Risk Assessment of Patients in an Acute Trust as a Means of Directing a Clinical Pharmacy Service

by

Emma Lucy Suggett

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Contents

Abstract

The aim of this research was to develop a new work model for hospital pharmacists based on risk assessment of patients using an electronic prescribing and administration system (EPMA).

Systematic review was performed to identify risk factors associated with clinical pharmacy intervention. Those factors which can be measured by the EPMA in a UK teaching hospital were subsequently identified. Data was extracted from the EPMA relating to risks in intervention recipients on medical and surgical wards and those patients present concurrently.

Univariable and multivariable analysis was performed and a risk score calculated. Receiver operating curves (ROCs) determined predictability of the score.

Risk factors for pharmacist intervention were: age, female gender, patient compliance, unavailable stock, prescription of warfarin, number of allergies, comorbidities, regular prescriptions, anti-epileptics, thrombolytics/anticoagulants, central nervous system agents, and chemotherapy / immunosuppressants. The area under the ROC for the risk score was 0.61.

Multiple factors were significantly and independently associated, with an increased intervention rate. However, it was not possible to generate a useful model for directing clinical pharmacy services. Inverse relationships were demonstrated between some risk factors usually associated with problems with medicines use.

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Background

In the United Kingdom (UK), the general public's perception of the role of the pharmacist is most frequently manifested through their interaction with their local community pharmacist found in the high street. A general concept of the "chemist", who supplies medicines against prescriptions from general practitioners and who at times, may advise on the treatment of minor ailments, may be the extent of the layman's understanding of a pharmacist's role. However, pharmacists are extensively trained healthcare professionals who perform many different highly skilled tasks not only in a community environment, but in research, industry, educational and hospital settings. To practice as a pharmacist, candidates must obtain a four-year masters degree in pharmacy (MPharm) and in addition, spend 6 to 12 months working in a patient facing setting working towards performance standards set out by the regulatory body, the General Pharmaceutical Council (GPhC). In addition, successful completion of a pre-registration examination is required before candidates may be entered onto the GPhC register as a pharmacist. This tight regulation and ongoing requirement for continuing professional development (CPD) post registration is intended to ensure that all pharmacists deliver a high quality service to safeguard the public.

Whatever the chosen practice setting for a pharmacist, the core aim, either directly or indirectly, is to ensure that patients receive the right medicine, to the right patient, at the right dose, by the right route at the right time (a traditional concept termed The Five "Rights" of Medicines Administration[1,2]). Whether it be through research to develop effective medication education for pharmacists or student pharmacists or through the

widely recognised process of prescription checking, pharmacists have medication efficacy and patient safety at the very heart of their practice.

In the hospital setting, the core pharmacist role is involved with confirming the appropriateness of medicines prescribed for in- and outpatients. In the UK, hospital pharmacists visit inpatient wards and confirm that any patient medication is appropriate, ensuring that all relevant monitoring occurs and amendments to prescriptions have been made in response to any clinical changes in the patient. This form of pharmacy is most often referred to as “clinical pharmacy” and those pharmacists practicing in this way as "clinical pharmacists”.

Hospital pharmacists are unique amongst other healthcare workers in that they are rarely referred patients for review. Physiotherapists, speech and language and occupational therapists are frequently referred patients by either medical or nursing staff. In effect, patients are triaged prior to referral with respect to services provided by the professions allied to medicine (AHPs). For most clinical pharmacists practising in the UK’s National Health Service (NHS) however, local policy requires that they review all inpatient charts daily on the wards, which they are allocated. However, in the UK there is no national guidance which dictates how frequently pharmacists must review inpatient medication charts. In addition, with a shortage of doctors and nurses in the NHS, the role of the clinical pharmacist has been expanding. Many pharmacists are now non-medical prescribers and some are being trained as advanced clinical practitioners (ACPs) capable of clinical assessment of patients and diagnosis. Consequently, in recent years, owing to increasing bed numbers and rising expectations in terms of practice with no corresponding increase in resources, hospital pharmacists have sought to find ways of

becoming more efficient in their way of working while still retaining the quality of service they have been bound to deliver by their professional responsibilities.

The aim of the present research is to develop a new work model for the review of inpatients by hospital clinical pharmacists based on risk assessment of patients generated by an electronic prescribing system. The intention is to identify evidence-based risk factors for review of inpatient medication and use these risk factors to develop a form of clinical pharmacist triage, directing pharmaceutical expertise to those who are most in need.

CHAPTER 1

INTRODUCTION

1. Introduction

1.1. History of Clinical Pharmacy

1.1.1. Background

During the past three decades there has been growing evidence that the safe, effective and efficient management of medicines improves outcomes for patients by delivering high quality patient centred care[3–5]. In most hospitals in the United Kingdom (UK), Pharmacy Services are responsible for delivering medicines management through a variety of initiatives involving the procurement, supply and use of medicines.

Since the 1970s Pharmacists have been responsible for the delivery of most hospital pharmaceutical services. During the 1960s much of the role of the hospital pharmacist was involved in extemporaneous preparation and supply of pharmaceutical products. A pharmacist could rarely be seen conversing with patient and the majority of hospital pharmacies were located in hospital basements well away from key services and the multidisciplinary team.

Figure 1.1 shows some of the activities and environment in the Pharmacy Department at Queen Elizabeth Hospital in Birmingham, UK, in the 1960s. The pictures show an emphasis on compounding, aseptic preparation and wide-scale manufacture of sterile fluids.

Figure 1.1 Queen Elizabeth Hospital Birmingham (UK) in the 1960s

However in the 1970s and 1980s the role of the hospital pharmacist in the UK expanded to meet the increasing requirement for quality and productivity in the hospital setting. The expansion of large scale manufacturing of medicines by pharmaceutical companies quashed the necessity for the relatively small-scale production by local hospital pharmacies. Hospital pharmacists began to expand their role.

Hospital pharmacists are no longer simply the providers of a medicines supply function but are responsible for many aspects of pharmaceutical care requiring detailed knowledge of medicines, medicines action and use. The development of pharmacists' clinical expertise over the past three decades, supported by the introduction of new postgraduate qualifications, has improved the quality of these services. Examples include ward based pharmacy, therapeutic drug monitoring (TDM), pharmacist prescribing, support to pre-admission clinics, medicines reconciliation, antimicrobial stewardship, management of electronic prescribing systems, governance of medicines and advanced clinical practitioner roles (ACPs). Almost all of these initiatives require a degree of clinical expertise acquired currently in a post graduate role and most are termed under the umbrella of "Clinical Pharmacy" as opposed to the more traditional function of "supply" which remains a core function of most Pharmacy Departments.

In 2008 the Department of Health issued a White Paper[6], which recognised the significance of clinical pharmacist expertise in improving patient services, this was further reinforced in 2010[7] when their role in refining treatment through medicines optimisation was supported. Despite government support, the benefits of clinical pharmacy have been notoriously difficult to demonstrate and high quality research difficult to find. Research is

complex mainly owing to the fact that almost all of the functions performed by clinical pharmacists overlap with responsibilities of other healthcare professionals and in most cases, the pharmacists role is preventative in nature which makes the measurement of outcomes difficult. There has however, been some work which has demonstrated the worth of clinical pharmacy through a reduction in adverse drug events (ADEs), reduction in the length of hospital stay, reduction in readmission rates and lower overall treatment costs[3–5].

1.1.2. What is Clinical Pharmacy?

Clinical Pharmacy is defined as a health science discipline in which pharmacists provide patient care that optimises medication therapy and promotes health, wellness and disease prevention[8]. In practice, pharmacists are by definition "clinicians" and as such Clinical Pharmacy includes all services performed by pharmacists practising in hospitals, community pharmacies, nursing homes and any other setting where medicines are prescribed and administered.

Clinical pharmacy services are a combination of medicines management (which includes how medicines are procured and supplied) and pharmaceutical care. Pharmaceutical Care defined by Hepler and Strand[9] as "the responsible provision of drug therapy for the purpose of achieving outcomes which improve the patient's quality of life", put the patient at the heart of care through the development and implementation of pharmaceutical care involving both the patient and the multidisciplinary team. It is this patient centred approach, which makes clinical pharmacy differ from the discipline of

"pharmacy" which simply embraces the knowledge of synthesis, chemistry and preparation of drugs. Clinical pharmacy is directed to the needs of patients with regards to medicines use, methods of administration, adverse drug effects, patterns of use and patient outcomes.

1.1.3. Ward- Based Clinical Pharmacy Services

In the United Kingdom (UK) during the 1960s and 70s, advances in the numbers and range of medicines available and an increasing awareness of adverse drug events led to the use of ward-based prescriptions in the hospital setting[10]. This in turn led to pharmacists expanding their more traditional roles of dispensing and manufacturing by leaving the pharmacy department to practice ward based pharmacy.

Through direct contact with both the patient and the multidisciplinary team in the ward environment, clinical pharmacists have been able to demonstrate their knowledge and skills concerning medicines and prove their worth in the hospital setting. Most ward-based pharmacy services generally include a clinical pharmacy review for every patient on a ward and aim to do this daily. The review generally consists of confirming the appropriateness of all the medicines prescribed for the patient starting with medicines reconciliation. Medicines reconciliation on admission includes confirming, comprehensively, the patient's medicines prior to admission and reconciling them with those prescribed as an inpatient. Acting in an advisory role, pharmacists will then communicate with prescribers and nursing staff regarding any inaccuracies and make recommendations for the administration and supply of drugs, future drug treatment and

monitoring. Often a pharmaceutical care plan is developed for those patients with complex drug needs or monitoring to ensure appropriate follow up and communication with other pharmacy staff. Any intervention into a patient's treatment is recorded by the pharmacist as a clinical pharmacy intervention.

Ward based pharmacy provided the first evidence of pharmacists' clinical expertise, in the hospital setting. In 1986 the Nuffield Report[11] detailed the significance of clinical pharmacy. Today, it is the ward based pharmacy service which is the most common form of clinical pharmacy services.

Although hospitals in the UK have different operational systems in place for delivery of ward based clinical pharmacy services, almost all of them now deliver (or aspire to deliver) the following:

- Medicines Reconciliation as per National Institute of Clinical Excellence (NICE) guidance[12] which states that pharmacists should be involved with medicines reconciliation as soon as possible after admission
- Clinical pharmacist review, validation and sign off of medications
- An advisory role to prescribers and nursing staff
- Recording of pharmacist interventions
- Counselling of patients on new drugs or those with Committee on Safety of Medicines (CSM) or National Patient Safety Agency (NPSA) warnings
- Supply of the correct product, initiated by a member of the pharmacy team

These however, are considered core services and over time, clinical pharmacists have expanded their role owing to a demand for their expertise.

An increase in patient numbers coupled with an aging population, the increasing public demand for improved access to medicines, demand for improvements in quality and efficacy without a corresponding increase in pharmacy resources, have all put an increasing strain on clinical pharmacists. The pharmacist role, like many other healthcare professional roles, has developed in response to these pressures. Pharmacist prescribing has enabled pharmacists to work autonomously to "fine tune" patients' drug regimens, prescribe adjunctive treatments and to prescribe against agreed protocols. Counselling of patients at the bedside is routine. Despite these additional responsibilities, clinical pharmacists in most National Health Service (NHS) Trusts in the UK perform a daily pharmaceutical review on more patients than ever before, yet at the same time must retain and ensure the safety and quality of their review. It is not unusual for pharmacists to be responsible for the pharmaceutical care of more than a hundred patients daily as ward sizes increase in an attempt to improve efficiency.

1.1.4. Advances in Technology

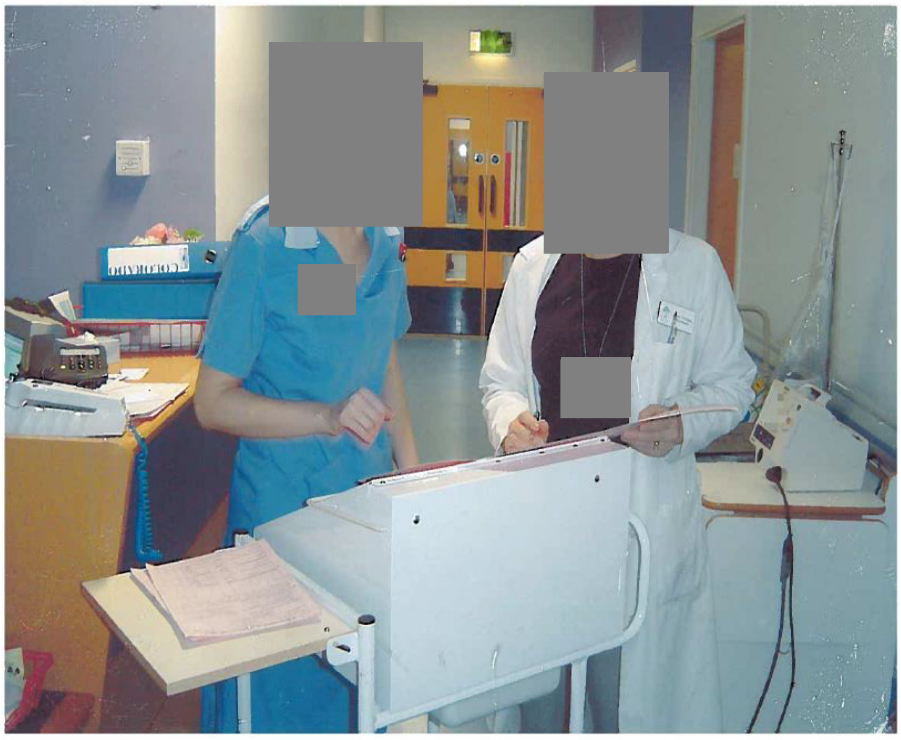
The number of admissions to secondary care has increased year on year over the last three decades, in the 5 years preceding 2013 alone, admissions to hospitals in England increased by 13 percent to on average 41,500 patients per day (data from the Health and Social Care Information Centre (HSCIC)). Consequently, coupled with rising patient expectations, and the increasing complexity of drug treatments and administration regimens, demands on clinical pharmacists have increased. However, despite this, pharmacists have managed to retain patient safety at the heart of their work even when

faced with additional necessity for documentation and expanded roles. It is possible that many of the operational changes, which have enabled these improvements, have been due to the advances in technology.

In the early 1990s ward based pharmacy was performed solely by reviewing paper prescription charts at the patient's bedside and reviewing the laboratory results at the nurse's station for any patients deemed to be at high risk of an ADE dependent on their test results.

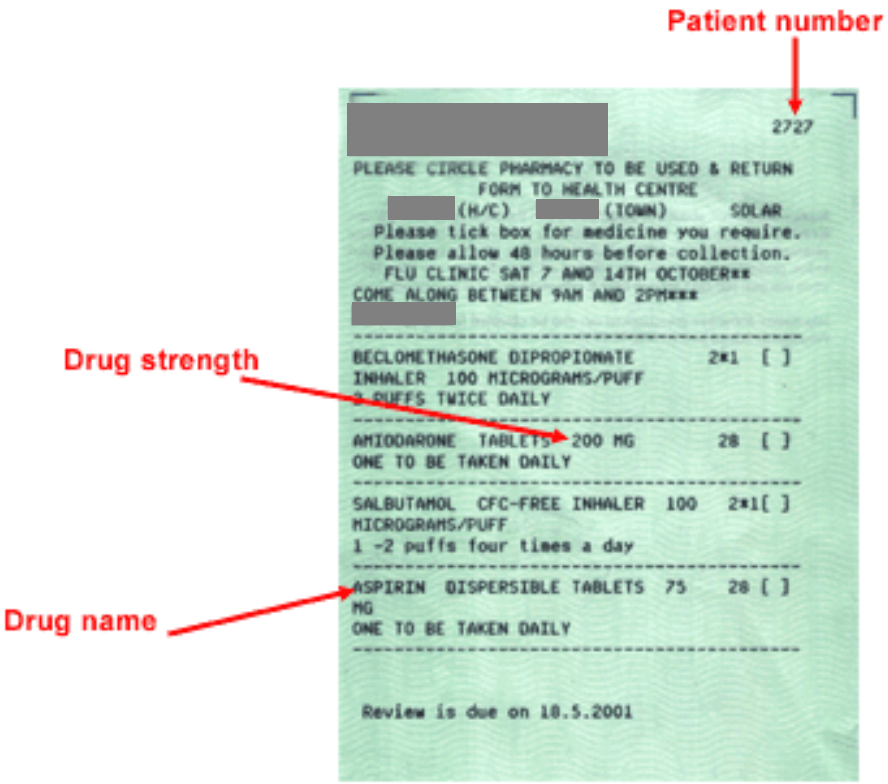
The use of paper documentation was inefficient as it was a time consuming process. Sometimes clinical notes would be difficult to locate or be in use by another member of the multidisciplinary team. If a patient was having a procedure or in theatre, then neither the patient's prescription chart or notes, would be available to the pharmacist.

Figure 1.2 Pharmacist review of a paper prescription chart in the ward environment in the 1990s



In the early 1990s, despite there being concerns regarding communication across the primary/secondary care interface, medicines reconciliation was not carried out as the norm. At this time, even FP10 prescriptions issued by general practitioners were not computer generated and did not include a tear off slip summarising medications (Figure 1.3) now used widely by clinical pharmacists to inform them of the patient's drug history when performing medicines reconciliation.

Figure 1.3 Repeat Prescription slip from FP10



As a result, communication of medicines related issues at the primary/secondary care interface was poor[13,14]. Between 1995 and 2000[15], prescribing in the community became solely electronic but despite widespread concerns, there was no corresponding move to electronic prescribing in the hospital setting.

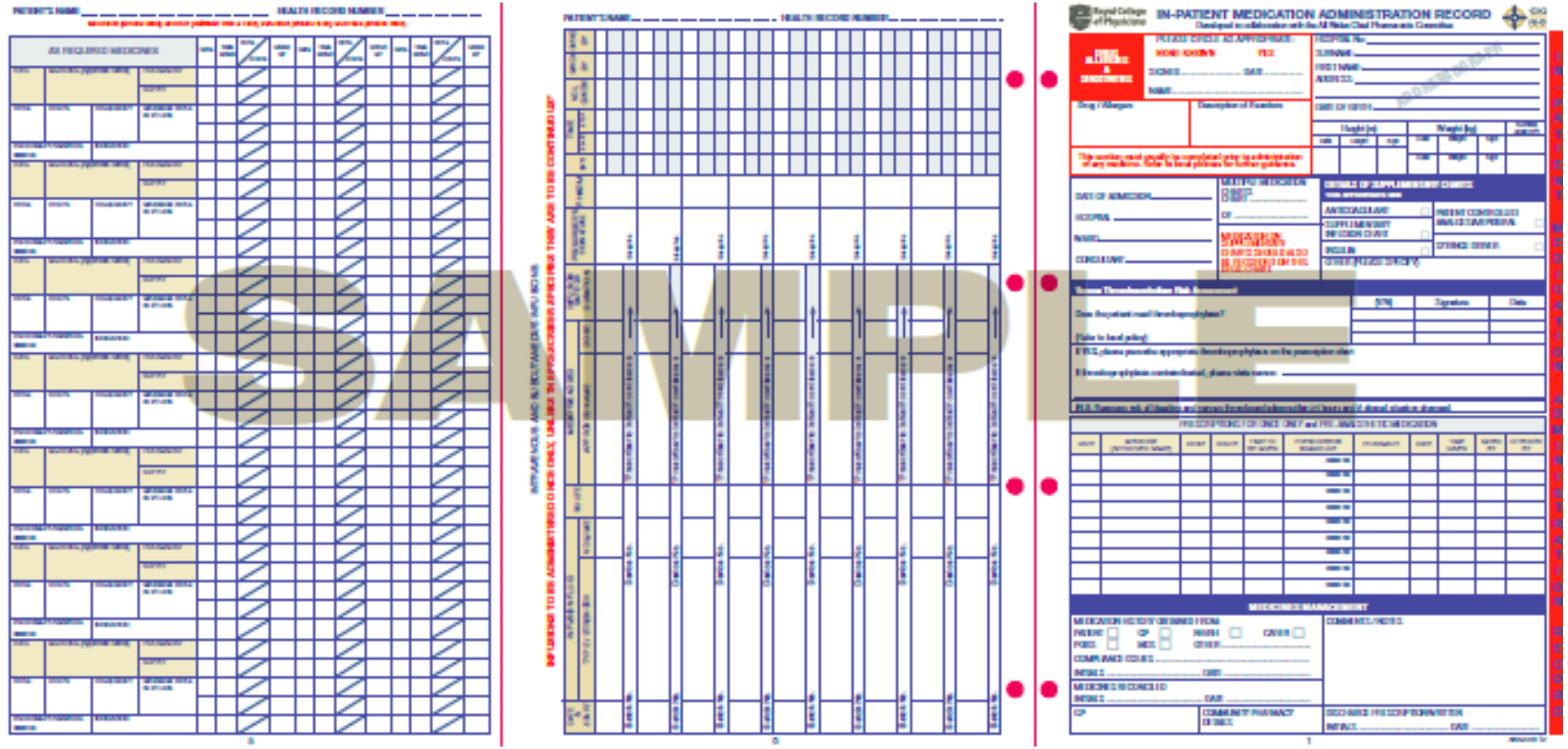
The quality of pharmaceutical review in the early 1990s was also poor in comparison to the reviews undertaken in most NHS Trusts today. Prescription charts, written by hand, were often illegible or ambiguous and since their design varied between settings, it was (and remains the case where they are still in use) difficult to educate prescribers in their use. Incidents frequently occurred owing to a breakdown of communication between healthcare professionals in the acute care setting and poor documentation was frequently a cause of drug errors[16].

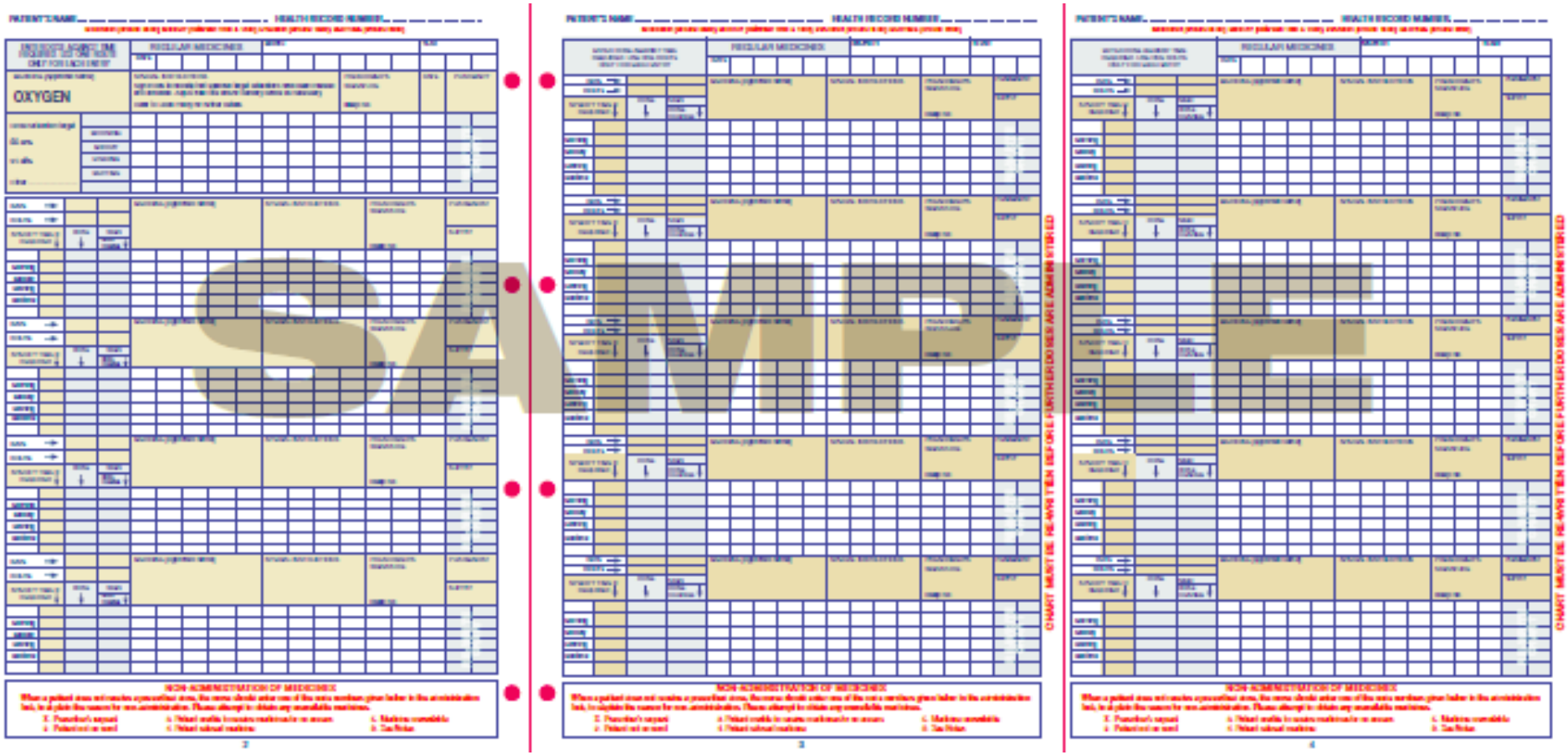
Despite these limitations, paper charts are still used in many settings where electronic alternatives are not available. To combat issues of errors arising owing to poor documentation and movement of prescribers (particularly locums) between settings, a decade ago, the NHS in Wales (advised by the All Wales Medicines Strategy Group) adopted an all Wales inpatient prescription chart (Figure 1.4) and like most prescription charts it was developed in collaboration with clinical pharmacists with the aim to reduce medication errors.

The EQUIP study[17], which was sponsored by the General Medical Council (GMC) to investigate the cause of prescribing errors amongst hospital doctors found that the causes of errors were multifactorial although much more could be done during undergraduate training to improve prescribing activity. The study did not investigate the effect of using a standardised prescription chart but it did advocate their standardisation. Movement of hospital doctors and now, non-medical prescribers is increasing between hospitals, which supports the case for greater commonality.

Despite the experience in Wales, elsewhere in the UK, owing to the increasing complexity of drug administration and changes to legislation and standards for patient assessment, the necessity for comprehensive documentation has resulted in drug charts which are technically challenging and far from intuitive for those using them. Over the past decade many acute Trusts in England have turned to electronic prescribing and administration systems (electronic prescribing and medicines administration (EPMA)) in an attempt to improve patient safety and efficiency. The Francis Report in 2012[18] called on the NHS to make better use of technology and in May 2013, the Health Secretary announced a £260 million technology fund set up to support his call for a paperless NHS by 2018. It was thought likely that most of the fund (called the "Integrated Digital Care Fund") would be spent on investment in electronic prescribing in acute Trusts.

Figure 1.4 All Wales Prescription Chart




PATIENT'S NAME
HEALTH RECORD NUMBER
REGULAR MEDICINES
OXYGEN
NON-ADMINISTRATION OF MEDICINES
CHART MUST BE RE-WRITTEN BEFORE FURTHER DOSES ARE ADMINISTERED
2
3
4

1.2. Clinical Pharmacy at University Hospitals NHS Foundation Trust (UHBFT)

1.2.1. Electronic Prescribing at UHBFT

Most acute trusts in the UK already employ at least some form of electronic prescribing documentation, mostly in a single speciality. However some Trusts use electronic prescribing and administration systems across the entire in - and outpatient population. The majority will also have access to other electronic databases enabling timely review of laboratory data at the patient's bedside enabling a more detailed and comprehensive clinical overview of the patient by clinical pharmacists. In some Trusts in the UK, EPMA systems include laboratory data, observations, assessments and much more in one single electronic system. Many of these more complex systems include prompts and alerts when prescribing and admitting patients providing decision support for users. Such systems are frequently termed clinical decision support systems (CDS or CDSS).

University Hospitals Birmingham NHS Foundation Trust (UHBFT) employs an EMPA system, which was built and developed in house which now has numerous CDS elements, inputted over the past 15 years by pharmacists and prescribers. The system, known as the Prescribing and Information Communication System (PICS), has transformed the way in which clinical pharmacy is delivered in the Trust. Prior to using the PICS, clinical pharmacists covering inpatient wards would be responsible for an average of 50 patients each day. Now, with access to reliable, comprehensive laboratory results, observations, assessments and admission details in the PICS, pharmacists may review 70-100 patients daily.

Figure 1.5 Review of a Patient's Medication Chart by a Pharmacist at the Patient's Bedside

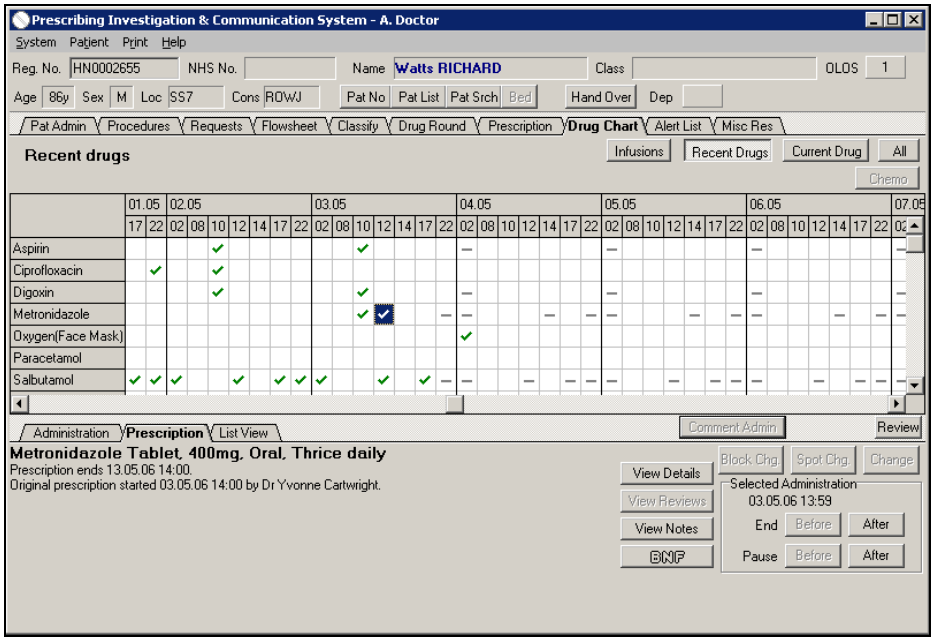
Using the PICS, the clinical pharmacy review is more visible and quantifiable than reviews using a paper chart. An individual pharmacists' performance can be measured by key performance indicators (KPIs) audited from direct outputs from the PICS such as; number of pharmacist sign offs, number of interventions, number of falls drug assessments and number of drug histories completed. Audit data to support educational initiatives concerned with most aspects of prescribing and administration of medicines is available to clinical pharmacists on request since every "click" in the system is auditable.

The PICS allows clinical pharmacists to carry out all of the functions they performed on a paper chart with improved access to additional patient information with the ability to educate prescribers "*en mass*" through a series of drug templates, prompts, warnings and

alerts built into the system by pharmacists and clinicians. However, in simple terms, the PICS has the benefits of legibility, accessibility and errors caused by erroneous or absent information on a handwritten chart. Figure 1.6a and 1.6b compare examples of a handwritten and electronic inpatient prescription charts respectively at UHBFT.

Figure 1.6a Handwritten inpatient chart in use in some UHBFT wards pre 2005

Figure 1.6b PICS inpatient chart in use in all UHBFT wards post 2005



However, despite these potential benefits it is important to recognise that there are also potential pitfalls to electronic prescribing[19–22]. Training of staff to use the system takes time and the implementation of such systems requires a great deal of planning to prevent adverse events during the switch from paper to an electronic system. Pre-set prescriptions may result in poor education of junior doctors when moving between clinical settings since they are no-longer required to learn doses and treatment regimens. It is also important that a system is not overloaded with warnings and alerts since "alert fatigue" can cause prescribers to dismiss alerts without considering their significance. It is imperative that these factors are taken into consideration when designing and programming an EPMA system.

1.2.2. The Clinical Pharmacist Review at UHBFT.

UHBFT consists of 30 inpatient wards each consisting of 36 beds and 7 specialist units, which are served by the clinical pharmacy service. Like most acute trusts, inpatient wards at UHBFT are allocated a pharmacist on a daily basis. The allocation is generally determined by the knowledge and experience of the clinical pharmacist with respect to the ward speciality and forms a daily rota.

Figure 1.7 Example of the Clinical Pharmacy Rota at UHBFT

More experienced pharmacists are usually allocated specialities and wards where patients with more complex medical issues are more likely to be sited, such as Critical Care Units and wards caring for transplant patients. Less experienced pharmacists are usually allocated elderly care and trauma specialities where drug regimens in the main, are less complex.

Unlike AHPs who are referred patients for review, pharmacists are responsible for reviewing every patient on their allocated ward on admission and in theory, again on a daily basis until discharge. Clinical pharmacy services use this method for allocation of workload in almost all trusts in the UK.

At UHBFT, pharmacists are required to comply with the local clinical pharmacy standards for review of each patient on their allocated ward/s. The standards require that for each patient the following is completed:

1. Medicines Reconciliation undertaken and recorded on the PICS
2. Validation and sign off on PICS of all medicines prescribed
3. Interventions into the patient's drug regimen documented on the PICS
4. Drugs assessed for risk of falls and recorded on the PICS for those patients at risk of falls
5. Patient counselled and recorded on the PICS for newly prescribed medicines or those with an NPSA or CSM warning referring to counselling points against them

Each pharmacist has around 2 hours allocated to review a 36 bed ward in order that a clinical pharmacy service is provided to all inpatient areas (with the exception of ambulatory care).

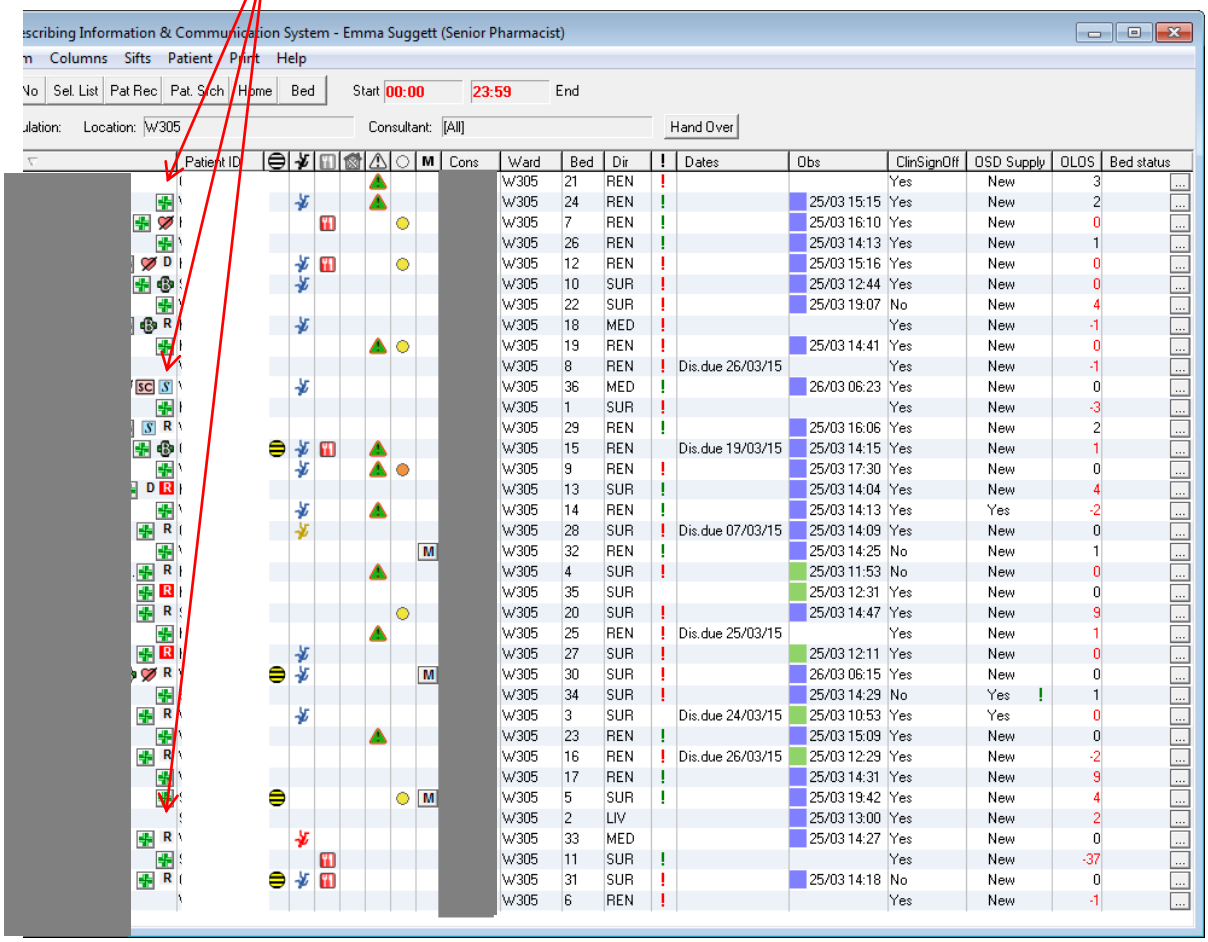
Medicines reconciliation alone takes an average 22 minutes to perform[23] so that where a ward has more than 5 new patients a day, pharmacists find it an almost impossible task to complete the quality of care they should be delivering as part of the local clinical pharmacy standards.

