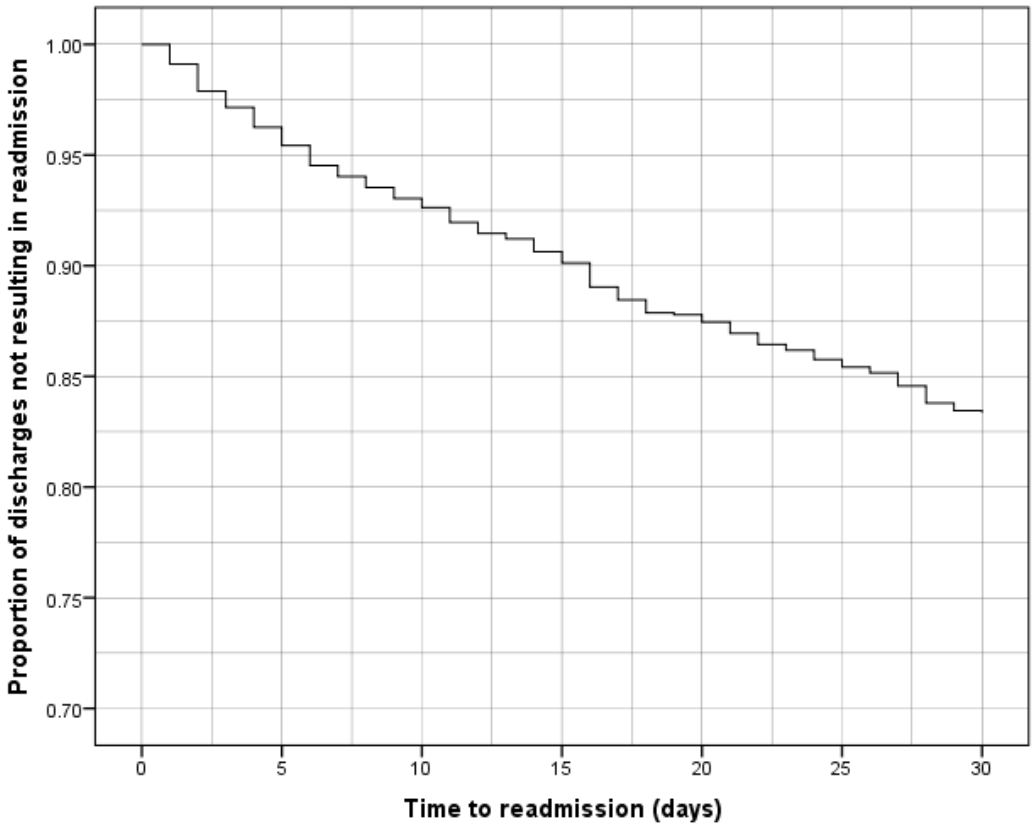


Figure 6.8: Cox regression for readmission behaviour at mean age and mean number of medicines prescribed

The Cox regression plot confirms that for a hypothetical 'average' case, readmission is most likely within the first week, with around one-third of patients who would be readmitted being readmitted within one week. Over half were readmitted within two weeks. Controlling for age, each additional medicine prescribed was associated with a seven per cent increase in readmission risk, and controlling for the number of medicines prescribed each ten additional years of age increased readmission risk by 10%; increases in either covariate resulted in reduced time to readmission.

6.4 Discussion

Appropriate intervention to prevent readmission is unlikely to depend on the characteristics of patient(s) at risk alone; whether readmission is avoidable and/or potential intervention is equally effective across the readmission interval must also be carefully considered. These analyses confirmed significant differences in readmission behaviour according to predictors of readmission from prescriptions: the predictors of readmission within 30 days identified by logistic regression analysis in Chapter 5, increasing number of medicines prescribed and increasing years of age, each reduced the time to readmission. Consistent with national trends, the greatest proportion of readmissions occurred within one week of discharge, accounting for around one-third of all readmissions (Friebel et al., 2018; Zerdevas & Dobson, 2008). This was observed consistently, albeit to differing extents, according to age and the number of medicines prescribed; reaffirming that it is necessary to apply any intervention to prevent readmissions early. Furthermore, evidence supports that early readmissions are more likely to be preventable (Clarke, 1990; Yam et al., 2010) Dobrzanska & Newell, 2006; Heggestad & Lilleeng, 2003; Sg2, 2011).

Increasing age is, in itself, unlikely to be the direct cause of older patients' increased risk of readmission. Increasing age is associated with increasing comorbidity and increased dependence on social support, each of which may increase readmission risk (Tan et al., 2013; Vest et al., 2010; Zerdevas & Dobson, 2008).

Increasing number of medicines prescribed may relate to readmission for a number of reasons, ranging from representing clinical complexity and/or comorbidity, the risk of adverse effects, to the consequence of non-adherence; as discussed in 3.2.2.2 b) MUR High Risk Medicines and 3.2.2.2 b) British National Formulary (BNF) chapter of prescribed medication, some medicines have an inherently greater risk of adverse effects which can result in hospitalisation than others. Introduction of new medicine(s) was found to be common practice on the MSSUs, and the average LOS indicated that patients were not

necessarily in hospital long enough for new medicine's effects to be fully assessed. The implications of this are that:

1- the intended effect may not be realised. In other words, the problem requiring medication may not be resolved while the patient is in hospital (or after discharge)
2- an adverse effect may develop after discharge.

It is probable that different interventions are effective in preventing early compared to late readmissions, and that patients involved in early and late readmissions have different characteristics; further research would be necessary to characterise avoidability and/or efficacy of potential intervention according to age and number of medicines prescribed in relation to the readmission interval.

6.5 Conclusion

The work presented in this chapter confirms:

Conclusion 3: Readmissions within 30 days of discharge home from an NHS medical short stay unit are most likely to occur within one week of discharge.

Conclusion 4: Time to readmission among adult patients discharged home from an NHS medical short stay unit decreases with increasing age and polypharmacy.

