ADVERSE DRUG REACTIONS IN HOSPITAL INPATIENTS

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Abstract

Adverse drug reactions (ADRs) are a significant public health problem. This thesis examined the incidence and nature of adverse drug reactions following admission to hospital. An initial pilot study was conducted to develop methodology, which was then utilised in a study of 3695 patients. Approximately 15% of patients experienced an ADR following admission, of which one-third were serious. Commonly used drugs such as opioids, diuretics and anticoagulants were the most frequent causes of ADRs. Bleeding, renal impairment and *Clostridium difficile* were the ADRs with the greatest impact on patient length of stay and thus should be key areas for intervention strategies. Adoption of methods used in the assessment of hospital patient safety incidents such as root-cause analysis may help in identifying underlying factors leading to ADRs as well highlighting the importance of ADRs to senior hospital managers.

One-fifth of patients readmitted to hospital within one year of discharge from their initial admission were readmitted due to an ADR, highlighting the need to effectively review patients' medicine both during the inpatient stay, and in primary care. The effectiveness of many medicines recommended as prophylaxis against ADRs is unknown. In a study of the relationship between opioids, laxatives and constipation in patients following neck-of-femur surgery, it was clear that the evidence base for using laxatives in the treatment and prevention of constipation was poor, making it difficult for prescribers to prevent opioid-related constipation.

Methodological difficulties in assessing the probability that a drug caused the identified adverse event were highlighted in the pilot, main admission and re-admission studies. An assessment of three published causality assessment methods found low-levels of reliability between the observers, questioning the validity of standardised causality assessments.

Future research in this area must focus on strategies to reduce the ADR burden and provide safer healthcare to patients.

Chapter 1: Introduction

1.1 Background

Adverse drug reactions (ADRs) have been described for as long as medicine has been practiced. In the modern era, serious adverse events, such as the development of phocomelia with thalidomide [1], the abrupt worldwide withdrawal of rofecoxib due to its association with increased cardiovascular risk [2, 3], and the controversy surrounding SSRIs and suicide [4] have publicly highlighted the need for pharmacovigilance. These events have attracted much publicity, but it should be recognised that ADRs are a common problem, which affect people in both primary and secondary care every day.

This introductory chapter will firstly examine terminology and methodology of ADR research relevant to this thesis and, then will focus on reviewing the literature surrounding ADRs in hospitals. An abridged version of this literature review was published in Current Drug Safety in January 2007 [5] (Appendix 1).

1.2 Definitions

Adverse drug reactions (ADRs) have been subject to several definitions. Early studies relied on definitions such as that of Cluff *et al* in 1964: "Any adverse response to a medication undesired or unintended by the physician" [6]. This definition and others from the same era are vague and encompass intentional and unintentional overdose as well as some administration errors [7, 8]. They are therefore less useful in analysing adverse reactions in drugs used at doses intended for therapy.

In 1972 The World Health Organization (WHO) defined ADRs as "any response to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [9]. This definition is intended to include all doses used clinically but exclude deliberate overdose and has been used widely in ADR studies [10-15], but was subject to criticism as is it includes all adverse reactions, no matter how minor, and thus may undermine current surveillance systems [16, 17]. Edwards and Aronson suggest the following as an alternative: "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a

medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [16]. This definition includes doses used clinically, but excludes reactions requiring no intervention, and has been used in ADR epidemiological research [18].

Other definitions used in some epidemiological studies which measure ADRs, have a broader scope and examine adverse drug events (ADEs) as a whole. ADEs have been defined as "injury resulting from the medical intervention relating to the drug" [19]. Therefore all ADRs are ADEs but not all ADEs are ADRs. The terms are not interchangeable as studies of ADEs can encompass errors of administration, prescription, and ordering and ADEs are not necessarily due to the drug itself. The disparity of terms is a major source of error when comparing studies and their methodology. A widely accepted, formal definition would allow for greater co-operation between those groups studying ADRs and their impact worldwide.

1.3 ADR Classification by mechanism

Rawlins and Thompson first formally classified the mechanisms of ADRs in 1977 [20] as Type A and type B reactions. Type A (Augmented) reactions are predictable through knowledge of the drug's pharmacology and dose - dependent e.g. hypoglycaemia with antidiabetic agents. Type B (Bizarre) reactions are unpredictable in relation to the known pharmacology of the drug and do not show a clear dose-response relationship, e.g. anaphylactic reactions to antibiotics. This classification system is the most widely accepted and recognized in the literature. This "A or B' classification system was extended and a further five categories (C-G) have been introduced by various authors (Table 1.1). These additional classifications are not universally accepted. With regard to the C (chronic) classification, e.g. skin discolouration with chlorpromazine, and D (delayed) classifications, e.g. teratogenic effects, both may be classifiable as a Type A reaction [21]. Genetic and genomic mechanisms can also be involved in type A and type B mechanisms. Systems that include failure of therapy as an ADR are controversial although interactions causing therapeutic failure in particular are of interest to ADR researchers.

Table 1.1: A-G Classification of ADRs

Type of Reaction	Features	Examples
A: Augmented [20]	Common Dose-related Related to pharmacology Predictable	Nausea and vomiting with digoxin
B: Bizarre [20]	Uncommon Not dose- related Not related to pharmacology Unpredictable	Anaphylaxis with penicillins
C: Chronic [22]	Uncommon Related to cumulative dose	Skin discolouration following long-term chlorpromazine therapy
D: Delayed [22]	Uncommon Usually dose-related Occurs a considerable time after drug has been stopped	Vaginal adenocarcinoma with diethylstilboestrol
E: End of Use [22]	Uncommon Occurs soon after stopping drug	Benzodiazepine withdrawal syndrome
F:Failure of Therapy [23]	Dose related Can be caused e.g. by interactions, tolerance, resistance	Oral contraceptive interaction with penicillins
G: Genetic/ Genomic Mechanisms [24]	Dependent on individual genome/	Malignant hyperthermia with suxamethonium

Aronson and Ferner found the above classification system limited and considered that other data such as the reaction properties (time course and appearance and severity), and the susceptibility of the individual (e.g. genetics and pathology) should be taken into account when classifying ADRs. DoTS (Dose, Time, Susceptibility) was the result of this thinking and produced a three dimensional classification system of ADRs, an interesting concept which has yet to be adopted by ADR studies [25].