On review, a pharmacist may deem a daily pharmacy visit to be unnecessary for patients who are unlikely to need pharmaceutical intervention in order they may prioritise their workload. Currently prioritisation predominantly involves targeting new patients and assessing their requirements for further pharmacy intervention. New patients can be identified from a list view on the PICS since they do not have a green cross next to their name denoting that a drug history has been documented as part of the medicines reconciliation process (Figure 1.8). The pharmacist will then perform an ad hoc risk assessment which includes checking clinical, biochemical, and pharmaceutical details in the PICS to determine whether or not the patient is receiving the appropriate choice of medicine, in the right dose, frequency and at the right time, if they are at risk of experiencing an adverse drug event (ADE) and crucially if the patient requires an intervention into their treatment.

However, since most of the information used by a pharmacist to risk assess a patient is held within the PICS, it may be more efficient if the information was used to develop a risk model in the PICS to highlight those patients at most need of pharmacist review. For example patients with certain complex medical issues or with certain demographics may predispose them as “high risk” for an ADE. If patients at high risk could be highlighted in the PICS, the information could be utilised to direct the pharmacy service to patients who are most likely to have a requirement for a pharmacist’s intervention.

Figure 1.8 Pharmacy Patient List View on PICS

Patients who have not yet had Medicines Reconciliation performed by Pharmacy will not have a Pharmacy “green cross” next to their name.



1.3. Risk Assessment and Pharmaceutical Risk Models.

1.3.1. Background to Risk Assessment.

The Oxford Dictionary defines risk assessment as "a systematic process of evaluating the potential risks that may be involved in a projected activity or undertaking." Risk assessment is the assessed potential for adverse consequences resulting from a hazard. A risk assessment process should distinguish between ***hazards*** (the potential to cause harm) and ***risk*** (the likelihood of that harm being realised during a specified amount of risk exposure).

Probably the most common example of formal risk assessment is a Health and Safety risk assessment which is carried out in the workplace and involves assessing the risk of harm to employees when undertaking their daily duties. However, it was the aviation industry who first introduced risk assessment more than 20 years ago[24] as a means of ensuring the safety of the general public and who today, employ multiple risk assessment processes at the core of complex Safety Management Systems. As patient and government expectations rise in terms of safety and quality in healthcare, there has been a move to replicate the experiences of the aviation industry.

1.3.2. Pharmaceutical Risk Assessment of Patients

Most clinical pharmacists who prioritise the pharmaceutical care of their patients will be unaware that they are effectively using their knowledge and skills to risk assess patients in order to determine which patient receives the benefit of a full and complete clinical pharmacist review. However, some clinical pharmacists are familiar with the concept and have developed local models to allow systematic risk assessment of patients. In some cases risk assessment has been used to identify those patients in the community and in the hospital setting who are at risk of experiencing a medication related issue[25] (Figure 1.9). In other cases, risk assessment has been used to identify low risk departments/wards from which the clinical pharmacy service can be withdrawn should the need arise (e.g. in the event of a pandemic) (Fig. 1.10).

Figure 1.9 Examples of Pharmaceutical Risk Assessment of Patients in the Community and in Hospital

The North West London Hospitals NHS Trust

PREVENT TOOL: "High Risk" patient REFERRAL FORM

Patient Name : Hospital Number: DOB: **Ward :** **Bed No:**	**Date of Referral :** **Name of Referrer :** **Bleep:** **Managed by :** **Referred by :** Ward Nurse ☐ Specialist Nurse ☐ Patient ☐ GP ☐ Hospital doctor ☐ Pharmacy ☐ OT ☐ Family ☐ Friend ☐ District Nurse ☐ Physio ☐ Readmission list ☐ Starrs☐ Primary Care list ☐
Date of Admission: **Date of Discharge:**	**For HIMMS Use Only:** **Referral Accepted : Yes ☐ No ☐** _____

This guide supports identification of patients with unmanaged complex pharmaceutical issues, at risk of preventable medicines-related readmission where the risk is modifiable through pharmaceutical care.

	Examples	Comment
Physical impairment [PHY]	Patient has difficulties with swallowing, impaired dexterity, poor vision, hard of hearing or poor mobility which will impact them taking medication	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐
Risk from specific med/medicines-related admission [RIS]	Patient is taking a high risk medicine (anticoagulants/antiplatelets, insulin /oral hypoglycaemics, NSAID, benzodiazepine, antihypertensives, opiates, methotrexate, injectable medicines, drugs requiring therapeutic drug monitoring with no monitoring) which the patient is unable to manage. Patient has a complex of medicine regimen or polypharmacy which the patient is unable to manage	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐
adh**E**rence issues [ADH]	Patient has not been taking their medicines e.g. various dispensing dates on medicines, no recent dispensing of medication, newly started on all medicines or cannot give names of medicines they are taking. Patient has decided to stop taking all or some of their medicines which has lead or will lead to worsening of their clinical condition.	Intentional Non adherence INT ☐ Unintentional Non Adherence UNI ☐ Intentional Non adherence managed IXM ☐ Unintentional Non Adherence managed UIM ☐
cogniti**V**e impairment [COG]	Patient is unable to take medication regularly without support as they have a condition which affects their memory e.g. delirium, dementia	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐
n**E**w diagnosis/exacerbation of disease/ [EEC]	Admission is related to poor management of medication for a long term clinical condition Previous admission or A&E attendance within 30 days Depression, high level of stress, psych issues, alcoholic	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐
complia**N**ce support [COS]	Refer all new requests	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐
socie**T**al/social [SOC]	Patient cannot manage daily activities independently or has carers to help with daily activities but not medicines. Patient has social issues such as no fixed abode, unkempt etc which impacts them taking medication	Unmodifiable UNM ☐ Modifiable MOD ☐ Unmodifiable - Managed UXM ☐ Modifiable – Managed MXM ☐

Additional Comments:

NHS
Midlands and East
West Midlands Strategic Health Authority

Risk Indicator for Medicines-related Problems

This tool has been developed to help identify those people who might be at an increased risk of medicines-related problems. It has been developed and tested in a range of care settings. Suggestions on how it might be used are provided on the back of this form.

Patient Identifier :		Date
Date of Birth	Care home resident (Yes/No)	Assessed by:

Risk Factors (score 1 for each risk factor present)	Score	Notes
1. Aged over 65 years		
2. Taking more than five medicines each day **OR** more than 12 doses of medicines each day		
3. Recent change in medicines Medicine added Medicine stopped Dose changed		
4. Higher risk medicines (score 1 for each) • Non-steroidal anti-inflammatory drugs[1] (see list below) • Aspirin • Diuretic [2] (see list below) • ACE Inhibitor or Angiotensin II receptor antagonists [3] (see list below) • Digoxin • Warfarin • Drugs for diabetes including insulin • Lithium • Methotrexate		
5. Difficulty in taking medicines as prescribed eg. swallowing problems, forgetfulness, unable to open medicines containers etc.		
6. Kidney or liver problems		
7. Dependant on support to take medicines (eg. care home resident, pill dispenser aid, carer)		
8. Has had medicines-related problems in the past eg. drug allergy, fall, hospital admission related to medicines		
Total score (max 18) NB lower Score = lower Risk		

Lower risk	0-6
Moderate risk	7-12
Higher risk	12-18

1. **NSAIDs**: aceclofenac, acemetacin, azapropazone, celecoxib, dexibuprofen, dexketoprofen, diclofenac, etodolac, etoricoxib, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefanamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid

2. **Diuretics**: bendroflumethiazide, chlortalidone, cyclopenthiazide, indapamide, metolazone, xipamide, furosemide, bumetanide, torasemide, amiloride, triamterene, eplerenone, spironolacone, mannitol.

3. **ACE Inhibitor or angiotensin II receptor antagonists**: captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramilpril, trandolapril, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan.

In the case of review of patients by AHPs, the referral process to AHPs serves as a risk assessment. A medical practitioner or nurse will review the patient holistically and make referral to an appropriate AHP if required. An intervention made by the AHP may subsequently mitigate the risk. The prescription of a medicine is by far the commonest intervention in healthcare and as such over 99% of the inpatient population will be prescribed a medicine. To prevent all patients with a prescription from being referred to a pharmacist, referral by another healthcare professional would require knowledge of the medicines prescribed and the quality of referral likely to be dependent on the pharmaceutical knowledge of the referrer. An alternative may be to provide a detailed checklist for completion by the referrer but this may be time consuming and eventually lead to failure of the referral system. However, an automated risk assessment model in PICS, developed using the expertise of pharmacists and based on evidence would enable high risk patients to be highlighted (or referred) to clinical pharmacists and potentially pharmacy technicians, enabling the pharmacy team to direct services to those patients in greatest need.

The pharmacy department at UHBFT has already used models for risk assessment of wards to determine whether the department should provide a clinical pharmacy service to the areas assessed, particularly at times when pharmacist resource was stretched e.g. winter pressures. The audit tool has been used across the West Midlands and in the North West of England (Figure 1.10).

Figure 1.10 Pharmaceutical Risk Assessment of Departments / Wards.

Risk Score (score a + score b)

a) NATURE OF PATIENT

Bed no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Over 65 yrs?																																				
Renal/Liver impairement?																																				
Co-morbidity? eg cardiac, COPD, diabetes etc																																				
Pt prescribed Unlicensed/Off label meds?																																				
Poly-pharmacy? (> 5 drugs)																																				
TDM requirement?																																				
Medical outlier?																																				
Critical Care level (0-3)																																				

b) NATURE OF THE WARD (score ward according to category from list below) – CIRCLE NEAREST DESCRIPTION OF WARD

1. day surgery
2. rehabilitation or day areas with more complex patients
3. low risk surgery / stable medical
4. high risk surgery / acute medical/HDU/admissions wards
5. Critical care

The tool assesses patients in the clinical areas against a number of risk factors thought to contribute to the need for a clinical pharmacist review (such as age, number of medicines the patient is taking, renal and liver function), and combines this with a score determined by the respective speciality and collates the results to produce an overall risk score for the ward concerned. The higher the risk score, the greater the need for a clinical pharmacy service in that area. The hazards included in the tool have been defined by clinical pharmacists as those recognised as potential risk factors when performing clinical pharmacy duties; and although the potential risks are similar to those used in the tool represented in Figure 1.9, there is little evidence to support the choice of hazards in any of the tools developed and it is not clear if the list of hazards are comprehensive.

In 2011 UHBFT used the tool in Figure 1.10 to assess the need for a clinical pharmacy service across the Trust. Data was gathered using a paper-based method with manual extraction of the necessary data from PICS. The results were collated and compared against the current clinical pharmacy service. However, it came as little surprise to find that those areas which were not covered by a clinical pharmacy service had an extremely low risk score and those with a high risk score such as critical care and renal wards, already had a high pharmacist to patient ratio. Pharmacy managers had already used their pharmaceutical knowledge to direct services to those areas in greatest need without the use of the tool. Subsequently there was no change to the clinical pharmacy service and despite an increase in the number of beds across the trust, there was no corresponding increase in pharmacist numbers.

It was clear that a new way of working was required for clinical pharmacists but a number of questions would need to be answered in order that an evidence base could be established for clinical pharmacy services and the assurance of patient safety.

1. What are the evidence based risks associated with patients experiencing an adverse drug event in hospital?
2. Can patients be risk assessed individually for their requirement for a clinical pharmacy review in the same way that whole wards have been risk assessed previously?
3. Can this risk assessment be achieved in real time using an electronic prescribing system (PICS) at UHBFT?
4. Can a triage/referral system be developed in PICS to direct clinical pharmacy services to those patients at risk of experiencing a problem with their medicines and send more experienced pharmacists to those patients in greatest need?

1.4. Research Question

Is it possible to develop an electronically generated “risk score” based on an individual’s pharmaceutical and clinical risk, which is capable of directing a hospital clinical pharmacy service to those inpatients most in need of pharmaceutical intervention?

1.5. Aims

The research topic aims to:

- Develop a risk assessment tool as a safe and effective method of delivering a clinical pharmacy inpatient service in which the need for a clinical review by a member of the pharmacy team, is clearly defined, based on pharmaceutical and clinical risk as determined through an electronic prescribing system.

1.6. Objectives

Research objectives will be to:

- Determine which parameters are associated with the risk of patients experiencing an adverse drug event using a systematic review of the literature.
- Determine whether the risk parameters identified can be quantified through University Hospitals Birmingham's (UHBFT) electronic prescribing system (Prescribing and Information Communication System (PICS)).
- Quantify risk factors using analysis of clinical pharmacy interventions as a possible predictor of a preventable drug related problem.
- Design a risk management model based on a numerical risk score for hospital inpatients to determine which patients are most in need of intervention by a member of the pharmacy team in order to reduce risk.

CHAPTER 2

RISK FACTORS ASSOCIATED WITH THE REQUIREMENT FOR PHARMACEUTICAL INTERVENTION IN THE HOSPITAL SETTING: A SYSTEMATIC REVIEW OF THE LITERATURE

2. Risk Factors Associated with the Requirement for Pharmaceutical Intervention in the Hospital Setting: A Systematic Review of the Literature.

2.1. Introduction

2.1.1. Background.

There are many studies which aim to determine the risk factors which lead to patient admission to the hospital setting and indeed these studies are valuable in meeting the QIPP agenda[26] in the United Kingdom (UK) by preventing admissions into secondary care. QIPP is a national policy driver in the UK, which seeks to reduce costs in the UK National Health Service (NHS) through improving **Q**uality, **I**nnovation, **P**roductivity and **P**reventing (QIPP) readmission to hospital.

It has been shown that more than 6% of all hospital admissions are due to adverse drug events (ADEs)[27] with the result that there have been an increasing number of community based methodologies trialled internationally to identify and target patients displaying risk factors for intervention.[28–33] Most of these studies have used incident report review, prescription chart review, direct observation or trigger tools to identify at-risk patients. The trigger tool method in which patients are screened for perceived risk factors for

ADEs, has been shown to be the most effective and labour–efficient method for identifying vulnerable patients[34]. At the same time, the availability of electronic prescribing systems (EP) and clinical decision support (CDS) has resulted in the development of a number of "trigger tools" for adverse drug events driven by rule based alerts programmed into a CDS system[35–37].

However, research into drug related problems post hospital admission is not so accessible and the use of a number of different terminologies and definitions such as ADEs, Adverse Drug Reactions (ADRs), Drug Errors, Drug Related Problems (DRPs) and Medication Related Problems (MRPs) make it difficult to make comparisons between studies available. As a result there are fewer studies in secondary care, which seek to determine the causative factors of adverse outcomes from the use of drugs.

A number of corporate approaches to assess risks associated with drug usage exist. Retrospective assessment of incident reports in the hospital setting in the UK is widespread with the majority of acute trusts identifying local trends in drug-related incidents. Reporting ADRs to the Medicines and Healthcare Regulatory Agency (MHRA) and drug related incidents to the National Patient Safety Agency (NPSA) (replaced by the NHS Commissioning Board Special Health Authority and now, NHS England) has been the norm for many years with the result that there has been an increasing awareness of high risk prescribing areas amongst pharmacists and prescribers. The NPSA have issued alerts[38] in this area including those pertaining to high risk drugs, drug omissions, patients who are nil by mouth and the administration of medicines using syringe drivers. Similarly, the Institute for Safe Medicines Practices (ISMP) in the United States[39] and the Australian

Commission on Safety and Quality in Health Care (ACSQHC)[40] have used a similar system of alerts raising awareness of the risk of ADEs in organisations internationally.

This increasing awareness of risk in the hospital setting has led researchers in the UK to pilot a national trigger tool, The Medication Safety Thermometer[41], which seeks to identify patients at risk of harm from omission of high risk drugs using data pooled from reports to the NPSA. This may prove to be a valuable tool in reducing patient harm but does not address all of the risks that a pharmacist should target.

In most UK hospitals, clinical pharmacists aim to review all in-patient prescription charts with the intention of identifying any medicines related problems and performing any necessary intervention into the patient's care by making recommendations for changes in drug therapy or further monitoring of the patient. By performing such pharmacist interventions, pharmacists have become familiar with certain types of medicines or patient factors, which more often predispose the patient to intervention and may endeavour to ensure that all patients with such factors receive an in-depth review of their medicines chart. Essentially as part of their daily review, pharmacists already perform a risk assessment of sorts when reviewing patients' drug charts. As a result, patients with impaired renal or liver function, those taking anti-epileptics or medication for Parkinson's disease or displaying polypharmacy, may already be in receipt of increased pharmacist monitoring albeit *ad hoc* and qualitative. Assessment of the impact of pharmaceutical intervention is also usually qualitative with the result that the value of clinical pharmacy services is not well documented, communicated or perceived by hospital managers in the UK.

Patients are unlikely to be documented as “high risk” for medicines related problems and / or in need of targeted intervention by the pharmacist with the possible exception of cases where a pharmaceutical care plan has been employed. However, producing a pharmaceutical care plan is extremely labour intensive and is therefore often only completed for the most complex cases in the acute setting. National initiatives such as reduction of dosage omissions, targeting high risk drugs, supporting patient adherence and expanded roles are increasingly taking up the time of the clinical pharmacist. In a risk driven, resource limited environment, targeting clinical pharmacy services to ensure safe, timely, high quality services centered on patient safety should be paramount.

2.1.2. Aims

The purpose of this systematic review is to determine the evidence base for measurable risk factors that pre-dispose to the requirement for an intervention by a pharmacist or to the development of a drug related problem (DRP). The review seeks to list those risk factors for pharmaceutical intervention or DRPs with the intention that they may be used in further research to build an evidence-based trigger tool, targeting individuals at risk of DRPs in the hospital setting. In particular, the aim is to target high-risk patients on general medical and surgical wards rather than patients in specialist settings where the presence of specialist equipment and personnel may already mitigate the risks associated with the use of medicines.

The aims of this systematic review are to search the international literature to:

a) Determine factors associated with the requirement for pharmaceutical intervention and prevention of potential subsequent DRPs;
b) Determine measurable risk factors for DRPs;
c) Document the frequency and critically review papers reporting such risk factors.

2.1.3. Objective

The objective is to document all primary research identifying measurable risk factors for pharmaceutical intervention or drug related issues which may be retrieved prospectively from a patient's clinical records during their inpatient stay in hospital whether these be demographic, clinical or otherwise.

The intention is that the results may be used for further research to identify patients at risk of experiencing problems with their medicines and requiring intervention with a view to targeting pharmaceutical input in the hospital setting. To search for potential risk factors for interventions only would depend upon an assumption that pharmacists are comprehensively targeting all issues related to adverse outcomes associated with the use of medicines.

2.2. Methods

Identification of measurable risk factors associated with adult hospital inpatients on non-specialist wards, which affect the number (or type) of pharmaceutical interventions or drug related problems.

A literature review was conducted systematically using the principles and checklist set out in the PRISMA statement[42] in order to source all primary research identifying measurable risk factors for drug related problems or pharmaceutical interventions. The term "drug related problem" (DRP) in this review included all definitions of adverse drug events (ADEs), adverse drug reactions (ADRs), drug related errors, medication related problems (MRP) or drug related problems (DRP) in the literature. No date or language restrictions were applied during the review. However, the search was closed in July 2013 and identified no papers prior to 1966.

Paper Inclusion Criteria: Measurable risk factors, patients over 16 years, inpatients in secondary or tertiary care centres, all definitions of ADEs, ADRs, MRPs, DRPs and clinical pharmacy interventions, inpatients in medical and surgical wards, all primary research and systematic reviews.

Paper Exclusion Criteria: Qualitative risk factors (e.g. patient's previous knowledge of medicines), studies reporting outcomes indirectly associated with pharmacist interventions or adverse events associated with medicines e.g. medicines adherence, studies of patients 16 years or less, outpatients, ambulatory care and community based studies, studies solely in patients in specialist care settings e.g. intensive care, summary articles (with the exception of systematic reviews) and discussion articles.

Initially on-line searches were conducted of databases 1-10 included in Table 2.1. Searches were undertaken in the chronological order of inclusion in the table.

The PICOS method[43] was used to formulate the review question and identify free text search terms through a combination of mind-mapping by the primary author and a focus group consisting of 10 members of the UK West Midlands Clinical Pharmacy Group:

- Population - adult hospital inpatients
- Intervention – unknown risk factors
- Comparison – no risk factors
- Outcomes – a problem associated with medicines use or the requirement for pharmaceutical intervention
- Study design – Primary research and systematic reviews

Free text search terms included: Risk, Risk Assessment, Clinical Risk, Susceptibility, Drug, Medicine, Medicines Reconciliation, Drug History, Clinical Check, Age, Elderly, Adult, Compliance Aids, Medicines Adherence, Comorbidity/ies, Long term conditions, Therapeutic Drug Monitoring, Renal Function, Liver function, prescription, Early warning score, Dose/Dosage, Pharmacy Review, Biochemistry, Urea and Electrolytes, Tests, Microbiology, Intervention, Adverse Drug Event, Adverse Drug Reaction, Drug Error, Medication Error and Pharmacy Service.

MeSH descriptors were identified from free text terms inputted into the databases listed in Table 2.1 and included: Risk, Risk Factor, Hospital Risk, Risk Assessment, Lifestyle Risk Reduction, Risk Reduction, clinical prediction rule, clinical prediction, health risk, health

risk appraisal, Pharmaceutical Preparations, medicine, Drug Administration Schedule, Drug administration routes, Drug Combinations, Drug Hypersensitivity, Drug Interactions, Drug Synergism, Drug Therapy Drug toxicity, Medical history taking, Drug prescriptions, Decision Support techniques, clinical pharmacy, Medical informatics, Pharmacists, Pharmacy service Hospital**,** Pharmacy Service, Hospital, Clinical Pharmacy Information Systems, Drug Utilization Review, Pharmaceutical services, intervention studies, Pharmacy Service, Hospital, medication errors.

Following the database search a manual search was conducted of Journals 11-21 in Table 2.1 using on-line access.

Initial searches found no papers linking risk factors with the requirement for a pharmaceutical intervention. Further on-line searching was conducted for grey-literature using the free text search terms listed above, and in particular for Internet publications linked to pharmaceutical interventions, using Google and Firefox as a browser.

Table 2.1 Databases and Journals Searched

Name of Database	Location	Description	Pros	Cons
1. Medline	www.ncbi.nlm.nih.gov/PubMed	Bibliographic records (with and without abstracts) of biomedical literature from 1966 onwards.	Extensive electronic database with literature from 1966. Clinical Pharmacy not in practice prior to 1966	North American emphasis? Less International studies and non-English language.
2.EMBASE	www.embase.com	Biomedical literature from 1974 onwards	Greater European emphasis	Greater European emphasis. ?international studies. Has a high pharmacological content.
3.Cochrane Data Base of Systematic Reviews	http://www.cochrane.co.uk/en/index.html	Database of systematic reviews, includes reviews of work in progress	Cochrane reviews base their findings on research that meets certain quality criteria and authors of reviews apply methods which reduce the impact of bias	Includes only systematic reviews and trials which meet strict criteria, will exclude grey literature and papers with a weaker evidence base which may be a problem if there are few papers available on the subject
4.CINAHL	www.cinahl.com	Records of literature on all aspects of nursing and allied health disciplines	May cover qualitative studies	Unlikely to include clinical pharmacy as not a true AHP
5. Dissertation Abstracts	http://www.umi.com/en-US/catalogs/databases/detail/pqdt.shtml	Dissertation Abstracts, Dissertation Abstracts International (DAI) or the ProQuest Dissertations and Theses (PQDT) database is a bibliography of American (and international) dissertations published by University Microfilms International (UMI) / ProQuest, Ann Arbor, since 1938.	It covers doctoral dissertations accepted at an accredited American institution since 1861. Selected Masters theses have been included since 1962; since 1988, the database includes citations for dissertations from 50 British universities that are available at The British Document Supply Centre.	UMI has changed it's name and owner several times and the bibliographical data therefore appears under different labels. It also covers few dissertations outside US and UK.
6.Science Citation Index	http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/web-of-science-core-collection.html		Relevant studies found through electronic or manual searches can be used to identify further relevant citations on the same topic through citation search on Science Citation Index	Requires thorough searches before using the citation Index
7.Conference Papers Index	http://ca2.csa.com/factsheets/cpi-set-c.php	Records of conference presentations	Will cover some unpublished work presented at conferences	Unpublished work may be of poorer quality than published peer reviewed work
8.uk Clinical Research Network: Portfolio Database	http://public.ukcrn.org.uk	Details of research in progress	Gives details of work underway which may not yet be published	only covers research in the UK. Since work may be unpublished, no indication of the quality of the research. Does not include any projects listed before 2007
9.National Research Register Archive	http://www.nihr.ac.uk/Pages/NRRArchive.aspx	Details of research documented prior to CRN in 2007	Covers work not included in CRN portfolio	Only covers research in the UK. Requires follow up to indicate if any papers were published and the quality of this work

10.SIGLE (System for Information on Grey Literature)	http://www.opengrey.eu	Bibliographic database covering European non-conventional literature in the field of pure and applied natural sciences and other areas	Quick method for searching grey literature	Database for grey literature can never be comprehensive (like other databases). Does not cover non-European grey literature
11.Clinical Pharmacist	http://www.pharmpress.com/product/13527967/clinical-pharmacist	Leading British clinical pharmacy journal. Founded in 2009	May show work not yet published to database and grey literature of relevance	Quality of work may be variable. Only covers British research post 2008
12.Hospital Pharmacist	http://www.pharmj.com/backissues/hp.html	Leading British clinical pharmacy journal. Founded in 2000	May show grey literature of relevance	Quality of work may be variable. Only covers work 2000-2008
13.British Journal of Clinical Pharmacy	http://www.clinicalpharmacy.org.uk/home	British Journal founded in 2009	May show grey literature of relevance	Quality of work may be variable. Only covers British research
14.British Journal of Clinical Pharmacology	http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2125	Journal from the British Pharmacological Society. One of the world's leading clinical pharmacology journals.	Publishes papers, original papers, short communications, correspondence, and reports on all aspects of drug action in man. Peer reviewed.	Quality of work may be variable. Mainly British research.
15.European Journal of Hospital Pharmacy	http://ejhp.bmj.com/	The premier communication platform for European hospital pharmacists, EJHP Science and Practice is a major source for continuing education as well as updates on advances in the practice and standard of pharmaceutical care for patients	Peer-reviewed papers, features, conference reports and more on topics covering all aspects of hospital pharmacy from both a scientific and practice perspective	International work not included
16.American Journal of Hospital Pharmacy	currently without website accessed at: https://www.researchgate.net	Monthly Journal from the American society of Hospital Pharmacists.1958-1994 only	Includes American innovation	Details work only until 1994. Excludes international work
17.American Journal of Health - System Pharmacy	http://www.ajhp.org/content/by/year	Current journal from the American Society of Hospital Pharmacists from 1994-date	Includes American innovation	Excludes international work
18.Australian Journal of Hospital Pharmacy	Currently without website accessed at:http://search.informit.com.au/browseJournalTitle;res=IELHEA;issn=0310-6810	The *Australian Journal of Hospital Pharmacy* was the official journal of The Society of Hospital Pharmacists of Australia (SHPA) from 1996 to 2001, succeeded by the *Journal of Pharmacy Practice and Research*	Includes Australian work	Only includes work until 1996
19.Journal of Pharmacy Practice and Research	http://search.informit.com.au/browseJournalTitle;res=IELHEA;issn=1445-937X	Australian Pharmacy Practice Journal from 2002 to date	Includes Australian work	Excludes international work

20. International Journal of Clinical Pharmacy (Known as Pharmacy World and Science Prior to 2011)	http://www.springer.com/medicine/internal/journal/11096	International Journal which includes Australian work of clinical pharmacy and related practice orientated subjects	Includes Australasian work	? Biased towards work reported in English language
21. International Journal of Pharmacy Practice	http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)2042-7174	Produced by the Royal Pharmaceutical Society, Medline-indexed, peer reviewed, international journal.	One of the leading journals publishing health services research in the context of pharmacy, pharmaceutical care, medicines and medicines management. Regular sections in the journal include, editorials, literature reviews, original research, personal opinion and short communications.	? Biased towards work reported in English language

After screening the abstracts, all potentially relevant full text publications were evaluated through intensive reading. Citations included in the retrieved articles were reviewed and if relevant, were sourced, evaluated and citations checked.

All sourced articles were tabulated to allow validation of a final list of citations and a final list of included papers drawn up. The validation of this final list was carried out by a pharmacy research graduate. Using the tabulated list of sourced articles and the agreed inclusion/exclusion criteria, the research graduate independently evaluated the articles against their respective abstracts. Where the abstract did not provide sufficient information for the article to be evaluated against the inclusion/exclusion criteria, the full text was provided to the research graduate.

Finally, the research graduate and primary author met to discuss any remaining articles where an agreement had not been reached during the independent evaluation until final concurrence was achieved.

In order to quantify the results of the review, a thematic analysis was undertaken. Through intensive reading, risks were identified as such as those listed as independent risk factors in the research conclusions and subsequently tabulated to allow for common themes (risks) to be identified.

Statistical identification of the risk factor as an independent risk factor was not required for identification in the review results table although where statistical methods excluded or included a risk factor as an independent risk factor, this was noted in the conclusions. Positive and “negative” associations of risk factors were also noted in the results table. A “negative” association was not a risk factor with a protective association but noted as such where the research had shown there to be no association between the risk factor and DRPs or the requirement for a pharmacist intervention.

Positive and negative associations with risk factors were documented in Table 2.2 as reported in the text and totaled in order to identify the most commonly reported risk factors.

All risk factors identified in the literature by more than 1 primary research paper were listed and all others noted as “other”.

Those studies which demonstrated an association between certain drugs or drug classes and risk of problems associated with medicines were further tabulated in Table 2.3 to identify which drugs are most commonly associated with DRPs (all definitions included).

2.3. Results

Figure 2.1 indicates the publication outputs at each stage of the review process.

Using search terms “risk” and “adverse drug events”, 44,731 articles were identified initially from online searches. This was reduced to 7,720 through the use of “AND” as the Boolean operator to link to a 3rd relevant search term.

All resulting titles were viewed and 120 abstracts identified for possible inclusion in the review from searching online search engines.

A further 29 full text papers were identified from manual searching Journals 11-21 in Table 2.1. In total 149 full texts were sourced.

A preliminary screen of the sourced texts and cross referencing of citation by the primary author resulted in a list of 82 papers which were tabulated and sent for independent evaluation by a pharmacy research graduate.

Intensive reading by the primary author of the resulting 82 papers eliminated a further 46 in accordance with the study inclusion/exclusion criteria.

The same 46 were independently eliminated by the research graduate, while 2 papers of the 82 were included back into the final results after discussion and agreement with the primary author.

The resulting 38 papers were tabulated in Table 2.2.

Figure 2.1 Systematic Review Process

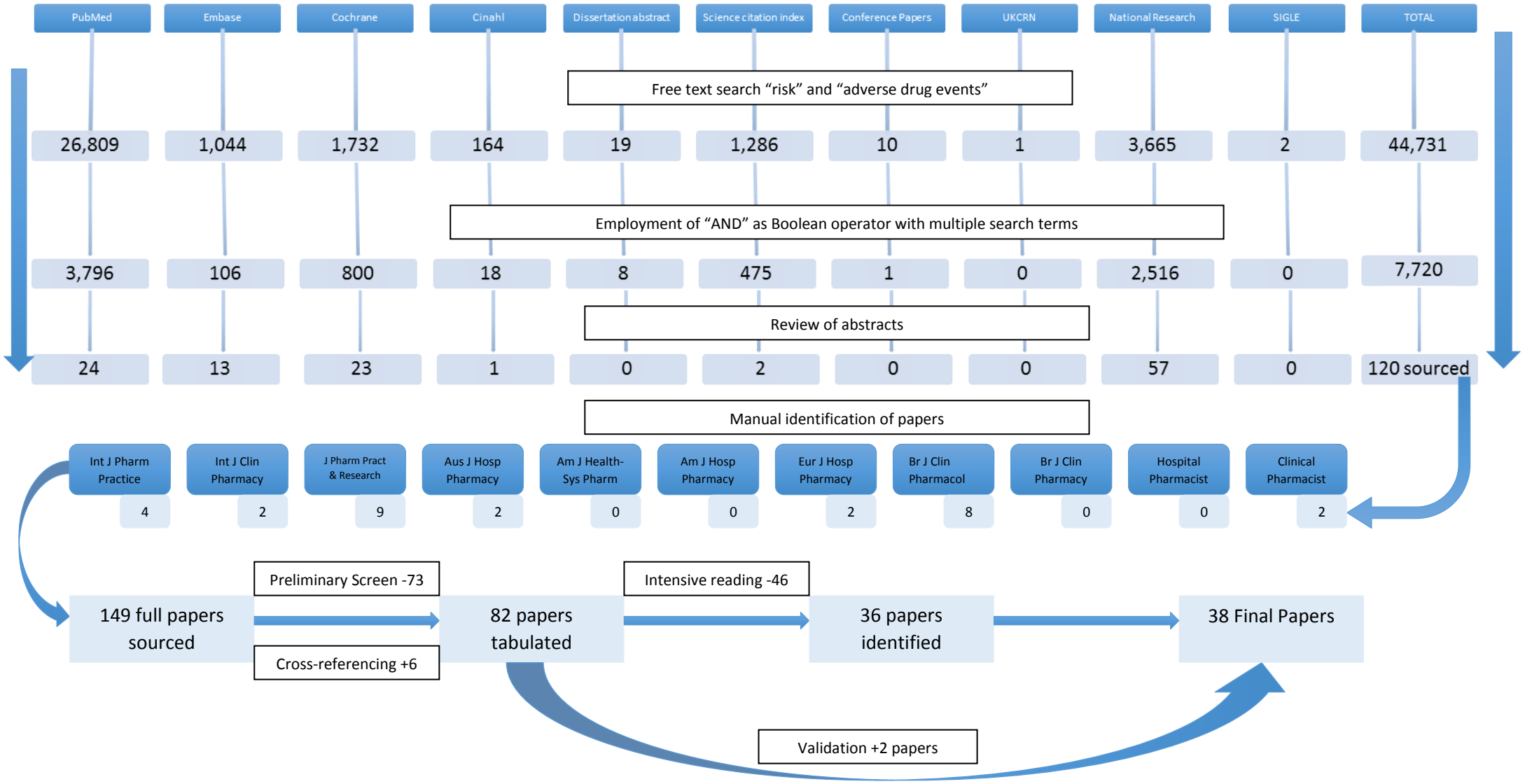


Table 2.2 Overview of Studies of Patient Risk Factors for Drug-related Problems

Reference	Study Setting	Study Design SCS = Single Centre Study MCS = Multicentre Study	Size of Sample	Drugs	PolyPharm	Age	Renal	Female	Co-morbid's	Stay length	Hx of allergy	Liver	Compliance	Other	Limitations to Study
Alderman, C.P. and Farmer, C. (2001) [44]	Australian teaching hospital	SCS Prospective study of prevalence of pharmacy interventions with manual collection of data.	67 interventions	✓											SCS only. Sample size very small. No denominator (no. of interventions may be affected by prescription rate)
Al-Hajje, A.H., Atoui, F., Awada, S., et al. (2012) [45]	Beruit university hospital	SCS Prospective study involving clinical pharmacy students trained to identify DRPs on a medical ward round and analysis of resulting interventions	90 DRPs in 572 patients	✓											No denominator (increase in percentage of DRPs related to a particular drug may be due to an increased number of prescriptions for that drug)
Bates, D.W., Miller, E.B., Cullen, D.J., et al. (1999) [46]	US. Medical and surgical inpatients	2 Tertiary care hospitals – 2 methods used: 1. Cohort study 2. Nested matched case control study	Cohort Study 2109 Case Control 247 of 4108 total admissions		✓	✓	✓								Only 2 tertiary centres which may hinder generalizability to other care settings. Cohort analysis looked only at information available electronically.
Blix, H.S., Viktil, K.K., Reikvam, \A Asmund, et al. (2004)[47]	5 general hospitals - Norway.	MCS -Medical inpatients excluding A&E departments Prospective manual recording of assumed clinical and pharmacological risk factors. Impact of various risk factors on occurrence of different categories of DRPs using multivariate analysis	827 patients	✓	✓	✓	✓		✓		✓	✓	✓		
Bowman, L., Carlstedt, B.C., Hancock, E.F., et al. (1996)[48]	US general hospital	SCS medical inpatients. Prospective drug chart review. Univariante logistic regression to identify covariate predictors of ADR from laboratory, demographic and total drug exposure. Stepwise multivariate logistic regression to identify those univariate indicators that best predict ADR occurrence	1024 patients		✓	✓	✓	✓							SCS only.
Bowman, L., Carlstedt, B.C. and Black, C.D. (1994)[49]	US general hospital	SCS medical inpatients. Prospective observational study using manual chart review by pharmacists	304 ADRs in a total of 1024 patients	✓				✓		✓					The study is quite old and SCS only so that drugs used in the study may differ somewhat from those used 20 years on.
Calderón-Ospina, C. and Bustamante-Rojas, C. (2010)[50]	US university hospital	SCS Prospective study including manual assessment of adult inpatients. All reports of ADRs subsequently evaluated by 3 independent researchers	102 patients	✓		✓			✓						Small sample size may have led to overestimation of percentage of cases
Camargo, A.L., Ferreira, M.B.C. and Heineck, I. (2006)[51]	Brazilian university hospital	SCS Cohort study using logistic regression analysis to identify risk factors. Factors demonstrating significant association with an ADR were included in the multivariate logistic regression model.	360 ADRs	✓	✓	✓		✓	✓	✓					19.7% of the ADRs were prior to admission, this review is primarily focused on ADRs in the inpatient setting
Carbonin, P., Pahor, M., Bernabei, R., et al. (1991)[52]	Italy – general hospital- medical and geriatric wards	MCS Prospective study using clinician identification of ADR, logistic regression to determine risk factors and multivariate logistic regression to identify independent risk factors	788 ADRs from 9,148 admissions		✓	✓			✓	✓			✓		ADRs may have been under reported as relying on physician reporting.