There were significant differences in readmission behaviour according to the number of medicines prescribed and years of age, which were identified as predictors of readmission within 30 days by logistic regression analysis in Chapter 5. Both covariates were positively associated with readmission, with increasing values decreasing the time to readmission. The greatest proportion of readmissions occurred within one week of discharge; supporting that it is necessary to identify those at risk of readmission and provide preventative intervention early. The implications of the findings of this study for practice are discussed in Chapter 7.

Chapter 7 Discussion

Having introduced the research topic in Chapter 1 and assessed the context and evidence base for the potential of predicting readmissions using routinely recorded information from discharge prescriptions in Chapter 2, prescription data were collected, processed and examined as described in Chapter 3 and Chapter 4 to characterise the cohort and determine the suitability of discharge prescription variables for inclusion in logistic regression analysis presented in Chapter 5, as well as enabling consideration of the potential generalisability of the resulting model. The age of the patient and the number of medicines prescribed on admission contributed significantly to the predictive model, with increases in each being independently associated with an increasing risk of readmission; survival analysis presented in Chapter 6 confirmed that readmissions tended to occur within one week, and increases in each covariate decreased the time to readmission. Analysis-specific discussion has been presented in the corresponding chapters (see 4.3 , 5.3 and 6.4); the purpose of this chapter is to discuss the implications for practice. The study objectives addressed in this chapter are:

Objective 7 To review the study results in the context of the relevant literature and policy, and

Objective 8 To provide recommendations for practice and future research.

7.1 Predicting readmission using prescription information

Two main models for predicting readmission risk based on prescription information available on admission and discharge were developed. Although the model based on discharge information had potential to be slightly more effective in predicting readmission than the model based on information available on admission, the difference was marginal and the confidence intervals for the models' c-statistics indicated that either may prove the most

effective. Furthermore, as described in 5.2.2 (Multiple logistic regression), the model based on information available on admission had the practical advantage of being more practically useful as it would enable earlier identification of those at risk and thus support the prompt delivery of preventative intervention (see also 5.2.2 Multiple logistic regression). The model based on information available on admission was selected as the main model on this basis.

The positive relationship between age and polypharmacy with readmission within 30 days and time to readmission is consistent with the findings of Gildersleeve and Cooper (2013) and, more broadly, in line with the common finding that older patients with more comorbidities are more likely to be readmitted (Gildersleeve & Cooper, 2013; Tan et al., 2013; Vest et al., 2010; Zerdevas & Dobson, 2008). Considering that more readmissions occurred within the first week among older patients/those prescribed more medicines compared to younger patients/those prescribed fewer medicines, and that such early readmissions are more likely to be preventable (Sg2, 2011); Zerdevas and Dobson (2008), it may be the case that readmissions among older patients and/or those prescribed more medicines are more likely to be preventable; further research would be necessary to confirm whether this is the case. Stepwise prescribing approaches, as set out in 4.2.3.4 , can result in prescriptions for patients being treated for some conditions being prescribed many medicines from the same BNF chapter to treat one condition. In such cases the number of medicines prescribed may represent disease severity rather than comorbidity. Considering the proportion of CV, CNS, and GI medicines prescribed, it seems these being the most commonly implicated in hospital prescribing errors (Lewis et al., 2009) probably reflects their prevalence. The fact that both age and number of medicines prescribed each contributed significantly to the multivariable models confirmed that age was not a proxy for polypharmacy and vice-versa: the independent, positive relationship between age and readmission, having accounted for the influence of the number of medicines prescribed, which is expected to reflect comorbidity to some extent (see also 3.2.2.2 b) Number of medicines prescribed); indicates that age could serve as a marker for increased frailty and dependency on social or community care, given that increasing age itself is unlikely to be a

cause of readmission. Tan et al. (2013) interpreted to their finding that patients with a *LACE* score [42] greater than 10 tended to be older as consistent with current understanding of burden and complexity of chronic disease in the elderly, with such patients being more likely to have limited resources and poor social support.

The final model demonstrated a 36% improvement in accuracy compared to indiscriminate intervention whilst correctly identifying 70% of patients who would be readmitted. It represents a dynamic, point-of-care tool to stratify readmission risk and support clinical decision-making based on information routinely recorded in the course of care, which could be automated and integrated into clinical systems to enable intuitive application by clinicians. The model could inform appropriate prioritisation by the clinical pharmacy team of potential intervention to prevent readmission by enabling those least likely to be readmitted to be effectively ruled-out, thereby facilitating the conservation of preventative effort for those most likely to require it, improving efficiency as well as clinical outcomes. This would be consistent with Eapen et al. (2013)'s recommendation of a risk-specific approach to deployment of intervention, targeting services to those who will benefit most, Gildersleeve and Cooper (2013)'s suggestion that efficiently identifying those at risk would enable intervention to be focussed in a more effective manner, and Singal et al. (2013)'s endorsement of targeted allocation of resource-intensive intervention to high-risk patients. The model could facilitate such prioritisation being undertaken early due to its suitability for use on admission, realising opportunity for clinicians to engage patients in relevant discussion to strengthen shared decision-making (as sanctioned by Eapen et al. (2013)), and thus enabling the provision of effective intervention during their hospital stay and/or through the transition home to prevent deterioration after discharge resulting in readmission. Further research would be necessary to evaluate whether the implementation of any such predictive model meaningfully impacts upon readmission rates.

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[42] increases with increasing length of stay, acuity of admission, comorbidity and emergency department visits in the previous 6 months (van Walraven et al., 2010a)

The model's discriminative capability was comparable to some of the models included in the literature review that were undertaken for the purpose of predicting readmission; these were described by their authors as exceeding, or comparable with, existing models (Rothman et al., 2013; Singal et al., 2013) (see also 0
Model performance). However, considered objectively, the model was disappointing and was not considered appropriate for further development. This occurred because variation in the outcome was not sufficiently explained by variation in routinely recorded prescription information. It may be possible to improve performance by re-specifying the model with more and/or better predictors (Garson, 2016); however, such re-specification is outside the scope of this study because all reliable information available using the Trust's electronic discharge prescriptions was considered. In other words, more and/or better predictors are not available among routinely collected data from discharge prescriptions. The model's performance was insufficient to warrant progression to implementation and evaluation of impact; which patients will be readmitted cannot be accurately predicted on the basis of routinely collected prescription data alone. Among studies included in the literature review that were undertaken for the purpose of predicting readmission, all but one of model involving application or further development of existing models performed better than those involving derivation of a new model; it was also noted that among studies involving application or development of existing models:

- more than half incorporated prior health care utilisation; indeed, Eapen et al. (2013) reported a c-statistic of 0.62 based on prior hospitalisation alone, and
- half incorporated variables reflecting socioeconomic status.