1.4 Detection and monitoring of ADRs: pharmacovigilance

Pharmacovigilance has been defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" [26]. Following the thalidomide disaster in the early 1960s, legislation requiring pre-marketing efficacy and safety data for medicines was introduced, including amendments to the US Federal Food and Drugs Act in 1962, and the introduction of the Medicines Act in the UK in 1968.

Due to the relatively small, well-selected, patient populations in clinical trials, post-marketing surveillance is essential to identify ADRs with a relatively low incidence or long latency period, or those which mimic common non drug-related conditions in the community [27]. Effective pharmacovigilance post-marketing helps to develop a full drug-safety profile for medicines. A formal system to monitor the adverse effects of drugs was set up in the UK in 1964. The "Yellow Card" scheme allowed for the spontaneous reporting of suspected adverse drug reactions by doctors. The scheme continues and it later allowed pharmacists and nurses to report. In 2005 it first permitted members of the public to report adverse events.

There have been successes with the Yellow Card scheme; for example, warnings were added to the summary of product characteristics regarding myocarditis caused by clozapine, and the antipsychotic remoxipride was withdrawn worldwide following reports of aplastic anaemia [28]. Clearly, the scope of the information received depends on the willingness of reporters to co-operate and between 85 and 98% of doctors, depending on the country, never report an adverse event to their national authority [29]. Under-reporting is harmful as it delays the time taken for signals indicating the presence of serious ADRs to be identified in the wider population. Low reporting rates also make spontaneous reports unsuitable for recording epidemiological data (i.e. incidence) of ADRs. Detailed case reports of notable adverse drug reactions are published in medical journals, but these anecdotal reports have been found to be of little value because reports are rarely investigated further, or incorporated into drug reference sources [30].

In order to fully assess the impact of ADRs, comprehensive surveillance of all patients in a population is required. This surveillance can be done retrospectively or prospectively. Retrospective analysis relies on review of medical records and

chart review. As information recorded in patient notes is often incomplete [31], and access to the patient and relevant staff for further information is less likely, retrospective analysis is generally less capable than prospective monitoring of identifying all ADRs in a study population, although several studies have successfully used retrospective methods [32-34]. Retrospective studies using discharge coding found very low ADR rates. Data from an Australian study over a 20-year period to 2002 showed that 0.8% of all inpatient stays were associated with ADRs [35]. Data from a UK coding study showed that 0.35% of admissions were drug-induced [36], in contrast with a UK prospective study showing the incidence to be 6.5% [18]. Despite this, discharge coding has been shown to highlight more ADRs than spontaneous reporting by healthcare professionals [37].

Prospective surveillance of a patient population is thought to be the most appropriate method for assessing the incidence of ADRs [38]. It involves collection of ADR data regularly, often daily, by a trained healthcare professional on selected wards or departments over a restricted time period to record all patients and all events [39].

Examples of early prospective studies include those conducted by the Boston Collaborative Drug Surveillance Program (BDSCP) [40-42]. where nurse monitors identified ADRs on a daily basis for the study period and the monitor and a physician then made a judgement regarding causality based on the collected data [41, 42]. Similarly, in a recent study in the UK of ADRs leading to hospital admission, a study pharmacist or nurse assessed all admissions to two hospitals for ADRs over a six-month period. ADRs were then assessed for causality, severity and avoidability [18]. Different healthcare professionals have collected the data in different studies although whether or not the profession of the investigator has an impact on quality or number of ADR reports has not been investigated. Use of multiple data sources, including computerised surveillance of laboratory reports, medical records and prescriptions have also been suggested as methods of detecting ADRs in hospital [43-47].

Patients can be very useful in identifying ADRs. This is reflected by the fact that patients are now permitted to spontaneously report ADRs in the UK via the Yellow Card scheme. Studies of inpatients and patients in the community have shown

they are able to identify ADRs successfully [48-50]. Reports of subjective ADRs e.g. headache and dizziness can only be obtained from the patient in the first instance, and the patient should, where possible, be involved when considering an ADR as a likely diagnosis. Differences in ADR perception between clinician and patient were highlighted in a study of patients taking clozapine. Clinicians generally estimated greater incidence and severity of adverse drug reactions compared with patients, particularly extra-pyramidal side effects, although they underestimated the incidence of polyuria by 41% [49]. This may reflect different perceptions of ADRs and also the limitations of the clinic setting, where visible reactions may have greater impact on the clinician than those which can only be described by the patient.

An ideal method for detecting ADRs in inpatients would be prospective and ongoing, use trained staff to collect ADRs whilst encouraging ward staff to be involved in ADR detection and allow independent review of each ADR by senior trained staff, such as clinical pharmacologists. Embracing technology and developing an integrated approach to ADR detection may help to reduce the workload that typifies intensive prospective review [51].

The variability in data collection methods, definitions and analysis contribute to varying conclusions of ADR studies, and result in subsequent difficulties in pooling data. Individual studies and meta-analyses of ADR studies should therefore be evaluated cautiously and critically. Before discussing these studies, this review will focus on three main areas of ADR assessment, causality, severity and preventability.

1.5 Causality assessment

In reality, a drug either caused a reaction or it did not. However, there are many variables in making this decision. In the large majority of cases, due to the lack of available evidence, an absolute decision as to causality cannot be made. Estimations of the likelihood that an adverse reaction was caused by a drug are made based on the study of the available facts surrounding each case.

A recent systematic review found 34 different methods for assessing causality [52], highlighting the extent and complexity of the research in this area. There are

principally three types of method for causality assessment which are practical for regular use; thesé are unstructured assessment by an evaluator or a panel of evaluators (global introspection), semi-structured assessment using pre-set guidelines, and standardised assessment using decision tables or algorithms [53]. A fourth method, using the application of Bayesian statistics (Bayesian Adverse Reaction Diagnostic Instrument: BARDI) has also been devised but its complexity may limit its use [54].