Reference	Study Setting	Study Design SCS = Single Centre Study MCS = Multicentre Study	Size of Sample	Drugs	PolyPh'm	Age	Renal	Female Gender	Co-morbid's	Length of Stay	Hx of allergy	Liver	Compliance	Other	Limitations to Study
Classen, D.C., Pestotnik, S.L., Evans, R.S., et al. (2005)[53]	US tertiary care centre	SCS Prospective study of all patients admitted over an 18 month period	648 patients with ADEs in a total of 36,653 admitted patients	✓		✓				✓					Authors acknowledge that age may not be an independent risk factor. Further studies required to investigate this. Number of ADEs identified appears low and potentially, minor ADEs may have been undetected by this method
Claydon-Platt, K., Manias, E. and Dunning, T. (2012)[54]	Australian teaching hospital	SCS conducted over 2 years Retrospective cohort study of medication related problems in inpatients with diabetes. Risk factors associated with medication-related problems were identified using random effect logistic regression	571 patients in a total of 5205 admitted patients			✓		✓	✓					✓	Data used was collected for other purposes so links to other risk factors may have been omitted. Risk factors in diabetes may not be valid in other cohorts.
Davies, E.C., Green, C.F., Taylor, S., et al. (2009)[55]	UK university hospital	SCS over a six month period Prospective cohort study of ADRs. Risk factors for ADRs were identified using multivariable analysis.	545 patients from 3695 patient episodes	✓	✓	✓		✓						✓	SCS, likely to be variation between different hospitals because of the differences in the local population characteristics and specialities within the hospitals
Dequito, A.B., Mol, P.G.M., van Doormaal, J.E., et al. (2011)[56]	Holand –general hospitals	2 Dutch hospitals using CPOE - 5 month data collection .Prospective cohort study. Univariante analysis followed by multivariante analysis analysis was performed using a logistic regression to establish independent risk factors for preventable ADEs and non-preventable ADRs	349 patients from 603 admissions	✓	✓	✓		✓	✓	✓				✓	Only gastroenterology, rheumatology, geriatrics and internal medical patients included. Results may not be transferable to other specialities and hospitals.
Fattinger, K., Roos, M., Vergères, P., et al. (2000)[57]	Switzerland teaching hospital	2 teaching hospitals. Prospective cohort study using a purpose built database. Clinical events were reported in a separate database by separate personnel to avoid bias. Regression analysis used to identify risk factors.	2102 patients of 4331 admissions	✓	✓	✓		✓							ADRs included "accepted" side-effects e.g. Nausea and vomiting from chemotherapy
Fields, W., Tedeschi, C., Foltz, J., et al. (2008)[58]	United States – community hosiptal	2 community non-teaching hospitals Prospective study using a multi-method approach - voluntary self-reports, e-prescribing, laboratory triggers and pharmacist intervention surveillance.	1052 medication safety events- of these 318 were classified as errors				✓								Analysed data from medication errors only and did not address other ADEs
Gurwitz, J.H. and Avorn, J. (1991)[59]	United States	Literature review examining the association of age with ADRs Medline search for articles between 1966 and 1990.				✓									Review over 20 years old but principles likely to still apply
Hoonhout, L.H., de Bruijne, M.C., Wagner, C., et al. (2010)[60]	Netherlands	MCS Analysis of medication-related adverse events (MRAEs) identified by retrospective chart review of patients admitted to 21 hospitals in 2004	140 patients of 7889 admissions	✓		✓									Difficult to make comparisons to other studies due to differing definition of MRAEs however, conclusions look similar to other studies
Hurwitz, N. (1969)[61]	Irish university hospital	SCS Prospective study using a rank correlation to determine relationship between age, sex, length of stay in hospital, no. of drugs, history of previous drug reactions, allergic disease, jaundice, diabetes and renal disease.	118 ADRs from 1,160 patients		✓	✓		✓			✓				SCS from 1969. Are the same factors relevant with the differing drug groups available in the inpatient setting today?

Reference	Study Setting	Study Design SCS = Single Centre Study MCS = Multicentre Study	Size of Sample	Drugs	PolyPh'm	Age	Renal	Female Gender	Co-morbid's	Length of Stay	Hx of allergy	Liver	Compliance	Other	Limitations to Study
Hurwitz, N. and Wade, O.L. (1969)[62]	Irish general hospital	SCS Prospective study of patients admitted to surgical and medical wards by means of case note review and patient interview	118 patients of 1,160 patients receiving drugs	✓											SCS from 1969. Are the same factors relevant with the differing drug groups available in the inpatient setting today?
Johnston, P.E., France, D.J., Byrne, D.W., et al. (2006)[63]	US University Hospital	SCS Prospective analysis of AE reports. A three stage logistic regression model used to evaluate key indicators of the most vulnerable patient populations	59,531 admissions, including 782 AEs which included 83 ADRs and 699 errors	✓	✓	✓		✓						✓	The number of ADRs in this study was small (only 83) while the study mainly collected data on medication errors.
Kanjanarat, P., Winterstein, A.G., Johns, T.E., et al. (2003)[64]	United States	Literature Review Key word search of Medline and International Pharmaceutical Abstracts and by manual search.	Ten studies between 1994 and 2001	✓											Only 10 studies reviewed. Does not include more recent work and therefore does not cover newer therapies.
Kelly, W.N. (2001a)[65]	Study from Clin-Alert, an abstracting service in the US.	Retrospective study of case reports of fatal ADEs published between 1976 and 1995.	447 cases involving a fatal ADE.	✓		✓									No denominator. An increase of fatal ADEs may have been attributable to the number of prescriptions in the respective class.
Kelly, W.N. (2001b)[66]	Study from Clin-Alert, an abstracting service in the US.	Retrospective study of case reports of drug-induced permanent disabilities published between 1978 and 1997.	227 cases involving a drug-induced permanent disability	✓		✓									No denominator. An increase in disabilities may have been attributable to the no. of prescriptions in the respective class. Study includes children which this systematic review excludes
Krähenbühl-Melcher, A., Schlienger, R., Lampert, M., et al. (2007)[67]	Switzerland	Literature Review Electronic Search using Medline and Embase for articles published between 1990 and 2005. Subsequent manual search of resulting articles for original research.	11 studies reporting risk factors for ADRs.	✓	✓	✓	✓	✓						✓	Comprehensive review but excludes drugs to market post 2005.
Marcellino, K. and Kelly, W.N. (2001)[68]	Study from Clin-Alert, an abstracting service in the US.	Retrospective study of case reports of drug-induced threats to life published between 1977 and 1997.	846 drug-induced life threats.	✓											No denominator. An increase in life threats may have been attributable to the number of prescriptions in the respective class or that the associated condition treated was a risk to life.
O'Connor, M.N., Gallagher, P., Byrne, S., et al. (2012)[69]	Irish University Hospital	SCS. Study to examine the GerontoNet ADR risk score in elderly patients. Prospective study, ADRs identified through patient and physician consultation and case note analysis. Multivariante logistic regression examined influence of individual variables on ADRs	135 ADRs from 513 acutely ill patients	✓	✓	✓	✓								Sample size quite small and single centre only
Onder, G., Petrovic, M., Tangiisuran, B., et al. (2010)[70]	Italy	MCS - 4 European university hospitals .Data from an Italian research group used to identify variables associated with ADRs using stepwise logistic regression and used to compute the ADR risk score. The risk score was then validated in a sample of older adults.	383 ADRs in 5936 patients		✓		✓		✓		✓	✓			Risk score may not be relevant in the under 65 age group and the risk score excludes any other risk factors.
Pearson, T.F., Pittman, D.G., Longley, J.M., et al. (1994)[71]	US community hospital	SCS. Retrospective analysis of ADRs through internal voluntary reporting system. Patient characteristics compared for patients experiencing preventable and non-preventable ADRs	203	✓			✓				✓			✓	Reliance on voluntary reporting of ADRs. Actual number of ADRs may have been much higher resulting in a small sample size. Although the ADRs were all independently reviewed, all the reviewers were pharmacists which may have introduced bias. Single centre only

Reference	Study Setting	Study Design SCS = Single Centre Study MCS = Multicentre Study	Size of Sample	Drugs	PolyPh'm	Age	Renal	Female Gender	Co-morbid's	Length of Stay	Hx of allergy	Liver	Compliance	Other	Limitations to Study
Runciman, W.B. (2003)[72]	Australia	Literature review of systematic reviews and national data collections	53, 388 ADRs	✓											Review does include community data but the studies are separated out in the review to detail specifics in secondary care
Samuel, S.A., Rajendran, S.D., Ebenezzar, S., et al. (2002)[73]	2 general hospitals in India	2 sites. Prospective study post introduction of an ADR monitoring programme. Manual reporting of ADRs and patient interview.	152 ADRs	✓											Includes some data from the outpatient setting. No denominator i.e. number of ADRs recorded with probable causative agent but no record of number of prescriptions for respective agent.
Schimmel, E.M. (2003)[74]	US university hospital	Reprint of Annals of Internal Medicine, 1964, volume 60, pages 100-110. Prospective study. Recording by house officers of all noxious events in patients admitted under them	119 ADEs	✓	✓										Excludes ADEs which did not have a harmful outcome e.g. if the house officer altered treatment before an adverse incident occurred. Does not report a rate of ADEs for each drug i.e. no denominator. Relevance now with new drug groups available? Also single centre.
Smith J.W., Seidl, L.G. and Cluff, L.E. (1966)[75]	US university hospital	SCS. Prospective study with manual chart review	151 drug reactions in 900 patients	✓	✓		✓				✓	✓		✓	Only rate of reactions reported, multivariante logistic regression required to determine if independent risk factors. 1965 study and drug groups used today have altered somewhat.
Steel, K. (2004)[76]	United States	Reprint of the New England Journal of Medicine, 1981, volume 304, pages 638-42. Prospective study of medical pts. - manual review of case notes vs. a standardised 27 item instrument to identify iatrogenic issues. Hospital interventions categorised and included no. and type of drugs	290 pts experiencing iatrogenic illness. 208 caused by drugs	✓											Study from 1979. Drugs prescribed today may result in greater or less risk. No denominator included to determine rate of ADRs. Unclear if the study covered ADEs such as hypoglycaemia with insulin? Is this covered by the definition of iatrogenic illness?
Tegeder, I., Levy, M., Muth-Selbach, U., et al. (1999)[77]	University Hospital, Germany.	SCS. Retrospective case note analysis to assess if changes in lab data due to ADR and if physician recognised this	294 patients											✓	Small sample size. Changes in lab data may be a consequence of the ADR and not a pre-disposing risk factor for developing an ADR.
Van den Bemt, P., Egberts, A.C.G., Lenderink, A.W., et al. (2000)[78]	.Dutch general hospital.	Study in 2 Dutch general hospitals	149 ADEs in 538 patients	✓	✓									✓	Study from 1996 so groups of drugs prescribed may now be a little outdated.
Van Kraaij, D.J., Haagsma, C.J., Go, I.H., et al. (1994)[79]	Dutch general hospital.	SCS- Patients 65 years and over Naranjo's algorithm used to estimate the probability of adverse event being attributable to a drug. Multiple regression analysis used to measure interrelationships between variables	120 ADRs in 105 patients	✓		✓									Study only includes patients 65 years and over. Only single centre and medical patients only included
Viktil, K.K., Blix, H.S., Moger, T.A., et al. (2007)[80]	Norwegian general hospitals	MCS - 5 sites. Prospective cohort study using manual case note/chart review by the MDT. Univariante analysis and a multivariante logistic regression to assess influence of gender, age and clinical risk factors on no.s of drugs prescribed.	827 patients		✓										Drug discontinuations during hospital stay not recorded
Wiffen, P., Gill, M., Edwards, J., et al. (2002)[81]		Systematic review of the literature .Comprehensive search of MEDLINE (1966-1999), EMBASE (1980 -1999) and International Pharmaceutical Abstracts (1970-1999)		✓	✓	✓		✓	✓				✓	✓	Excludes studies post 2000. Most studies cited refer to elderly pts only which excludes drugs and characteristics common in the young.
				28	18	14	9	9	7	5	4	3	3	10	Positive Associations
				0	0	7	0	2	1	0	1	0	0	0	Negative Associations

Ten risk factors were identified in more than 1 primary research paper (see below in descending order of prevalence):

Prescription of certain drugs or classes of drugs, polypharmacy, elderly patients (defined as over 60-75 years or older), female gender, poor renal function, the presence of multiple co-morbidities, length of patient stay, history of drug allergy or sensitivity, patient compliance issues and poor liver function.

Table 2.3 lists the 28 studies that reported that the prescription of certain drugs or classes of drugs were a risk factor in the development of drug related problems. The ten most common classes of drugs reported to be associated with DRPs in the hospital setting are, in descending order of prevalence:

Intravenous antimicrobials, thrombolytics/anticoagulants, cardiovascular agents, CNS agents, corticosteroids, diuretics, chemotherapy, insulin/hypoglycaemics, opiates and antiepileptics.

Table 2.3 High Risk Drugs for Drug-related Problems

Reference	Antimicrobials	Thrombolytics/ Anticoagulants	Cardiovascular	CNS Agents	diuretics	Corticosteroids	Chemo	Opiates	Antiepileptics	Insulin / hypoglycaemics	Anti-inflammatories/ NSAIDs	Other
Alderman, C.P. and Farmer, C. (2001)[44]		✓	✓									
Al-Hajje, A.H., Atoui, F., Awada, S., et al. (2012)[45]		✓	✓			✓						
Blix, H.S., Viktil, K.K., Reikvam, \AAsmund, et al. (2004)[47]		✓	✓			✓			✓			theophylline, allopurinol, potassium, and levothyroxine
Bowman, L., Carlstedt, B.C. and Black, C.D. (1994)[49]	✓		✓		✓							
Calderón-Ospina, C. and Bustamante-Rojas, C. (2010)[50]	✓	✓	✓ Betablockers		✓				✓			
Camargo, A.L., Ferreira, M.B.C. and Heineck, I. (2006)[51]	✓			✓								
Classen, D.C., Pestotnik, S.L., Evans, R.S., et al. (2005)[53]	✓	✓	✓					✓				
Davies, E.C., Green, C.F., Taylor, S., et al. (2009)[55]	✓	✓			✓	✓		✓				
Dequito, A.B., Mol, P.G.M., van Doormaal, J.E., et al. (2011)[56]				✓								
Fattinger, K., Roos, M., Vergères, P., et al. (2000)[57]							✓					
Hoonhout, L.H., de Bruijne, M.C., Wagner, C., et al. (2010)[60]	✓	✓					✓					
Hurwitz, N. and Wade, O.L. (1969)[62]												Digitalis, bronchodilators and ampicillin
Johnston, P.E., France, D.J., Byrne, D.W., et al. (2006)[63]	✓	✓	✓				✓		✓	✓		lorazepam, theophylline, cyclosporin

Reference	Antimicrobials	Thrombolytics/ Anticoagulants	Cardiovascular	CNS Agents	diuretics	Corticosteroids	Chemo	Opiates	Antiepileptics	Insulin / hypoglycaemics	Anti-inflammatories/ NSAIDs	Other
Kanjanarat, P., Winterstein, A.G., Johns, T.E., et al. (2003)[64]	✓	✓	✓	✓				✓				
Kelly, W.N. (2001a)[65]	✓		✓	✓			✓					
Kelly, W.N. (2001b)[66]	✓			✓			✓					Vaccines
Krähenbühl-Melcher, A., Schlienger, R., Lampert, M., et al. (2007)[67]		✓			✓				✓			
Marcellino, K. and Kelly, W.N. (2001)[68]	✓			✓								
O'Connor, M.N., Gallagher, P., Byrne, S., et al. (2012)[69]					✓			✓				Benzodiazepines
Pearson, T.F., Pittman, D.G., Longley, J.M., et al. (1994)[71]		✓										
Runciman, W.B. (2003)[72]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Samuel, S.A., Rajendran, S.D., Ebenezzar, S., et al. (2002)[73]	✓			✓		✓					✓	
Schimmel, E.M. (2003)[74]	✓	✓		✓		✓	✓			✓		
Smith J.W., Seidl, L.G. and Cluff L.E. (1966)[75]	✓		✓	✓	✓	✓				✓	✓	
Steel, K. (2004)[76]	✓	✓	✓	✓								Aminophylline
Van den Bemt, P., Egberts, A.C.G., Lenderink, A.W., et al. (2000)[78]	✓	✓	✓	✓								GI Drugs
Van Kraaij, D.J., Haagsma, C.J., Go, I.H., et al. (1994)[79]	✓											
Wiffen, P., Gill, M., Edwards, J., et al. (2002)[81]	✓	✓			✓	✓				✓	✓	
	19	**16**	**13**	**12**	**8**	**8**	**7**	**5**	**5**	**5**	**4**	**Total number of studies with positive association with the drug group**

2.4. Discussion

2.4.1. High Risk Drugs

The ten risk factors most frequently associated with drug related problems are not unsurprising and yet are poorly documented as such in the literature. The identity of the drugs themselves and the associated class effects are the most commonly reported risk factor for DRPs and yet it is not possible to quantify the risk associated with the use of an individual drug or drug class. For example, intravenous antibiotics are the most frequently reported drug class increasing the risk of DRPs, while thrombolytics and anticoagulants constitute the second most prevalent group. However, none of the publications identified by the systematic review quantify those risks. Further research would be beneficial to identify a risk score for each drug class to facilitate comparisons and measures for prevention. Similarly there is no information that compares risks associated with drugs within each class.

The four most commonly named groups were antimicrobials, anticoagulants and thrombolytics, cardiovascular drugs and drugs acting on the central nervous system (CNS). Definitions of these classes of drugs were not included in almost all of the papers reviewed. While definition of antimicrobials, anticoagulants and thrombolytics are quite well defined in reference sources such as the British National Formulary (BNF), cardiovascular and CNS drugs are more difficult to define with some drugs belonging to more than one category. Without clear definitions of drug categories, interpretation of the findings and further research could be problematic. In the case of antimicrobials, none of the researchers considered the possibility that the presence of infection may

have been the causative factor leading to a DRP. Further, without a specific definition of antimicrobials it is not clear whether a distinction should be made between the risks associated with the use of intravenous antimicrobials, compared to oral and topical forms.

It is important to identify that any conclusions taken from this review are interpreted in general medical and surgical settings only. In order to obtain meaningful data, researchers have investigated groups of patients taking widely available and frequently prescribed medicines in hospital. None of the review papers reported the frequency of prescribing for a particular drug class i.e. there was no reported denominator. It is possible that the large number of DRPs associated with diuretics for example is associated with their widespread use. Some of the newer drugs to the market which the researcher would expect to be associated with a large number of DRPs compared to the number of prescriptions such as monoclonal antibodies, anti-retrovirals and anti-rejection drugs, are not included in any of the review papers and the results do not mirror alerts for high risk drugs issued nationally and internationally[38–40].

The present review did not impose a date restriction on papers despite concerns that this might have a direct impact on the range of drugs identified as high risk. However, only the inclusion of diuretics as a high-risk category seemed unexpected. On review of the date of the articles citing diuretics as a high risk drug category, four of the eight publications were published post 2005; should all papers prior to 2005 in the review been excluded, diuretics would remain as a top ten high risk drug.

One approach to increasing awareness of the risks associated with individual medicines could be that in the future, all drugs are risk assessed before they come to the market as

part of the clinical trial process. Products could be assigned a risk score prior to issue of market authorisation using a process similar to that undertaken for intravenous medication under UK NPSA Alert 20. In light of post marketing studies and national incident reporting systems, modifications of risk scores could accompany national patient safety alerts.

2.4.2. Polypharmacy

It is widely accepted and undisputed in the literature, that polypharmacy has a direct effect on the number of drug related problems. Polypharmacy has also been shown to be an independent risk factor for the development of DRPs[47,48,51,52,55–57,69,70,78,80]. Various definitions of polypharmacy exist ranging from prescription of 2 to 6 or more medicines[82]. However, it is more likely that there is a continuous relationship[80], possibly exponential[81] between the number of drugs taken and the risk of developing a drug related problem.

2.4.3. Age

Older age (definitions vary from over 60 years[50,61,63,67] to over 75 years[69]) was reported as a risk factor for drug related problems in 14 studies, however a further 6 studies[47,48,51,52,57,79] reported that age is not an independent risk factor for DRPs. The 6 studies which demonstrated that age is unlikely to be an independent risk factor used multi-variant analysis and logistic regression to show that the association of older age with DRPs is more likely to be associated with the increased incidence of multiple co-morbidities, multiple medications, poor renal function and compliance issues in elderly persons rather than a direct association with their age *per se*. This was supported by a literature review[59] over 20 years ago which recognised that most studies examining age and ADRs (including all definitions) failed to control for multiple drugs and multiple co-

morbidities. As the elderly population increases and research in this area continues, it is likely that the risks associated with the use of drugs in old age will become clearer. However, it seems logical that as life expectancy increases, exceeding the age of 65 years is unlikely to influence the likelihood of suffering an adverse drug reaction whereas the prevailing general state of health will.

One study[54] reported that the age group 18 -50 years was a risk factor for ADEs, but it is likely that this was due to the fact that the study group comprised only diabetic patients.

2.4.4. Renal Function

Poor renal function was the 4th most frequently reported risk factor, listed in nine papers[46–48,58,67,69–71,75]. However, as long ago as 1966, Smith[75] recognised that this risk factor is only likely to increase the rate of ADRs when using certain groups of drugs that are eliminated renally. However, any patient with poor renal function may have the potential to be prescribed one of these drugs and, as such, may already be deemed at risk of a DRP prior to prescription. The recommended dosage or frequency adjustments in renal failure are well documented for affected agents so that this risk may be minimised if appropriately identified. This was supported by Fields and co-workers[58] who recognised the importance of early estimation of creatinine clearance (CrCl) through computerised order entry to identify renal function as a risk factor for preventable adverse drug events.

2.4.5. Gender

Female gender is the 5th most frequently reported risk factor for experiencing drug related problems with nine papers reporting an association[48,49,54–57,61,67,81]. However, it is

possible that the link between DRPs and female gender may be weak since one paper demonstrated that gender was not an independent risk factor for ADRs[51] while another reported that adverse drug events occurred more often in men than in women[63]. However, numbers in the latter study[63] were small and most adverse events were due to drug errors, which are unlikely to be affected by the gender of the patient. Further detailed research is required to define the precise relationship.

2.4.6. Co-morbidities

Seven papers included multiple co-morbidities as a risk factor for DRPs [21,26,28,30,44,55,24]. However, Camargo[51] used multivariate logistic regression and identified that multiple diagnoses were unlikely to be an independent risk factor for ADRs. It is possible that the increased number of medicines taken by patients with multiple co-morbidities could have a bearing on the number of DRPs experienced by patients. Conversely, it is also possible that a patient's susceptibility to ADRs is increased by their poor overall health, that their metabolism of drugs may be affected by their condition or additional unknown factors. It would be advisable for more research to be carried out in this area.

2.4.7. Length of Stay

Length of hospital stay was reported as a risk factor[49,51–53,56] for DRPs. This seems a logical connection in that any adverse event (drug related or otherwise) is more likely to occur the longer the patient is observed, which in the case of hospital inpatients would be dependent on their length of stay. However, it was reported in a single paper[51] that there is an association between the follow-up period (period of time as an inpatient after an

ADR). In this case it is possible that the occurrence of an ADR caused the increase in length of stay through treatment failure, drug toxicity or other factors. None of the review papers reported that patients were more likely statistically to experience a DRP the longer the patient stayed in hospital i.e. the intra-patient risk at any point in time does not increase with the length of inpatient stay. However, it is also likely that patients who have longer hospital stays suffer from complex conditions or are more unwell, making them more susceptible to drug related problems throughout their stay: under such circumstances length of stay would be unlikely to be an independent risk factor.

2.4.8. History of Allergy and Compliance Issues

Other risk factors for DRPs included in the literature were previous history of allergy or ADR and compliance issues listed as risk factors in four[47,61,70,71] and three[47,52,81] papers respectively. Patients who may have a genetic predisposition to ADRs or who display atopic characteristics may be more likely to experience ADRs. Smith[75] noted that although there was not an overall increase of ADRs in this group, there was an increase in allergic reactions.

Compliance issues included assumed non-compliance, low cognition, and other factors affecting patients taking their medicines such as alcohol abuse and swallowing difficulties. Such barriers to compliance intuitively would predispose patients to DRPs.

2.4.9. Liver Function

The association of deteriorating liver function with DRPs is less well documented. Only 3 papers[47,70,75] list deteriorating liver function as a risk factor. In an analogous situation to those with renal impairment, poor liver function is likely to only be associated with an increased risk of DRPs when certain drugs are used i.e. those whose elimination or distribution is hepatic or affected by the reduction in protein metabolism which accompanies deterioration of liver function. Again this relationship was recognised by Smith[75] who noted in his study that although the overall rate of ADRs was not increased by decreasing liver function, the rate for certain groups of drugs was slightly increased.

Drug management in hepatic failure generally differs to therapy in renal failure. Often the risks of hepatotoxicity drive the decision to treat with a drug or not, in contrast to dosage or frequency adjustments required to avoid immediate toxicity or treatment failure encountered in renal failure. Prescribers often only have one of two options when considering a drug for use in liver failure: “to use or not to use?” - essentially a 50 percent chance of making the correct decision and avoiding toxicity which may (or may not) result in an adverse drug event. The likelihood of ADEs in patients with renal failure as opposed to liver failure seem much greater owing to errors in prescribing. These issues are compounded in renal failure owing to drug accumulation or treatment failure as CrCl reduces.

2.4.10. Other Risk Factors

Other risk factors which were uniquely identified (and were therefore not tabulated as top 10 risk factors in this review) included admission to a medical ward[55], elderly care ward, rheumatology ward or gastroenterology ward[56], source of admission (e.g. from home, general practitioner, clinic etc.)[63], insurance class (U.S)[63], infection[75], changes in patient's biochemical/haematological parameters[77], new drug initiation in hospital[78], single marital status[27], use of drugs with a narrow therapeutic index[67] and therapeutic drug monitoring (TDM) requirement in the absence of a pharmacokinetics service[71]. Since these associations were only reported in single studies, there may have been explanations for the reported risk factors. It seems likely that drugs with a narrow therapeutic index or requiring TDM are indeed generic risk factors in all specialities and that starting a new drug in any setting poses a risk owing to drug error or poor compliance. However, it is less obvious that factors such as single marital status are independent risk factors for drug related problems. Perhaps married patients may be older and their lifestyle more predictable providing a supportive environment for improved compliance.

2.4.11. Limitations to the Review

The search methodology relied on appropriate links being created from databases to key-words in the literature. When the full texts were evaluated, 44 citations were identified from cross-referencing. It was found that 30 of these papers were available through databases listed in Table 2.1 indicating that the online database search had not captured

all relevant papers. However, these databases were rechecked using various other combinations of the search terms listed in an attempt to confirm that no other papers remained. In particular, cross-referencing identified a number of older articles which have been included in this review but whose significance may be debatable owing to differences in drug treatments available historically.

Most notably, no outputs listing risk factors requiring intervention by a pharmacist were detected using these methods. It is possible that research into pharmacist interventions would assume a direct correlation between pharmacist intervention and an adverse drug event. Researchers may deem it more appropriate to assess risk factors leading to the latter since the presence of an adverse event suggests that either there has been no preventative intervention or an intervention has been unsuccessful in prevention of the adverse event. Whichever is the case, without a proven correlation between pharmaceutical intervention and the outcome of an adverse event, research methodology may be better directed at risk factors leading to adverse events caused by medicine use.

Similarly, research into pharmacist interventions is more likely to be carried out by pharmacists themselves who already target patients perceived to be at risk, this may result in bias. Intervention research is more likely to be targeted at those areas pharmacists may be missing i.e. actual reported DRPs rather than pharmacist interventions i.e. the near miss. Pharmacists may wish to determine whether DRPs are preventable, non-preventable or partially preventable through pharmaceutical intervention before targeting clinical pharmacy services to patients with risk factors for

DRPs. Certainly, research in this area is lacking and has resulted in difficulties in quantifying the worth of clinical pharmacy services.

There were further limitations to the review in that the search method employed relied on the use of a number of electronic databases (Table 2.1) all of which used English as the primary language. Similarly, all of the journals searched were publications in the English language. As a consequence, although the databases included citations from international journals, it is likely that there is a bias towards publications in the English language and that other work, in particular from the Far East may have been overlooked.

The review which was completed in 2013, imposed no date restriction on papers included however, the oldest paper identified was from 1966, papers prior to this date are less likely to be comprehensively included in the electronic databases searched. It is recognised that this may have a bearing on those drugs included as high risk. Further, up-to-date research is required in this area since inclusion of current, accepted high risk drugs are conspicuous in their absence from recent literature e.g. monoclonal antibodies, anti-retrovirals and biosimilars. There is currently little difference in those drug groups associated with DRPs and those included in the literature prior to 2005. It is also possible that the lack of inclusion of a denominator in papers reporting classes of high-risk drugs caused some of the newer drug classes to be absent from the more recent research papers.

2.5. Conclusions

Review of the literature found 38 papers, which detailed 10 measurable risk factors linked with drug related problems in hospital inpatients. Each were identified in the literature by more than one primary research article. There were no papers which detailed the risks associated with the likelihood of experiencing a pharmaceutical intervention. More research is required in this area as although it is likely that interventions are carried out where there is a risk of a problem associated with the use of medicines, this cannot be assumed. It is possible that there are additional factors, which cause pharmacists to intervene which have not been previously identified.

All of the risk factors for DRPs are potentially identifiable from an individual patient's records on admission to hospital and it is hoped that these risk factors may be used to identify patients at risk with a view to targeting pharmaceutical input in order to minimise the risk of a DRP. Risk factors include older age, polypharmacy, presence of multiple comorbidities, poor renal function, poor liver function, compliance issues, female gender, length of hospital stay, previous history of allergy or ADR and class of drug prescribed.

Prescriptions which are associated with a high risk for DRPs include antimicrobials (intravenous antibiotics), anticoagulants and thrombolytics, cardiovascular drugs and drugs acting on the central nervous system (CNS). More research is required to ensure that newer drug classes are included in research into risks associated with DRPs and whether the risks associated with the use of high-risk drugs are preventable.

CHAPTER 3

IDENTIFICATION OF COMMON CATEGORIES OF PHARMACIST INTERVENTIONS

3. Identification of Common Categories of Pharmacist Interventions.

3.1. Introduction

3.1.1. Background

A pharmacy intervention can be defined as:

'An intervention which results in the correction of a prescribing/transcribing error or the provision of pharmaceutical advice which optimises the patient's care'[83].

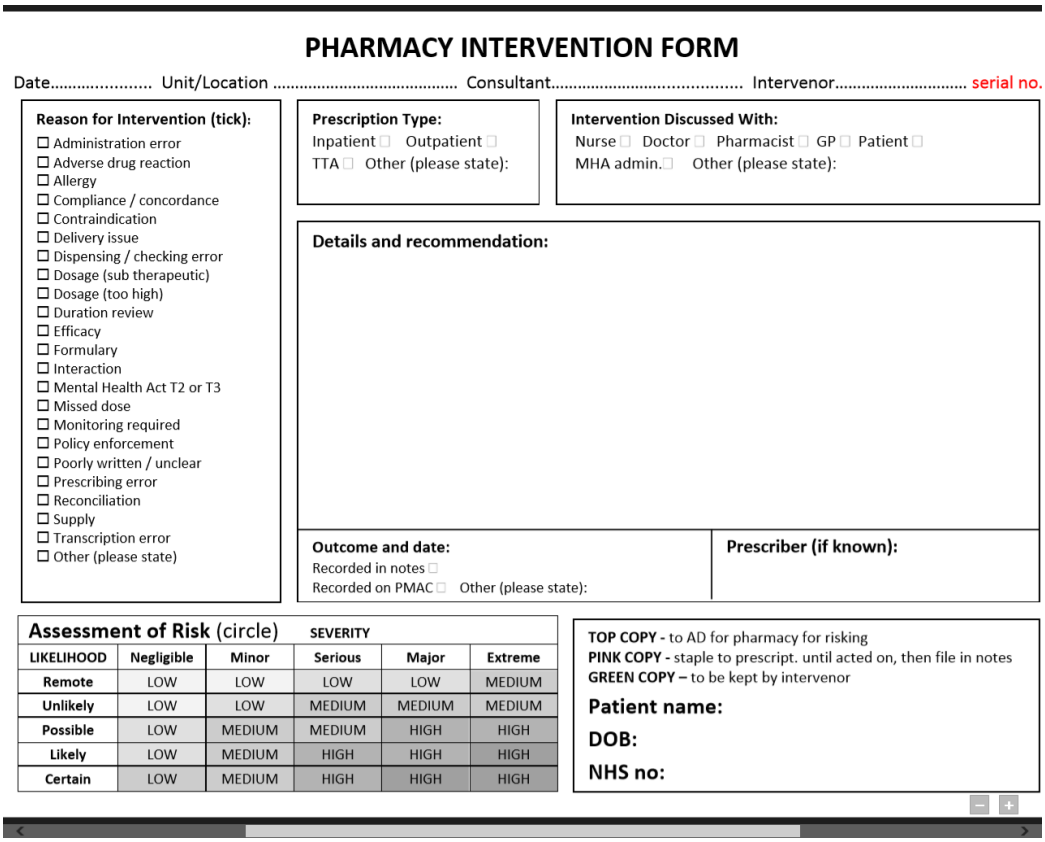
A pharmacist intervention is not a clinical pharmacy review of a patient's medication but an intervention into their treatment as a consequence of such a review. Not all inpatients in hospital in the UK will be the recipient of a pharmacy intervention but most will receive a pharmacy review of all their medications.

Chapter 2 concluded that there were no studies within the limitations of the systematic review, which identified risk factors leading to pharmacist interventions. It is possible that this is due to poor association between pharmacist interventions and adverse drug events (ADEs) with the result that research into risk factors leading to outcomes for patients is more likely to be directed at adverse events in order to achieve reliable research outcomes. Historically, this poor association may be for a number of reasons but it seems logical that when conducting research regarding risks associated with ADEs or other drug related problems to review data where events actually occurred rather than pharmacist interventions, which in essence, constitute a "near miss".

However, although evidence of a direct correlation between pharmacist interventions and medicines related incidents is poor, there is increasing evidence that pharmacist interventions in certain settings, do or can, lead to a reduction in ADEs[3,84–87]. As a practicing pharmacist in a tertiary care setting, the researcher is also aware that it is common place for pharmacists to record the circumstances which lead to an intervention and the precise detail of the respective intervention. In comparison ADEs are often poorly recorded and at worse, undocumented[88,89]. This wealth information regarding pharmacist interventions gives a unique opportunity for analysis of the circumstances peri-intervention and potentially (assuming we accept the hypothesis of a "near miss"), the circumstances prior to an ADE.

Pharmacist interventions are usually recorded on intervention forms which prompt the intervening pharmacist to record specific details of the intervention and outcome. Documentation forms may be paper based (e.g. Figure 3.1), paper based with later transfer to electronic database or more recently directly into an electronic database (e.g. Figure 3.2).

Figure 3.1 Example of Hard Copy Intervention Documentation Tool [90]



PHARMACY INTERVENTION FORM

Date..... Unit/Location ..... Consultant..... Intervenor..... serial no.