This indicates that despite prior utilisation being identified as an impractical choice of predictor for readmission (see also 3.2.2.2 b) Discharge variables), and reliable postcode/address data not being available among the Trust's routinely collected prescription data (see also 3.3.1 Reliability), these may each represent important factors in readmission that were not accounted for. This is consistent with the concepts: that:

- potentially important clinical, psychosocial and/or economic predictors are not captured in existing datasets (Eapen et al., 2013),
- behavioural and social variables are potentially not captured accurately in electronic medical records (Singal et al., 2013), and
- models for readmission do not often achieve a c-statistic greater than 0.70; the minority which incorporate functional status, overall health, social determinants of health or illness severity tend to achieve better performance than the majority which do not (Kansagara et al., 2011).

It was found that pharmacists have a tendency to prioritise their attention towards older patients who are prescribed more medicines, highlighting that clinical intuition may be as, if not more, effective than statistical modelling for predicting readmission. Given the similar performance of the final model developed in this study to that demonstrated by intern physicians predicting readmission among the elderly (Allaudeen et al., 2011a), the results of this study may simply provide assurance about the appropriateness of pharmacists' intuitive prioritisation.

7.1.1 Analysing existing data from NHS discharge prescriptions

Although an abundance of information was available, many of the prescription variables were found to be related to one another, as described in sections 4.3.6 4.3.7 and 5.2.1.1 Thorough exploratory analysis was necessary to properly assess which variables were suitable for use; cross-checking the independent variables with one another enabled relationships between them to be explored, and careful interpretation was required to ensure that variables included in the predictive model were suitably independent of one another to maintain the validity of the model. The quality of the data available for analysis was found to be relatively poor. In particular, prescription and pharmaceutical intervention data for discharge prescriptions that were not validated was unreliable or absent, as the pharmacy team solely populated some aspects. As described in 4.2.4.2 (Medicines

reconciliation), variability was also evident in pharmacists' interpretation of what confirming the medicines reconciled meant, and it is probable that such inter-practitioner variability affected other, potentially unmeasured, aspects of patient care. It was noted that 'home' was by far the most commonly selected discharge destination among discharges, and that despite there being codes for nursing homes (NHS and non-NHS), 'home' was often selected for addresses that were 24-hour care, indicating such coding was not applied consistently. Although variables such as age, date of admission, and date of discharge would be expected to be more reliable than other more subjective fields, one readmission was recorded as occurring after a patient's date of death; Rosen et al. (2013) described excluding such admissions as they represented data error. The Health & Social Care Information Centre's Specification for Emergency readmissions to hospital within 28 days of discharge stated the indicator had potential value to stimulate discussion and encourage local investigation to lead to improvements in data quality as well as quality of care (Health & Social Care Information Centre, 2013c); evidence from this project support that improvements in data quality are necessary. Data quality could be improved by information technology system design e.g. forcing functions and standardising terms, ideally within an electronic prescribing platform, as well as standardisation of practice, i.e. careful definition of clinical intervention in policy. In the meantime, it is important that those interpreting such data are aware of its limitations.

It was acknowledged in sections 3.2.2.1 a) and 3.2.2.5 a) that conducting the analysis on a large sample involved a risk of detecting small, albeit statistically significant, differences which may be of limited clinical relevance, and the results were consequently interpreted in the context of their potential clinical significance. Also due to the size of the sample, it is probable that a portion of discharges may not have met the necessary standard. Inadequate discharge could result in adverse outcomes such as readmission; yet, inadequacy would not necessarily be evident in the discharge prescription data. In addition to inadequacies at discharge which may not be reflected in the documentation, it is probable that prescribing errors affected around 7% of medication orders, or around half of patients admitted (Lewis

et al., 2009); prescriptions that were not validated and/or reconciled by a pharmacist would be particularly vulnerable to undetected prescribing errors. Some such errors were evident in the data, for example apparently look-alike-sound-alike drugs selected in place of a drug for the indication and dose intended, e.g. co-amilozide 625mg TDS for 3 days to treat pneumonia and cholecystitis (presumably intended/provided co-amoxiclav which was available on the ward; co-amilozide would have required dispensing by pharmacy). It is also possible that discharges could have involved other errors, for example, dispensing errors, which affect up to an estimated 2.7% of dispensed medicines (James et al., 2009). Furthermore, dispensing errors could originate on the ward as well as in the pharmacy department. It is not known whether any of the discharges were unplanned/against medical advice and it can be expected that this would affect the likelihood of adverse outcomes such as readmission (Hwang et al., 2003). Variation was evident in the way that discharge prescriptions were written, for example, a single medicine prescribed three times a day could be expressed as a single entry, or as three separate entries with specific reference to time of day (e.g. gabapentin capsules 300mg three times a day or gabapentin 300mg capsule in the morning, gabapentin 300mg capsule at lunchtime, and gabapentin 300mg capsule in the evening). Similarly, doses comprising multiple strengths could be written as a single entry stating the total dose, or as separate entries relating to the separate components (e.g. levothyroxine tablets 75 micrograms in the morning or levothyroxine 25 microgram tablet in the morning and levothyroxine 50 microgram tablet in the morning). Such discrepancies would reflect in the variables representing the number of medicines prescribed. Nonetheless, the data are the information contained in the discharge summaries that were provided to the patient, their GP and other primary care providers by secondary care at the care transition.

It is not known whether patients referred to their discharge summaries, how the discharge summaries were processed in primary care, or whether patients were under any admission avoidance schemes; whilst is it acknowledged that all of these may influence whether a patient is readmitted, such information is unlikely to be routinely available to the pharmacist

during the patient's episode of hospital care and it would therefore be inappropriate for it to be included in a predictive model designed for use by the clinical pharmacy team before discharge.