1.5.1 Global introspection

This method of causality determination is based on the personal judgement of each ADR report by the investigator, following careful study of the case notes and application of clinical opinion. The early studies of the BCDSP used the assessment of the attending physicians, whereas others have used clinical pharmacologists. In a 1976 study comparing clinical pharmacologist and physician assessment of suspected ADRs, complete agreement between the clinical pharmacologists and the treating physicians occurred in less than half (47%) of the cases [55]. More recent work found poor agreement ($\kappa = 0.2$) between expert judgements when assessing 150 drug-effect pairs by global introspection, particularly at the intermediate levels of causality [56]. Poorer agreement at lower levels of certainty is logical due to the increased subjectivity involved in making assessments of ADRs, when clear evidence is absent [56-57]. The character traits of the evaluators may also influence their assessment of the ADR [58]. This "global introspection" has been described as inappropriate as a serious scientific method for assessing adverse drug reactions [59], although despite its subjectivity and lack of transparency, this method of assessment is the one that is most binding for the evaluator [53].

1.5.2 Semi-structured assessment

This method provides guidelines for assigning a causality term, i.e. 'definite', 'probable', 'possible' and 'unlikely' ADR, without providing specific rules as to how the causality assessment should be carried out. The World Health Organization - Uppsala Monitoring Centre (WHO-UMC) has provided a tool for the assessment of case reports (Table 1.2), giving guidance to the general arguments that should be used to select one category over another [60]. Its application has advantages over the unstructured method in that the guidelines for categorisation of an ADR are

clear, and this will allow other observers to have an indication as to how a conclusion was drawn.

Table 1.2: WHO-UMC Causality Categories [60]

1.5.3 Standardised assessment

The use of unstructured and semi-structured methods of assessment leads to causality evaluations where the exact methods of determining causality are not clear. The relative importance of different factors such as the temporal relationship between drug and effect and the recognition of a possible ADR in the product literature, to the evaluator is not clear. This variation, confounded by the evaluators' belief system and prior knowledge means that the use of an evaluator's opinion is neither reproducible when several evaluators assess the same data, nor it has it been validated. Many algorithms have been developed to assess the causality of ADRS. Three of these algorithms, Karch [61], Kramer [62], and Naranjo [63], are discussed. The development of these methods shows progression from large decision tables to a concise algorithm, although there are inherent problems in their design and validation.

1.5.3.1 Karch and Lasagna decision tables

Karch and Lasagna produced an algorithm for causality assessment in 1977 [61]. This algorithm was designed around three decision tables intended to assess potential ADRs, the certainty of the link between the event and the agent, and evaluate the underlying causes of the identified untoward events.

If the possibility of a link was established, it was determined as definite, probable, possible, conditional, or unrelated according to evaluation criteria. These criteria include knowledge of the reaction, temporal relationship, presence of known alternative causes, dechallenge and rechallenge information. Events due to alcohol or recreational drugs were distinguished from medicines related events. Compliance, drug choice and dose, drug interactions, medication errors and treatment of terminal illness were incorporated within the algorithm, and the method was used to determine whether or not an ADR occurred, or the untoward event had another root cause.

The accuracy of the analysis was evaluated by comparison of 60 assessments with the consensus assessment agreed by a group of three clinical pharmacologists. The use of consensus as a standard against which the algorithm is assessed was flawed, but using a consensus of three experts minimises

individual bias and the algorithm evaluations agreed with the consensus of the clinical pharmacologists on 45 evaluations (71%) [61].

The algorithm was intended as a method whereby the result is reproducible, but the algorithm still requires the evaluator to make certain judgements. Therefore it will not always produce the same answer from the same report. There were two main problems with the algorithm; that the limits or identifying 'possible' ADRs were found to be so wide that no ADR cases were excluded, and that the criteria for determining a 'definite' ADR were very narrow. Because of this, quantitative data based on 'definite', 'probable' and 'possible' ADRs overestimated the number of ADRs, yet those excluding 'possible' ADRs underestimated the overall number of ADRs [61].

This algorithm therefore has its problems, although it provides a framework for the systematic evaluation of ADRs with a greater degree of transparency than less structured approaches.

1.5.3.2 Kramer algorithm

In an attempt to expand on the work of Karch [61], Kramer *et al* [62] produced a set of diagnostic criteria providing specific rules for the assessment of ADRs. The criteria are arranged as an algorithm with a numerical scoring system for 56 questions over six axes of decision strategy: previous general experience with the drug, alternative etiologic candidates, timing of events, drug levels and evidence of overdose, dechallenge and rechallenge. The algorithm is then applied to rate the candidate ADR as definite, possible, probable or unlikely [62]. Judgement still plays a part in the algorithm particularly with regard to the evaluation of diagnostic evidence.

When the above methods were compared, assessing 200 reports, the methods were not significantly different in the proportion of cases they deemed definite ($p=0.5204$) or probable ($p=0.2972$). However, for possible and unlikely ADEs, the Kramer algorithm was more likely to assign a risk of possible ($p=0.0001$), while the Karch instrument was more likely to assign a risk of unlikely ($p=0.0001$). The algorithms disagreed with each other 59% of the time. It is apparent that the results from these algorithms are not directly comparable [64].

1.5.3.3 Naranjo algorithm

The above algorithms go some way to achieving reproducible assessment, but the algorithms are long and time-consuming to complete. Naranjo *et al* therefore set out to develop a simpler method [63]. They developed the ADR Probability Scale (Table 1.3). When six observers tested this scale, a rise in agreement was found between the observers using the algorithm, compared with use of conventional definitions [63]. The validity assessment of this algorithm used the consensus assessment of three experts using semi-structured assessment as an external standard. When the experts' results were compared with those of the observers, the percentage agreement between the observers and the experts was 70% to 84%. Furthermore, when one of the experts re-assessed the events using the algorithm and his results were compared with those of the observers, the agreement increased to between 86% and 95%. The scores produced by the algorithm also correlated with the scores produced by the Kramer algorithm when it was used to score the same cases ($r=82$, $p<0.001$) [65].

Question 5 in the algorithm (regarding alternative causes) resulted in the most disagreements [63], which may be due to the complex clinical situations and differences in training of the observers. This serves to demonstrate that algorithms such as these still require the need for a degree of clinical judgement and therefore 100% reproducibility between observers is impossible.