Reason for Intervention (tick):

- ☐ Administration error
- ☐ Adverse drug reaction
- ☐ Allergy
- ☐ Compliance / concordance
- ☐ Contraindication
- ☐ Delivery issue
- ☐ Dispensing / checking error
- ☐ Dosage (sub therapeutic)
- ☐ Dosage (too high)
- ☐ Duration review
- ☐ Efficacy
- ☐ Formulary
- ☐ Interaction
- ☐ Mental Health Act T2 or T3
- ☐ Missed dose
- ☐ Monitoring required
- ☐ Policy enforcement
- ☐ Poorly written / unclear
- ☐ Prescribing error
- ☐ Reconciliation
- ☐ Supply
- ☐ Transcription error
- ☐ Other (please state)

Prescription Type:
Inpatient ☐ Outpatient ☐
TTA ☐ Other (please state):

Intervention Discussed With:
Nurse ☐ Doctor ☐ Pharmacist ☐ GP ☐ Patient ☐
MHA admin. ☐ Other (please state):

Details and recommendation:

Outcome and date:
Recorded in notes ☐
Recorded on PMAC ☐ Other (please state):

Prescriber (if known):

Assessment of Risk (circle) SEVERITY

LIKELIHOOD	Negligible	Minor	Serious	Major	Extreme
Remote	LOW	LOW	LOW	LOW	MEDIUM
Unlikely	LOW	LOW	MEDIUM	MEDIUM	MEDIUM
Possible	LOW	MEDIUM	MEDIUM	HIGH	HIGH
Likely	LOW	MEDIUM	HIGH	HIGH	HIGH
Certain	LOW	MEDIUM	HIGH	HIGH	HIGH

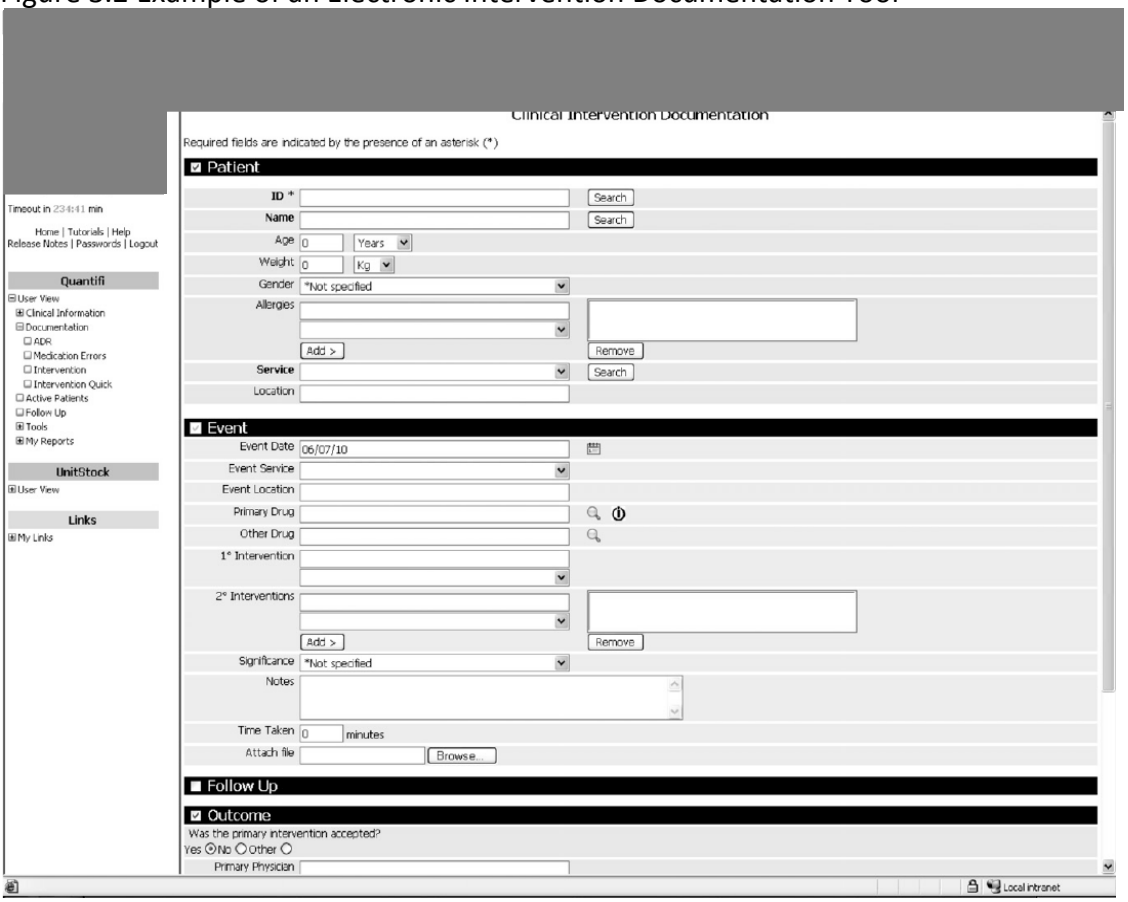
TOP COPY - to AD for pharmacy for risking
PINK COPY - staple to prescript. until acted on, then file in notes
GREEN COPY – to be kept by intervenor

Patient name:

DOB:

NHS no:

Figure 3.2 Example of an Electronic Intervention Documentation Tool [91]



The main purpose of documentation of pharmacist interventions is twofold. The first from an operational perspective, is that they provide evidence of service or individual performance and the second is to provide analytical data for research into the interventions and the ADEs which, in theory, they prevent. Consequently pharmacists have developed numerous different tools to record interventions, which enable retrospective data analysis. However, there is no national or international guidance on what should be documented and the categories of information documented vary. Pharmacists use their own pharmaceutical knowledge and expertise to determine the local procedure for documentation and usually adapt a regional or a prestigious centre's approach and categorisation to suit local initiatives.

What shouldn't be ignored is that almost always, one of the purposes of documentation of pharmacist interventions is to enable analysis of the documentation to find "patterns" in the intervention data either after local informal review (which is most often the case) or after formal research. These "patterns" potentially identify where most frequently interventions are occurring with a view to putting preventative measures in place. For example, a simple analysis of intervention data might show that prescribers consistently prescribed the incorrect dose of drug x, on finding this "pattern" in the data, the pharmacy team may issue guidance on dosage for the drug.

In essence, pharmacists have developed intervention documentation forms to analyse not only what happens when they perform an intervention for operational purposes but where and why they are performing interventions. Assuming that interventions are a "near miss" for an ADE the categorisation of "where" and "why" of Pharmacist intervention documentation may constitute perceived risk factors for ADEs.

3.1.2. Aims

The purpose of this systematic review is to identify which categories are most commonly used when documenting pharmacy interventions in secondary or tertiary care. These categories may also be risk factors for ADEs.

All categories of interventions will be included, not just those which are thought to identify risk factors for intervention or ADE. This is because there may be risk factors which have not been previously identified in the literature or recognised by researchers but have been used as categories for analysis for other purposes (e.g. financial and economic evaluation).

The intention is that the results together with those risk factors identified in Chapter 2, may be used for further research to identify patients at risk of problems associated with the use of medicines and requiring intervention with a view to targeting pharmaceutical input in hospital.

3.1.3 Objective

The primary objective is to identify and document all measurable categories of pharmacist interventions in secondary or tertiary hospital settings which may be retrieved prospectively from a patient's clinical records during their inpatient stay in hospital whether these be demographic, clinical or otherwise.

Objectives include:

a) Identify all measurable categories by searching the literature and tabulating the results;

b) Determine which of these risk factors may be retrieved from clinical documentation through intensive reading.

3.2. Methods

Identification of quantitative and measurable categories used when documenting or analysing pharmacist interventions in the adult inpatient setting in secondary care.

A systematic review was conducted to source primary research identifying measurable categories for pharmacist interventions. All definitions of pharmacist interventions were included. No language restrictions were imposed however publications prior to the year 2000 were excluded.

The author used mind mapping to identify the following free text search terms: pharmacy intervention, pharmacist intervention, pharmaceutical intervention, categories, categorization, analysis, documentation, review, recording.

Paper Inclusion Criteria: Measurable intervention categories, patients over 16 years, inpatients in secondary or tertiary care centres, all definitions of pharmacy interventions, inpatients in medical and surgical wards, all primary research and systematic reviews.

Paper Exclusion Criteria: Qualitative categories, studies of patients 16 years or less, outpatients, ambulatory care and community based studies, studies solely in specialist care settings dealing with narrow group of patients e.g. intensive care and diabetes

patients, summary articles (with the exception of systematic reviews) and discussion articles. Table 3.1 details the databases searched.

Table 3.1 Databases Searched to Identify Common Categories of Pharmacist Interventions

Name of Database	Location	Description
1. Medline	www.ncbi.nlm.nih.gov/PubMed	Bibliographic records (with and without abstracts) of biomedical literature from 1966 onwards.
2.EMBASE	www.embase.com	Biomedical literature from 1974 onwards
3.Cochrane Data Base of Systematic Reviews	http://www.cochrane.co.uk/en/index.html	Database of systematic reviews, includes reviews of work in progress

3.3. Results

An initial search (Figure 3.3) of the online databases using the free text search terms listed identified the following number of articles, the title of which was reviewed by the researcher:

PubMed- Initial, 146 articles

Embase – Initial, 236 articles

Cochrane Database – Initial 14 reviews

The web was also searched using a domestic search engine, to identify any grey literature. One study was identified by this method.

Forty two articles were identified from the title alone and this was reduced to 31 after review of the abstract. A further 6 articles were removed owing to publication prior to the year 2000 and consequently a total of 25 full text articles were sourced for intensive reading. Of the remaining articles, 6 were discarded at intensive reading since they did not document the classification system used in the study or were discussion articles concerning the principles of and necessity for comprehensive and retrievable documentation of clinical interventions by pharmacists.

The final 19 articles are listed in Table 3.2. As part of the intensive reading process, the categories of interventions used both at the documentation stage of the intervention and during analysis which took place as part of the study was recorded in Table 3.3.

Figure 3.3 Review Process

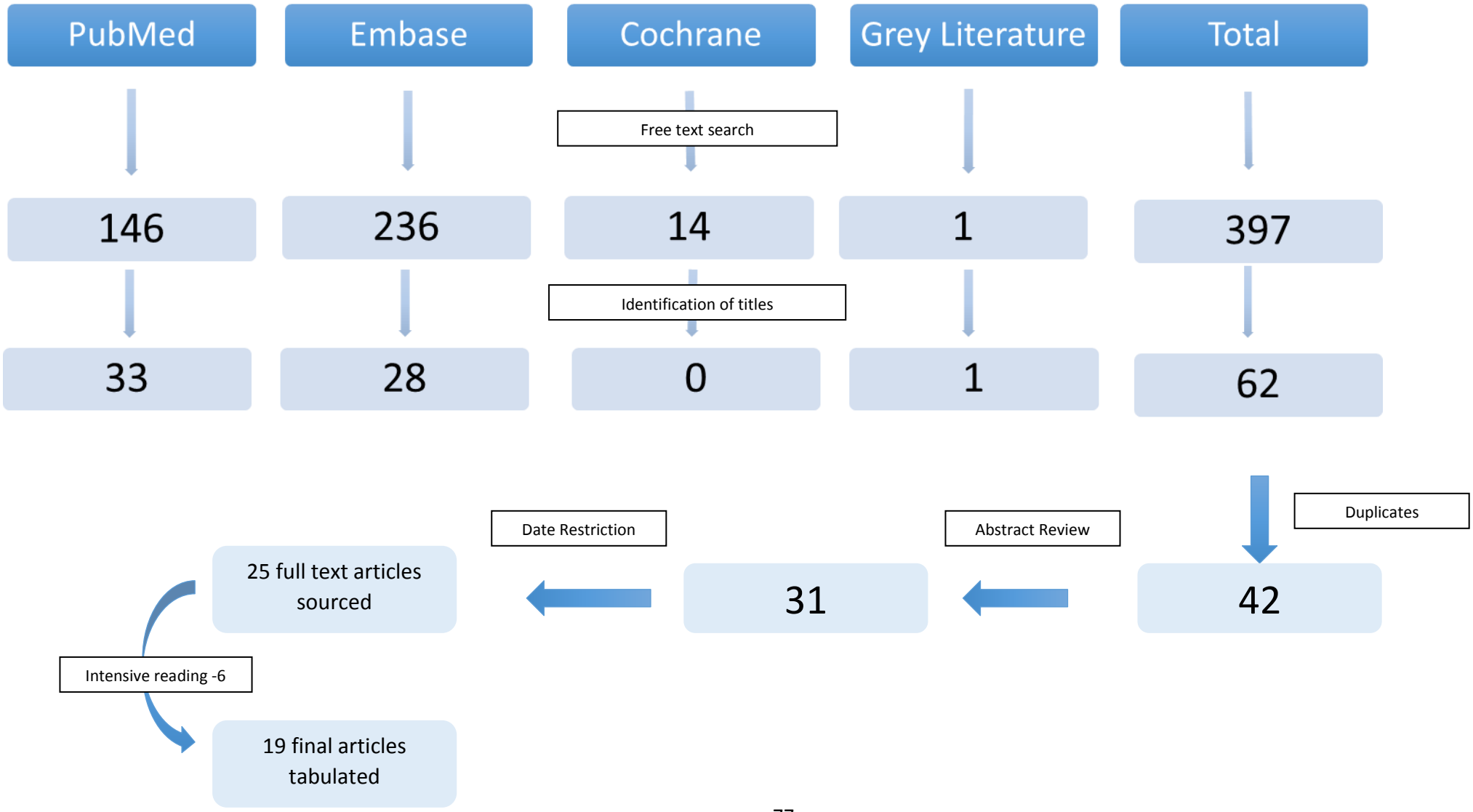


Table 3.2 Studies Using Categorisation of Interventions.

Author, Year	Country	Study Type	Study Aim	Intervention definition	Method of Recording	Classification Source
Alderman et al., 2001[44]	Australia	Prospective analysis of intervention considered to have the potential to cause considerable harm over a 30 day period	To study the "near miss" scenarios detected in the course of clinical pharmacy practice, providing the opportunity to implement systemic solutions	"Any action by a clinical pharmacist which directly results in a change in patient management or therapy"	Paper-based	Demographics, not referenced. DRP categories from Strand et al.[92]
Allameh et al., 2013[93]	Iran	Retrospective, descriptive study of 2,227 interventions from 3,152 records.	To assess the impact of clinical pharmacy services by categorising into, types, severity, resolution and accuracy	No definition	Paper-based	Severity score based on Knudsen et al.[94] Other categories not referenced
Allenet et al., 2006[95]	France	Prospective study including design and validation of intervention form	To validate an instrument for documentation of clinical pharmacy interventions in French speaking hospitals	"A change in drug therapy initiated by the pharmacist"	Paper- based	DRP categories adapted from Strand et al.[92]
Amara et al., 2010[91]	United States	Retrospective analysis of web-based documentation tool for intervention recording	To assess the first 6 years of documented interventions after introduction of a Web-based documentation tool	No definition	Web-based	*Quantifi®* clinical intervention monitoring tool
Bedouch et al., 2012[96]	France	Prospective cohort study in 7 wards of a French teaching hospital using computerised physician order entry (CPOE)	To analyse pharmacist interventions in a setting using CPOE and ward-based pharmacy	"Any action initiated by a pharmacist directly resulting in a change of the patient's management or therapy"	CPOE	DRPs and interventions categorised according to a validated tool used by the French Society of Clinical Pharmacy- Allenet et al 2006[95]. However, categories have been amended since 2006
Boardman H and Fitzpatrick R. , 2001[97]	United Kingdom	Prospective observational study in 4 acute trusts	To determine what activities pharmacists actually undertook on a clinical pharmacy ward visit and to compare this to the usual method of measuring clinical pharmacist performance, self-reported pharmacist interventions	"those activities where the pharmacist was involved in a query about the patient's treatment whether that be a change or an alteration in drug therapy or advice for doctors or nurses to monitor a patient for possible problems"	Paper-based and observational	Categories derived from observation pre-study and analysis post result collection
Divall et al., 2010[98]	United States	Development of a Pharmacy School wide intervention form by Pharmacy practice Faculty consensus and upload to a secure Website	To implement and evaluate a school wide, web-based clinical intervention form to document types and impact of pharmacy students' clinical activities during advanced pharmacy practice experiences	No definition	Web-based	No source stated as developed "in house"

Author, Year	Country	Study Type	Study Aim	Intervention definition	Method of Recording	Classification Source
Dornan T et al., 2009[17]	United Kingdom	EQUIP Study - Mixed method study including literature review and comprehensive quantitative and qualitative studies on prevalence and causes of prescribing errors	To explore the causes of prescribing errors made by FY1 doctors concentrating on the interplay between the doctor's educational backgrounds and factors in the practice environment	No definition	Paper-based	No source stated, developed to gather information required for study
Donyai et al., 2008[99]	United Kingdom	Prospective, comparative study in a tertiary care centre	To determine the effects of electronic prescribing on quality of prescribing as indicated by prescribing errors and pharmacists' clinical interventions	"any proactive or reactive (in response to a question from another healthcare professional) activity undertaken to suggest changes to drug therapy or monitoring that involved contacting healthcare staff"	Paper-based	Prescribing error type and stage was classified according to Dean et al. 2002[100] as was stage of intervention. Severity of prescribing error classified according to Dean et al. 1999[101]
Dooley et al., 2004[102]	Australia	Prospective study examining resource implications of pharmacist's interventions assessed by an independent clinical panel	To determine the cost savings of pharmacist initiated changes to hospitalised patients drug therapy or management in 8 acute teaching hospitals	"any action which directly resulted in a change to patient management or therapy"	Paper-based	No source referenced
Fernandez-Llamazares et al., 2012[103]	Spain	Prospective descriptive study in a teaching hospital	To validate the inter-rater reliability of the method used to record interventions at the research hospital with a view to ensure consistency in recording	No definition	Paper- based then transferred into Microsoft Access	Based on Overhage and Lukes, 1999[104] and the Third Consensus Conference of Granada.
Khalili et al., 2011[105]	Iran	Prospective interventional study in an Iranian teaching hospital	To determine the frequency and type of medication errors and the pharmacists role in detection and prevention	No definition	Paper based	Medication errors classified according to Pharmaceutical Care Network Europe Foundation.
Kucukarslan et al., 2003[3]	United States	Prospective, single-blind, standard care controlled study	To evaluate the impact of having a pharmacist participate in a physician's ward round and to document the interventions made when doing so	No definition	Paper based	Intervention type classified according to Leape et al., 1999[84]
Lada and Delgado., 2007[106]	United States	Prospective study evaluating documented pharmacy interventions	To analyse pharmacist interventions and resuscitation experiences involving pharmacists to assess the potential cost avoidance associated with pharmacist interventions	No definition	Paper based and entered into database weekly	No source referenced for intervention type. Severity score as per Lee et al., 2002[107]

Author, Year	Country	Study Type	Study Aim	Intervention definition	Method of Recording	Classification Source
MacKinnon, 2003[108]	United States	Prospective descriptive study of pharmacy interventions	To analyse pharmacist interventions using an internet based documentation system	No definition	Web-based	Elements of intervention recording form developed over a 10 year period testing paper collection forms. Mackinnon, 2002[109]
Millar et al., 2007[110]	New Zealand	A questionnaire based cross-sectional survey of all pharmacy managers in publically and privately funded hospitals	To investigate the perceived value and the recording, storage and use of pharmacists' clinical data in New Zealand hospitals	"any action taken by a pharmacist that aims to change patient management or therapy"	NA- Survey requesting details of recording methodology nationwide	NA- Survey requesting details of recording methodology nationwide
Nurgat et al., 2011[111]	Saudi Arabia	Retrospective comparative study of a web-based tool versus multi-user PC software	To develop a database for documenting pharmacist interventions through a web based application and to determine if the new tool had benefits in terms of documentation compliance and ease of calculating cost savings	No definition	Web-based	Developed in house from a previous paper-based system
Olson et al., 2005[112]	Canada	Retrospective pilot study to analyse documented clinical interventions	To identify benefits of pharmacists by determining their impact on patient care and to identify potential problems with data collection and cost estimation to improve future documentation of services	No definition	Paper-based	Interventions classified according to Leape et al., 1999[84]. DRPs which led to these interventions classified according to Overhage and Lukes, 1999[104].
Stevenson et al., 2011[113]	United States	Descriptive prospective study of development of a web-based documentation tool	To evaluate the effectiveness and impact of a web-based tool for documentation of clinical interventions by pharmacy PharmD students.	No definition	Web-based	*Quantifi®* clinical intervention monitoring tool

Table 3.3 Categories Used in Documentation and Analysis of Interventions

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Alderman et al., 2001[44]	✓	✓		✓		✓	✓										✓				6	**DRP – 7:** No indication, Unfulfilled indication, Suboptimal dose, High dose Drug interaction, Adverse drug reaction, Inappropriate drug selection
Allameh et al., 2013[93]	✓	✓	✓																	✓1 Accuracy	4	**Severity – 3:** Minor potential inconvenience to pt Potentially influence treatment of pt but correctable Potentially influence treatment of pt, intensive treatment is required **DRP – 7** ("improper medication use" further subdivided into 11 categories): Dose adjustment, Improper medication use, Monitoring Recommendations Interaction, ADR, Peri-operative, Order clarification/ pt education **Intervention/Action type – 5:** Counselling, Recommendations to the Pt Recommendations to the Prescriber, Recommendations to the Nurse ADR Reporting
Allenet et al., 2006[95]	✓	✓			✓												✓				4	**DRP -10:** Non-conformity with guidelines or contraindication, untreated indication Subtherapeutic dosage, Supratherapeutic dosage, Drug without indication Drug Interaction, Adverse Drug Reaction, Improper administration Failure to receive drug, Drug monitoring **Intervention/Action – 7:** Addition of a new drug, Drug discontinuation, Drug switch Change of administration route, Drug monitoring Administration mode optimisation, Dose adjustment

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Amara et al., 2010[91]	✓		✓	✓	✓	✓	✓	✓		✓						✓					9	No DRP category. However, the intervention type/Action is definitive of the DRP e.g. "unapproved abbreviation clarified". The intervention type being subdivided into a "drop down" menu from which the intervention type may be selected. The paper does not specify how many subcategories are in this drop down.
Bedouch et al., 2012[96]	✓	✓		✓	✓														✓	✓1 Mode of communication	6	**DRP- 10:** as per Allenet et al.; 2006 **Action - 4:** Drug Choice, Dose adjustment, Drug monitoring, Optimisation of administration **Mode of Communication:** Computer, Oral, Ward round
Boardman H and Fitzpatrick R. , 2001[97]	✓	✓		✓	✓				✓											✓2 Desired outcome and Info. gathered	7	**DRPs – 13:** Omission/legality, Dose, Duration, Administration, Adverse Effect, Interaction Choice of Drug, Formulary, Pharmacokinetics, Other, Supply issue Request for information, Addition of cautionary labelling
Divall et al., 2010[98]	✓		✓	✓	✓			✓	✓		✓										7	**Intervention Type/Action- only top 5 listed in paper:** Dose Adjustment, Education of (patient) or (prescriber) New drug for untreated indication, Subtherapeutic regimen Drug information **Acceptance – 6:** Recommendation accepted as is, accepted with modifications, DI or education provided, intervention completed/Rejected, Unable to follow up or unresolved, Left blank/not documented **Severity (clinical significance) -5:** No significance, Somewhat significant, Significant Very significant, Left blank/not documented
Dornan T et al., 2009[17]		✓	✓	✓		✓	✓	✓			✓		✓					✓	✓	✓3 Dose, Frequency and Actual or potential harm	13	**Severity of DRP – 4** Major (Potentially Lethal), Serious (Potential for harm) Significant (clinical affect but unlikely to cause harm) Minor (no clinical affect, no harm) **Grade of Prescriber – 8** Foundation year 1, Foundation year 2, Specialist trainee Staff Grade, Consultant, Pharmacist, Nurse, Other

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Donyai et al., 2008[99]	✓	✓	✓															✓			4	Unclear from paper if other information was gathered
Dooley et al., 2004[102]	✓	✓	✓		✓	✓	✓					✓								✓2 Details of therapy before and after intervention and therapy at discharge	9	**Purpose of intervention - 9** Decrease of potential side effects, Increase of efficacy Reduced mortality and morbidity, Symptom control, Cost savings Decreased actual adverse drug effects, Assist compliance Formulary reasons, Other **Intervention type/ Action - 6** An alteration to patient monitoring, Initiation of therapy Discontinuation of therapy, Change of a drug, Change of dosage, Other **Severity - 4** Life Threatening, Major, Moderate, Minor
Fernandez-Llamazares et al., 2012[103]	✓	✓	✓	✓	✓	✓	✓	✓												✓2 Cause of DRP & Type of prescription	10	**DRP (termed negative outcome associated with the use of a medicine (NOM) in this study – 7** No NOM. No medicine related problem identified Potential or real NOM, related to untreated health problem Potential or real NOM, related to the effect of unnecessary medication Potential or real NOM, related to qualitative lack of effectiveness Potential or real NOM, related to the quantitative lack of effectiveness Potential or real NOM, related to the qualitative lack of safety Potential or real NOM, related to the quantitative lack of safety
Khalili et al., 2011[105]				✓		✓	✓				✓		✓								5	**DRP – 4** Drug Choice Problem (subdivided into 6 further categories) Dosing Problem (subdivided into 4 further categories) Drug Use Problem (subdivided into 2 further categories) Interactions (subdivided into 2 categories)

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Kucukarslan et al., 2003[3]	✓	✓		✓		✓	✓				✓		✓							✓2 Race and No. of co-morbidities	9	**Intervention Type – 9 (Leape et al.)** Clarification of drug order, Provision of drug information Recommendation of alternative therapy, Identification of drug interaction Identification of systems error, Identification of drug allergy Approval of a non-formulary use of a drug, Provision of special order drug Identification of an ADE
Lada and Delgado., 2007[106]	✓		✓		✓															✓1. Time of day	4	**Intervention Type - 15** Provision of drug information, Recommendations for dosage adjustment Formulary interchange, Initiation of medications, Alternative drug therapy Discontinuation of drug therapy Changes in medication therapy due to allergy notification Drug therapy duplication prevention, Changes in the route of administration Questions from Nursing Staff, Order clarification, Drug compatibility issues Patient information, Toxicology, Drug interaction identification
MacKinnon , 2003[108]	✓	✓	✓	✓	✓				✓			✓									7	**DRP Classification – 8** Order clarification, Drug product selection, Wrong drug, Dosage Adverse drug reaction, Contraindication, Inappropriate compliance Referral needed **Severity – 3** Significant, Moderate, Mild **Acceptance/ Outcome – 2** Expected outcome, Results
Millar et al., 2007[110]	✓ 88%	✓ 63%	✓ 63%	✓ 88%	✓ Acceptance 54% Outcome 20%			✓ 88%	✓ 88%	✓ 75%		✓ 50%		✓ 96%	✓ 75%	✓ 10%	✓ 25%	✓ 20%		✓3 Effect on cost saving 33%, Info sources used 10% and Other info 10%	17	**Intervention type – 2** Sub-classified 88% Free-typed 88%

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Nurgat et al., 2011[111]	✓	✓	✓		✓			✓	✓	✓				✓	✓					✓1 Other drugs prescribed	10	**DRP – 9** No indication, No drug order for medical condition, Formulary duplication, Inappropriate drug selection, Inappropriate dosage regimen (subdivided into dose, frequency, duration, route and rate), Prescribed drug not administered, Potential/Actual (ADR/Allergy/Toxicity) Potential/ Actual Drug interaction (subdivided into drug-drug, drug-food, drug-disease, drug-lab test), Miscellaneous (subdivided into lab, pt counselling, answer question, other) **Type of Intervention - 4** Pharmacokinetics, Pharmacotherapeutics, Drug information, Miscellaneous **Severity - 3** Potentially severe/high, Important/moderate, Minor/low **Acceptance - 4** Accepted, Modified then accepted, Denied, Unknown **Expected outcome - 4** Cost saving (subdivided into unnecessary drug, change to dosage regimen, change to less expensive drug, indirect cost saving), Enhanced therapeutic effect, ADR/Toxicity prevented/resolved
Olson et al., 2005[112]	✓	✓	✓			✓						✓		✓	✓					✓2 Date of admission and Estimated cost	9	**Intervention type – (adapted from Leape et al.)** Order clarification or correction, Provision of drug information, Formulary management, Assessment of adverse drug event, Assessment of drug interaction, Consideration of special order or investigational drug Recommendation of alternative medication, Other **DRP – (adapted from Overhage and Lukes)** Sub-therapeutic dose, Untreated disease state, Potential overdose, Failure to receive drug, Non-formulary agent, No indication for use of prescribed drug, Distributional error, Inappropriate drug choice, Adverse drug event, Drug interaction, Inappropriate frequency, Inappropriate duration, Inappropriate monitoring parameters, Inappropriate combination, Inappropriate admission time

Study	Intervention type/ Action	DRP	Severity/risk	Drug Name	Acceptance / outcome	Gender	Age	Location/ Speciality	Pharmacist ID	Consultant ID	Disease state	Time taken	No. of drugs	Date	Patient ID	Allergies	Drug Class	Stage of stay	Seniority of prescriber	Other	No. of Categories	No. of sub categories
Stevenson et al., 2011[113]	✓		✓	✓	✓	✓	✓	✓		✓						✓					9	Intervention type subdivided into a "drop down" menu from which the intervention type may be selected. The paper does not specify how many subcategories are in this drop down.
Total:	**17**	**14**	**13**	**12**	**12**	**9**	**8**	**7**	**5**	**4**	**4**	**4**	**3**	**3**	**3**	**3**	**3**	**2**	**2**	**11 studies 20 "Other" categories**		

The four most common categories of intervention were intervention action/type, drug related problem (DRP), severity of near miss and drug Involved. All of the studies categorised interventions with respect to the DRP, intervention action or both. In all studies, DRP and/ or intervention action categories had at least 4 subcategories.

Severity of the “near miss” was subcategorised into at least 3 categories.

In order to make comparisons between the subcategories used for DRP and intervention action categories, the subcategories were tabulated in Tables 3.4 and 3.5 in order of frequency used.

It was noted that DRP subcategories included the following, which were in fact, intervention actions taken by the pharmacist as a consequence of a DRP and therefore were not included in Table 3.4:

Clarification of order; Addition of cautionary labelling; Referral needed; Patient counselling/education; Answer to a question provided.

It was noted that intervention action/type subcategories included the following which were actually descriptions of the subcategories of DRPs which led to the intervention action and therefore were not included in Table 3.5:

Sub-therapeutic regimen; Identification of drug interaction; Identification of systems error; Identification of drug allergy; Identification of an ADE; Drug therapy duplication prevention; Drug compatibility issues; Toxicology; Drug interaction identification; Pharmacokinetics; Pharmacotherapeutics; Assessment of adverse drug event; Assessment of drug interaction.

Table 3.4 Comparison of DRP Categories

Study	Interaction	ADR	Wrong Drug	Wrong Dose	No indication	Untreated Indication	Administration problem	formulary/ Guidelines	Monitoring	Dose too High	Dose too Low	omission	Duration	Frequency	Compliance	Pharmacokinetics	Distribution	Request for Information	Supply issue	Incomplete /legality	Peri-operative
Alderman et al., 2001[44]	✓	✓	✓		✓					✓	✓										
Allameh et al., 2013[93]	✓	✓		✓			✓		✓												✓
Allenet et al., 2006[95]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓									
Bedouch et al., 2012[96]	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓									
Boardman H and Fitzpatrick R. , 2001[97]	✓	✓	✓	✓			✓	✓					✓			✓		✓	✓	✓	
Fernandez-Llamazares et al., 2012[103]				✓	✓	✓															
Khalili et al., 2011[105]			✓	✓			✓														
MacKinnon, 2003[108]		✓	✓	✓											✓						
Nurgat et al., 2011[111]	✓	✓	✓	✓	✓	✓		✓	✓			✓									
Olson et al., 2005[112]	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓			✓				
Total:	**8**	**8**	**6**	**6**	**6**	**5**	**5**	**5**	**5**	**4**	**4**	**4**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**

Table 3.5 Comparison of Categories of Intervention Action/Type

Study	Change of drug	Drug information	Addition of drug	Dose adjustment	Clarification	Counselling	Discontinued drug	Formulary management	Change of route	Drug monitoring	Information given to nurse	Change due to allergy	Provision of a special order drug	Optimisation of admin.	Information given to prescriber	ADR Reporting
Allameh et al., 2013[93]						✓					✓				✓	✓
Allenet et al., 2006[95]	✓		✓	✓			✓		✓	✓				✓		
Divall et al., 2010[98]		✓	✓	✓	✓	✓										
Dooley et al., 2004[102]	✓		✓	✓			✓			✓						
Kucukarslan et al., 2003[3]	✓	✓			✓			✓				✓	✓			
Lada and Delgado., 2007[106]	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓				
Nurgat et al., 2011[111]		✓														
Olson et al., 2005[112]	✓	✓			✓			✓					✓			
Total:	**5**	**5**	**4**	**4**	**4**	**3**	**3**	**3**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**1**

3.4. Discussion

In general the results indicated that there is no universal consensus regarding the categorisation and recording of pharmacy interventions. This may be partly due to the fact that none of the 19 papers identified in the search were designed to identify an appropriate categorisation system for the documentation and analysis for interventions. Categories were mainly determined in response to the objective of the research; for example, Dooley et al., 2004[102] had the objective of determining the cost savings of pharmacist initiated changes to drug therapy and therefore the categories included in the study were those allowing calculation of the associated costs and potential cost savings as a result of intervention i.e. time taken for the intervention, whether or not the intervention was actually accepted, details of therapy before and after the intervention and therapy at discharge.

A number of studies had a similar objective of validating a documentation tool[95,91,98,103,111,112,113]. However, "validation" and therefore the categories used are dependent on the detailed objective of the study or the purpose for which documentation is stored and analysed. Validation to determine if the new tool has benefits in terms of documentation compliance and ease of calculating cost savings (Nurgat et al.[111]) requires different categories for analysis than validation to determine the inter-rater reliability of the method used to ensure consistency in recording (Fernandez-Llamazares et al.[103]).

Some studies referenced categorisation of severity of DRP/intervention, DRP and intervention action/type to previous categorisation systems.

Severity of the DRP was referenced in 3 studies[93,99,106] using previous systems used by

Knudsen[94], Dean[101] and Lee[107]. However, all of the studies adapted the scoring system before use. Similarly where DRP categories and intervention categories were referenced[44,95,96,99,103,105,3,108,112], the categorisation systems where adapted before use in all but one study[96], demonstrating the lack of consistency and agreement regarding intervention categorisation and documentation.

Where defined, the studies agreed regarding the definition of a pharmacist intervention, with all definitions being based on "Any action initiated by a pharmacist directly resulting in a change of the patient's management or therapy". Twelve of the nineteen studies did not however explicitly define pharmacist intervention, which the author interprets as a likely reflection of widespread acceptance of the definition.

One of the studies conducted by Millar et al.[110], was of particular interest since it investigated categories used to record pharmacy interventions via a questionnaire to all hospital pharmacy managers. It is likely that this study gives a more detailed and comprehensive description of intervention categories used in hospital practice since investigational studies using interventions may not always list the detail of categories, which are not relevant to the study. For example, Millar's study[110] identified that the date and pharmacists' identification was recorded in 96% and 88% of hospitals respectively and it is probable that due to Millar's study design (where managers were specifically asked if these categories were included), the percentages are an accurate reflection of documentation rate. However, despite this high percentage, very few investigational studies recorded the documentation of date or pharmacist's identification. Only 2 other papers[111,112] listed date and 4 listed, pharmacists' identification[97,98,108,111] as a category for intervention documentation. In general, papers describing investigations using interventions listed the categories used for analysis rather than those which were actually

documented when recording the intervention such as who performed the intervention and when. Date, pharmacists' identification and patient identification are recorded as standard in UK hospital pharmacy to allow for follow up and accountability of the pharmacist. Millar's study[110] also indicates categories which pharmacy managers have determined may be of practical use to a clinical pharmacy service. For example, a third of hospitals documented intervention-associated cost savings; 88% documented where these interventions were being made while only 63% documented the severity/risk of the potential DRP. This is surprising as severity/risk was one of the most frequently recorded categories in the other papers identified.

The results of the present investigation indicated some consensus in categorisation of pharmacists' interventions. Categories which were documented in more than 50% of papers included drug name (12 papers), DRP (14 papers), Severity/ Risk (13 papers), Intervention Action/Type (17 papers), and whether or not the intervention was accepted/outcome (12 papers).

The recording of drug name which would allow further categorisation to drug class (recorded as an alternative to drug name in a single paper[95]) is fundamental to the analysis of pharmacy interventions for a variety of reasons such as identifying the potential risks associated with drugs/ drug classes, identifying the need for education and training around specific drugs, identifying specific specialities requiring increased pharmaceutical input/monitoring and quantifying cost savings associated with interventions. Where the drug name has not been documented as a separate category it may have been recorded as a free text entry. It is likely that the recording of drug name/class is included in much nearer to 100% of intervention documentation systems as

it is very difficult to document a meaningful intervention without mentioning the name of the drug involved.

Thirteen of the 19 papers categorised the intervention according to the potential severity/risk of the drug related problem. Most severity/risk categories were subcategorised into their "potential to cause harm" or their "clinical significance". However, it is likely that pharmacists recording interventions would interpret and therefore categorise "clinical significance" according to the potential for the DRP to cause harm to the patient so that the two categories are probably equivalent. In five of the papers[91,98,108,111,113], detailed explanation of each subcategory was poor with the use of "minor", "moderate" or "severe" giving little guidance as to their definition. As such, these may be open to inter-pharmacist interpretation for many reasons, which may include experience, clinical knowledge and specific circumstances of the intervention e.g. clinical details of the respective patient and others. Where there is a clear definition for each subcategory, it is less likely that there will be variance in pharmacist interpretation. Dornan et al.[17] used a simple 4-point scale combining the description of clinical significance and the potential to cause harm and validated the intervention scores using a panel of 2 independent pharmacists and 2 clinicians.