7.1.2 Appraisal of the study design

A prospective research design would have enabled potentially pertinent variables which were not routinely recorded to included, as well as enabling the data to be analysed in the clinical context that was lacking due to the retrospective design. However, this would have resulted in impractical findings given the aim was to use existing data to develop a predictive model in order to augment existing systems. Correlational[43] analysis under a postpositive paradigm enabled rigorous assessment of association between prescription variables and readmission without the ethical implications of an experimental design (see also 3.2.1 Strategy of enquiry). Utilisation of routinely recorded data:

- Ensured the practicality of the resulting model
    - Guidance for health care commissioners in the UK encourages the selection of tools for predictive risk based on routinely recorded data to enable future cases to be identified (Lewis et al., 2011)
    - The model produced would be suitable to incorporate into existing systems, avoiding the need to record additional data for its development or clinical application, thereby preventing any additional burden to practitioners
- Ensured representativeness (see also 3.3.2 Validity)
    - Loss to follow up was minimised and the study was not susceptible to response bias, thus maximising the data available for analysis
    - The data were a genuine representation of the information provided to primary care after discharge. Moons et al. (2015) highlighted that clinical

[43] Observational research to identify relationships between naturally occurring variables (Field, 2018)

predictors drawn from observational data can be stronger than for those derived from studies with a randomised design, possibly owing to the extensive exclusion criteria often applied in randomised controlled studies.

- Enabled the assessment of a range of relevant variables/potential confounders (see also 3.2.2.2 b) Independent variables)
- Prevented observer bias (see also 3.3.1 Reliability)
    - Consistency was ensured by mandatory fields and structured data collection
    - Systematic, objective analysis ensured rigour
- Was an economical use of resources
    - Use of existing resources enabled relatively fast data acquisition and prevented any additional burden to practitioners
    - Enabled a large sample to be used, supporting the inclusion of all relevant independent variables and minimising the risk of type II error (see also 3.2.2.1 b) Participants, 3.2.2.5 a) Exploratory analysis and 3.2.2.5 b) Model specification)

Selection of the Trust-wide medical short stay cohort ensured the model developed would be relevant to a substantial population. Furthermore, cluster sampling minimised the risk of overfitting (see also 3.2.2.1 a) Setting); data loss was also minimised by employing pairwise deletion in the exploratory analyses (see also 3.2.2.5 a) Missing data and 3.3.2.2 Internal validity).

Evidence-based selection of candidate predictor variables encouraged inclusion of relevant and exclusion of irrelevant variables (Garson, 2016), fostering meaningful results.

Defining the outcome and independent variables according to national policy and standards enabled comparison with similar studies, maximising the potential for generalisability (see also 3.3.2.3 External validity).

The correlational approach did not enable:

- Causality to be inferred

- The Trust was actively working towards a goal of reducing readmissions and it is possible that unaccounted for changes outside the scope of the study could have influenced the outcome (see also 3.3.2.2 Internal validity). Characteristics of discharge prescriptions overlapped with delivery of services such as whether medication required dispensing, the phase of the study, and/or the whether the patient was discharged at the weekend. Discharge prescriptions that were not validated could therefore be expected to have different characteristics than those that were. This complicates the interpretation of any association with readmission identified, because it could be due to unmeasured variation in the related characteristics, such as necessary social support not being available at the weekend, rather than the discharge prescription not being validated. Similarly, characteristics tended to exist in combinations, and services tended to be delivered in 'bundles'. Without randomisation and control it is difficult to quantify the contribution of individual characteristics and/or intervention to the risk of the outcome.
- Randomised control would not be ethically justifiable as it would only be possible by excluding patients from receiving standard services, as well as causing operational challenges. Furthermore, controlling for pharmaceutical intervention during the hospital stay would not control for pharmaceutical services accessed outside of the hospital system. This limitation is common in similar studies: Bradley et al. (2013) and Mather et al. (2014) each specifically identified being unable to account for whether patients accessed primary care services as a limitation of their studies, and no study included in the literature review that was undertaken for the purpose of predicting readmission described accounting for this. There was no reason to expect any particular group among the cohort in this study to be more likely to be affected, and the results were interpreted with consideration for this limitation.

- Potentially pertinent variables that were not routinely recorded to be captured, such as medication adherence, counselling/verbal instructions provided, and/or whether social support was required and/or provided. In common with Bradley et al. (2013) and Gildersleeve and Cooper (2013), it was considered undesirable to produce a model which required data collection or manipulation additional to that necessary to deliver clinical care because the goal of the study was to utilise routinely-recorded information to augment existing systems; inclusion of such variables would have required prospective collection of data and would not have met the study's objectives.

The pre-existing data had limitations in terms of (see also 3.3.2.1 Construct validity):

- Quality

  For example, address data collected were not ultimately suitable for analysis due to potential inaccuracy resulting from an information governance safeguard intended to prevent confidential patient information being inadvertently posted to a previous address. This meant that the address displayed on the EDMS represented the patient's address at the time of data collection which was not necessarily their address at the time of discharge; 24 hour care and postcode district data were consequently disregarded, and the intended evaluation of socioeconomic factors was not possible.

  The quality of prescribing was not assessed. As discussed in section 3.3.2 (Validity), it is probable that the discharge prescriptions contained discrepancies/errors and these would not necessarily be identified on data collection due to the lack of clinical context.

- Detail

  For example, as described in 3.2.2.2 b)(Number of medicines prescribed) and British National Formulary (BNF) chapter of prescribed medication, the indication for which the medicines were prescribed was not known, and this is a known risk factor for readmission.

- BNF chapter was considered a proxy for comorbidity.

It was not possible to calculate precise medication course lengths as often only the total was detailed, rather than the duration remaining.

- Context

For example, practitioner variability, i.e. what practitioners meant when they indicated a pharmaceutical service had been provided (prescription validation, medicines reconciliation, MCAs), appeared to vary, although this was not specifically assessed (see also 4.2.4 Pharmaceutical intervention).

The data represented entries on discharge prescriptions and not observed actions. For example, the prescription data were an accurate representation of the written information provided on discharge, but not necessarily of the medicines the patient was taking (see also 3.3.2.1 Construct validity). Adherence to the prescribed regimen was not assessed, and could be expected to influence readmission risk.