As the Naranjo algorithm produces results that are highly correlated with Kramer's and also takes a significantly shorter time to complete [66], it would seem more appropriate to use Naranjo's algorithm on a daily basis. However, a study which applied the Naranjo algorithm to ADRs in an intensive care unit found poor inter-rater agreement [67] perhaps reflecting the difficulties in assessing 'real-life situations' as opposed to the detailed case reports used in the initial validation of the Naranjo scale [63].

Table 1. 3: ADR Probability scale: Naranjo *et al* [63]

A consensus has not been reached on which algorithm should be used universally and many others have also been devised e.g. Jones's algorithm has been used by The Food and Drug Administration (FDA) for many years [68]; Ciba-Geigy Ltd (now Novartis) used the method devised by Venulet *et al* [69, 70]. Other general methods have been devised [71, 72] as well as more specific systems, for example, Maria and Victorino's scale for the diagnosis of drug-induced hepatitis [73]. Different authors tend to apply similar parameters (experience, timing, rechallenge, dechallenge, alternative causes), but have disagreed on the weighting given to certain events and devised their own algorithms in an attempt to improve on what has been done previously.

The problem is that despite attempts made to compare some of these algorithms, it is impossible to prove one is better or than the others because the truth (i.e.

whether or not the drug caused the event) is not known. Agreement between methods is not to be assumed. A computerised assessment of 6 causality assessment procedures (including those of Karch, Kramer and Naranjo [61-63]) found that the rate of agreement between any two methods fluctuated between 26% and 65% [74]. It can however be argued that one method is easier to use and less time consuming than another, and that its results are more reproducible than another. When comparing studies it is important to recognise that different causality assessments may have been applied in each study. In France, all causality assessments must be done using the same method, that of Begaud *et al* [75]. This helps to standardise the research. A consensus of international opinion regarding the 'best' algorithm for everyday use would enable easier comparison of international studies.

1.5.4 Bayesian methods

Standardised assessment methods were criticised most effectively by Hutchinson and Lane [59, 63]. They described that typically, the evaluator is asked if the timing of the reaction is consistent with drug causation, but the issue of the consistency of this relationship is ignored. Also, the algorithms ask if the event is a known occurrence as a result of the drug, but do not ask how frequently it is described. When validating algorithms, most authors attempt to compare the results with the opinions of experts, but it was the poor reproducibility of unstructured and semi-structured assessment that led to the development of standardised methods.

A different approach (Bayesian Adverse Reaction Diagnostic Instrument (BARDI)) was proposed to determine causality based on Bayes' theorem [76, 77]. It applies logic of uncertainty to the problem of causality assessment. Its goal is to calculate the posterior odds that a drug caused a particular event. This is the probability that a drug causes an adverse event given all the background and case information, divided by the probability that it did not cause the event given the same information. The goal of the assessment is to collect all relevant information as input and deliver as output the posterior odds. There is no limit to the number of factors that can be incorporated into the assessment and the mathematics involved is complex.

It has been successfully applied in several instances to individual ADRs, for example, with haematologic dyscrasia associated with ticlopidine therapy [78], and with Guillain-Barre Syndrome and zimeldine [79]. The complexity of the instrument means that it is unsuitable for routine use in clinical practice and epidemiological studies. When BARDI and the Naranjo method were compared it was found that assessments using both tools were significantly correlated (r_s= 0.45, p<0.0001) [54]. The BARDI instrument was better at distinguishing cases that were highly probable or highly improbable whereas the Naranjo scale rated the majority of these cases in the mid range. A simple algorithm incorporating Bayesian concepts to assess ADRs in clinical trials has been developed [80], although whether this method provides a better simple algorithm than those already described is unlikely. In comparison to the most sophisticated measurement of causality, Naranjo yielded satisfactory results, which is positive, as this algorithm is more practical in everyday use than BARDI.

As Hutchison said: "it is a strange and counterintuitive practice to apply numbers to subjective judgements" [81]. Assessment of causality is complicated and confounded by many factors. Whichever system is in a study, it is vital that as much information as possible about each event is gathered and consistency of approach is applied.

1.6 Severity assessment

As part of a study of iatrogenic hazards in 1973, Schimmel classified 'episodes' as minor, if they were short and subsided without treatment; as moderate, if they required significant treatment, or if they prolonged hospitalisation by a day or more; and as major if they were life-threatening or contributed to death [82]. These definitions are principally adapted in later severity scales.

1.6.1 Hartwig ADR Severity Assessment Scale

Hartwig *et al* [83] produced a simple method of determining the severity of ADRs. It was adapted from a severity-ranking scale already being used to review significant medicines-administration errors [84] and the principles are similar to those of Schimmel, with length of stay, treatment required, and prognosis being the main axes of severity assessment. The scale has seven levels ranging from

level 1 (where the ADR requires no change in the drug treatment), to Level 7 (where the ADR is fatal). The advantages of this scale are its ease of use, and clear definitions; it has been applied in a prospective study of ADRs in hospitalised patients [13].

1.6.2 Dormann Adverse Drug Reaction Severity Score

Dormann *et al* [14] more recently devised an Adverse Drug Reaction Severity Score (Table 1.4). It classifies the severity of the adverse drug reaction as mild, moderate or severe depending on the numerical score obtained when the algorithm is applied to the ADR. It incorporates quality of life assessment and ability to work and therefore provides a more patient-focused judgement of severity. It may be inappropriate to use this scale routinely in inpatients, as assessment of a patient's long-term ability to work would be impractical.

1.6.3 The CHM/MHRA Yellow Card Criteria

The CHM/MHRA require 'serious' adverse reactions to established drugs (and all reactions to new drugs) need be reported to the CHM/MHRA Yellow Card reporting scheme. As in the above scales, serious reactions are defined as those which cause death, are life-threatening or cause permanent disability; those resulting in or prolonging hospitalisation, and those which are medically significant [85].

Table 1.4: Adverse drug reaction severity score [14]

1.6.4 World Health Organisation (WHO) Criteria

The World Health Organisation guidance for definitions for seriousness of ADRs differentiates between serious, moderate and minor ADRs as follows [86].