All of the studies attempted to subcategorise either "DRP" or "intervention type/action" or both. Most hospital pharmacies are aware that analysis of the cause of interventions (the DRP) and the resulting actions (intervention type/action) may allow patterns to be identified in order that preventative measures may be implemented e.g. education and training of prescribers and pharmacists or both. However, it is surprising to note that consensus regarding the sub-categorisation of DRPs was poor (Table 3.4.) with only 5 sub-

categories used in more than 50% of studies which subcategorised DRPs (interaction, ADR, wrong drug, wrong dose and no indication). Furthermore, there were 5 subcategories which were inappropriately used to document DRPs since they were actions taken as a consequence of a DRP namely, clarification of order; addition of cautionary labelling; referral needed; patient counselling/education and answer to a question provided. This appears to demonstrate confusion between sub-categories used for DRPs and those used for intervention action/type. This was particularly evident in studies assessing sub-categories used for intervention action/type (Table 3.5). Thirteen subcategories were used which were DRPs rather than intervention action/type and, of the remainder, only 2 sub-categories (change of drug and drug information) were common to more than 50% of studies.

3.5. Conclusions

Currently there is little agreement in the literature regarding categorisation for analysis or standardisation of documentation of pharmacy interventions. It is possible that the routine documentation of hospital pharmacy interventions does have a degree of standardisation indicated by Millar et al.[110] but further research is required to identify which categories would be beneficial to record in order to allow analysis to improve patient safety and improve pharmacy services.

Most intervention categories recorded as part of research studies are directly related to the objective of the study and are determined at the time of the study design, which limits the design to prospective analysis in some cases. If standardisation of documentation could occur such that it were possible to achieve most common study

objectives using an agreed proforma, this would allow retrospective analysis of interventions without time consuming coding and thus the inclusion of larger sample sizes.

In particular, there is little consensus and some confusion regarding the sub-categorisation of the drug related problem precipitating the intervention and the resulting intervention action with subsets of each category often included in the alternate set. Standardisation of these sub-categories would provide a platform to identify patterns, which may allow prevention of the DRP.

Prevention of DRPs is of particular interest, since analysis of pharmacist interventions as "near miss" incidents would allow the identification of patient risk factors. Categories used by the studies identified in this search which may be used to identify individual patients prior to the intervention occurring using most electronic prescribing systems include: gender, stage of stay, age, allergies, consultant ID, drug class/name, no. of drugs, disease state, administration problems (identified using missed doses on drug chart), monitoring issues and use of a non-formulary drug. Most other DRPs can only be identified by detailed analysis of the medication chart by a clinical pharmacist.

CHAPTER 4

DEVELOPMENT OF
A DATASET REQUEST

4. Development of a Dataset Request.

4.1 Introduction

4.1.1. Background

4.1.1.1. Information Identified from Chapters 2 and 3.

Chapters 2 and 3 identified possible risk factors for pharmacy intervention into patient treatment from the literature using a systematic review of measurable risks associated with DRPs and review of categories of pharmacist interventions respectively.

The systematic review in Chapter 2 identified a number of measurable risks for DRPs (all definitions included) which are well known yet poorly documented as such. However, the link between these risks and an intervention by a pharmacist is unproven. Although identifying and rectifying any issues related to the use of medicines, is a fundamental part of a pharmacist's role, in practice, there is no evidence to confirm that pharmacists comprehensively identify all DRPs. It is also possible that pharmacists identify a number of issues with drugs and prevent some DRPs which are subsequently never identified by the literature or similarly they intervene in situations which are not identified as DRPs by the literature. Without further research it cannot be assumed that risks associated with DRPs are identical to those factors which cause a pharmacist to intervene into a patient's treatment.

In contrast, the systematic review of common categories of pharmacist interventions identified factors which clinical pharmacists record for later review which may (or may not) be well known as risk factors for DRPs but have direct links to pharmacist

interventions. Some of the categories/factors recorded by pharmacists are the same factors identified by the systematic review of Chapter 2 but also a number of additional factors were identified. These additional factors may or may not be risk factors for pharmacist intervention and the possible associated DRPs which these interventions aim to prevent. However, pharmacists record this data for the purposes of research, audit, analysis or review and have (in most cases) used their experience and pharmaceutical knowledge to determine the detail of interventions which it may be necessary to record. Senior hospital pharmacists in the UK regularly perform informal analysis of their intervention data to identify any local patterns in interventions performed. As a result, risk reduction measures may be put in place. For example, where interventions are repeatedly associated with a particular drug, education of prescribers provides a form of risk reduction. In the United States, clinical pharmacists have already recognised that categories of pharmacist interventions may also be risk factors for patients experiencing DRPs. The American Society of Health-System Pharmacists use an intervention form which identifies some categories as risk factors but it is unclear what the evidence base for this is.[114]

However, it may be that where pharmacists record an intervention category for another purpose, that category too may also constitute as a risk factor. For example, pharmacists may record details of the consultant ID in order to refer serious interventions to the consultant team concerned, however, the prescribing consultant (team) may also be a risk factor. This could be for a number of reasons: as an independent risk factor, e.g. should the team be prone to making prescribing errors, or a dependent risk factor, e.g. should the team be prescribing high risk drugs or prescribing in more complex cases etc..

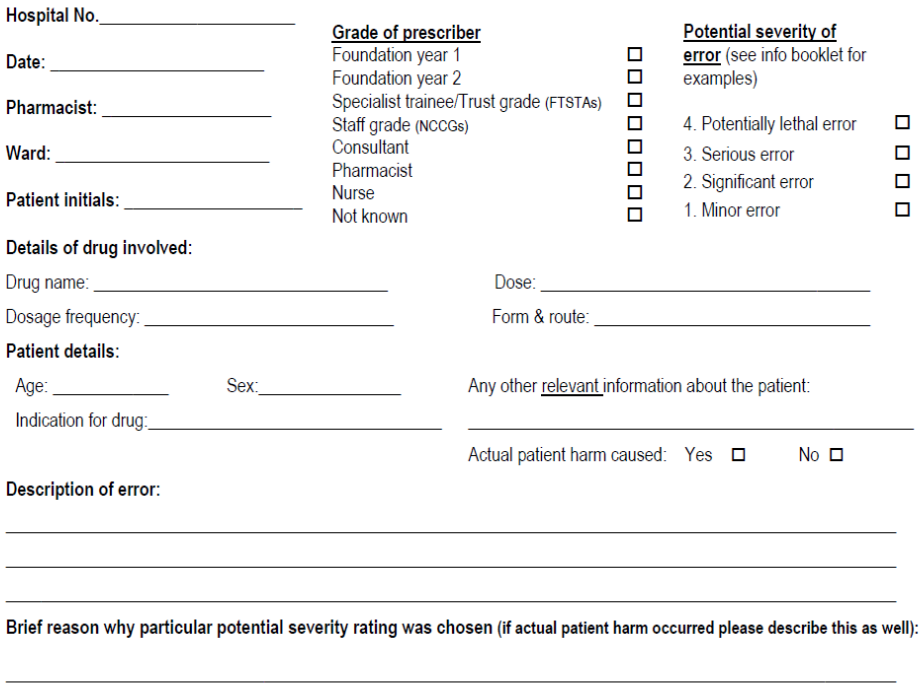
As such, it would be appropriate to review all quantifiable and measurable categories of pharmacist interventions identified in the previous chapters in order to determine whether or not they are risk factors which may be identified prior to intervention.

4.1.1.2. Data Available at University Hospitals NHS Foundation Trust

At University Hospitals NHS Foundation Trust (UHBFT) pharmacists record their interventions on the Prescribing and Information Communication System (PICS) which is an electronic prescribing and clinical decision support system (CDS) which also includes many of the clinical features included in an electronic patient record (EPR) such as biochemistry, microbiology, observations, assessments, therapy records, admission and discharge details.

Pharmacists at UHBFT are requested to record interventions in the PICS which enables data extraction to fulfil the requirements of the EQUIP study[17], the Trust having been involved in gathering follow up data during 2011. Early in 2012 the UHBFT Clinical Pharmacy Standards were developed and launched which standardised the way in which pharmacists in the Trust recorded their interventions in the PICS. This electronic recording of interventions precluded the necessity for the clinical pharmacy team to record their interventions on paper. Figure 4.1 details the form which the team used prior to electronic recording.

Figure 4.1 Intervention Form used in the EQUIP Study and by UHBFT prior to Electronic Recording



Hospital No._____

Date: _____

Pharmacist: _____

Ward: _____

Patient initials: _____

Grade of prescriber

- Foundation year 1 ☐
- Foundation year 2 ☐
- Specialist trainee/Trust grade (FTSTAs) ☐
- Staff grade (NCCGs) ☐
- Consultant ☐
- Pharmacist ☐
- Nurse ☐
- Not known ☐

Potential severity of error (see info booklet for examples)

- 4. Potentially lethal error ☐
- 3. Serious error ☐
- 2. Significant error ☐
- 1. Minor error ☐

Details of drug involved:

Drug name: _____ Dose: _____

Dosage frequency: _____ Form & route: _____

Patient details:

Age: _____ Sex:_____ Any other relevant information about the patient:

Indication for drug:_____ _____

Actual patient harm caused: Yes ☐ No ☐

Description of error:

_____

_____

_____

Brief reason why particular potential severity rating was chosen (if actual patient harm occurred please describe this as well):

_____

There is no pharmacy intervention form programmed into the PICS. Pharmacists use their pharmacist messaging system to record interventions as a free type entry (Figure 4.2). Interventions are recorded contemporaneously and as such, data extraction at the time of the intervention documents clinical details of the patient such as biochemical and haematological parameters and demographics such as ward, age, gender and hospital number. Details of the intervention included in Figure 4.1 which cannot be extracted without a standardised intervention entry into PICS are:

1) **Potential severity of DRP**
2) **Name of the drug (since the entry in PICS appertains to the patient and not the respective drug)**
3) **Brief description of the intervention**

Thus, pharmacists document “Intervention 1, 2, 3 or 4” to indicate the severity of the DRP, followed by the name of the drug and a brief description of the intervention.

Figure 4.2 Example of Documentation of Pharmacy Interventions at UHBFT

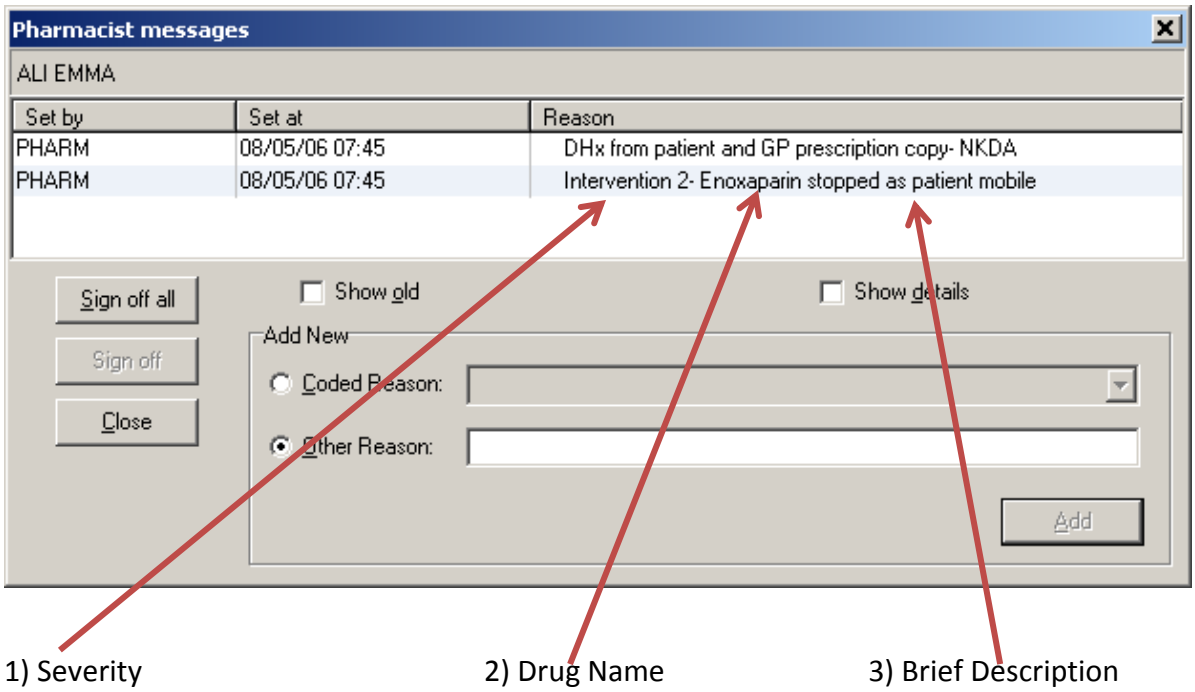
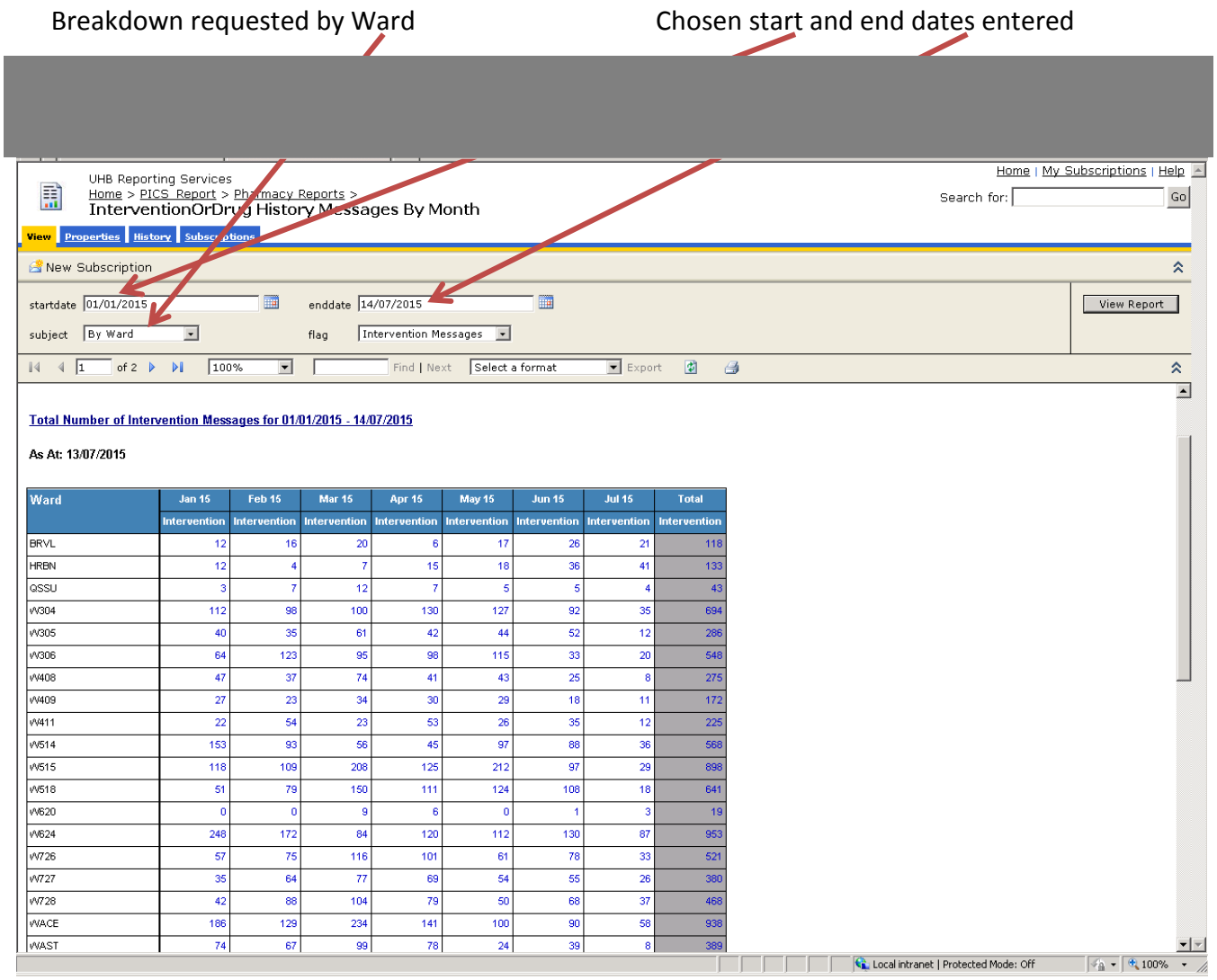


Figure 4.2 clearly demonstrates the simplicity of pharmacy intervention documentation at UHBFT and as such intervention recording in the Trust jumped in May 2012 to on average, 1,500 interventions per month compared to 20 per month when using paper based recording.

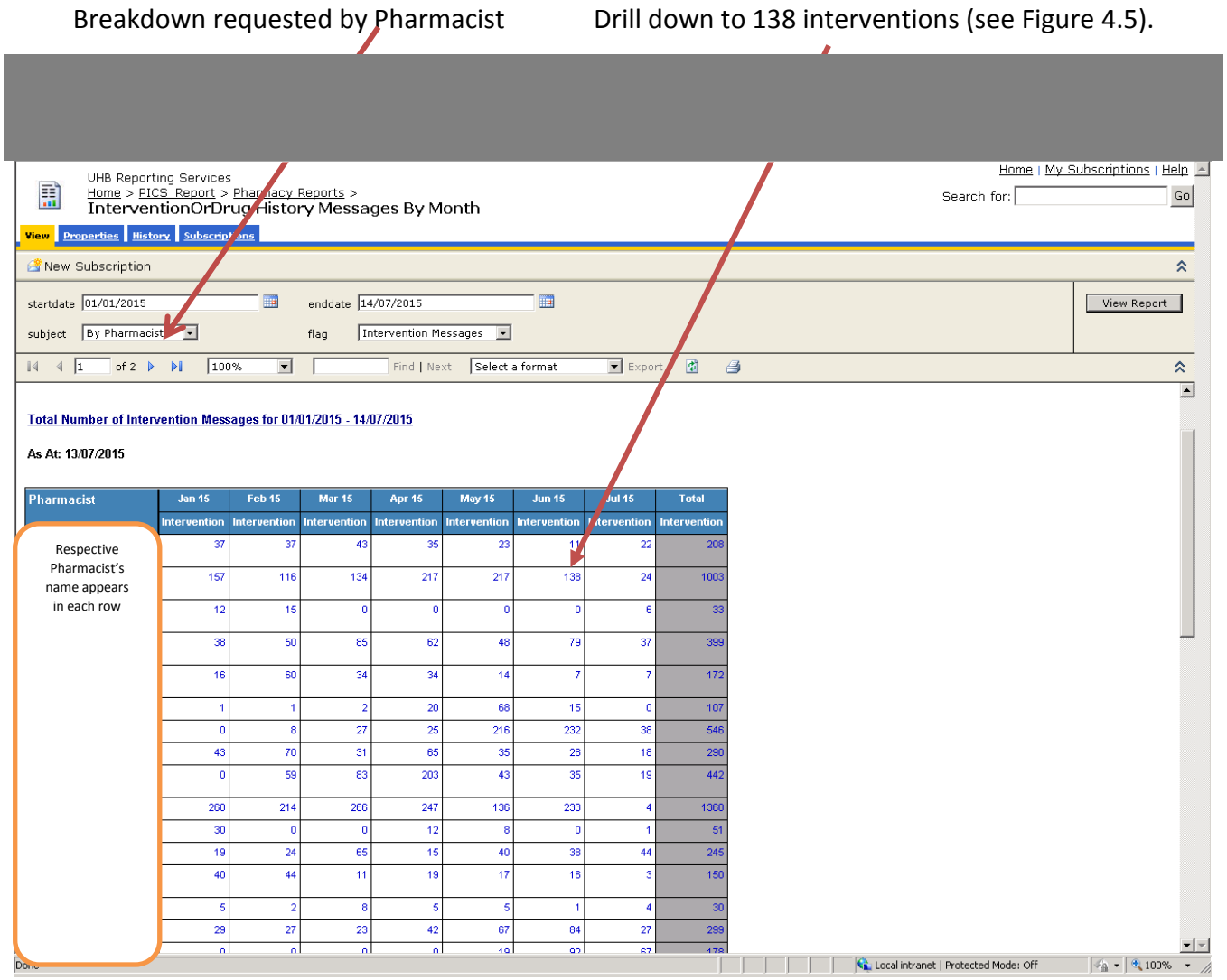
At the same time of the launch of the standardised intervention recording in the PICS, the informatics department at UHBFT was asked to develop a monthly report which detailed interventions by ward and by pharmacist. The report is produced by searching for the word “Intervention” in the pharmacist messaging system. Figure 4.3 shows a screen shot of the report with outputs detailed by respective ward at UHBFT and Figure 4.4 when generated by clinical pharmacist undertaking the intervention. The report may be generated between any respective chosen dates as required for audit or review.

Figure 4.3 Monthly Intervention Report by Ward.



Ward	Jan 15	Feb 15	Mar 15	Apr 15	May 15	Jun 15	Jul 15	Total
	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention
BRVL	12	16	20	6	17	26	21	118
HRBN	12	4	7	15	18	36	41	133
QSSU	3	7	12	7	5	5	4	43
W304	112	98	100	130	127	92	35	694
W305	40	35	61	42	44	52	12	286
W306	64	123	95	98	115	33	20	548
W408	47	37	74	41	43	25	8	275
W409	27	23	34	30	29	18	11	172
W411	22	54	23	53	26	35	12	225
W514	153	93	56	45	97	88	36	568
W515	118	109	208	125	212	97	29	898
W518	51	79	150	111	124	108	18	641
W620	0	0	9	6	0	1	3	19
W624	248	172	84	120	112	130	87	953
W726	57	75	116	101	61	78	33	521
W727	35	64	77	69	54	55	26	380
W728	42	88	104	79	50	68	37	468
WACE	186	129	234	141	100	90	58	938
WAST	74	67	99	78	24	39	8	389

Figure 4.4 Monthly Intervention Report by Pharmacist.



Analysis of the data contained in these reports has provided multiple benefits. Not only does the report allow intervention review for a particular ward which gives insight to the DRPs noted by pharmacists in a particular speciality but also they allow for an individual pharmacist's performance to be reviewed. Pharmacists are reviewed on a bimonthly basis by senior colleagues, not only reviewing the number of interventions undertaken in comparison to their peers but also as to the complexity and quality of their interventions in terms of clinical pharmacy outcomes. Figure 4.5 shows how it is possible to closely examine the data from Figure 4.4, to identify the wards on which the respective pharmacist has made their monthly interventions.

Similarly, it is possible to further examine the report shown in Figure 4.5, to view the detail documented in Figure 4.6. The view in Figure 4.6 allows the reviewer to consider the specific detail of each intervention made by the respective pharmacist.

Similar close examination of the report data is available when the report is generated by ward giving the opportunity to review the specifics of interventions in each clinical area.

Each report may be exported into a database for manipulation for review, audit or presentation and as such provides a wealth of data for the purposes of research. Raising awareness, feedback to clinical pharmacy staff and ease of reporting has increased the numbers of interventions reported so that by June 2015 the total number of interventions being reported on a monthly basis reached almost an average 3,000 in total (Appendix 1 - Extract from Intervention Report July 2015). The interventions electronically recorded in this manner provide an opportunity for research into the factors which lead to pharmacists intervening in a patients care to avoid subsequent DRPs.

Figure 4.5 Examination of June data from One Pharmacist detailing Wards where Clinical Interventions Occur

Examination of 44 interventions gives descriptive detail of interventions recorded in the pharmacist message (see Figure 4.6)

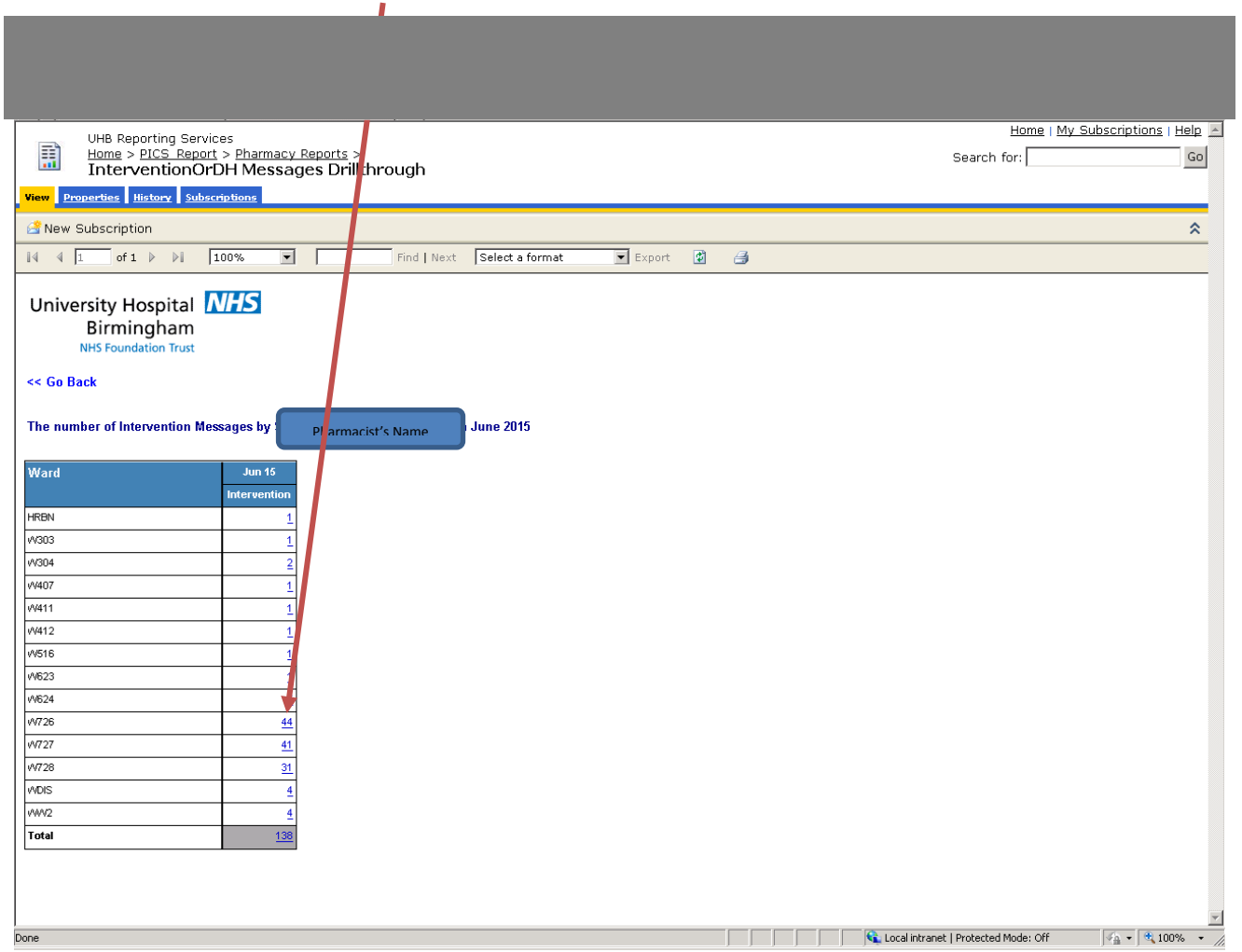
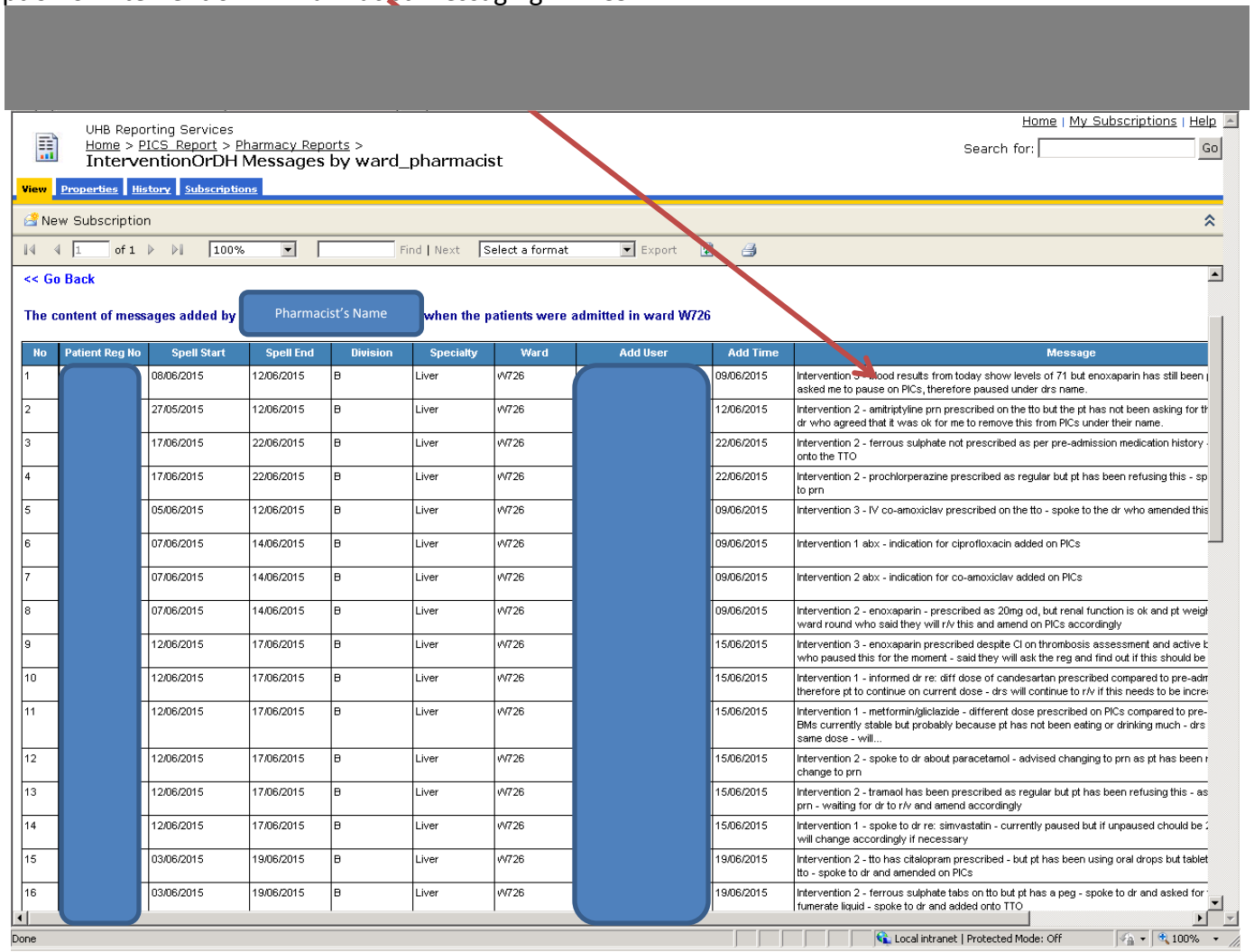


Figure 4.6 Examination of a single Ward's Interventions by one Pharmacist

"Free Type" description of intervention in Pharmacist Messaging in PICS



Analysis of the data from these reports may also help to determine at what point in the patient's stay they are most likely to have issues which require pharmacy intervention. With up to 6% of hospital admissions attributed to a medicine related issue[1], pharmacists are already targeted by NICE guidance to perform medicines reconciliation on patients within the first 24 hours post admission[12]. Medicines reconciliation on admission includes (as described in Chapter 1) confirming comprehensively, the patient's medicines prior to admission and reconciling them with those prescribed as an inpatient. Acting in an advisory role, pharmacists will then communicate with prescribers and nursing staff regarding any inaccuracies and make recommendations for the administration and supply of drugs, future drug treatment and monitoring. This makes the first 24 hours of admission crucial in terms of pharmacist intervention. Figure 4.2 shows how a patient drug history is recorded in PICS as part of the reconciliation process. To identify if the time of medicines reconciliation is closely associated with the likelihood of intervention, comparison is required between the timing of drug histories and any pharmacist interventions.

However, it is also likely that the point of discharge poses another risk to patients. Their medicines will be re-prescribed and re-defined as appropriate to take home which may put the patient at risk of DRPs and prompt a pharmacist intervention.

4.1.2. Aims

To determine if there is an association between potential risk factors identified in Chapters 2 and 3 and the characteristics of inpatients on whom interventions are performed.

To analyse the data to determine if these risk factors and categories can identify patients requiring intervention and therefore highlight their need for a pharmaceutical review.

4.1.3. Objectives

The objectives are to:

a) Develop a request for data (dataset request) for the informatics department at UHBFT which obtains the retrospective data required from PICS. There are three clear objectives when developing the data set:

1) Define the population from which the retrospective data is to be extracted
2) Combine results from Chapters 2 and 3 to determine which potential risk factors are to be included in the dataset request and identify if these risk factors may be identified from PICS
3) Produce a clear, concise and comprehensive written request for data which can be interpreted by informatics personnel who have little clinical knowledge or understanding of pharmacist interventions but who have a working knowledge of extracting data from PICS. The request must include clear explanation or definitions, for the following:

- How pharmacist interventions are recorded in PICS
- The population to be included in the data extraction
- The time of the data extraction in relation to a patient's admission
- The description of each risk factor (and therefore the data to be extracted)

b) Statistically analyse the data to determine risk factors which may identify patients who are most likely to require a pharmacist intervention. Chapter 5 will detail the statistical analysis of the data.

4.2. Methods

4.2.1. Identification of Population to be Studied

The objective is to provide data which can be statistically analysed to determine if there is an association between the potential risk factors (identified in Chapters 2 and 3) and the characteristics of those patients who are recipients of pharmacist interventions at UHBFT.

Analysis will be of data derived from a retrospective comparative study of characteristics of patients who had an intervention with those who did not. Therefore, the simplest population to review would be:

All inpatients admitted within a defined timeframe.

A comparison could then be made between the incidence of potential risk factors for intervention in those patients in the population who *did* have an intervention during their admission with those who *did not*. However, a number of variables needed to be considered:

- Clinical Pharmacy Services are not provided in all clinical areas (wards) of UHBFT and as such an intervention may not occur owing to the fact that the medication chart has not been reviewed by a Pharmacist.
- Patients may be admitted and discharged in less than 24 hours and therefore medicines reconciliation and full pharmacist review may not occur.
- Patients may be admitted into complex settings such as ITU where the presence of experts in the speciality (sometimes providing one to one care), may reduce the likelihood of a DRP and the possibility of a pharmacist intervention.
- Patients may not be the recipient of a pharmacist intervention if a pharmacist did not visit the ward during their ward stay (e.g. at the weekend where no clinical pharmacy service is provided)

To ensure that an appropriate population was identified, agreement was sought from a Professor in Clinical Pharmacology at Birmingham University with a practical knowledge of prescribing using the PICS and a specialist interest in drug safety and clinical pharmacy services, a statistician from Birmingham University and a senior member of the UHBFT informatics team.

Agreement was sought for:

1. The study population admitted to the Trust in a specified time period
2. A list of exclusion criteria for the population
3. The time of data extraction in relation to a patient's admission

4.2.2. Identification of Potential Risk Factors for Inclusion in Dataset Request

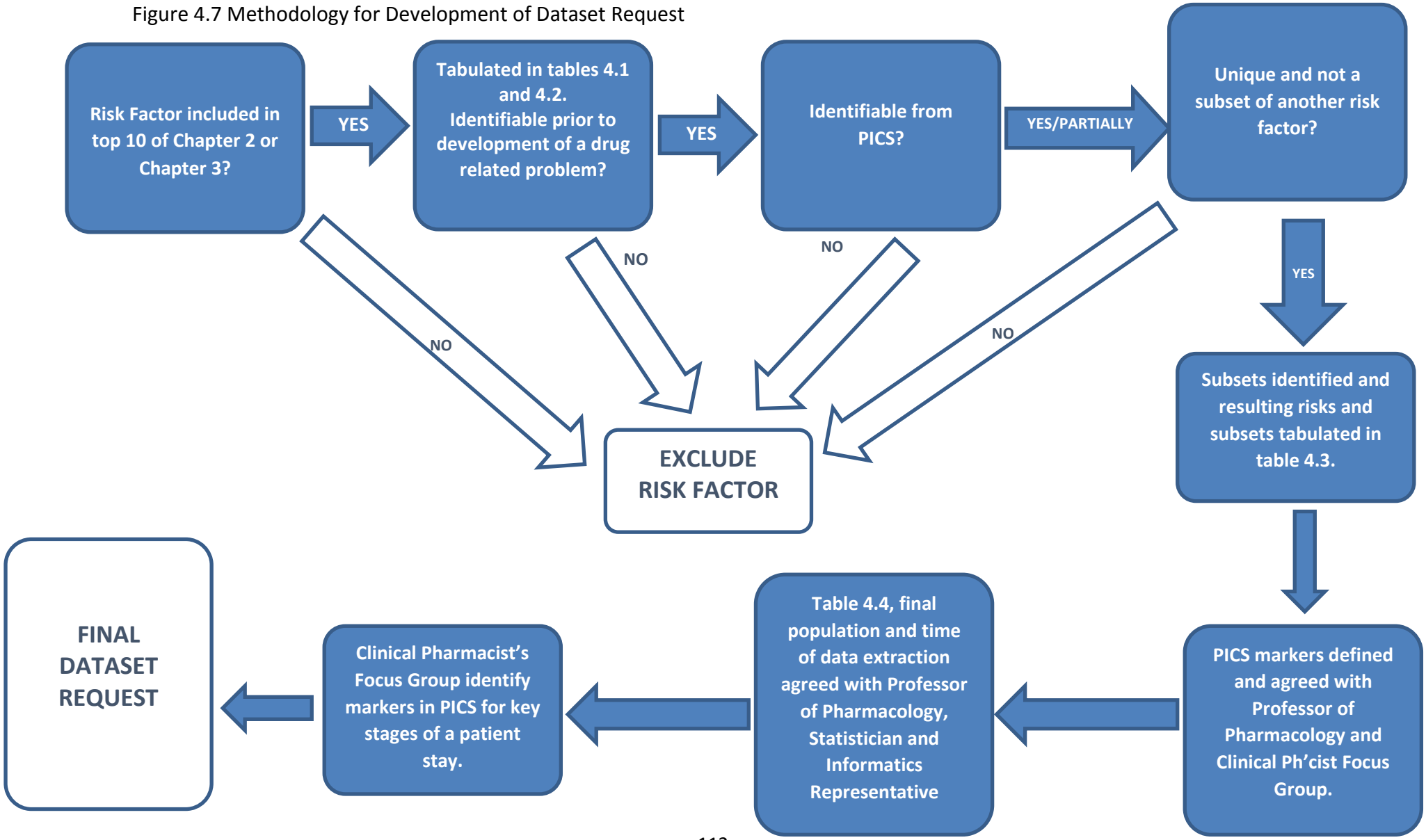
Factors identified in the Systematic Review (Chapter 2) as risk factors for DRPs and the factors identified as common categories recorded when documenting interventions (Chapter 3) were reviewed.