Care/services available/accessed in the observation period were not known and it is probable that this could influence readmission risk (see also 3.2.2.1 Sampling, 3.3.2.2 and Internal validity), and similarly the cause and appropriateness of readmission was not assessed; this is consistent with the policy for financial penalty.

These limitations are consistent with those recognised in many similar studies (Bradley et al., 2013; Eapen et al., 2013; Gildersleeve & Cooper, 2013; Haas et al., 2013; Lee, 2012; Singal et al., 2013), and the disadvantages were considered to be outweighed by the advantages of the intended approach; the limitations were acknowledged and the results were interpreted in context.

Consideration for whether readmissions were avoidable, their root cause, whether readmissions were medicines-related or potentially preventable by pharmaceutical intervention was outside the scope of this study; further work is necessary in this area to justify continued efforts to prevent readmission by pharmaceutical intervention.

The predictive model produced was based on a sample from one specialty in one NHS Trust, and would require external validation to determine its suitability for application outside of

the setting in which it was derived. Data quality was relatively poor; some potentially pertinent variables such as the patient's address, medicines reconciliation, medication communication/education/counselling and adherence were not captured reliably and therefore it was not possible to assess their association with readmission. Conducting the observational research project in a genuine clinical setting had challenges in common with other studies of pharmaceutical intervention e.g. Scullin et al. (2012), including the reliance on effective delivery of intervention and accurate recording of information by practitioners, as well as naturally-occurring comparison groups; the comparator in studies of intervention to reduce readmission is typically 'usual care', and this is poorly defined and highly variable between providers. In this study, considering that the study wards had daily pharmacist cover, it could be expected that patients who had been on the ward for more than one day would have had their prescription reviewed by a pharmacist, although this would not necessarily be reflected in the discharge prescription.

Nonetheless, readmission was modelled based on prescription information routinely available on admission. The model would rule-out many patients who would not be readmitted, as well as identifying some who would; thereby enabling preventative intervention to be targeted more efficiently to those likely to require it before discharge home. The model's performance was, however, insufficient to warrant progression through external validation to implementation and evaluation of impact.

7.2 Readmission as an outcome measure

As described in 1.3 (Readmission rate calculation) and 2.3.3.1 (Identifying readmissions), substantial inconsistency in the way readmission rates were calculated was apparent in the literature, including whether:

- Admission or discharge served as the denominator
    - Patients who died in hospital or the observation period were accounted for
    - Transfers to other hospitals; intermediate, nursing, residential or hospice care were excluded from the denominator

- Exclusion criteria were consistent with national policy (Monitor, 2016)
- Planned admissions within the observation period were included in the numerator
- Readmissions within a day or two of discharge were considered 'failed discharges' rather than readmissions
- Readmissions were also counted as index admissions
- Admissions to other hospitals/health systems were accounted for
- Readmissions were qualified by their cause e.g. limited to admissions for the same cause as the original admission

Indeed, in their *Service Kit* for reducing 30-day hospital readmissions Sg2 (2011) identified that emergency readmission rates among UK hospital trusts ranged from 2.9% to 9.1%, and this is consistent with a similar report produced by NHS Confederation (2011), yet, CHFT identified their readmission rate was in line with the national average at just over 10% at that time (Calderdale and Huddersfield NHS Foundation Trust, 2013a). It is perhaps telling that despite emergency readmission within 30 days of discharge first appearing in the December 2013 NHS Outcomes Framework (Health & Social Care Information Centre, 2013a), the 2011/12 data originally presented remain the most recent data published, and NHS Digital described the indicator as being on hold due to a methodology review at the conclusion of this study (NHS Digital, 2016).

7.2.1 Ease of measurement

Ease of measurement is a key appeal of readmission rate as an outcome measure (Benbassat & Taragin, 2000; Benbassat & Taragin, 2013; Health & Social Care Information Centre, 2014b); however, the rate of unnecessary or avoidable readmissions seems a much more appropriate gauge of care quality. Halfon et al. (2006) advocated readmission as a measure of hospital care quality on the condition that avoidability is accounted for. Concluding their analysis of potential avoidability of readmissions using administrative NHS data, highlighted the need to improve medical coding to rule out readmissions that are data artefacts or the result of choice. However, Lewis et al. (2011) highlighted that the

consequences of using predictions that may be subject to inaccuracies in available data should be balanced against the consequences of not using predictions, and that if a model contains systematic error, provided this remains consistent, then the predictions of the model remain so. Although avoidability is a vital factor in the validity of readmission as an indicator of care quality, it is subjective, and establishing it can be resource and labour intensive because factors that may be important in predicting avoidable readmission are not easily measured.

7.2.2 Avoidability

In their guide for commissioners *Choosing a predictive risk model in England*, Lewis et al. (2011) highlighted that predictive models should be useful for predicting events meeting four criteria:

- Undesirable to the patient - prevention improves health status of quality of life
- Significant to the health service - preventative intervention needs to at least break even accounting for its success rate and cost
- Preventable – preventative efforts should be conserved for preventable events
- Routinely recorded – to enable future cases to be identified from administrative data

All-cause 30 day readmissions do not necessarily meet the third criteria because only a portion of readmissions are preventable, and only a portion of these may be preventable by the actions of the hospital.

7.2.3 Competing outcome measures

Laudicella et al. (2012) pointed out that conventional calculation methods can underestimate relative readmission rates of hospitals with lower survival rates, resulting in an upward bias in their relative ranking due to sample selection bias. The authors proposed a bivariate sample selection model for calculating readmission rates, and demonstrated that accounting for the bias inherent in the conventional univariate calculation not only resulted in material change in hospital performance rankings, but also clarified that much of the annual rise in readmission rate was due to improved performance in terms of mortality. The

authors of the *HOMER* trial suggested that the counterintuitive increase in readmissions among elderly patients provided domiciliary medication review provided by community pharmacists could be attributable to a combination of increased help-seeking behaviour and increased survival in the cohort, although the difference in mortality was not significant (Holland et al., 2005). Concluding their meta-review of meta-analyses of clinical interventions' effect on readmissions, Benbassat and Taragin (2013) stated that provided future research confirms efforts to reduce readmissions do not adversely affect other patient outcomes such as mortality, functional capacity and quality of life, hospital readmission rate may be considered as a publicly reported quality indicator of community care for patients with heart diseases and bronchial asthma. Rothman et al. (2013) interpreted the decline in readmissions among patients with a *Rothman Index* (representing patient condition) value below 30 as due to increased mortality among those patients whose condition was poorest. In this study the view of Keenan et al. (2008), that failure to exclude those who died during the observation period from the analyses would be effectively treating death as a non-event, was adopted; consequently the readmission rate denominator comprised those who survived for 30 days after discharge.