Serious: Any untoward medical occurrence that at any dose results in death, requires or prolongs hospitalisation, results in persistent or significant disability/incapacity, and/or is life-threatening

Moderate: The symptoms are marked, but the involvement of vital organ systems is only moderate. No loss of consciousness, no circulatory failure. Antidotes may be necessary. The development of certain biochemical or structural changes may justify classification in this category.

Minor: Incidental, no antidote needed. Does not substantially complicate the original disease.

These definitions are clear and understandable, and all WHO 'serious' ADRs, and several 'moderate' ADRs would require a yellow card report in the UK. In common with all classification scales studied, the initiation or extension of hospitalisation are among the most important factors when considering the seriousness of an ADR.

1.7 Avoidability assessment

We can simply classify which ADRs are preventable by their mechanism, and deduce that a Type A reaction is pharmacologically predictable and therefore, is preventable. Type B reactions are not judged to be predictable and are therefore not preventable [20]. This is not realistic in a clinical situation. Though steps can be taken to reduce type A ADRs, sometimes there is little clinical alternative but to use the drug in the patient. Type B reactions can also be avoided if previous history of allergy or predisposition to an ADR is confirmed prior to administration.

Structured questions to assess the preventability of a reaction were designed by Schumock and Thornton in 1992 [87] (Figure 1.1). They ask the assessor to consider possible reasons for the ADR, including appropriateness of prescribing and monitoring, relevant history, and compliance.

Figure 1.1: Schumock and Thornton Preventability assessment [87]

Hallas *et al* provided definitions to assess preventability, or 'avoidability' [88]. These are shown in Figure 1.2.

Figure 1.2: Hallas Avoidability Definitions [88]

The Hallas definitions [88] are more flexible than those of Schumock and Thornton [87] and how to differentiate between definitely or possible ADRs is open to interpretation by the assessor. However, the Hallas criteria are more structured and generate greater accountability in a study than merely stating that Type A ADRs are preventable and Type B ADRs are not.

Having examined different methods of detecting and assessing ADRs, this review will examine the literature surrounding studies of ADRs in hospitalised patients.

1.8 Overview of ADR literature

Despite the difficulties in pooling data, Lazarou and colleagues published a meta-analysis of 39 prospective US studies in 1998. The analysis spanned four decades and combined the incidence of ADRs resulting in admissions and those occurring whilst patients were in hospital. The authors deduced an overall incidence of serious ADRs of 6.7%. The more controversial conclusion of the analysis was the incidence of fatal ADRs as 0.32%. When extrapolated to the hospitalised patient population of the US, ADRs were determined to be between the 4th and 6th leading cause of death in the USA [89]. The study was heavily criticised for its methodology and inappropriate extrapolation [90], but work from Sweden suggests that ADRs may be responsible for approximately 3% of all deaths, placing it as the 7th most common cause of death in the Swedish population [91] which corroborates the findings of Lazarou. Regardless of the controversy, the Lazarou analysis highlighted the enormity of the ADR burden in hospitals.

A review by Wiffen *et al* in 2002 [92] examined prospective and retrospective studies from across the world (mainly North America) for incidence data, and focussed on the impact of ADRs in the UK, their risk factors and preventability. They reviewed 69 studies (54 prospective, 15 retrospective), with a total of 413,000 patients. Incidence of admissions to UK hospitals due to ADRs was estimated as 2.6%, with those in inpatients estimated as between 3.5 and 7.3%. The cost of ADRs to the NHS in England in 1994 was estimated as £380million, with 4% of bed days being taken up by patients with an ADR [92]. As with the Lazarou study, it is difficult to draw any exact conclusions and comparisons between studies. Wiffen *et al* examined only 9 UK studies to extrapolate the above figures. The inherent differences in study methodologies make generalisations difficult. It is interesting and useful therefore to look at individual studies when

discussing incidence and risk factors for ADRs, recognising that each has its own limitations but also a contribution to the ADR literature.

1.9 Incidence of ADRs

There are two main groups of patients when examining ADRs in hospital patients: those experiencing ADRs in the community which result in admission to hospital, and those who develop an ADR during their stay as inpatients. Two recent large UK prospective studies demonstrated that 6.5% of patients admitted to hospital were experiencing an ADR [18, 93]. This is two and a half times the estimate by Wiffen and colleagues, but that estimate was based on largely North American studies, where the ADR rate appears to be approximately half that of Europe [92]. It is unclear whether this is a true difference between continents or merely reflects methodological problems.

The incidence of ADRs in hospital inpatients varied widely in the different studies examined. Early studies from the 1960s suggest that ADRs occurred in 10-20% of hospital inpatients [8, 94, 95]. Further research has resulted in widely varying estimates of prevalence, from 0.86% in one Australian study [96], to 23% in an American study of elderly patients [97], to 37% in a Netherlands-based study, also of the elderly [98]. There are no current reliable figures available for UK inpatients.

Not all patients are equally susceptible to ADRs and the potential risk factors for ADRs are discussed below.

1.10 Risk factors for ADRs

1.10.1 ADRs in the elderly

Elderly patients are rarely included in clinical trials. This makes the determination of age effects impossible. Where there is an adequate age range, most studies fail to control for important clinical differences among subjects of different ages to distinguish the independent effects of chronological age [99], and therefore the reporting of ADR incidence post-marketing is even more important. Most studies have shown an increase in ADRs among the elderly population [10, 100] and ADRs have been shown to be responsible for repeated admissions to hospital in the elderly [101]. Reasons for this increased rate of ADRs include polypharmacy,

poor prescribing, poor compliance, concurrent medical illnesses, and alterations in pharmacokinetic and pharmacodynamic parameters [10].

Pharmacokinetic changes occur with age as a result of the inevitable anatomical and physiological changes which occur with time, such as loss of an organ's functional units (e.g. nephrons, neurones) and a disruption of some regulatory processes between cells and organs, resulting in a decrease in function of bodily systems [102]. For example, first pass metabolism decreases due to a decrease in liver mass and blood flow [103], resulting in an increase in bioavailability of drugs such as propranolol which undergo extensive first pass metabolism [104]. By contrast, pro-drugs such as perindopril will experience slower or reduced first-pass metabolism [105], although the influence of ageing on the normal liver is smaller than the effects on the kidney and less significant in drug metabolism [106]. Renally cleared drugs undergo reduced clearance due to reduced renal plasma flow and glomerular filtration. This increases the potential for toxic effects particularly with those drugs with a narrow therapeutic window, such as digoxin and lithium [102]. Changes in body composition such as increases in body fat proportion and decreases in total body water result in a decreased volume of distribution for water soluble drugs such as digoxin, which increases their serum concentrations and potential for adverse effects. Changes in the handling of the drug by the body can also result in changes in the pharmacodynamic response. Thus pharmacodynamic changes with ageing include increased sedation and postural sway with diazepam, increased anticoagulant effect with warfarin, and an increased analgesic effect with morphine [102].