Criteria for inclusion of a potential risk factor in the dataset request were agreed with the Professor in Clinical Pharmacology as:

- The factor prevalence must be in the 10 identified by the Systematic Review (Chapter 2) or a result of the Search for Common Categories of Interventions (Chapter 3)
- The factor must be identifiable prior to the development of a DRP
- The factor must be identifiable from data recorded within PICS
- The factor must be unique and not a subset of another factor previously identified

Figure 4.7 details the methodology used to develop the final dataset request.

Figure 4.7 Methodology for Development of Dataset Request



4.3. Results

4.3.1. Identification of Population.

In order to ensure that the absence of pharmacy interventions was not due to the fact that a pharmacist had not visited the ward during their stay, it was decided that the population would include all patients present on a respective ward during the stay of individuals who were the recipient of a pharmacist intervention:

1) All patients who had one or more pharmacist interventions between 01/04/2013 and 31/03/2015 on wards visited by a pharmacist (CDU, Burns Unit, CCU, 302, 303, 304, 305, 306, 407, 408, 409, 410, 411, 412, 513, 514, 515,516, 517, 518, 519, 620, 621, 622, 623, 624, 625, 726, 727, 728, Edgbaston, Harborne, Bournville, West 1 and West 2 (excluding Critical Care Units) (**"Lead Intervention" patients**)

And

2) All patients who were present on the respective ward within the lead intervention patient's ward stay (ward stay is termed "spell" in the PICS) (**"spell" patients**)

Exclusions:

- Patients whose pharmacist intervention occurred while on a Critical Care Unit
- Patients with an admission duration <24 hours
- "Spell" patients whose ward stay began prior to commencement of the lead intervention patient's ward stay
- "Spell" patients whose ward stay ended after the end of the master patient ward stay

4.3.2. Tabulation of Potential Risk Factors to Determine Inclusion in the Dataset Request

Tables 4.1 – 4.3 detail the tabulation of potential risk factors in order to determine their appropriateness for inclusion in the final dataset request.

Table 4.1 Potential Risk Factors Identified from the 10 most prevalent in Systematic Review

Category	Identifiable prior to DRP?	Identifiable in PICS?	Unique?	Included Yes/No
Drug Class	✓	✓	✓	Yes
Polypharmacy	✓	✓	✓	Yes
Older Age (?>65 years)	✓	✓	✓	Yes
Gender	✓	✓	✓	Yes
Number of co-morbidities	✓	✓✗	✓	Yes
Length of pt stay	✓	✓	✓	Yes
History of Drug Allergy/Sensitivity	✓	✓✗	✓	Yes
Patient Compliance Issues	✓	✓✗	✓	Yes
Poor Renal Function	✓	✓	✓	Yes
Poor liver function	✓	✓	✓	Yes

Key (Table 4.1 and 4.2): ✓Yes X = No ✓X = Partially

Table 4.2 Potential Risk Factors Identified from Chapter 3 -Search for Common Categories of Interventions.

Category	Identifiable prior to DRP?	Identifiable in PICS?	Unique?	Included Yes/No
Intervention type/ Action	X	X	✓	No
DRP	X	X	✓	No
Severity/Risk of DRP	X	X	✓	No
Drug Name	✓	✓	X (Drug Class in table 4.1)	No
Acceptance/outcome	X	X	✓	No
Gender	✓	✓	X (included in table 4.1)	No
Age	✓	✓	X (included in table 4.1)	No
Location/Speciality	✓	✓	✓	Yes
Pharmacist ID	X	✓	✓	No
Consultant ID	✓	✓	✓	Yes
Disease state	✓	✓	✓	Yes
Time taken for Intervention	X	X	✓	No
No. of drugs	✓	✓	X (included in table 4.1 as polypharmacy)	No
Date	X	✓	✓	No
Patient ID	X	✓	✓	No
Allergies	✓	✓✗	X (included in table 4.1)	No
Drug Class	✓	✓	X (included in table 4.1)	No
Stage of Stay	✓	✓	✓✗ (similar to length of stay)	Yes
Seniority of prescriber	✓	X	✓	No
Interaction	✓	X	✓	No
ADR	X	X	✓	No
Wrong Drug	✓	X	✓	No
Wrong Dose	✓	X	✓	No
No indication	✓	X	✓	No
Untreated Indication	✓	X	✓	No
Administration problem	✓	✓✗	✓✗ (similar to compliance issue and omission)	Yes
Non-formulary/Guidelines	✓	✓✗ (non-formulary possible not guidelines)	✓	Yes
Monitoring	✓	✓✗ (relies on previous documentation in PICS)	✓	Yes
Dose too High	✓	X	✓	No
Dose too Low	✓	X	✓	No
omission	✓	✓	✓	Yes
Duration	✓	X	✓	No
Frequency	✓	X	✓	No
Compliance	✓	✓✗	X (included in table 4.1)	No
Pharmacokinetics	✓	X	✓	No
Distribution	✓	X	✓	No
Request for Information	✓	X	✓	No
Supply issue	✓	✓	✓✗ (similar to compliance issue and omission)	Yes
Incomplete order/legality	✓	X	✓	No
Peri-operative	✓	X	✓	No

Table 4.3 Summary of Potential Risk Factors for Inclusion in Dataset Request

Category	Subsets if Applicable
Drug class	IV antimicrobials
	thrombolytics/anticoagulants
	cardiovascular agents
	Central Nervous System (CNS) agents
	corticosteroids
	diuretics
	chemotherapy
	insulin/hypoglycaemics
	opiates
	Anti-epileptics
Polypharmacy	Number of drugs
Older Age (?>65 years)	Age in years
Female gender	Male/Female
Number of co-morbidities	-
Length of pt stay	Stage at which intervention made
	Total length of stay
History of Drug Allergy/Sensitivity	Number of allergies
Patient Compliance Issues	-
Poor Renal Function	Mild/moderate/severe or continuum?
Poor liver function	-
Location/Speciality	Ward
	Speciality
Consultant ID	-
Disease State	-
Administration Problems, Omissions and Supply Issues	Reasons for omissions
Non-Formulary Medication	-
Monitoring Issues	-

4.3.3. Identification of Potential Risk Factors in PICS

To extract data at the time of the Lead Intervention patient's intervention would produce data which would require highly complex data analysis and to do so add variables to the resulting data since spell patients would have variable lengths of stay at the time of data extraction.

Data extraction would need to be at:

- The same length of time post admission for all patients in the data set
- Less than the average length of stay for the patient population

- At a point in time in the patient's stay that it is practical for a pharmacist to visit (since the resulting model from the research may be used to direct pharmacist interventions)

It was agreed with the Professor in Clinical Pharmacology and the statistician that the dataset request to informatics would request data from each patient at 24 hours after admission (Time of data Extraction). Each potential risk factor was then discussed and agreement reached as to how the factor would be measured using the PICS (Table 4.4). In the case of disease states, a focus group of 5 senior clinical pharmacists at UHBFT identified the common disease states which in their experience, may increase incidence of interventions and the most common points during a patients stay at which patients are vulnerable to intervention.

Table 4.4 Detail of Data Representing each Potential Risk Factor in PICS

Potential Risk Factor	Data Representing Potential Risk Factor in PICS	Comments
Drug class	**Number regular drugs prescribed from each of the following PICS drug categories (report each category separately):** **Thrombolytics/anticoagulants:** to include PICS drug classes ANTICOAG (except enoxaparin), NOAC, ANTIPLATE, THROMBO and ANTIFIB **IV antimicrobials:** to include PICS drug classes AMINOGLYC, ANTIMICC, ANTIMIC3, OTHER ANTI, ANTIBIO, ANTIMIC2, PENICIL, PENICILLIN, MACROLI, CARBAPEN, AMINOGLYC, TETRAC, ANTIFUN, IMIDAZOLES, POLYMYXINS, TB DRUG, ANTIMAL and QUINOL plus individual drugs Chloramphenicol IV, Vancomycin IV, Teicoplanin IV, CO-TRIMOX, Anidulafungin, Griseofulvin and Micafungin **Cardiovascular agents:** to include PICS drug classes ANTI-ARRY, CARD GLYC, CARDIAC, INOTROPE, BETA BLOC, CA CHAN, VASODI, VASOCON, ANTIHYP-CA, AD NEUBLOC, APLHA BLOC, ACE INHIB, ANGIOII and ANTIHYPO plus individual drugs ILOPROST, nicorandil, adenosine, ranolazine and milrinone **CNS agents:** to include PICS drugs classes HYPNO, ANTI-PSYCH, ANTIDEP, MAOIS, SSRIs, TRICYC, LEVODOPA, BENZO, C.N.S, PHENO, MAOIS plus individual drugs flupentixol, pericyazine, pimozide, valproic, lithium, Atomoxetine, Dexamfetamine sulphate, Lisdexamfetamine mesilate, Methylphenidate hydrochloride, Modafinil, tolcapone, ENTACAPONE, PRAMIPEXOL, ROPINIROLE, rotigotine, bromocriptine, cabergoline, pergolide, Apomorphine, amantadine, PIMOZIDE, ACAMPROSATE and Disulfiram **Corticosteroids:** to include PICS drug classes CORTICO, GLUCO, HYDROCOR and MINCORTICO **Diuretics:** to include PICS drug classes DIURET, LOOP DIUR, THIAZ and POT-SPAR **Chemotherapy/immunosuppressants:** to include PICS drug classes ANTINEO, CYTO, CYTO2, CYTOMOD, MABS, MALIG, INTERMIT, DIETHYLSTILBESTROL, PKINHIB, IMMUNO, TACRO, METHOTREX,SIROL and CICLOSPORIN plus individual drugs Fingolimod, Glatiramer, Lenalidomide and thalidomide **Insulin/hypoglycaemics:** to include PICS drug classes INSIMP12, INSIMP2, INSIMP23, INSIMP3, INSIMP4, INSUL, DIABET, SULPHONYL, BIGUAN, GLIPTINS and ORALHYPOG **Opiates:** to include PICS drug class OPIOID **Anti-epileptics:** to include PICS drug classes ANTICONVUL and ANTIEPIL **NB**. Include regular medications only prescribed at the time of data extraction (exclude when required (PRN), one off (OOF) and take home medication (REGT, PRNT).	The British National Formulary BNF definition of drug category was used. PICS has its own unique drug categories and drug dictionary. The drug dictionary was reviewed and each drug code identified for the respective BNF class. Any additional individual drugs in the BNF class not identified by the PICS drug class code were included. Where drugs are in more than one section in the BNF, the main section of classification (bold type in BNF index) was used. PICS drug classes were requested from informatics and reviewed to ensure they corresponded to BNF classification.
Polypharmacy	Number of regular drugs prescribed at time of data extraction (exclude when required prescriptions, one offs and any prescriptions which do not require a pharmacist sign off e.g. TEDS, dietary supplements)	PICS includes some “prescriptions” for non-medicinal products which act as prompts for nursing to administer and provide documentation of administration.

Potential Risk Factor	Data Representing Potential Risk Factor in PICS	Comments
Age	age (in years) of patient at the time of data extraction	Definition of elderly varies in the literature and with an ageing population the definition may need revision. In addition, the systematic review excluded paediatric papers as "specialist" and therefore age reported as a continuum was felt to be more appropriate than defined age groups.
Female gender	gender	Documented in the PICS
Number of co-morbidities	number of ICD10 codes documented in PICS at the time of data extraction.	PICS uses ICD10 codes to code for co-morbidities. When a co-morbidity is entered, PICS translates into the respective ICD10 code.
Length of pt stay	total spell length.	"Stage" of intervention can be extracted from PICS but will require precise definition and study of time of the intervention in relation to other clinical pharmacy activities
History of Drug Allergy/ Sensitivity	number of allergies/sensitivities recorded	Documented in the PICS
Patient Compliance Issues	number of missed doses due to "pt refused" against all regular prescriptions within 24 hours prior to time specified for data extraction Identify patients who have a blister pack icon at the time specified for data extraction (Yes/No)	When recording a drug omission in PICS, staff administering must include a reason for non-administration. A "drop down" selection includes "patient refused" as a reason for documentation of non-administration. PICS includes a Blister Pack Icon. Pharmacists may denote patients in need of a blister pack as a form of compliance aid.
Poor Renal Function	GFR or eGFR reported as the most recent prior to 24 hours post admission. Where there is none reported prior to the data extraction, use GFR or eGFR up to 72 hours post admission. **NB.** Use GFR wherever possible instead of eGFR. If there is a GFR then use this even if there is a later eGFR. Only use eGFR if no GFR has been reported prior to 24 hours post admission (in the same admission) or 72 hours post. Where there is NO GFR or eGFR on that admission prior to 72 hours post admission, record pt as "**NA".**	None of the studies identified in the systematic review defined renal function as mild/moderate or severe but reported renal function as a continuum.
Poor liver function	Identify patients (Yes/No) who at the specified time of data extraction are either: ➢ in Liver directorate (Medicine or Surgery) ➢ have a liver "declared interest" recorded or ➢ have ICD10 codes: o C22 Malignant neoplasm of liver and intrahepatic bile ducts. o D13.4 Liver. o D37.6 Neoplasm of uncertain or unknown behaviour of oral cavity and digestive organs // Liver, gallbladder and bile ducts. o K70-K77 Diseases of liver. o R94.5 Abnormal results of liver function studies. o B18.0 Chronic viral hepatitis B with delta-agent. o B18.1 Chronic viral hepatitis B without delta-agent. o B18.2 Chronic viral hepatitis C. **NB**. Patients must only be counted once if they are in more than one of the categories (e.g. they may be in the Liver directorate AND have one or more of the respective ICD10 codes).	There is no direct relationship between liver function tests and the degree of liver failure observed. Indicators of diagnosis of poor liver function in PICS were agreed to be more reliable.

Potential Risk Factor	Data Representing Potential Risk Factor in PICS	Comments
Consultant ID	consultant ID	Documented in the PICS
Ward / Speciality	Ward and speciality of patient	Documented in the PICS
Disease state	Identify patients (Yes/ No) with the following ICD10 codes for **Insulin dependent diabetes**: **E10** Type 1 diabetes mellitus or **O24.0** Pre-existing type 1 diabetes mellitus Identify patients (Yes/ No) with the following ICD10 codes for **epilepsy**: **G40** Epilepsy or **G41** Status epilepticus Identify patients (Yes/ No) with the following ICD10 codes for **parkinsons' disease**: **G20** Identify patients (Yes/ No) with the following ICD10 code for **tuberculosis**: **A15, A16, A17, A18** or **A19** Identify patients (Yes/ No) with the following ICD10 code for **Acute MI**: **I21** Identify patients (Yes/ No) with the following ICD10 codes for **stroke**: **I60** subarachnoid haemorrhage, **I61** Intracerebral haemorrhage, **I62** other non-traumatic intracranial haemorrhage, **I63** cerebral infarction, **I64** stroke, not specified as haemorrhage or infarction **G46.3** Brain stem stroke syndrome, **G46.4** Cerebellar stroke syndrome, **I69.4** Sequelae of stroke, not specified as haemorrhage or infarction Identify patients (Yes/ No) with the following ICD10 codes for **PE or VTE**: **I26** Pulmonary embolism, **I74** Arterial embolism and thrombosis, **I82** other venous embolism and thrombosis Identify patients (Yes/ No) with the following ICD10 code for **alcoholic liver disease**: **K70**	A focus group of 5 clinical pharmacists determined the main disease states which they felt would make patients vulnerable to pharmacist intervention.
Administration problems/omission and supply issues	number of missed doses recorded on PICS. Include only regular prescriptions within first 24 hours of admission to Trust number of missed doses recorded on PICS due to "drug out of stock". Include only regular prescriptions within first 24 hours of admission to Trust	Comment as per "Patient Compliance Issues". "Drop down" includes "drug out of stock"
Monitoring issues	Identify patients (Yes/No) who have the following recorded during the respective admission: 1. INR recorded AND warfarin prescribed OR 2. Any record on PICS Drug results tab	PICS includes a separate section ("tab") for drug level results. INR is not included in this tab as is not actually a drug level but a marker of drug activity. INR may be taken when pt is not prescribed warfarin so the combination would need to be evident to highlight patients at potential risk.
Non-formulary medicine	Identify (Yes/No) if patients have a "dot" prescription (either regular, prn or otherwise) at the specified time of data extraction	The majority of medicines in the drug dictionary are UHBFT formulary drugs. Non-formulary drugs need to be prescribed on the system using a dot before free-typing the name of the drug.

4.3.2. Identification of Key Stages of Intervention

The clinical pharmacist focus group identified 3 key points in time in which intervention from a pharmacist was most likely to occur:

1) At the time of Medicines Reconciliation
2) Long-term patients (staying more than 2 weeks) who require repeat review of medicines
3) At the point of prescription of discharge medication (termed at UHBFT To Take Out medicines (TTOs)

In response to the feedback from the focus group, it was agreed with the Professor in Clinical Pharmacology and the statistician that the dataset request to informatics would include the following information for both "lead intervention" and "spell" patients:

- Date of admission to trust
- Date of discharge from trust
- Date and time "DH or DHx" appears in pharmacist message (upper or lower text) – i.e. time of medicines reconciliation
- Respective ward name during the spell in which lead intervention patient and corresponding spell patients, were identified
- Date and time of all interventions during their respective admission

4.3.3. Compilation of Results to Provide Final Dataset Request

The final dataset request is shown in Appendix 2.

4.4. Discussion

Perhaps the most complex and controversial aspect of the dataset design was identification of the population for study. The most simple design would have been to review all patients admitted to the Trust in a given timeframe and compare the characteristics of those patients who had a pharmacist intervention with those patients who did not. However, there are a large and statistically relevant, number of patients who are admitted to UHBFT who are never reviewed by a pharmacist. As a consequence, these patients may never become the recipient of a pharmacist intervention, not due to their lack of potential risk factors, but owing to the fact, a pharmacist was not present to undertake such an activity.

A crude reflection of the percentage of patients reviewed by pharmacists is the percentage of prescriptions validated and subsequently signed off on the PICS by pharmacists. Figure 4.8 details the number of prescriptions written in the PICS and shows in 2014 more than 2 million prescriptions were entered into the PICS.

Figure 4.8 Number of Prescriptions entered into PICS between 2010 and 2014.

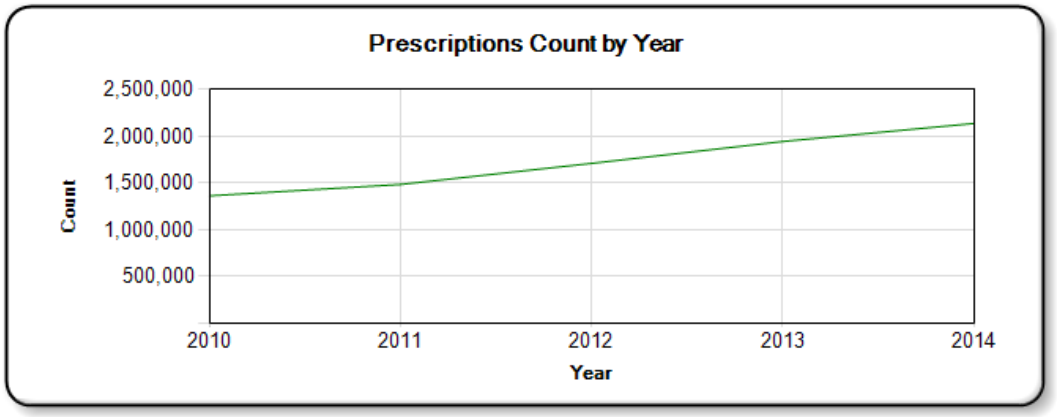
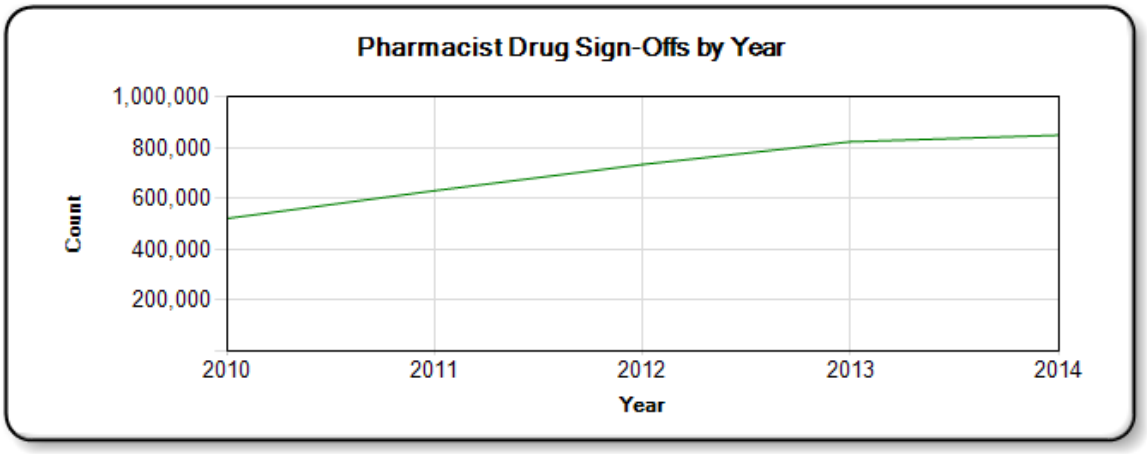


Figure 4.9 Number of Prescriptions Signed Off (validated) by a pharmacist in PICS



In comparison, Figure 4.9 details the number of prescriptions signed off (validated) by pharmacists in the Trust. In 2014, of the 2.2 million prescription entered into PICS, approximately 850,000 prescriptions were signed off by pharmacists (less than 40%). This percentage precluded the study from including all patients admitted to the Trust as the population for the study.

Although, it was accepted that there may be a large number of outpatient prescriptions in the data included in Figure 4.9, there are still numerous other reasons why pharmacists are not present to review prescription charts and therefore would not have the opportunity to intervene in a patient's treatment. As such, it was felt that a more accurate method of identifying patients who would be present on a ward and subject to pharmacist review was required to ensure a statistically relevant outcome. The final method which was agreed upon was to identify all patients ("spell" patients) present on a ward in the same ward spell as a patient who was the recipient of a pharmacist

intervention (the “lead intervention patient”). By using this method, in most instances, it would be valid to assume a pharmacist was present and able to review all patients’ medication in the respective ward stay. Exclusions included;

1) “lead intervention” patients admitted to wards not covered by the clinical pharmacy service (since it is possible that the intervention occurred in the pharmacy dispensary, which would mean that “spell” patients on the respective ward were not subject to pharmacist review)
2) All patients with an admission length <24 hours (since it is possible that they could have been admitted and discharged without a pharmacist review)

It was however, concluded that however complex the method of identifying the patient population there may still be inaccuracies. For example, patients admitted on a Friday evening and discharged on a Monday morning would be included in the population requested but are unlikely to be subject to a pharmacist review since the clinical pharmacy team currently only work from Monday to Friday. However, advice was sought from the statistician and the Professor in Clinical Pharmacology and it was agreed that the method of identifying the population was as near accurate as could be gleaned from the available data.

The time of the data extraction was also difficult to determine. Ideally, a review of all the patients’ potential risk factors at the time of the master patient’s intervention would be thought to be most accurate. However, in this case, the characteristics of each patient “spell” and “lead intervention” would need to be compared in a comparative study for every intervention in the determined time scale. This would mean tens of thousands of

comparative studies within a 2 year dataset. In addition, “lead intervention” patients may appear more than once in the data, if they are the recipient of more than one intervention, likewise “spell” patients may appear as “lead intervention” patients if they are the recipient of an intervention. If the time of data extraction (and resulting measurement of the potential risk factor) changed each time a patient was recorded in the dataset, statistical analysis of such data would be extremely difficult. It was agreed to extract data for all patients at 24 hours after their admission with the view that later work could be centred on analysing data later in patients’ stay. Twenty-four hours was chosen since;

1) All patients included in the study would have data at this time. If a later time for data extraction was chosen, some patients may be excluded from data extraction due to shorter lengths of stay.
2) Pharmacists aim to review all patients within 24 hours of admission to perform medicines reconciliation so it is likely that more interventions are performed around this time.

Finally it is acknowledged that not all of the potential risk factors could be comprehensively and accurately determined from PICS.

For example with respect to accuracy, when looking for non-formulary drugs on PICS the dataset request asks for the number of “dot” prescriptions. A “dot” prescription denotes a free-typed prescription in PICS which is generally used for a non-formulary drug as this set of drugs are not usually programmed into the drug dictionary forcing a free-typed prescription by a senior medical practitioner. However, free-typed prescriptions (“dot”

prescriptions) may also be used for other prescribing issues where the drug dictionary templates do not fit the current licensing or approval of the drug in the Trust e.g. a prescriber may want to nebulise an antibiotic but the drug template for the respective drug on PICS does not allow nebulisation. In such instances, prescribers may use the free-type facility.

Another limitation with respect to the comprehensive nature of the dataset request includes as an example, the dataset request for patient compliance issues. Patients may have numerous other compliance issues other than those which lead to the use of a blister pack or cause the patient to refuse medications and any interpretation of the extracted data should take this into account.

Since there was an awareness that the data extracted from the PICS as a result of the dataset request may have limitations, the resulting data required review and validation prior to statistical analysis.

One of the main inaccuracies found in the resulting dataset was the use of ICD10 codes to identify disease states. The International Statistical Classification of Diseases and Related Health Problems (ICD) is a comprehensive classification of causes of morbidity and mortality. All inpatient episodes and attendances that contain diagnoses must be recorded to the mandated version of ICD. The ICD-10 refers to the tenth revision. The World Health Organisation (WHO) is responsible for publishing the ICD-10 classification.

On reviewing the data generated from the dataset request, it became obvious that disease state recorded as an ICD10 code on the electronic prescribing system was unreliable. It was evident that when comparing the number of patients taking treatment for a given condition with the number of patients allocated the appropriate ICD10 code,

the number of patients with the ICD10 code was significantly lower. For example the demographics indicated that 9,755 patients were prescribed insulin or hypoglycaemics in the total population but only 673 were denoted by the respective ICD10 code for diabetes at 24 hours after admission. It is possible that this may be because admitting doctors tend to include only the presenting complaint on admission rather than a full scope of the patient's co-morbidities. Therefore, at this stage it was decided not to include disease states in the analyses and exclude this data going forward. However, were the research to be repeated using different methodology for data collection, disease state should be considered alongside all other potential risk factors.

In addition, it was decided not to include consultant ID in the data analysis since with over 350 different consultants within the data set it became apparent that any statistical analysis to determine any one of the individual consultants would not be significant.

Further chapters will discuss the limitations of data analysis in greater detail.

CHAPTER 5

ANALYSIS OF RISKS ASSOCIATED WITH CLINICAL PHARMACY INTERVENTIONS AT UHBFT

5. Analysis of Risks Associated with Clinical Pharmacy Interventions at UHBFT.

5.1 Introduction

5.1.1 Background

Data generated as a result of the dataset request detailed in Appendix 2 were presented by the informatics department in the form of an Excel spreadsheet. Initially, data was extracted from the PICS for a single ward only, and the records for 20 randomly selected patients were compared to that in the PICS, to assess the accuracy of the extraction. Any inconsistencies were reported to the informatics department, so that the data extraction could be refined. This process was repeated for several months, until validation indicated that the extracted data representing all sixteen risk factors was shown to be accurate (with the exception of the disease state variables, which were excluded as explained in Chapter 4). The informatics report was then generated for all wards as detailed in the dataset request.

The resulting dataset reported 58,918 rows of data (i.e. 58,918 patient admissions). Rows detailed a “lead intervention patient” who had been the recipient of an intervention and all the patients who had been present on the respective ward during the period of their ward stay “spell patients”. Each row detailed whether or not the patient had had an intervention, as well as all of the data requested, as detailed in Chapter 4.

5.1.2 Aims

To statistically analyse the dataset (extracted from the dataset request in Appendix 2) detailing potential risk factors for pharmacist intervention to:

- Identify any significant differences between the potential risk factors in patients who have been the recipient of a pharmacist intervention, and those who have not.
- Identify if there is a point in time after the patient's admission at which an intervention is more likely to occur.
- Identify if any point in time in the patient's stay determined above, is related to the time at which a drug history is taken by a member of the pharmacy team.
- Develop a "risk score" for patients as the potential recipients of a pharmacist intervention.

5.1.3 Objectives

- To "clean" and validate the dataset in an Excel spreadsheet to provide the necessary input data for analysis using IBM SPSS Statistics software.
- To perform a survival analysis to determine the point in time of a patient's stay at which an intervention is most likely to occur and whether the stage of a patient's stay is related to the time at which a drug history is taken by a member of the pharmacy team.

- To perform univariable analyses to determine whether each potential risk factor is significantly associated with the likelihood of the respective patient receiving a pharmacist intervention.
- To perform a multivariable analysis to identify independent predictors of the need for pharmacist intervention, and to convert the final model into a risk score.
- To validate the above risk score against retrospective data.

5.2 Methods

5.2.1 Data Cleansing and Validation

5.2.1.1. Data Cleansing

The original data set included “lead intervention patients” who had received an intervention and “spell patients” who were present on the ward during the stay of the lead intervention patient.

Spell patients were duplicated;

1. If they had received an intervention during their hospital stay, then they would also appear as a lead intervention patient.
2. If they were present on wards where multiple patients received interventions (i.e. lead intervention patients), then they would appear as a spell patient for each of these interventions.
3. If they were readmitted, duplication as in 1 and 2 above may apply.

In order to ensure that the cases in the data were independent, to meet the assumptions of the statistical analyses used, patients who had already appeared in the dataset in the same admission were removed from the data. For lead intervention patients, only the first interventions for an admission were included in the analysis, and any cases where the patient was a spell patient to another patient were excluded. For spell patients, only the first appearances in the data during each admission were included, with all subsequent duplications excluded. Repeated admissions to hospital were treated as being independent; hence if a patient was discharged and readmitted, they would be included in the data once for each admission.

5.2.1.2. Validation of Final Dataset

Once the exclusions had been made, the final dataset was compared back to the original, to ensure that no errors had been introduced, using the process below:

1. Twenty five patients were randomly selected from the original dataset which included all duplicated entries

2. For each patient, it was confirmed that:
    - The patient and their respective characteristics appeared in final dataset
    - Where there was duplication of the patient number in the final dataset, the duplication was only in the case of readmission
    - All column entries detailing the patient's characteristics were the same as the data in the original dataset for the respective admission

- Where the patient had intervention/s:
    - The number of interventions was the total for that admission in the final data set (original data set had given total for each ward stay)
    - The total number of pharmacist visits was correct according to original dataset time of intervention.

5.2.2 Statistical Analysis

5.2.2.1 Statistical Methodologies Compared

The outcome being considered in the analysis was whether or not a patient received an intervention during their stay. This was a binary outcome, as patients either did or did not receive an intervention. However, there was also the added complexity introduced by the fact that the length of stay for patients varied. The longer that a patient stayed in hospital, the greater the opportunity for an intervention to occur, as it gave pharmacists more time to review their case and identify any interventions that would be necessary.

If the duration of a patient's stay was independent of other confounding factors, then the differing length of stay would introduce no bias to the analysis. However, this was unlikely to be the case, as patients with longer hospital stays are likely to be more complex than those with shorter stays, hence patients with longer stays may differ with respect to a range of the factors being considered (e.g. age and comorbidities). As a result, treating pharmacist interventions as a simple binary outcome could introduce bias into the analysis.

Treating pharmacist interventions as a simple binary outcome also does not account for the timing of these interventions. The data for the characteristics being considered in the analysis were recorded at 24 hours after admission, and some of these may vary over time, such as GFR. For this reason, for interventions that occurred several weeks after admission, the recorded characteristic data may not reflect a patient's characteristics at the time of the intervention.

The simplest way to mitigate these two issues was to introduce a time limit at which the intervention status of a patient would be assessed. The average length of stay at UHBFT is between 5 and 7 days, so seven days after admission was selected as a sensible point of assessment. For each patient, it would then be identified whether an intervention had occurred within seven days of the first admission. Any patients for whom first interventions occurred after this point were classified as being in the non-intervention group. In addition, any patients with a length of stay that was less than seven days were excluded from this analysis, as their intervention status at seven days was unknown.

This approach reduced the total period of follow up, preventing the issues relating to interventions occurring a considerable time after admission not being reflective of a patient's baseline characteristics. Any bias from including patients with differing lengths of stay was also eliminated, as the length of stay considered in the analysis was now seven days for each patient. However, this approach also had limitations, the major one being that, since patients with shorter lengths of stay had been excluded, a biased subset of the original cohort of patients was now being considered. As a result, whilst analysis of

this data would be valid for patients with hospital stays of seven days or more, it was not necessarily generalizable to the population as a whole. Excluding such a large number of patients would also reduce the sample size, resulting in lower statistical power.

The third potential approach would be to use a time to event methodology. This would consider, for each patient, the period of time that they were "at risk" of an intervention, and the timing of the intervention, where this occurred. Patients would then be included in the analysis for the period of their stay, before being "censored" (i.e. excluded) at the point that they were discharged. The total period of follow up could be truncated, for example to seven days, for the reasons detailed above.

The benefit of this approach is that is accounts for both the timing of the intervention, and the differing lengths of stay for patients, without making any exclusions. The main limitation is the assumption of non-informative censoring. Time to event analyses assume that censoring of patients is a random process that is not related to factors associated with the study. In the case of the present investigation, this would involve making the assumption that a patient's length of stay is independent of the characteristics being considered, which is unlikely to be the case. Where this assumption is not met, the strength of the associations between the characteristics being considered and pharmacist interventions may be under- or over-estimated, depending on the strength and direction of any associations between the characteristics and length of stay.

A summary of the benefits and limitations of the three approaches is reported in Table 5.1.

5.2.2.2 Univariable Analysis

Owing to the limitations of method 1 detailed in Table 5.1, this approach was not used in the analysis. Methods 2 and 3 were deemed to be valid approaches to the analysis, and so univariable analyses were performed using both of these methodologies, and the results compared.

Analysis 2 (Table 5.1) was termed the “binary outcome analysis” and analysis 3 (Table 5.1) was termed the “time to event analysis”:

Table 5.1 Statistical Methods Compared

Analysis	Tests Used	Benefits	Limitations
1. Comparison of patients with interventions to patients without interventions for all patients	**Univariable:** Kendall's tau-b, Chi^2 **Multivariable:** Binary logistic regression	Includes all patients in analysis	Does not account for the timing of the interventions Does not account for the length of stay (LOS) (patients with a shorter LOS may be more "healthy"/younger etc. leading to bias) Includes interventions that occur weeks after admission which may be less likely to be related to the characteristics of patients at 24 hours.
2. Comparison of patients with interventions at 7 days to patients without interventions at 7 days, excluding patients with <7 days LOS	**Univariable:** Kendall's tau-b, Chi^2 **Multivariable:** Binary logistic regression	Does not include interventions that occur weeks after admission Standardises the follow up for each patient	Excludes short stay patients, so is looking at a biased sample of patients
3. Time to event analysis, looking at the time to intervention over the first 7 days	**Univariable:** Kaplan-Meier curves **Multivariable:** Cox regression	Includes all patients in analysis Does not include interventions that occur weeks after admission Considers the timing of interventions, so may be more powerful	Potential issues with informative censoring, which may overestimate the rate of interventions, and give unreliable comparisons

1. **"Binary Outcome Analysis"** – Patients with a length of stay less than seven days were excluded. The incidence (in percentage of population) of patients at seven days who had received an intervention displaying the respective characteristic was determined. P-values comparing patients with different characteristics were calculated using Chi-square and Kendall's tau-b for binary and ordinal data respectively.