7.2.4 Appropriateness as a measure of care quality

Concerning readmission risk being considered by some to encompass quality of care, Curry et al. (2005) expressed that such nebulous elements are not easily incorporated into quantitative models. Indeed, there is evidence that hospital performance inferred by readmission rates can be misleading (Gorodeski, Starling, & Blackstone, 2010; Stefan et al., 2013). Stefan et al. (2013) identified that hospitals with higher performance in meeting care quality targets did not generally have fewer readmissions, and in areas where statistically significant reductions were identified, the differences were too small to be of any clinical significance. Halfon et al. (2006) raised that inadequate risk-adjustment of readmission rates could lead to inappropriate conclusions about hospitals, and Kansagara et al. (2011) expressed concern that the risk-standardised readmission rates against which

hospitals' performance was being gauged were based on administrative models with relatively poor discriminative ability. The authors of many studies of readmission characterisation and/or reduction have expressed that readmission may not be an appropriate indicator of care quality (Cotter et al., 2012; Lindquist & Baker, 2011). The findings that whether standard components of the discharge process were delivered or not did not affect the likelihood of readmission (Hansen et al., 2011), and that hospitals' overall readmission rates are not indicative of the proportion that are avoidable (van Walraven et al., 2011a) support that readmission rate may not be an effective indicator of hospital care quality. Joynt and Jha (2012) proposed a number of reasons for considering readmission problematic as an outcome measure for hospital performance, including:

- much variation being explained by patient- and community-level factors,
- preventability and accountability thereof,
- interaction with mortality rates, and/or accessibility of care.

Indeed, Clarke (2004) raised a similar argument years prior, proposing that "we must give up measuring unsatisfactory performance indicators simply because they are available and, instead, concentrate harder on allowing for known valid measures of the quality of care to be collected as a matter of routine". Joynt and Jha (2012) concluded that these reasons may explain why despite persistent efforts to understand and reduce readmissions, readmission rates have remained relatively stable. Recent, national-scale readmission research undertaken in the UK supports that although numbers have increased, rates remain relatively stable (Friebel et al., 2018; Morris, 2018). Irrespective of the validity of readmission as a measure of care quality, it is in routine use and forms the basis of an NHS performance indicator with policy for non-payment. As stated by Blunt et al. (2014): "these are the data that are currently being used in the NHS to make decisions on whether readmissions are eligible for payment or not". Certainly, preventable readmissions should be prevented, and thorough characterisation of readmission enables better accuracy of risk-adjustment which is essential to minimise inappropriate application of penalty.

7.2.5 Responsibility and financial penalty

NHS Confederation (2011) proposed a number of exclusions to original the policy for non-payment (Department of Health, 2011) including cancer patients, patients admitted for end of life care, and children under 17, to minimise penalties for appropriate readmissions.

Consistent with the findings of Jencks et al. (2009), Halfon et al. (2006) identified that on average, around a fifth (ranging from zero to 88%) of potentially preventable readmissions among Swiss acute care hospitals were to a different hospital than the index admission. Whilst it is accepted that the UK health system could differ too greatly from the US or Swiss system to generalise the estimates, it must also be considered that the variation in proportion of readmissions presenting at a different hospital than the index admission will depend on a number of factors, and some of these will be relevant to the NHS. Consequently, the financial penalty of withholding payment for readmissions may be misdirected. Furthermore, it seems doubtful that secondary care's influence extends as far as 30 days. The results of this study support that the greatest proportion of readmissions occur within one week; and there is evidence that readmissions with a shorter interval are more readily acceptable as related to the index admission and/or avoidable (Clarke, 1990). Whilst increased time to rehospitalisation has been achieved by pharmacist intervention (Sanchez, Douglass, & Mancuso, 2015), studies which have investigated the effect of intervention on the time to readmission as well as the likelihood of readmission within 30 days have shown that reductions achieved at 14 days were not sustained at 30 days (Kilcup, Schultz, Carlson, & Wilson, 2013), and 30 days were not sustained to 60 days (composite outcome with ED visits) (Koehler et al., 2009). It must therefore be considered that studies identifying reductions in 30-day readmissions may represent delay to, rather than prevention of, readmission, and whether this represents an improvement.

7.2.6 The role of primary care and community services

The Indicator Quality Statement for emergency readmission within 30 days of discharge acknowledged that social care, as well as healthcare, is a major determinant of how well a

patient recovers following illness or injury, and referred to a number of trade-offs, including:

- factors outside the control of hospitals and differences in case-mix contributing to variation in readmission rates
- variation in the patterns of care e.g. transfers to other providers prior to discharge possibly affecting organisations' readmission rates
- variation in length of stay possibly leading to variation in the number of complications occurring in hospital or in the community
- variation in coding possibly affecting readmission rates
- discharges against medical advice possibly preceding readmission, and crucially,
- that readmissions may reflect the level of primary and community care resources available to manage care outside of hospital (Health & Social Care Information Centre, 2014b).