Onder found age to be an independent risk factor for ADRs [107] but other studies have disputed this [108-110]. Carbonin *et al* [110] studied the risk factors associated with ADRs in over 9000 patients and found the independent risk factors to be staying in a medical ward, drinking alcohol, staying in a hospital longer than 14 days, and having more than four active medical problems. Age, gender, smoking and previous history of falls, were not determined to be independent risk factors.

Variations in the rate and severity of ADRs, as well as the type of ADR and drugs implicated, can be attributed to many factors. Onder *et al* have looked at the

incidence of ADRs in older patients with depression [111], and with cognitive impairment [107]. Depression was associated with a higher incidence of ADRs. Neurologic and neuropsychiatric ADRs were more common (p=0.001) among depressed patients, but other types of ADRs, e.g. cardiovascular and gastrointestinal ADRs, showed no significant differences in incidence between the two groups, although the level of co-morbidities were similar [111]. There are multiple hypotheses as to why depressed patients may experience more ADRs. Depressed patients may amplify somatic symptoms leading to a higher rate of ADRs [112], or psychological distress may activate neurally regulated biological processes, diminishing the ability to combat pathologic processes, favouring the onset of negative outcomes such as ADRs [111]. Alternatively, depression may occur as a consequence of ADRs and the high co-morbidity associated with them [111].

Studies in elderly patients have shown that cognitive impairment is associated with a lower incidence of ADRs [107, 113]. However, this may be misleading. These patients may be unable to communicate their illness; there may also be a greater difficulty in distinguishing ADRs from the symptoms of the underlying disease [107]. This was supported in further studies, which suggested that ADRs in geriatric patients were difficult to recognise, and may be interpreted as senile loss of function [114].

1.10.2 Polypharmacy

It is accepted that patients taking more medicines suffer more ADRs [13, 110, 115, 116]. Polypharmacy is commonly defined as patients taking four or more medicines [117], but attempts to define polypharmacy are problematic. Current research suggests that ADR risk increases linearly with the number of drugs being taken, therefore polypharmacy cannot be defined by a certain number of drugs [118].

Polypharmacy is likely to increase as therapeutic guidelines often promote the use of two or more therapies to control disease, for example myocardial infarction, heart failure and type 2 diabetes [119]. These guidelines are based on clinical trials where study patients have fewer co-morbidites and fewer concomitant

medicines than many of the 'real-life' population, thus the impact of additional medicines in these patients is unknown at the licensing stage [120].

The prescription of multiple drug therapies increases the risk of drug-drug interactions. Studies have shown that 5-15% of elderly patients suffered clinically significant adverse effects due to interactions, with the number of elderly patients exposed to potential drug-drug interactions estimated to be between 35 and 60% [13, 121].

1.10.3 Renal function

The impairment of renal function, which occurs naturally with time, and when renal function is compromised by diseases such as diabetes, is an important factor in the increased risk of ADRs. If doses are not adjusted accordingly, this can result in more Type A, pharmacologically predictable [20] reactions for renally excreted drugs. It should therefore be possible to reduce the number of ADRs in elderly patients, and others with impaired renal function, by providing appropriate care [97]. Older patients with concealed impairment of renal function (i.e. reduced estimated glomerular filtration rate (GFR) and normal serum creatinine) are exposed to a greater risk of ADRs with water soluble drugs, which clearly highlights the need for monitoring of full renal parameters in the elderly patients when prescribing [122]. Steps should be taken to adjust doses and minimise the number of drugs taken by the renally impaired patient.

1.10.4 Influence of Gender on ADRs

Several studies have found that more females than males experience ADRs [10, 97, 108]. Examination of spontaneous reports found that more neuropsychiatric reactions were reported in women, and more cardiovascular reactions in men [123]. Reasons suggested for differences such as these include differences in perception of ADRs, pharmacology of ADRs, differences in kinetics such as volume of distribution leading to gender associated differences in drug exposure, polypharmacy and hormonal differences between men and women [124-126]. For example, female gender is associated with greater risk for drug-induced torsade de pointes [127]. The corrected QT interval is longer in women generally, but women are also more likely to respond adversely to drugs that can potentially block cardiac potassium channels such as sotalol. The reason for the gender

difference has been suggested to be due to specific regulation of ion channel expression by sex steroids [125, 128]. A study of gender differences in analgesic response to morphine found that women experienced significantly more side effects with morphine although both genders experienced equi-analgesic effects [129]. A pilot study examining sexual dysfunction in depressed patients treated with Selective serotonin reuptake inhibitors (SSRIs) raises interesting question regarding perception of symptoms in relation to disease state and adverse effects [130]. It was found that women generally had an increase in sexual function following treatment with SSRIs as they experience greater sexual dysfunction with their illness. Any adverse effects on sexual functioning experienced as a result of the SSRI were overshadowed by the positive effects associated with treating depression, whereas sexual functioning in men significantly worsened, possibly due to the SSRI [130]. The numbers in this study were small, but they reflect the possible differences in response to illness, medicines and perception of ADRs that can exist in men and women.