2. **"Time to Event Analysis"** – All patients in the data were included. Kaplan-Meier curves were produced, and used to estimate the rate of intervention within seven days. Patient follow up started at the time of admission, with the event of interest

being pharmacist intervention. Patients were censored at the point that they were discharged, or after seven days of follow up without a pharmacist intervention. Comparisons between groups were then made using the log-rank test, which is a non-parametric test that addresses the null hypothesis that there are no differences in the survival times in the groups being studied, and compares events occurring at all time points on the survival curve.

For both approaches, continuous variables were divided into ordinal categories prior to analysis. This was a requirement for the Kaplan-Meier analysis, as continuous variables cannot be analysed using this approach. The creation of categorical variables was also for consistency with the later multivariable analysis. For analyses involving a binary outcome, where continuous factors are considered, an assumption is made about the relationship between the factor and the outcome. If the assumed shape of this relationship is incorrect, the then results of the analysis will be misleading. Treating the factors as categorical prevents this issue from occurring. Categorical variables also mean that the resulting risk score can be calculated using an additive approach when used in practice, with no multiplication necessary, making manual calculation easier.

For the continuous variables, if a national or international standard grouping was known, then this grouping was used, otherwise the data was tabulated and the population divided into approximately equal groupings, based on rounding the percentiles of the data to the nearest meaningful values. For the remaining ordinal variables, groups were combined where the numbers of patients were small, in order to maximise the within-group sample sizes, to give a more precise estimate of outcome rates. The final groupings are detailed in Table 5.2.

Table 5.2 Subgrouping of Potential Risk Factors

Potential Risk Factor	Data	Subgrouping
1. Drug class	• Number regular drugs prescribed from PICS drug categories	No formal grouping. 0,1, 2 and 2+ (3 approximately equal groups)
2. Polypharmacy	• number of regular drugs prescribed	5 or more drugs cited[80] but most likely to be linear relationship. <5, 5-9, 10 and 10+ (3 approximately equal groups)
3. Age	• age (in years)	</=40, 41 -55, 56 – 70, 71 -80, 81+ (4 equal groups rounded to nearest 5 years)
4. Female gender	• gender	Binary
5. Number of co-morbidities	• number of ICD10 codes documented	0, 1 or 2, 3 or 4, 5 and 5+[115]
6. Length of patient stay	• Date of admission and discharge (to calculate length of stay in days)	Linear. No subgroups as used as accounted for by survival analysis
7. History of Drug Allergy	• number of allergies/sensitivities recorded	Multiple Drug Intolerance Syndrome defined as 3 or more unrelated drug class allergies 0, 1, 2, 3 and 3+
8. Patient Compliance Issues	• number of patient refusals	0, 1, 2 and 2+ (3 approximately equal groups)
	• identify patients who have a blister pack icon	Binary
9. Poor Renal Function	• GFR	**NICE Guidance 2014:** ≥90 Normal and high 60–89 Mild reduction related to normal range for a young adult 45–59 Mild to moderate reduction 15–29 Severe reduction 30–44 Moderate to severe reduction <15 Kidney failure
10. Poor liver function	• Identify patients (Yes/No)	No clear grouping classification using markers of disease. Binary.
11. Consultant ID	• consultant ID	Over 350 consultants made any statistical analysis impossible –removed from analysis
12. Disease state	• Identify patients (Yes/ No) with the respective ICD10 codes.	Binary
13. Administration problems/omission and supply issues	• number of missed doses	0, 1, 2 and 2+ (3 approximately equal groups)
	• number of “drug out of stock”	0, 1, 2 and 2+ (3 approximately equal groups)
14. Monitoring issues	• Identify patients (Yes/No): INR recorded AND warfarin prescribed OR Any record on PICS Drug results tab	Binary
15. Non-formulary medicine	• Identify (Yes/No) if patients have a “dot” prescription	Binary

5.2.2.3 Receiver Operating Characteristic (ROC) Curves

In order to further quantify the ability of the characteristics being considered to predict the need for pharmacist intervention, receiver operating characteristic (ROC) curves were produced for each characteristic. Since ROC curves can only be applied to binary outcomes, this analysis was based on the data from the "Binary Outcome Analysis". The areas under the ROC curves (AUROCs) were then calculated, as well as the standard errors (SEs), and associated p-values.

5.2.2.4 Multivariable Analysis

The two methodological approaches gave similar results in univariable analysis, so the multivariable analysis was performed using the "Time to Event" methodology, to maximise the sample size. Prior to performing the analysis, Spearman's correlation coefficients were calculated between the factors, in order to determine any pairs that were strongly associated. Where strong correlations were detected, factors were excluded prior to the multivariable analysis, in order to reduce the risk of multicollinearity, as this can result in poor model fit. The data were then randomly divided into two subsets. The modelling set consisted of 75% of the patients, and was used in the multivariable analysis. The remaining 25% of cases made up the validation set, which were used to validate the findings of the analyses, to ensure that overfitting had not artificially inflated the accuracy of the analysis.

A multivariable cox regression model was produced from the cases in the modelling set, with patients followed up from admission until the point of pharmacist intervention, and censored either at discharge or after seven days without an intervention. A backwards stepwise approach was used to select the variables for inclusion. This started with a model containing all of the factors, with an iterative process used to remove non-significant factors ($p>0.05$), until the final model only included significant independent predictors of pharmacist interventions. The benefit of this stepwise approach is that those factors that do not add significantly to the prediction of pharmacist interventions are removed, simplifying the resulting risk score.

A risk score was then produced based on the final model. The log-hazard ratios for each category were used as a basis for the score. This meant that the reference category for each factor would be given a score of 0, and the other categories would be given a positive or negative score, depending on whether interventions were more or less likely to occur for patients in this category. In order to simplify the score, each of these values was rounded to the nearest integer, after multiplying by 20 to minimise rounding errors. The total score for a patient could then be calculated by looking up the score for each of their characteristics, and adding together the resulting values.

The resulting score was then validated, in order to assess how accurately it could identify those patients at risk of requiring pharmacist intervention. ROC curves were produced, as detailed previously, for both the modelling and validation sets of data. The latter was intended to give a reflection of the predictive accuracy of the score if used in practice, as it was based on data that were not used in the multivariable analysis. In order to visualise

the accuracy of the score, the rates of pharmacist interventions within seven days were calculated for the range of possible values, and plotted separately for the modelling and validation sets.

ROC curves for both sets of sample data were also drawn up to determine the predictability of the score.

5.3 Results

5.3.1 Demographics

Data were available for 58,918 patients, the demographics of whom are reported in Table 5.3. Additional factors relating to comorbidities and medication usage are detailed in Appendix 3.

Table 5.3 Demographics of Population

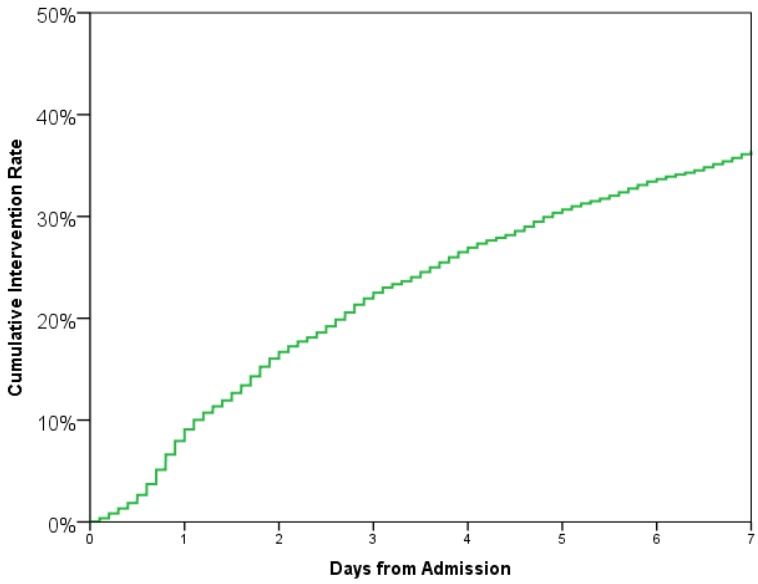
Demographic		N/Median (IQR*)
Gender	Male	31247
	Female	27671
Age (years)		62 (45 - 76)
Number of Regular prescriptions		7 (4 - 11)
Length of Stay (days)		5 (3 - 11)

*Inter Quartile Range

Pharmacist interventions occurred in a total of 34.9% (n=20582) of cases. However, this simplistic rate does not account for the differing lengths of follow up for patients. Since patients are only “at risk” of having an intervention for the period that they were in

hospital, a Kaplan-Meier curve was produced, in order to estimate the probability of an intervention occurring over the course of hospital stays of varying lengths (Figure 5.1). This plot illustrates that pharmacist interventions occur at a reasonably constant rate over the first seven days of a patient's hospital stay. For patients still in hospital seven days after admission, the Kaplan-Meier analysis estimates that 36.4% will have received an intervention by a pharmacist. The median time to the first intervention, namely the point at which half of all admitted patients would be expected to have received an intervention, was found to be 15.7 days (95% CI: 15.2 – 16.2).

Figure 5.1 Rate of Interventions over the first seven days of Admission



A similar analysis was performed to assess the proportion of patients where drug histories were recorded. This occurred in a total of 48207 patients, giving a simplistic rate of 81.8%. A Kaplan-Meier analysis (Figure 5.2) found that, after seven days in hospital, 91.5% of patients would have had a drug history taken, with the median time being 36.0 hours (95% CI: 35.5 – 36.5) after admission.

Figure 5.2 Rate of Drug Histories (DHx) over the first seven days of Admission

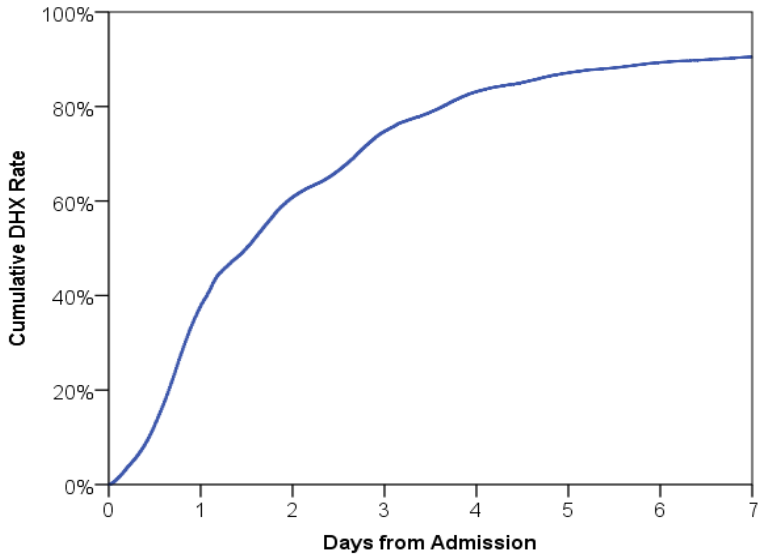
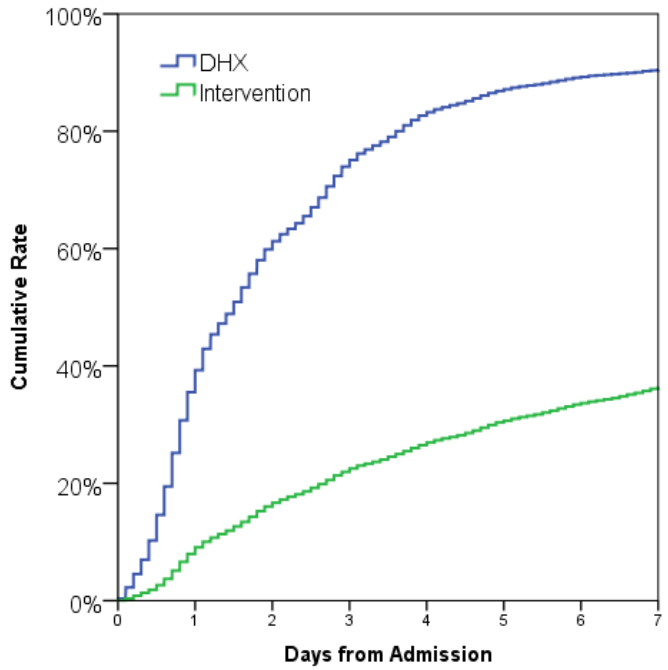


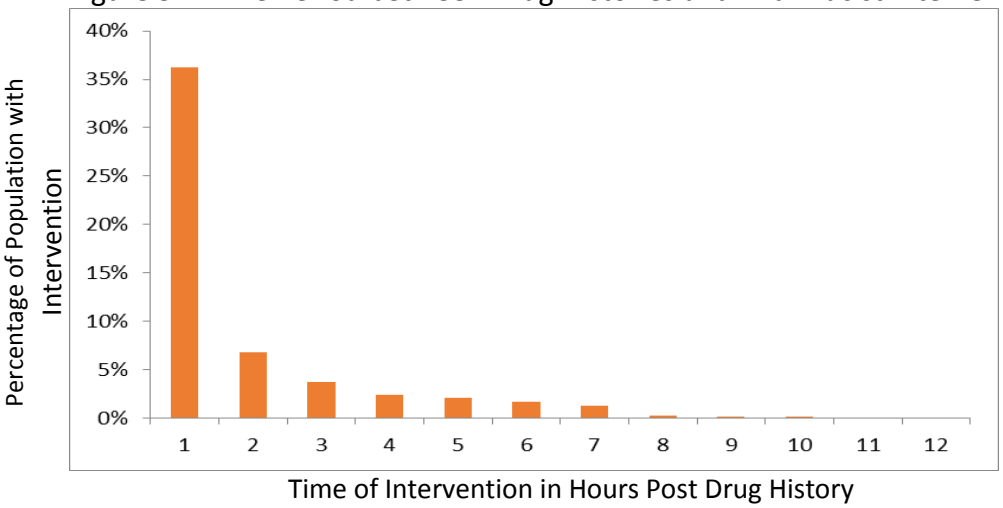
Figure 5.3 Plots the cumulative rate of interventions and drug histories on the same axis in order to make a comparison between the two curves and determine the likelihood of a relationship between the timing of drug histories an interventions.

Figure 5.3 Cumulative Rate of Interventions and Drug Histories over the first seven days of Admission



For the 19258 patients who received both a drug history and a pharmacist intervention, the time between these two events was calculated and compared (Figure 5.4). In this subgroup of patients, the majority of interventions occurred within the first 12 hours after completion of the drug history (55%), with 43% of interventions within two hours, and 36% within one hour of the drug history.

Figure 5.4 Time Period between Drug Histories and Pharmacist Interventions



5.3.2 Univariable Analysis

5.3.2.1 Summary of Univariable Analysis

Univariable analyses were then performed, in order to identify potential predictors of pharmacy intervention. As outlined in the methods, two alternative approaches were used, which dealt with the issue of variable length of stay in different ways:

1. **"Binary Outcome Analysis"** – Patients with a length of stay less than 7 days were excluded and rate of intervention calculated at 7 days. This was

then compared across factors using Chi^2 tests for nominal variables, and Kendall's tau for ordinal variables.

2. **"Time to Event Analysis"** – All patients were included and the rate of intervention at 7 days was calculated using Kaplan-Meier curves, some of which are detailed in Figure 5.5. Comparison across factors were performed using log rank tests.

Results for the two methods are detailed in Tables 5.4 – 5.11. The overall intervention rate at seven days was estimated to be 31.4% using the binary outcome approach, and 36.4% for the time to event methodology. This variation is a reflection of the different populations being studied and the different assumptions being made in the two analytical approaches. The factors identified as significant were generally consistent for the two methods.

Table 5.4 Intervention Rate at 7 days according to Patient Demographics

Demographics	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	P-value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	P- value (Log Rank)
Gender			<0.001[Chi2]			<0.001
Male	12010	3582 (29.8%)		31247	35%	
Female	11149	3687 (33.1%)		27671	38%	
Age			<0.001[K]			<0.001
<= 40	2875	580 (20.2%)		11944	26%	
41 - 55	3873	1035 (26.7%)		11375	33%	
56 - 70	6063	1920 (31.7%)		15278	38%	
71 - 80	4698	1642 (35.0%)		10082	41%	
81 and 81+	5650	2092 (37.0%)		10239	42%	
Regular Prescriptions			<0.001[K]			<0.001
< 5	4405	1090 (24.7%)		15812	28%	
5 - 9	9746	2898 (29.7%)		24481	35%	
10 and 10+	9008	3281 (36.4%)		18625	44%	

Table 5.5 Intervention Rate at 7 days according to Non-Formulary Prescription

Non-formulary Drug Prescribed	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Dot Drugs			0.129[Chi2]			<0.001
No	22450	7028 (31.3%)		57442	36%	
Yes	709	241 (34.0%)		1476	39%	

Table 5.6 Intervention Rate at 7 days according to Allergies/Co-morbidities

Number of Allergies/ Comorbidities	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Allergies			<0.001[K]			<0.001
0	15172	4625 (30.5%)		39310	35%	
1	4999	1617 (32.3%)		12292	38%	
2	1739	591 (34.0%)		4291	40%	
3 and 3+	1249	436 (34.9%)		3025	41%	
Comorbidities			<0.001[K]			<0.001
0	6772	1888 (27.9%)		20534	31%	
1-2	8905	2657 (29.8%)		22203	35%	
3-4	5121	1805 (35.2%)		11182	42%	
5 and 5+	2361	919 (38.9%)		4999	46%	

Table 5.7 Intervention Rate at 7 days according to Administration/Supply Issues

Administration and supply issues	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Total Missed Doses			0.507[K]			<0.001
0	8652	2693 (31.1%)		24071	35%	
1	4933	1552 (31.5%)		12778	37%	
2 and 2+	9574	3024 (31.6%)		22069	37%	
Missed Doses – Drug Out of Stock			<0.001[K]			<0.001
0	18854	5583 (29.6%)		49909	35%	
1	2507	945 (37.7%)		5321	44%	
2 and 2+	1798	741 (41.2%)		3688	47%	

Table 5.8 Intervention Rate at 7 days according to Liver/Renal Function

Liver/Renal Function	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Liver			<0.001[Chi2]			<0.001
No	21789	6920 (31.8%)		55692	37%	
Yes	1370	349 (25.5%)		3226	31%	
GFR			<0.001[K]			<0.001
< 15	728	202 (27.7%)		1391	30%	
15 - 29	1882	667 (35.4%)		3200	40%	
30 - 44	2744	996 (36.3%)		4997	41%	
45 - 59	3103	1097 (35.4%)		6488	42%	
60 - 89	5676	1817 (32.0%)		14373	38%	
90 and 90+	8546	2393 (28.0%)		25235	36%	

Table 5.9 Intervention Rate at 7 days according to Requirements for Drug Monitoring

Requirements for Drug Monitoring	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
INR			<0.001[Chi2]			<0.001
No	10834	3734 (34.5%)		31679	39%	
Yes	12325	3535 (28.7%)		27239	34%	
Warfarin			<0.001[Chi2]			<0.001
No	22398	6978 (31.2%)		57103	36%	
Yes	761	291 (38.2%)		1815	49%	
Drug Monitoring			0.665[Chi2]			0.001
No	22910	7194 (31.4%)		58413	36%	
Yes	249	75 (30.1%)		505	42%	

Table 5.10 Intervention Rate at 7 days according to Drug Class

Number of Regular Drugs Prescribed from each Class	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Anti-epileptics			<0.001[K]			<0.001
0	19763	6110 (30.9%)		51370	36%	
1	2875	974 (33.9%)		6275	40%	
2 and 2+	521	185 (35.5%)		1273	42%	
Thrombolytics/ anticoagulants			<0.001[K]			<0.001
0	15010	4454 (29.7%)		41672	34%	
1	6718	2358 (35.1%)		13824	42%	
2 and 2+	1431	457 (31.9%)		3422	42%	
CNS agents			<0.001[K]			<0.001
0	17540	5254 (30.0%)		46350	35%	
1	4181	1498 (35.8%)		9428	41%	
2 and 2+	1438	517 (36.0%)		3140	45%	
Cardiovascular agents			<0.001[K]			<0.001
0	10795	3212 (29.8%)		32396	33%	
1	5043	1662 (33.0%)		10860	39%	
2 and 2+	7321	2395 (32.7%)		15662	41%	
Corticosteroids			<0.001[K]			<0.001
0	18476	5620 (30.4%)		47827	35%	
1	4431	1563 (35.3%)		10522	42%	
2 and 2+	252	86 (34.1%)		569	41%	
Opiates			<0.001[K]			<0.001
0	15733	5302 (33.7%)		42180	38%	
1	6116	1697 (27.7%)		14150	33%	
2 and 2+	1310	270 (20.6%)		2588	28%	
Diuretics			<0.001[K]			<0.001
0	17215	5189 (30.1%)		47304	35%	
1	4934	1734 (35.1%)		9833	42%	
2 and 2+	1010	346 (34.3%)		1781	40%	
Chemotherapy/ immunosuppressants			<0.001[K]			<0.001
0	18121	5471 (30.2%)		46987	35%	
1	3680	1345 (36.5%)		9323	43%	
2 and 2+	1358	453 (33.4%)		2608	39%	
0020/.;…Insulin/ hypoglycaemics			<0.001[K]			<0.001
0	18494	5635 (30.5%)		49163	35%	
1	2533	853 (33.7%)		5110	41%	
2 and 2+	2132	781 (36.6%)		4645	43%	
IV antimicrobials			0.003[K]			<0.001
0	15051	4636 (30.8%)		40725	36%	
1	5021	1592 (31.7%)		12019	36%	
2 and 2+	3087	1041 (33.7%)		6174	40%	

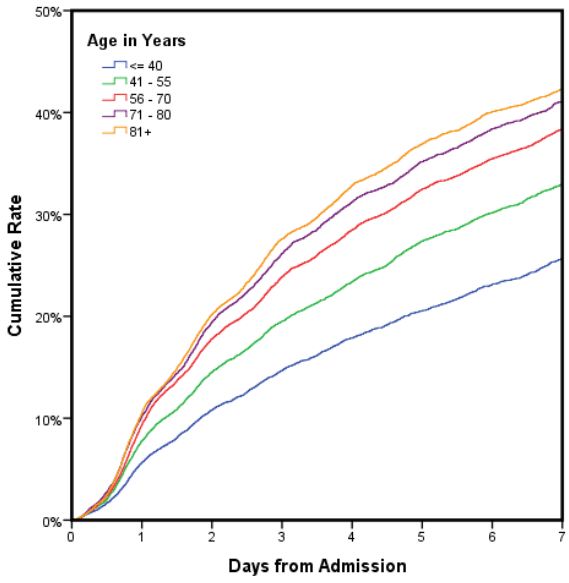
Table 5.11 Intervention Rate at 7 days according to Patient Compliance Issues

Patient Compliance Issues	Binary Outcome Analysis			Time to Event Analysis		
	Total N	Interventions at 7 Days	p value K = Kendall's tau Chi2 = Chi Square	N	Interventions at 7 Days	p value (Log Rank)
Blister Packs			0.004[Chi2]			<0.001
No	22823	7139 (31.3%)		58279	36%	
Yes	336	130 (38.7%)		639	50%	
Missed Doses - Patient Refused			<0.001[K]			<0.001
0	18268	5597 (30.6%)		45763	36%	
1	2668	871 (32.6%)		7365	38%	
2 and 2+	2223	801 (36.0%)		5790	39%	

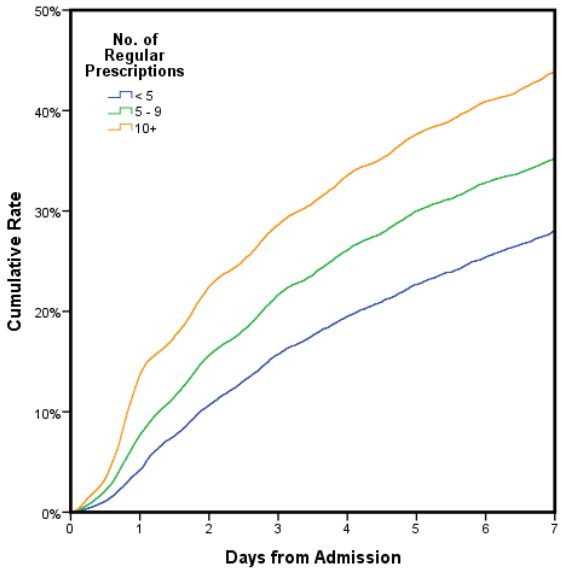
Figure 5.5 Time to Event Analysis – Kaplan Meier Curves

(Cumulative Rate of Interventions)

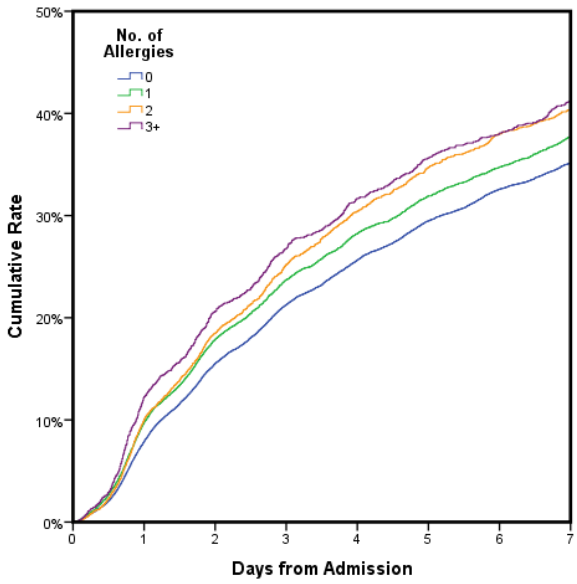
Age:



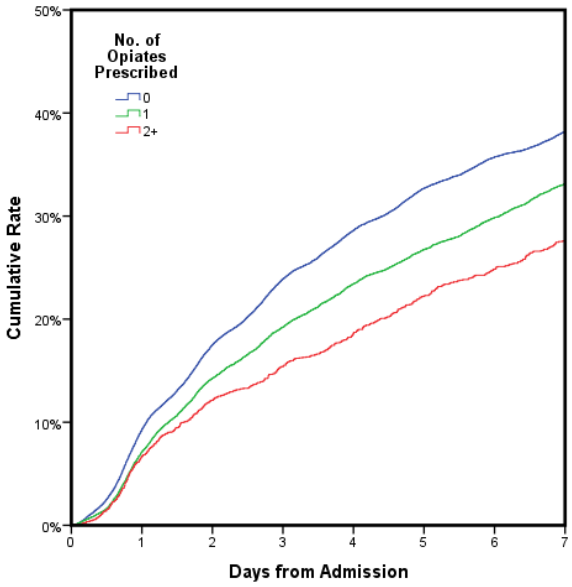
Regular Prescriptions:



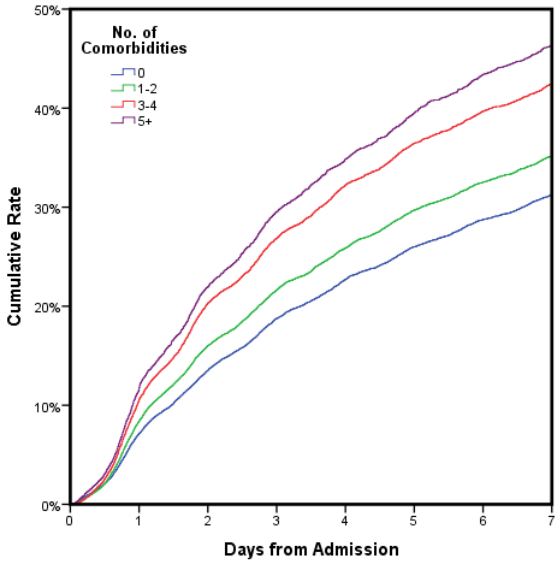
Allergies:



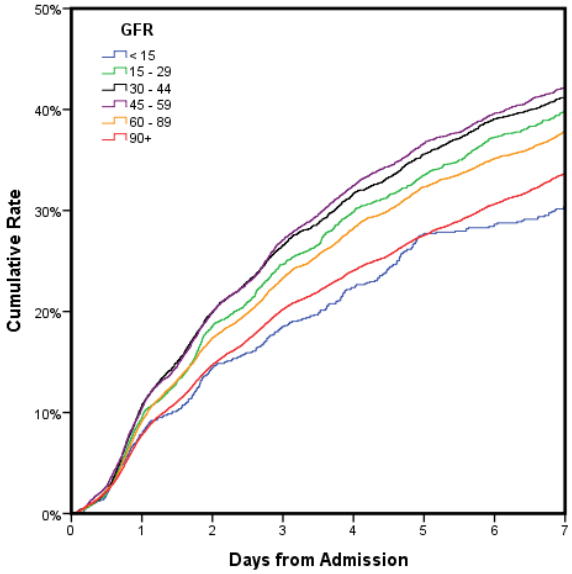
Opiates:



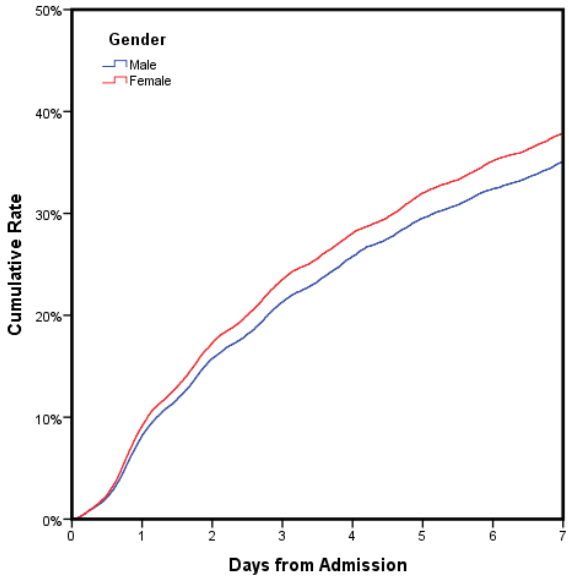
Comorbidities:



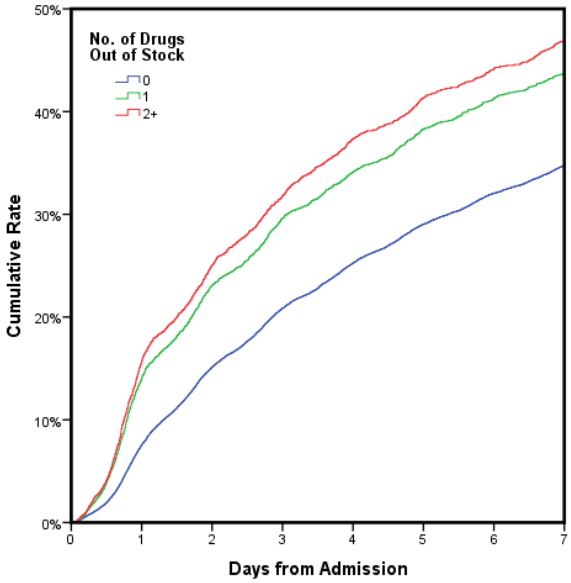
Renal Function:



Gender:



Drugs Out of Stock:



5.3.2.1 Patient Demographics

Of the demographic factors considered (Table 5.4), the intervention rate was found to be significantly higher in females, and increased significantly with patient age and the number of regular prescriptions.

5.3.2.2 Non Formulary Prescribing

Non formulary prescribing was found to significant increase the likelihood of pharmacy intervention in the time to event analysis ($p<0.001$), but not in the binary outcome analysis ($p=0.129$). Despite the difference in significances, the direction and magnitude of the difference in 7-day intervention rates was similar (39% vs. 36% in time to event analysis, 34% vs. 31% in binary outcome analysis), hence the non-significance of the latter

was likely to be as a result of lower statistical power, owing to the smaller sample size being considered.

5.3.2.3 Allergies and Comorbidities

Increasing number of allergies and comorbidities in patients were found to result in significantly increased intervention rates using both methodologies (Table 5.6).

5.3.2.4 Missed Doses

The number of missed doses in the first 24 hours (Table 5.7) was found to significantly increase the pharmacy intervention rate in the time to event analysis ($p<0.001$), but not the binary outcome analysis ($p=0.507$). This was due to a combination of the reduced statistical power of the latter, and the fact that the binary outcome analysis appeared to have selected a biased cohort for this analysis. Analysis of total missed dose rates by length of stay indicated that those patients who were admitted for less than seven days and, hence, were excluded from the binary outcome analysis, had a significantly higher rate of missed doses within the first 24 hours than those with longer lengths of stay (43.2% vs. 37.5%, $p<0.001$). It is possible that those patients with longer lengths of stay were more likely to be elective patients and patients with long term conditions who might be less likely to refuse their regular medication, while patients with shorter lengths of stay are more likely to result from acute, emergency admissions of younger patients who are less likely to be compliant with new medication prescribed and refuse when required analgesics. When considering the missed doses as a result of a drug being out of

stock, results from the binary and time to event analyses were consistent, with greater number of missed doses associated with an increased likelihood of pharmacy intervention ($p<0.001$).

5.3.2.5 Renal and Liver Dysfunction

Analysis of factors associated with liver function (Table 5.8) indicated that the presence of a liver comorbidity was associated in a significantly lower likelihood of pharmacy intervention ($p<0.001$). A significant association with GFR was also detected ($p<0.001$), with those patients with GFR<15 being the least likely to receive an intervention.

5.3.2.6 Requirements for Drug Monitoring

Of the drug monitoring requirements considered (Table 5.9), it was found that patients who had an International Normalised Ratio (INR) measurement were less likely to receive a pharmacist's intervention than those that who did not ($p<0.001$). This was a surprising finding, since in the present study, the prescription of warfarin (the use of which is usually monitored through the measurement and assessment of INR), increased the likelihood of an intervention being performed ($p<0.001$). Analysis of whether drug monitoring had taken place gave inconsistent results for the two methods, with no significant association with pharmacist intervention in the binary outcome analysis ($p=0.665$), but a significant increase was observed in the time to event analysis. ($p=0.001$). As with the missed dose analysis, this was attributed to reduced statistical power in the former analysis, owing to the very small proportion of patients who had

drug monitoring performed, and a biased patient selection, with 1.1% of patients with a length of stay of 7 or more days having drug monitoring, compared to 0.7% of shorter stays ($p<0.001$). It is possible that this may be due to the fact that more monitoring takes place in those patients with long term prescriptions who tend to have longer stays, and that many drugs which require Therapeutic Drug Monitoring (TDM) take several days to reach steady state (the optimum time for drug monitoring). Therefore, patients who have shorter stays and are excluded from the binary outcome analysis may be less likely to be the recipients of TDM.

5.3.2.7 Class of Drug Prescribed

The frequency of prescribing of a range of drug classes over the first 24 hours of a patient's stay were then considered (Table 5.10). All of those analysed were found to be significantly associated with pharmacy intervention rates, with rates increasing with the number of prescriptions for the majority of classes considered. The only exception was the prescription of opiates, where pharmacy intervention rates fell significantly from 38% for patients not prescribed opiates, to 28% where two or more opiates were prescribed (time to event analysis, $p<0.001$).

5.3.2.8 Patient Compliance

The final class of factors considered was those relating to patient compliance (Table 5.11). Use of blister packs and increasing number of doses missed owing to patient

refusal were both found to be associated with significantly increased pharmacy intervention rates.

5.3.3 Multivariable Analysis

Since the two approaches to the univariable analysis had returned broadly similar results, the "time to event" methodology was used in the multivariable analysis. This was because it maximised the available sample size (since no patients needed to be excluded), and took into account the timing of interventions, both of which would result in greater statistical power.

Prior to the analysis, correlations between the factors being considered were assessed using Spearman's rank correlation coefficients (rho). A strong correlation was detected between the use of corticosteroids and chemotherapy / immunosuppressant drugs (rho=0.91). In addition, the total number of missed doses was correlated with the missed doses owing to patient refusal (rho=0.49) and drugs unavailable (rho=0.39). In order to minimise the risk of multicollinearity, the factors from these groups that had the weakest association with pharmacist interventions were excluded from the multivariable analysis, namely the number of corticosteroids and total number of missed doses.

The patients were then randomly divided using computer software, into two sets. The first was made up of 75% of the cohort to retain a large population for statistical analysis and was used to perform Cox regression (main data). The remaining 25% of patients (validation data) were retained to use in the validation of the risk scores.

A total of 23 factors were considered for inclusion in the original model. The stepwise procedure then iteratively removed four factors that did not add significantly to the predictive accuracy of the model, namely drug monitoring (p=0.253), and the number of prescriptions of dot drugs (p=0.216), cardiovascular medications (p=0.143) and insulin (p=0.240). Appendix 4, Table 5.12 details the final model, after excluding these factors. For each of the categories considered, the hazard ratio is quoted and alongside the beta coefficient (the natural log of the hazard ratio).