In recent years the readmission rate for complications of hospital care have remained stable; meanwhile, readmission rates for pressure sores and pneumonia more than doubled between 2010/11 and 2016/17 (Morris, 2018). Patients who utilise community nursing services have been identified as having an increased risk of readmission (Caplan, Brown, Croker, & Doolan, 1998; Williams & Fitton, 1988). Given that around a quarter of medical patients experience adverse events in the 30 days after discharge, and only 17% of these are readmitted (Forster et al., 2004), the majority of post-discharge problems must be resolved in the community; yet, readmission rates do not reflect health care utilisation outside of hospital. Marcantonio et al. (1999) proposed that readmission risk was influenced by the interaction between baseline patient vulnerability and key factors during hospitalisation that predispose to readmission; the influence of primary care services is another dimension to this complex interaction. It must be considered that readmissions for some long-term conditions have in fact reduced (Zerdevas & Dobson, 2008), and that this could be attributable to more simple cases being managed as day cases or in the community as time goes on, skewing the inpatient data to include more complex cases with

higher level of underlying readmission risk. NHS Confederation (2011) pointed out that encouraging more care to be undertaken in the community necessitates some risk that patients may need to return to hospital. Yam et al. (2010) categorised many readmissions due to relapse of the original illness as avoidable on the basis that they could have been managed in the community, providing yet more support that community services are an important factor in managing readmissions.

7.3 Pharmaceutical intervention

Studies evaluating pharmacists' activities tended to report errors, discrepancies, potential adverse drug events; however, it has been expressed that medicines-specific outcomes should not be considered in isolation from other factors that may influence the overall success of intervention, as focussing on a narrow range of outcome measures may lead to incomplete or misleading conclusions (Ryan et al., 2014). Kaboli, Hoth, McClimon, and Schnipper (2006) discussed the inconsistency in outcome measures among studies of pharmacist intervention, and suggested that process measures that are frequently used may not be related to outcomes, whereas health care utilisation can be easily quantified and is generalisable. Lewis et al. (2009) identified by systematic review of hospital prescribing error studies that studies tended to be process-based rather than outcome-based, and that outcome-based studies had much lower error rates: it was proposed this was because although a possibility, harm is not an inevitable outcome of prescribing error. The same sentiment applies to other outcome measures that may be intermediary to (re)admission such as ADRs, non-adherence, discrepancies etc.: although a potential consequence, it is relatively rare for such outcomes to result in (re)admission and consequently it is difficult to demonstrate readmission reduction for interventions which are effective in reducing these. Krska et al. (2007) proposed that number of admissions was not sensitive enough as an outcome measure for pharmacist intervention, and given that readmissions are a subset of admissions, it is unsurprising that a difference in readmissions was not detected in this study. It seems that only a small proportion of readmissions may be medicines-related and

preventable; consequently, even if pharmaceutical intervention were effective in preventing all preventable medicines-related readmissions, the reduction in overall readmission rate would be minimal. Figure 7.1 demonstrates that avoidable medication-related readmissions represent only a subset of health care utilisation:

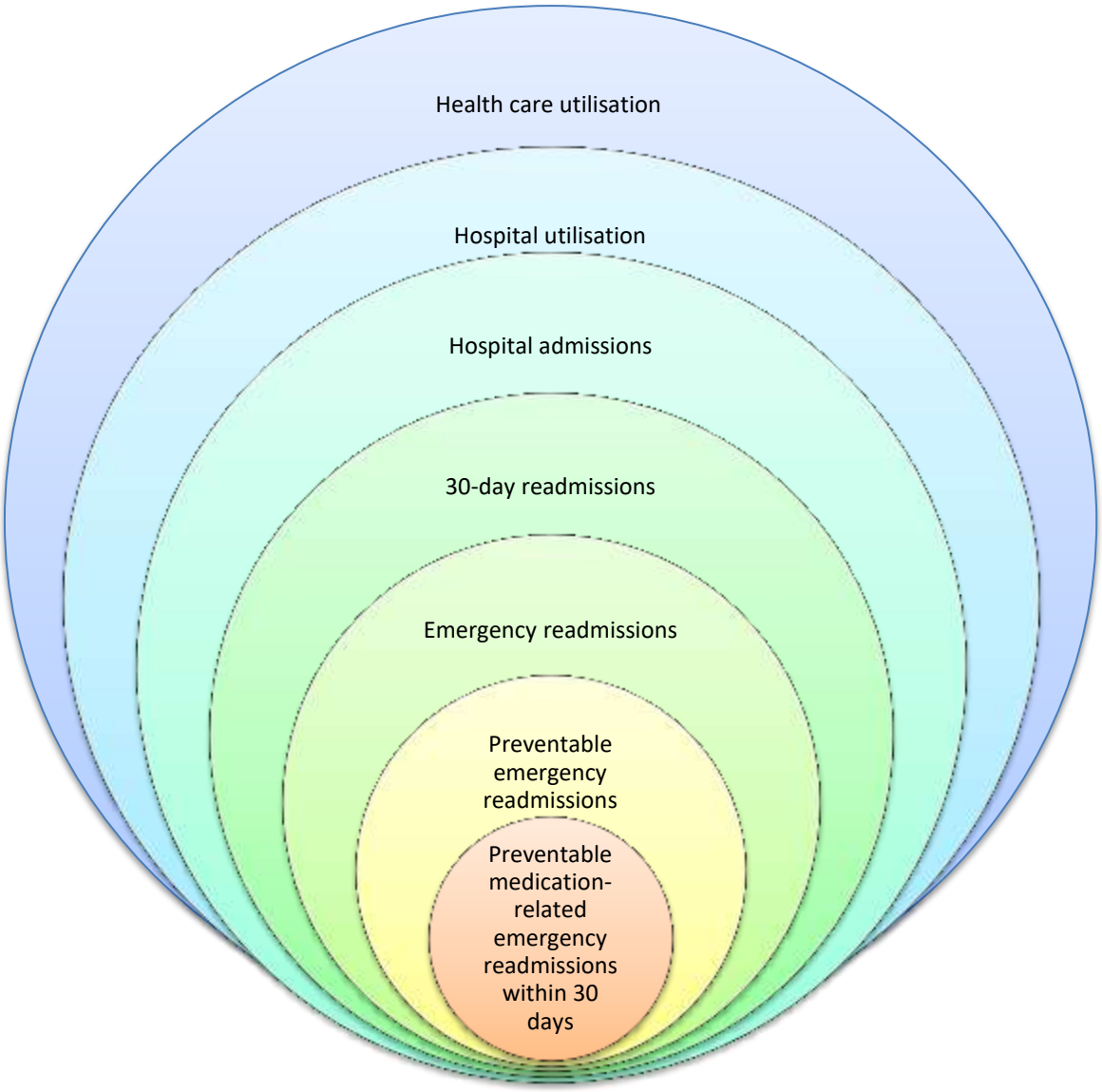

Figure 7.1: Avoidable medication-related readmissions in the context of hospital utilisation