1.11 Study settings

The majority of ADR studies have been undertaken in general medical units, although studies in other clinical areas have also provided interesting results. A 1982 multi-centre study of surgical patients demonstrated that ADRs were associated with 2.2% of prescriptions, although the majority of reactions were relatively minor [41]. The issues of polypharmacy are again reflected by a study of adverse drug events (ADEs) in intensive care units (ICUs). The rate of preventable and potential ADEs was twice as high in ICUs compared with non-ICUs, but when this figure was adjusted for the number of drugs ordered, there was no significant difference between the two types of unit [131]. However, a clearer picture can be obtained from the same study, reported elsewhere, which differentiates between medical and surgical ICUs. It shows that Medical ICUs had almost double the ADE rate per 1000 patient days (19.4) than Surgical ICUs (10.5) [43], whilst the figures for surgical ICUs were comparable with general medical and surgical units. When corrected for drug use, the ADE rate in medical ICUs was still almost double that of surgical ICUs. This may be due to various factors including the use of a larger number of drugs in medical ICUs where the patients may be sicker and suffering from more complex conditions than in surgical ICUs. It is important to note however that ADEs, encompassing all drug related adverse events, including

errors in administration and transcription, and not only ADRs, were studied. The results for ADRs were not presented separately. Most ADR research is undertaken in 'developed' countries but a study of ADRs in sub-Saharan Africa found that HIV status played a major role in risk and severity of ADRs with a younger demographic and an increased fatality rate compared to 'developed' countries [132] showing that the geographical setting may impact on the rate and type of ADRs reported.

1.12 ADRs in paediatrics

A meta-analysis of paediatric studies showed that ADR incidence in hospitalised children was 9.53%, and that 2.1% of admissions are due to an ADR [133]. This is comparable with the lower adult estimates for ADRs from prospective studies. As with the elderly population, few drugs undergo clinical trials in paediatric patients. Many drugs are used 'off-label' and ADR studies therefore can potentially identify previously undetected ADRs. Data from two retrospective studies of hospitalised children in the USA showed that the drug classes most frequently associated with ADRs in hospitalised children were antibiotics, opioid analgesics, anticonvulsants and anxiolytics [34, 134] with severe reactions most commonly linked to anticonvulsants and antineoplastic drugs [134]. European studies found an increased incidence of adverse drug reactions in patients using unlicensed or off-label drugs [135, 136]. Whilst it should be acknowledged that it is often clinically necessary to use unlicensed and off-label medicines in children, steps should be taken to monitor ADRs when drugs are used in this manner, in order to reduce the burden of these ADRs in paediatric patients. As with adults, the number of ADRs has also been shown to increase with the number of drugs taken in paediatric patients [135, 137, 138].

1.13 Drugs implicated in ADRs

Studies from hospitalised patients in the 1960s reported antibiotics, diuretics, cardiac glycosides, and antidiabetics as the drugs most frequently linked to ADRs [7, 82, 94, 95]. These drugs have remained amongst the most common causes of ADRs in the following decades [12, 115]. NSAIDs and opioids have been implicated, particularly in studies involving surgical patients [15, 43], with diuretics being prevalent as causative factors in elderly patients [10, 97, 111]. Similarly,

drugs implicated in patient admission to hospital have changed little, and are largely similar to causative drugs during hospitalisation, although NSAIDs, causing gastro-intestinal bleeding, and anti-hypertensives, causing hypotension and falls, have been more frequently implicated in causing admission [18, 93, 139-142]. Table 1. 5 summarises several studies and the drugs implicated in ADRs. A recent systematic review by Howard *et al* showed that four groups of drugs (antiplatelets, diuretics, NSAIDs and anticoagulants) were associated with greater than 50% of preventable drug-related admissions [143].

Table 1.5: Adverse drug reactions and causative drugs

Study	Population	Most frequent causative drugs/drug classes
Leach 1986 [10]	521 Admissions (elderly)	Antibiotics, diuretics, insulin, opioids
Evans 1994 [11]	79,719 Admissions and Inpatients	Antibiotics, digoxin, morphine
Bowman 1994 [97]	1225 Admissions and inpatients	Anticoagulants, cardiac drugs, diuretics
Dartnell 1996 [139]	965 Admissions	Antihypertensives, corticosteroids, diuretics, NSAIDs
Classen 1997 [12]	91 574 Inpatients	Antibiotics, digoxin, morphine
Moore 1998 [115]	328 Admissions and inpatients	Antibiotics, Antidepressants, antidiabetics, antihypertensives, digitalics, NSAIDs,
Suh DC 2000 [144]	9311 Inpatients	Antibiotics, anticoagulants, cardiovascular drugs
Dormann 2000 [14]	379 Inpatients	Antibiotics
Vargas 2003 [15]	401 Inpatients (Intensive care)	Opioids
Howard 2003 [93]	4091 Admissions	Antidiabetics, antiepileptics, diuretics
Pirmohamed 2004 [18]	18820 Admissions	Anticoagulants, diuretics, NSAIDs

If a drug frequently causes ADRs, this is important, but the severity of the ADR is also a crucial issue. If a drug causes few ADRs, but these ADRs tend to be serious, it is arguably more important to address means of preventing these ADRs than those of another drug that results in a larger number of minor ADRs. A study by Evans *et al* showed that morphine was both the most frequent causative drug overall and the drug which cause the most severe reactions, but only 1 in 50 ADRs with morphine were 'severe'. However the monoclonal antibody muromonab –CD3 had the greatest ratio of severe adverse events to all adverse events (1 in 3) [11]. Putting these results into context, it is important to be alert when morphine is administered, as there are a high number of adverse events, but also, vigilance should be heightened whenever muromonab – CD3 is administered due to the frequency of severe ADRs.

It is also important to note that inaccurate medication histories taken in hospital may result in possible ADRs being overlooked [145]. The use of complementary medicines and over-the-counter (OTC) medicines must also be assessed, as this is often not documented [145, 146]. Interviews have shown that patients have a very poor knowledge of possible ADRs relating to purchased OTC medicines, which is worrying due to the prevalence of ADR-related hospital admissions, particularly to NSAIDs, which are readily available over-the-counter [18, 147].

The benefits as well as the risks of drugs should be taken into account when prescribing. Clearly, for some drugs, there is growing evidence of their effectiveness, for example, aspirin to prevent cardiovascular events [148], but also of their potential to cause harm. The use of the drug in a patient should be accompanied by an assessment of relative harm-benefit ratio, and measures put into place to maximise benefits and minimise harms. This is not always easy to achieve. For example, some drugs will always cause adverse reactions to some extent, including idiosyncratic reactions. Nevertheless, it is disappointing that the same classes of drugs, which produce pharmacologically predictable ADRs [20], are still causing ADRs on a frequent basis. It is therefore imperative that we learn from our experiences of drug use in the real clinical world and attempt to implement prevention strategies for ADRs.