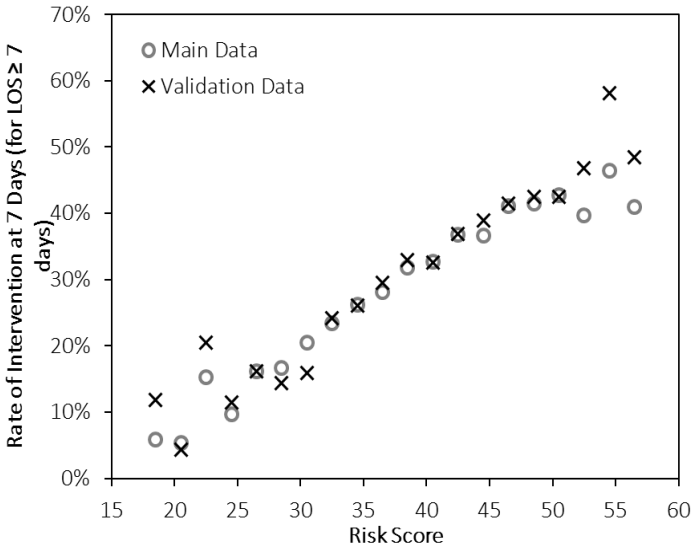
These beta coefficients were the basis of the risk score. Simply adding these values together for a patient would give the log-odds from the model, which could be used as an indicator of their risk of requiring pharmacy intervention. However, the beta coefficients were small, and so calculations would need to be performed using sub-unitary figures in order to produce an accurate risk score for a patient. In order to simplify the calculation and to make it more easily calculable should the results be used in practice, the beta-coefficients were multiplied by 20, and rounded to the nearest integer. This gave each category a score ranging from -9 to +10. In order to ensure that a risk score for a patient was always positive, a constant value of 28 was also included, giving a theoretic range for the score of 1 to 80. The greater the value of a patient's score, the greater the chance that they will require a pharmacist intervention.

5.3.4 Validation of Risk Score

In order to validate the risk score, it was applied to each patient in both the main and validation datasets. The resulting scores were then compared to the rates of pharmacy intervention at 7 days for those patients with at least 7 days of inpatient stay. Patients

were grouped by their risk score, with the intervention rates calculated within each category (Appendix 4, Table 5.14). This is shown graphically in Figure 5.6.

Figure 5.6 Rate of Intervention at 7 days Versus Risk Score.



LOS = Length of stay

A clear correlation between the risk score and intervention rate was observed in both the main and validation datasets. Intervention rates at 7 days increased from around 10% for the lowest risk patients, to almost 50% in those patients at the highest risk. However, risk scores in these extreme ranges were found in the minority of patients (<1%) shown by Figure 5.7.

In order to quantify the degree of predictive accuracy, ROC curves were produced, and the areas under these curves are reported in Table 5.15 below.

Figure 5.7 Number of Patients in Total Population (main and validation sets) Versus Risk Score

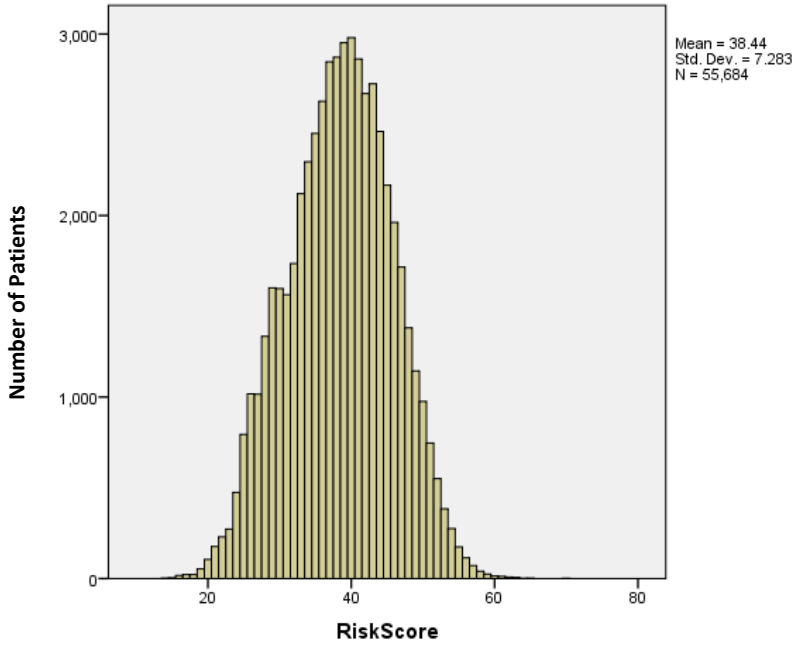


Table 5.15 ROC Curves – Main Data and Validation Data

	Areas Under ROC Curves*
Main Data	0.607 (SE=0.005, p<0.001)
Validation Data	0.616 (SE=0.008, p<0.001)
**For the prediction of intervention at 7 days (for Length of stay ≥ 7 days)*	

The areas under the ROC curves (AUROCs) were consistent for both the main and validation sets, indicating that overfitting to the data used to generate the score was not a major issue, and that the performance of the model when used in practice should be similar to that observed in this analysis. The AUROCs for both datasets were significantly greater than 0.5, hence the performance of the risk score was significantly better than would be expected by chance. Despite this, the AUROC of around 0.6 indicated that, whilst the score was significantly predictive of pharmacist interventions, the degree of predictive accuracy was low.

The performance of the risk score was also compared to that of the individual factors included in the univariable analysis. ROC curves were produced for all of factors considered for inclusion in the score, with the AUROCs reported in Appendix 5. Table 5.16. The strongest predictor of pharmacy intervention was patient age, with an AUROC of 0.57. This was of a similar magnitude to that observed for the risk score as a whole, indicating that the use of patient age in isolation would allow the prediction of pharmacy intervention with a similar degree of accuracy to that of the risk score.

5.4 Discussion

The original data set consisted of 58,918 patient admissions, which comprised only 63% of the total 93,239 admissions to the relevant wards during the study period. However, 32,850 of the total admissions were to the clinical decision unit (CDU) where more than 70% of stays are less than 24 hours which would result in these admissions being excluded from the study. The remaining exclusions were likely to be patients who were not present on the wards included in the study at the time of a pharmacist intervention.

A Kaplan-Meier survival curve was plotted for cumulative intervention rate against time to intervention. The graphic showed a smooth rise in cumulative intervention rate to 7 days post admission, at which point, just under 40% of patients would have received an intervention. The gradient of the curve was marginally steeper over the first day of hospital stay, but was near linear subsequently, indicating that the risk of intervention increased proportionally with the duration of stay.

The results from Chapter 4 identified three key stages of a patient's stay at which they may be at risk of intervention, namely, admission, discharge and during the two weeks post admission for long stay patients. When a Kaplan-Meier survival curve was produced for the rate of drug histories taken against time, the curve was steeper in the first 2 days, with 60.7% of patients receiving drug histories within this period. This initial rise is unsurprising as pharmacists aim to undertake medicines reconciliation in the first 24 hours post admission.

Using this methodology it was not possible to identify a particular stage of a patient's admission at which they would be more likely to experience an intervention. However, it is important to note that 43% of patients who receive at least one intervention will do so within 2 hours of having their drug history. This is an unsurprising finding, since once a drug history is taken by a member of the pharmacy team, it is at this point that reconciliation of the drug history against the patients current medication chart/order would occur and any discrepancies would be identified by the pharmacist. It is very likely that a large proportion of the 43% of interventions which occur within 2 hours of establishing the drug history, are directly attributable to errors in the prescription of medication which the patient usually takes at home, although further analysis of this subset of interventions would be required before this can be proven. Figure 5.3 plotted the cumulative rate of drug histories and cumulative rate of interventions on the same axis and shows how in the first 2 days of patient's admissions , there does appear to be a steep rise in both parameters which tends to tail off over time.

When performing univariable analysis, the rate of interventions was consistently lower using the binary outcome analysis. It is possible that this may be because the excluded patients experienced less complex conditions than those staying 7 days or longer. In which case, interventions to these individuals would be likely to be less complex and occur at an earlier stage in their stay, perhaps around the time of medicines reconciliation. Patients with more complex conditions are more likely to have interventions later in their stay. In particular, the number of patients in the respective age groups shows that the binary outcome analysis excluded a larger percentage of younger patients from the population than older patients: the under 40s were by far the smallest age group while in the time to event analysis, (where the whole population was included) the under 40s were the largest group. Younger patients might be healthier, take fewer medications and may have less comorbidity which could cause some bias in the binary outcome methodology. In addition, if the present research produced acceptable computable risk scores for patients admitted to a Trust, it is extremely unlikely that on calculation of risk scores at 24 hours, there would be an awareness of whether a patient would be likely to stay for 7 days. As such, the risk model would need to include all patients on admission irrespective of their length of stay supporting the time to event analysis as a method for determining significance of potential risk factors. However, both methods showed similar results, some of which were surprising and revealed some limitations to the data collected.

5.4.1 Risk Factors for Intervention

A random sample of 75% of the total population was used to perform multivariable analysis using Cox regression to determine independent risk factors for pharmacist interventions and their associated hazard ratios. The use of the beta coefficients from these models enabled calculation of a risk score.

The following risk factors were all shown to be independently and significantly associated with the outcome: **age, female gender, number of allergies, number of comorbidities, presence of liver dysfunction, presence of renal impairment, record of an INR, requirement for a blister pack, number of regular prescriptions, refusal of medicines by a patient, drug out of stock, prescription of warfarin, and number of anti-epileptics, thrombolytics/anticoagulants, CNS agents, opiates, diuretics, chemotherapy / immunosuppressants or intravenous antimicrobials prescribed.** This was generally consistent with the results of the univariable analysis.

Age was the dominant risk factor in the multivariable analysis with the highest risk score of 10 (hazard ratio of 1.63 for 81+years vs. <=40 years). This was in line with the univariable analysis, and many studies detailing age as a risk factor for issues related to medicines [46,50,53–56,60,61,63,65–67,69,81]. However, although the present study indicates that age is an independent risk factor, it is only independent of the other factors which were included in the analysis. There are likely to be many factors which may predispose an elderly patient to a pharmacist intervention which are not routinely recorded, and may be difficult to quantify such as hearing loss, dementia and general confusion. It remains highly likely that age is acting, in part, as a surrogate marker of these confounding factors,

which lead pharmacists to intervene more frequently into the care of older patients. The number of regular prescriptions (ten or more drugs) gave a risk score of 7 (hazard increases by 44% compared to patients on less than 5 drugs), which again was consistent with both the univariable analysis, and what is reported elsewhere in the literature[46–48,51,52,55–57,61,63,67,69,70,74,75,78,80,81].

Also with a risk score of seven in the multivariable analysis was the requirement of a patient to have a blister pack. As a measure of patient compliance, this score is supported by the positive associations reported in the literature[47,52,81] and by the univariable time to event analysis, which found that 50% of these patients were in receipt of intervention at 7 days.

Female gender was shown to be an independent risk factor in the multivariable analysis in line with risks associated with problems with medicines in the literature[48,49,54–57,61,67,81] but only with an approximate 6% increase in the hazard ratio compared with males. This small increase is not unsurprising, in that at least one study has indicated previously that female gender is not an independent risk factor for medicines related problems[51], while another reported that being male was a risk factor[63]. However, since the present study is determining risk factors for pharmacist intervention rather than the numerous potential issues associated with medicines, the increase in risk observed with female patients does give an example of the likelihood that risks for intervention may not be identical to those for drug related problems. It is possible for example, that females are (controversially and arguably) more likely to engage in conversation with pharmacists and discuss their medicines in more detail, which may lead to more interventions into their treatment than

males. Further research into the type of interventions carried out in both groups would be required to make any conclusions.

The increase in hazard seen in patients with allergies was in line with the literature[47,61,70,71]. However, the magnitude of the increased risk of intervention was similar for the patients with 1, 2 or 3+ allergies, implying that it is the presence of any allergies, rather than the number of allergies, that is important. Additionally, in line with the univariable analysis, the following showed statistically significant positive associations with intervention rates:

number of comorbidities[47,50,52,54,56,70,81], refusal of medicines by a patient, drug out of stock, prescription of warfarin, and number of anti-epileptics, thrombolytics / anticoagulants, CNS agents or chemotherapy / immunosuppressants prescribed.

However, as in the univariable analysis there was surprisingly, an *inverse* relationship between a number of factors and the likelihood of intervention. These factors included:

renal and liver dysfunction, prescription of opiates and diuretics, record of an INR and prescription of a single intravenous antibiotic.

In the univariable analysis, reduced GFR appeared to increase the likelihood of intervention in cases of minor and moderate renal impairment but, as renal dysfunction became severe, pharmacists were less likely to intervene. This is not in line with literature detailing risks associated with medicines related problems, which indicate an increase in problems as renal function declines[46–48,58,67,69–71,75]. It is possible that minor impairment is less well noted by prescribers and, therefore, in cases of minor renal impairment, pharmacists are likely to intervene when doses or frequencies have been unaltered in

reduced renal elimination. Patients who have severe impairment (GFR <15) are more likely to be treated by clinicians who have an awareness of their renal impairment or may be admitted to a renal speciality where expertise mitigates the risk of error, hence fewer interventions are required.

Notably, in the multivariable analysis, even mild and moderate renal dysfunction demonstrated an inverse relationship with the likelihood of pharmacist intervention. This may be due, in part, to the fact that renal function deteriorates with age, hence accounting for age in the model highlights the independent effect of renal function. With this in mind, the multivariable analysis demonstrates that pharmacists are not currently targeting patients with poor renal function at UHBFT. It is likely that this is because of other mitigating factors which are occurring which reduce the risk of medicines related problems at UHBFT in this group of patients. At UHBFT, patients whose presenting complaint is poor renal function are admitted to specialist renal wards where they are treated by specialist renal nurses and nephrologists who are familiar with drug treatment of the renally impaired patient. It is possible that as a result, drug errors are significantly less common in these patients at UHBFT. A similar argument could be made for the inverse relationship seen with poor liver function, as UHBFT has specialist liver wards. Liver patients are treated on a specialist ward and receive treatment from clinicians, many of whom are members of the Trust transplant team and as such, it is possible that there is little cause for pharmacists to intervene.

The other factors with inverse relationships are more difficult to explain. These were the prescription of opiates, an IV antibiotic or diuretic and the presence of an INR result. In all of these cases, it is unlikely from the previous research identified in the systematic review

(Chapter 2) that these risk factors for drug related issues *should* be inversely related to pharmacist interventions. However, these negative relationships were present in both of the univariable methodologies considered, as well as the multivariable analysis.

It remains possible that pharmacists are not intervening as frequently as perhaps they should in this group of patients and that the present research needs to be repeated on a set of data which has been verified for appropriate and comprehensive interventions by pharmacists. Currently with a hazard ratio of 0.657 and a risk score of -8, patients with GFR <15 have a reduction in their hazard ratio of approximately 34% compared to patients without renal impairment.

5.4.2 Risk Score as a Predictor of Intervention

In terms of predicting where pharmacists will direct their interventions, the risk score was calculated for a random subset of 25 percent of the population (validation data). When plotted against the rate of intervention at 7 days, the main data and validation data showed very similar, almost linear, results (Figure 5.6) indicating a clear relationship between the risk score and the intervention rate for the population at 7 days. However, a true linear relationship would result in the rate reaching 100% at some point in time which is unlikely. It is possible that not all patients will require intervention and even the highest risk score indicated a rate of 50% which suggests that there may be a rate at which an increasing score no longer increases the rate of intervention. Further research would be required to prove or disprove this theory.

On validation of the risk score, a four-fold increase (12% to 48%) in risk was observed between the groups with the highest and lowest risk scores. However, these rates were at the extremes and constituted less than 1% of the total population (Figure 5.7).

In the univariable analysis, age followed by number of regular prescriptions had the largest impact on the likelihood a patient would receive an intervention. However, AUROCs were disappointing at only 0.570 and 0.565 respectively showing the factors were poor predictors of intervention when used alone. The prescription of multiple central nervous system agents prompted pharmacists to intervene more than any other drug class. However, again the AUROC for prescription of CNS agents was only 0.525 indicating that the drug class was a poor predictor of intervention.

In the multivariable analysis, ROC curves were produced for both sets of data (main data and validation data) to indicate whether patients with a particular risk score are likely to experience an intervention at any point in time. The resulting AUROC was 0.607 for main data and 0.616 for the validation data, which is only a marginal improvement over using the individual factors alone as predictors of intervention. To use the score alone as a method of prediction of interventions, refining of the score to improve the AUROC would be required.

5.4.3 Limitations

Very early on in the collection and manipulation of the data, it became apparent that there were several different methodologies which could have been chosen for handling the data. The major difficulty was that there were several factors that could vary with

time. For some of the potential predictors being considered (e.g. GFR), measurements could be made at any point of a patient's stay, and there could potentially have been multiple measurements made, allowing for these factors to vary over time. In addition, the length of stay of patients varied widely, and any interventions could occur at any point during this period. Attempting to account for all of this variability would require a considerably more complex statistical approach, which would also require many more assumptions. In addition, the resulting risk score would have the potential to continuously vary over time, and give different intervention probabilities depending on a patient's projected length of stay, which would be more difficult to understand and implement in practice.

As a result, a more pragmatic approach was taken in the present study, where the effect of time based variability was minimised where possible. All of the potential methodologies would have limitations, which is why multiple approaches were utilised in specified cases, with acceptance of their potential benefits and limitations. The decision to collect data for the potential predictors being considered at 24 hours after admission was an attempt to reduce the aforementioned variability over time in these factors, and has been discussed further in Chapter 4. This had the effect of simplifying the analysis, and is also more in line with how the risk score might be used clinically, as identification of patients at risk of requiring an intervention would be most useful as early as possible in a patient's stay, in order to prevent possible harms of prescribing errors. However, the limitation of this approach was that some long stay patients and those patients whose stay is less than 24 hours have been excluded from the study, resulting in a biased sample, which may not be generalizable to the whole hospital population in practice.

It was not possible to analyse data associated with disease states as the recording of ICD10 codes on the PICS is poor, particularly where these were secondary to the main reasons for admission (e.g. diabetes). Prior to any future study, clinicians should be encouraged to improve ICD10 code recording rates.

It is extremely significant to this research to note that all of the data analysed consisted of data generated on the assumption that pharmacists were carrying out interventions where patients were at most at risk, and that the model developed would be ideal in determining where future services should be directed. However, when considering the factors which had an inverse relationship with the likelihood of a patient receiving an intervention, it is possible that pharmacists may not be carrying out interventions on all patients who are most at risk of a drug related problem. There may be numerous explanations for this. It may be that pharmacists are avoiding complex or palliative patients on significant numbers of opiates through a need for training or because of anxieties associated with treating this group of patients. Pharmacists who visit liver or renal patients may be less likely to make interventions than their peers or patients with INR results on admission are referred to the anticoagulant team and are not thoroughly reviewed by pharmacists.

It should also be considered that the markers chosen in the PICS to represent the predictors of intervention were either not sensitive or specific enough and therefore were not sufficiently accurate to measure the respective predictor. For example, in the case of renal function, it may be that a change in renal function is a more accurate marker of a drug related risk than GFR.

However, it is also possible that for other reasons, these groups of patients at UHBFT do not require intervention by pharmacists and that there are other factors mitigating the risk in these patients. For example, patients who are prescribed opiates are likely to be mainly in one of two categories, patients who have non-complex needs who are in pain post-surgery or patients with complex needs who have some sort of malignancy or are palliative. The non-complex prescriptions are simple and often short term prescriptions which may be less likely to be prone to intervention by a pharmacist whilst the pain control of a palliative patient is likely to have been prescribed by the chronic pain team who are experts in their field. Similarly, at UHBFT, patients with liver and renal dysfunction are mainly located on wards dedicated to the treatment of patients with hepatic and renal problems rather than on general medical wards. Therefore, unlike many other hospitals in the UK, liver and renal patients are treated by specialist professionals who may mitigate the risk of pharmacist intervention through a reduction of error in the treatment of patients with liver and renal dysfunction. Indeed, UHBFT is a tertiary centre offering solid organ transplant services and therefore patients are treated by the experts delivering these services.

It is also possible that risks associated with drug related problems are not identical to those risks leading to pharmacist intervention and further research would be required to identify the root cause of these inverse relationships. However, it remains possible that there is an error in the assumption that pharmacists are currently carrying out interventions comprehensively and adequately in all settings. In the present analysis, it is assumed that the outcome data collected, identified all of those patients who needed a pharmacist intervention. However, owing to the retrospective nature of the study, the only outcome available was whether an intervention occurred, which is a subtle, but

important difference. It is likely that some patients requiring interventions will have been missed, for example, because they were discharged before a drug history was recorded. As such, it would be advisable to repeat this research in a prospective study, where senior clinical pharmacists are asked to review respective patients without time constraints or interruption and their interventions validated by a senior clinician to seek to determine a "best case" scenario for targeting interventions. This would be time consuming, and be limited to a smaller quantity of data, but the quality of the data may be superior to that used in this analysis. A prospective study of this nature may also seek to verify the counterintuitive finding that patients who are prescribed no medications at all are more likely to receive a pharmacist intervention than a patient who is prescribed one or more opiates.

5.5 Conclusion

The primary aim was to develop a risk score for patients as potential recipients of pharmacist interventions. The intention was to then use these risk scores to identify patients who were at high risk of intervention and direct pharmacists as part of a clinical pharmacy service to those patients who had highest risk scores, whilst other patients could potentially be reviewed by another member of the pharmacy team (potentially pharmacy technicians). A risk score was successfully produced from the data, which was found to be significantly predictive of the requirement for pharmacy intervention, and remained significant when applied to a validation cohort. However, the score had two main limitations.

The first was that, although it was found to be significantly predictive of the need for pharmacy intervention, the degree of predictive accuracy was low. Although a small number of patients in the extreme ends of the score were found to have very low or high probabilities of requiring an intervention, the discrimination between high and low risk patients for the majority of the cohort was poor. In addition, the predictive accuracy of the score was only a small improvement over what could be achieved by some of its individual components (e.g. patient age). If the score is to be used in practice then it should be used as a guidance tool rather than directive policy.

The second limitation related to the fact that some potential risk factors were found to demonstrate inverse relationships with pharmacist interventions. This was unexpected since, as discussed in Chapter 2, all of the potential risk factors considered were identified as risk factors for problems related with the use of drugs. Although the link between pharmacist interventions and drug related problems has never been proven, there is an expectation that the role of the clinical pharmacist is to target medicines related issues in an attempt to avoid or minimise the impact of adverse incidents from the use of drugs. This concept is a fundamental part of clinical pharmacy training both at undergraduate and post graduate level. As such, it was a significant finding to identify that currently at UHBFT, there is an inverse relationship between pharmacist interventions and the following independent risk factors: renal and liver dysfunction, prescription of opiates and diuretics, record of an INR and prescription of a single intravenous antibiotic. This is potentially indicative of the fact that the outcome being analysed was not the need for pharmacist intervention, but whether a pharmacist intervention actually occurred. If pharmacists are intentionally avoiding interventions for subgroups of patients, then this

will introduce bias into the data, which could potentially result in the observed inverse relationships between use of specific drugs and intervention rates.

A question arises as to whether the analysis needs to be repeated using a dataset derived from an "ideal" population, who have been identified as recipients (or not) of pharmacy interventions by experts in the field, without the usual constraints imposed on a pharmacists time, and validated by at least one other expert. However, it is also possible to argue that the dataset used in this study was extremely large (58,918 admissions) and taken over a 2-year period and, as such, the current data analysis should give an excellent, albeit unexpected, picture of where pharmacists currently practice at UHBFT. It could be argued that they currently act safely and competently and they do so alongside other healthcare professionals who may, indeed, be mitigating the potential risks for the use of drugs by practicing as experts in their own field such as renal and liver transplant. In the unlikely event, the model developed as part of this present research were to be used in practice, then it may not be applicable to other hospitals as the risk mitigation in place at UHBFT would not be evident in other settings.

The combination of the poor predictive accuracy of the score, and the potentially misleading inverse relationships between interventions and prescriptions of specific drugs indicates that the score requires further refinement before use in practice. Use of the score as the sole method to identify patients likely to need review by pharmacists may mean that resources are used incorrectly, or may mean that patients requiring intervention are missed. However, using the score to identify those at the highest risk of intervention to be seen by promptly by a senior pharmacist, those with "average" scores

to be reviewed by a junior pharmacist and that those with a very low score to be seen by a pharmacy technician may have merit in practice.

Another aim of this chapter was to identify if there was a point in the patients stay at which they were more likely to experience a pharmacist intervention. When plotting a Kaplan- Meier curve detailing one-minus survival for the rate of interventions during the first seven days of a patient's admission, it was clear that there was a higher rate of interventions over the first 1-2 days after admission, which then stabilised to a gradual increase in rate of intervention, as shown by Figure 5.1. Although 36% of patients who had both a documented drug history and an intervention were recipients of the intervention within an hour of documentation of the drug history, the specific time of the intervention could not be pre-determined prior to taking a drug history. The Kaplan-Meier curve for drug histories did not indicate a sudden increase in the rate of drug history documentation making it difficult to determine the likely time of drug histories and most interventions.

CHAPTER 6

GENERAL DISCUSSION

6. General Discussion

6.1 Discussion

6.1.1 Review of Aim

The present research was undertaken with the primary aim to:

Develop a risk assessment tool as a safe and effective method of delivering a clinical pharmacy inpatient service in which the need for a clinical review by a member of the pharmacy team, is clearly defined, based on pharmaceutical and clinical risk as determined through an electronic prescribing system.

This present research explored the possibility that risks for experiencing a problem with medicines may be identified from a patient's electronic record on admission to hospital and the possibility that pharmacists might be directed to those most at risk by an electronic computable risk score. This potentially, would be a more efficient way of directing services, since the current service model requires pharmacists to visit every inpatient at UHBFT on a daily basis, irrespective of their requirement for a review. Some patients have more complex drug regimens than others, while other patients have a good understanding of their drug regimen allowing them to manage without intervention from a pharmacist. Patients are very complex in their needs, and there are multiple factors which affect their requirement for intervention by a pharmacist and the possibility of them experiencing an adverse incident related to the use of their medicines. As such, the present research partially met its primary aim.

6.1.2 Identification of Risk Factors for Drug Related Problems

The systematic review of the literature in Chapter 2 sought to identify what factors were likely to lead to a patient becoming a recipient of a pharmacist intervention or a problem with their medicines. Review of the literature found 38 papers, which detailed 10 measurable risk factors linked with drug related problems in hospital inpatients. All of the risk factors were potentially identifiable from an individual patient's records on admission to hospital. However, the search did not identify any papers which detailed the risk factors which were directly linked to pharmacist interventions. It was therefore identified that there was a need for further research to determine if there was a direct association with the risks documented in the literature for problems associated with the use of medicines such as adverse drug events, drug related problems, medicines related problems etcetera and pharmaceutical intervention. Certainly it is likely that there are a number of factors which are more "holistic" in nature which cause pharmacists to intervene that are unlikely to be included as risk factors for adverse outcomes from medicines. For example, patients with communication problems or learning difficulties are more likely to be targeted by pharmacists in order to determine if they have any compliance issues. However, patients with communication problems are also less likely to engage in conversation with a pharmacist, which may make them less likely to be the recipient of an intervention, while patients who enjoy engaging in conversation with the pharmacist are may be more likely to hold their attention. It is clear that causes of pharmacist intervention may not necessarily be bound purely by a patient's prescription and previous medical history. In particular, age was found to be an independent risk factor for pharmacist intervention in this study and although it is very unlikely that age *is* an independent factor *per se*, there are so many confounding factors which vary as

patients age and also may increase the likelihood of patients experiencing problems with their medicines such as hearing loss, deteriorating dexterity, sight impairment and memory loss, that it becomes irrelevant in practice, to prove that age is not an independent risk factor. In the main, older patients are more likely to be the recipient of a pharmacist intervention with patients over 81 years having a risk score of 10 in our risk model.

In order to identify factors, which lead to pharmacist interventions which may not be directly associated with drug related problems, Chapter 3 reviewed the literature. The aim was to identify if there was any consensus with regards to the recording of pharmacists' interventions with a view to determine whether or not factors recorded for the purpose of retrospective analysis of interventions were also risk factors for the interventions themselves. Compliance issues were the most notable addition to the potential risks for pharmacist interventions included at this stage.

6.1.3 Measurable Risk Factors In the Electronic Prescribing System

By combining potential risk factors identified by the reviews in Chapters 2 and 3, some work went into defining how these factors could be identified from the electronic prescribing system (PICS) at UHBFT. However, there was no assurance that the potential risks identified in Chapter 2 or 3 would have a direct association with clinical pharmacy intervention. Identifying some of the potential risk factors using an electronic prescribing system was in some cases, difficult. For example "compliance issues" were identified by only the requirement for a blister pack or refusal of medication recorded on the prescribing system. Patients may have numerous other compliance issues, such as problems opening medication containers or shift working on return home which would

not be identified by the PICS but may cause a pharmacist to intervene into a patient's treatment regimen as an inpatient.

Further work to improve the predictive accuracy of the risk score may include improving the sensitivity and specificity of the predictors of risk in the electronic prescribing system.

6.1.4 Statistical Analysis and Risk Score

Statistical analysis of the data produced some surprising results. Both univariable and multivariable analysis indicated that there were risk factors for problems with medication which had an inverse relationship with the likelihood of experiencing a clinical pharmacy intervention. At UHBFT patients who have a deteriorating GFR, have liver impairment or are taking opiates, diuretics or a single intravenous antibiotic are all less likely to have an intervention than those who do not. On analysis the risk score was shown to be a significantly associated with the need for intervention, but the degree of predictive accuracy was found to be poor. It is possible that the markers chosen in the PICS may require refinement to improve their accuracy as predictors of intervention.

Another limitation of the methodology was that the data representing each risk for intervention was measured at 24 hours after the patient's admission. It could be argued that the characteristics of all patients who were recipients of an intervention should have measured at the time of the respective intervention and compared with those who did not receive an intervention. However, this posed the question as to what time in the patient's stay should the patients who did not receive an intervention, have their characteristics compared. Twenty-four hours was chosen as this was thought to be the time at which most patients were reviewed by the pharmacy team for medicines

reconciliation and therefore likely to be associated with a high rate of interventions at this point in the patient's stay.

6.1.5 Use of the Risk Score in Practice

Although statistically the AUROC was poor, the score may be of use in practice as a guidance tool for clinical pharmacists, directing the team to those patients at high risk of intervention who have not been reviewed within the first 24 hours of their stay. Thereafter, a manual re-assessment of risk could be undertaken by the pharmacist in accordance with a guidance document detailing the high risk factors for intervention detailed in this present research.

In practice, the score would be best utilised in the early stages of a patient's stay and for those patients with stays of more than 24 hours for a number of reasons. Firstly, if programmed into the PICS, the score would not be visible until the patient had been admitted for at least 24 hours. Pharmacists will endeavour to see patients as soon as possible after their admission and start their daily round at 9am in the morning, at which time, only the scores for those patients admitted prior to 9am the previous day would be visible. In addition, for patients who stay much longer than 7 days, the score on admission would become less relevant over time as their treatment and clinical condition changes. As such it would seem sensible that scores should be recalculated for patients with longer lengths of stay. However, this would require additional data analysis not covered by this research and in which case, a manual risk assessment from a pharmacist could be employed for patients with longer lengths of stay until further research is completed.

In Chapter 4 some potential risk factors were excluded from the analysis as they could not be identified in the PICS e.g. interactions, untreated indication, dose too high or low, duration of prescription or request for information. These potential risks should be borne in mind for future development of the system. In the main, these excluded factors were factors which were directly attributable to pharmacist intervention, i.e. those factors which are recorded as part of the documentation of pharmacist intervention. They were not factors which may (or may not) lead to a problem with medicines such as poor renal function or polypharmacy. As such, it may be pertinent to also consider programming the electronic prescribing system to alert pharmacists to when there is an *actual* problem with a medicine in addition to highlighting patients at risk. Currently, prescribers receive alerts regarding interactions or they may need to confirm a high dose but where prescribers confirm that they wish to override an alert and continue with a prescription, pharmacists are not alerted. An alert to a pharmacist would serve as a potential referral system and with appropriate programming could allow referral requests from healthcare professionals and patients alike. However, such a system would require extensive programming and could potentially generate significant numbers of inappropriate alerts if it were to be a comprehensive enough to ensure patient safety. To avoid alert fatigue (i.e. ignoring potentially critical alerts due to the number of insignificant alerts generated), it would be appropriate that alerts were only generated when certain criteria are met prompting pharmacist review. Certainly, since commencing this research, there have been publications of such rule based clinical decision support systems improving the number/effectiveness of pharmacist interventions[116,117].

Ideally, an approach using both a rule based alert system to identify any patients who have already been prescribed a regimen identified as inappropriate used alongside a

potential risk score for those for the potential to experience a drug related problem should be developed.

6.2 Conclusions and Future Research

The poor statistical predictability of the score in an individual and the finding that there were inverse relationships with some of the factors examined, suggests that there may be scope for refinement of the score to improve its accuracy.

Prior to using the risk score, it would be important to ascertain whether or not the inverse relationship which consequently would be used to direct the pharmacy team away from this subset of patients was appropriate or not. It is possible that in the case of renal and liver dysfunction the treatment of patients on specialist wards mitigates the risk of pharmacist intervention. These wards receive input from senior specialist pharmacists so there is little reason to assume that there are a large number of drug related problems which go undetected by a pharmacist. It would be beneficial to generate the data again but exclude patients from Liver and Renal specialist wards. It may be the case that patients with renal or liver impairment who have been admitted to other wards at UHBFT (perhaps when their renal or liver impairment is not the presenting complaint) do in fact, have an increased risk of pharmacist intervention.

In the case of patients who have been prescribed opiates, diuretics or a single intravenous antibiotic, it is possible that at UHBFT there is a lack of expertise by the pharmacy team in the treatment of these patients. Further analysis would be required to

identify the true cause. If this was found to be the case, then a package of education and training should be instigated and the research repeated.

Future development of the score will focus on improving the sensitivity and specificity of individual predictors of intervention in an attempt to improve the AUROC of the score. For example, problems with renal function may be more accurately measured by a change in renal function rather than GFR and compliance may be better measured by a combination of the requirement of a blister pack with the refusal of medicines. With the refinement of the predictors of intervention, the score would then be recalculated with the expectation of an improved AUROC and therefore predictive accuracy.

Once a new risk score is developed, research should focus on how to use the score in practice. Scores of varying magnitudes need to give an indication to the pharmacy team as to the level of pharmaceutical input required in respective patients and currently this research has not addressed this issue.

As such, the PICS has been developed to allow manual risk assessment of patients by pharmacists who assign them to “HIGH”, “MEDIUM” and “LOW” risk categories. Future research will focus on using the data from manual risk assessment to undertake a comparative analysis of the manual risk categories assigned and the computable risk score to determine the range of scores in each category. Statistical analysis will then be used to indicate the risk score range for each category which can then be used to determine the level of pharmaceutical input required by the pharmacy team. It is likely that HIGH risk patients will be reviewed daily by a pharmacist, MEDIUM risk patients every 48 hours and LOW risk patients by a pharmacy technician.

It is also possible there are many other factors which are associated with pharmacist intervention which have not been highlighted by this research. These factors are also likely to be variables that are either not measurable, or are not currently recorded in patient notes. For example, patients when in conversation with pharmacists will often highlight issues with their medication which is not documented on the inpatient chart. It is possible that if an electronic prescribing system was used to direct the pharmacy team away from patients who were deemed to be low risk, that the opportunity for pharmacist intervention (unidentified by an electronic risk model) would be removed from these patients entirely. As such it is crucial that all patients are reviewed by a member of the pharmacy team (which could include a pharmacy technician for "low" risk patients) to allow the opportunity for conversation and identification of risks not apparent from this research therefore increasing the possibility of intervention.

In some cases, it is possible that carrying out one intervention may also increase a patient's chances of receiving multiple interventions as a pharmacist may return to confirm the outcome of intervention. Further investigation should seek to confirm if those patients who have received an intervention are more likely to be visited again by a pharmacist and consequently more likely to be the recipients of multiple interventions. It is also possible that patients with low risk scores may not only be less likely to be the recipient of an initial intervention but also subsequent interventions. As such, analysis of the current data may be warranted to determine if the risk score is a predictor of the total number of interventions in a patient's stay.

This research used the data generated from PICS to determine a risk score for patients as recipients of an intervention within the first 7 days of their stay. The records of

intervention at UHBFT also record a severity score based on the severity of the potential outcome in the absence of intervention. It may be advantageous to determine whether or not the risk score developed as part of this research could also be used to determine which patients are more likely to be the recipient of a potentially lifesaving intervention.

6.3 Summary

In summary, this evidence based risk score may be used as a useful guide to determine which patients are at highest risk of pharmacist intervention within their first 7 days of stay. Further refinement of the score and a comparative study with manual risk assessment by pharmacists may determine if it is possible for the score to indicate the level of service delivery.

This research may be of interest nationally and as such, publication of the development of the score will disseminate the findings in order that the conclusions and research and development opportunities may be shared amongst organisations.

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APPENDICES