Coleman et al. (2004) demonstrated that a multifactorial intervention including medicines reconciliation and counselling spanning the care transition, designed to empower patients to take an active role in managing their health, was effective in reducing readmissions well beyond 30 days in a select cohort of elderly patients. The authors proposed that due to the

sustained benefit, such interventions could be suitable to offer to patients who had not yet been admitted. This sentiment seems compatible with community pharmacists empowering patients to optimise their medicines use by medicines use reviews, for example. Indeed, it has been demonstrated that patients who received a consultation with a community pharmacist having been referred on discharge from hospital were significantly less likely to be readmitted (Nazar et al., 2016).

7.4 Conclusion

It was not possible to accurately predict which patients would be readmitted using routinely collected prescription information, although it was possible to rule-out those who were least likely to be readmitted, thereby contributing to appropriate prioritisation and conservation of preventative efforts for patients most likely to require them. The patient's age and the number of medicines they were prescribed each contributed significantly to the predictive models developed, confirming that they explained different variance in the outcome: increases in either were associated with increased risk of, and decreased time to, readmission. Overall, the performance of the final model was disappointing and it was not suitable for progression through implementation and evaluation of impact. The model was potentially no more effective than clinical intuition. The model was developed with the intention of informing clinical decision-making and not replacing clinical judgement. Comparing prescriptions validated whilst pharmacist validation was optional with those validated after it became mandatory demonstrated that pharmacists' efforts were focussed towards prescriptions containing more medicines which tended to belong to older patients prior to mandating validation. If pharmacist validation of discharge prescriptions had the intended effect of preventing errors, discrepancies, adverse drug reactions and medication-related problems, and consequently prevented readmissions that could otherwise have resulted, then it seems pharmacists' efforts were probably appropriately prioritised in the first place.

Conclusion 1: The likelihood of readmission within 30 days of discharge home from an NHS medical short stay unit can be estimated using routinely recorded prescription information; however, the accuracy of the resulting predictions is relatively poor and may not outperform those based on clinical intuition.

Conclusion 2: Likelihood of readmission within 30 days of discharge home from an NHS medical short stay unit increases with increasing age and polypharmacy

Conclusion 3: Readmissions within 30 days of discharge home from an NHS medical short stay unit are most likely to occur within one week of discharge.

Conclusion 4: Time to readmission among adult patients discharged home from an NHS medical short stay unit decreases with increasing age and polypharmacy.

Conclusion 5: It is unlikely that readmission as defined under PbR represents an appropriate outcome measure for pharmaceutical intervention.

7.4.2 Recommendations

Recommendation 1: Organisations considering implementing predictive models should ensure appropriate validation is undertaken to confirm generalisability to the intended population, and that the impact of any such implementation is effectively evaluated.

Recommendation 2: The positive relationship between readmission risk with age and polypharmacy among NHS medical short stay patients should be recognised by clinicians in order that, when appropriate, it may be inform their clinical decision-making

Recommendation 3: Further research should be undertaken to explore the extent to which adverse outcomes such as readmission can be predicted on the basis of clinical intuition

Recommendation 4: Patients who are likely to be readmitted should be identified promptly, ideally early during their hospital stay and certainly before discharge home

Recommendation 5: The NHS should invest in improving the quality of routinely-recorded data to support effective clinical care as well as service evaluation, improvement and research

Recommendation 6: The NHS should develop systems to monitor adverse outcomes such as readmission due to avoidable problems with medication; such systems could provide valuable data for future research and inform improvements in clinical practice

Recommendation 7: Further research is required to determine appropriate outcome measures for pharmaceutical intervention that foster genuine, sustainable improvements in quality

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Appendices

Appendix A Author's Relevant Publications

Upton, S., Culshaw, M., & Stephenson, J. (2014). An observational study to identify factors associated with hospital readmission and to evaluate the impact of mandating pharmacist validation of discharge prescriptions on readmission rate. International Journal of Pharmacy Practice, 22(Suppl. 2), 45-46. doi:10.1111/ijpp.12146

Upton, S. M., & Culshaw, M. S. (2014). The impact of pharmacist validation of discharge prescriptions on readmission. Poster competition winner presented at the Primary Care Pharmacists' Association Annual Conference, London.

Upton, S., & Culshaw, M. (2014, 8th-11th April). An investigation into the role of the pharmacy team in reducing avoidable hospital readmissions. Paper presented at the University of Huddersfield Research Festival, Huddersfield.

Upton, S., & Culshaw, M. (2014, 24th-25th September). The influence of pharmacist validation of discharge prescriptions on readmission. Paper presented at the NHS Research & Development North West Conference: Let's Talk Research, Bolton.

Upton, S., & Culshaw, M. (2014, 21st-22nd November). Compliance aids, readmission, and pharmacist validation of discharge prescriptions. Paper presented at the United Kingdom Clinical Pharmacy Association Autumn Symposium, Nottingham.

Upton, S., Culshaw, M., & Stephenson, J. (2015, 15th-17th May 2015). The role of the pharmacy team in reducing readmissions: general medical patients eligible for NMS not found to be at increased risk of readmission. Paper presented at the Guild of Healthcare Pharmacists and United Kingdom Clinical Pharmacy Association11th Joint National Conference, Leeds.

Upton, S., Culshaw, M. A., Culshaw, M. S., & Stephenson, J. (2015). A preliminary study identifying prescription factors associated with readmission. International Journal of Pharmacy Practice, 23 (Suppl. 1), 42.

Appendix B Electronic Discharge Medication Summary

DISCHARGE MEDICATION SUMMARY

Medicines Reconciled:

Medication	Dose	Direction	Status	Reason	Cont	Course	From Ward	From Pharm

STOPPED MEDICATION

Medication	Reason

APPROVAL

	Name	Date		Initials	Date		Initials	Date
Clinical Check/Approved By			Dispensed By			Checked By		