1.14 ADRs and length of stay

The financial burden of ADRs increases substantially when ADRs either cause or extend hospitalisation. The average additional stay resulting from an ADR is between 2 and 4 days, which has major cost implications for a health service [92]. Whilst ADRs may prolong hospital stay, it is important to appreciate that those patients who stay longer in hospital are at an increased risk of ADRs, and therefore an association of an ADR with longer stays does not necessarily reflect cause and effect [142, 149]. Moore *et al* found that patients admitted with ADRs did not stay in hospital significantly longer than patients without ADRs, whereas patients with ADRs in hospital did [115]. A study in surgical ICU found an ADR incidence of 9.3%, with an increase in length of stay for those suffering from ADRs of 3.39 days [15]. This increased length of stay may have been due to the ADRs themselves; an alternative explanation may be that patients who are in ICU for long periods are more severely ill and therefore require more medicines, increasing the possibility of ADRs [15].

Suh *et al* found no increase in length of stay (and total hospitalisation costs) in patients with ADRs aged over 65 compared with an age-matched control group without ADRs [144]. However, older patients also have greater rehabilitation and social needs compared with the younger patient population in terms of planning for hospital discharge. Therefore their discharge can be delayed because of a number of factors, which may make it difficult to assign an increase length of stay to an ADR.

1.15 ADRs and readmissions

A study of hospital admissions and readmissions undertaken in Germany found that of 1000 admissions (630 patients), 424 patients had a single admission and 206 patients were readmitted at least once in a 6-month period. Of these readmitted patients, 82 were readmitted more than once [150]. ADRs observed at admission occurred in 12.1% of all patients at the first admission, 9.3% at the first readmission, 7.3% at the second readmission, and 6.1% of patients readmitted three or more times. An Australian study which looked at repeat adverse drug reactions and admissions to hospital found that repeat ADRs causing admission are increasing, and in 2003, were responsible for one third of admissions related

to ADRs; the most common ADRs causing readmission were nausea and vomiting, haemorrhage with anticoagulants and 'poisoning' by cardiovascular agents [101]. The level of repeated admission due to ADRs shown suggests that prescribing issues contributing to the ADR could originate in primary or secondary care. The lack of monitoring of patients post-discharge was highlighted by a US study of 400 general medical patients; one fifth of whom experienced an adverse event following discharge, 66% of which were related to medicines [151]. Improvements in prescribing, monitoring and communication across the primary-secondary care interface are essential to help prevent future admissions due to ADRs.

1.16 Costs associated with ADRs

Readmissions and increased length of stay contribute to the considerable financial burden of ADRs. Direct costs are theoretically quantifiable and have been examined in several studies. Wiffen *et al* estimated that the annual cost of ADRs to the NHS in England in 1994 was £380million, with 4% of bed days being taken up by an ADR [92]. A US study showed that the costs in patients with ADEs in hospital were increased, with the greatest effect seen in those with preventable ADEs [19]; it is unclear whether this effect was also seen when ADRs alone were examined. In France, a study showed an increase in cost of €11,500 for ADRs that increase a patient's length of stay, which totalled approximately one third of the ADRs in that study [152]. Hospital charges for a 31-day inpatient stay for a case involving an interaction between azathioprine and allopurinol totalled $181,000 [153]. In addition, the threat of litigation has the potential to add to the high costs of preventable ADRs. Therefore, the financial burden of ADRs is significant; clearly, preventable ADRs provide the potential to save costs, and there is an urgent need to develop preventive strategies to reduce this cost burden. It is also important to note that studies to date have largely concentrated on direct costs, and there are no reliable estimates of the social and indirect costs of ADRs, making it difficult to measure the overall economic burden to the patient and society [154].

1.17 Prevention of ADRs

Historically, studies have shown that between 20% and 80% of ADEs and ADRs are preventable [43, 155-157] with the majority of latter studies showing around

60-70% preventability [13, 18, 93, 139, 142]. Although there are differences between studies in how preventability was determined, a recent systematic review has shown that over 70% of ADRs are preventable [143].

The benefits of drug use are evident, and when considering their hazards it is important not to become blinkered to their positive effects. The risk in different patients varies, and a prescriber must consider these before making a decision. The characteristics that differentiate preventable from non-preventable ADRs have been determined as appropriate prescribing, dosing, allergy reporting and monitoring [87]. These are logical conclusions as care in prescribing doses specific to the individual patient and careful documentation of medication history are core components of safe prescribing. Implementation of quality information technology (IT) systems has been proposed as a method for reducing ADRs. Evans *et al* significantly reduced the number of type B ADRs in their hospital by implementing three interventions [11]. They used computerised alerts of drug allergies, emphasised standardised administration rates for antibiotics, and notified staff of ADRs to increase their awareness. This is particularly important, as type B ADRs are proportionately more likely to cause serious illness or death than type A ADRs [158]. A computer alert system which alerted the physicians to potential drug related problems e.g. lactic acidosis with metformin, by analysis of multiple inputs e.g. laboratory results, drug orders, drug allergies, was shown to aid in the detection and therefore the prevention of ADEs. Almost half of the true positive reports were not recognized by the physician prior to the computer generated alert [159]. A system generating Automatic Laboratory Signals (ALS) for ADRs has been devised in Germany [46, 160, 161] which detects changes in laboratory values which may be indicative of ADRs. The computer-monitoring system, combined with chart review by study staff prospectively detected ADRs in 377 patients over 6 months. Thirty-nine of 109 ADRs were detected by the computer system alone, and only 9 were not alerted by the computerised system, thus increasing the overall detection rate of ADRs. The problem with a system such as this is that it generates a large number of false positive results. Integration of the ALS system with individual medicines data would allow more intelligent decision-support [160]. This would alert the prescriber when there is a real need, rather than continuously, which inevitably leads to "warning fatigue" and switching off of the decision analysis software. Drug-drug interactions are also potential causes of

ADRs [162, 163] and the incorporation of reliable decision support software into hospital information systems can be effective in averting dangerous drug combinations [164, 165].

Prescription of inappropriate medicines is prevalent, particularly in the elderly [166]. Application of the Beers criteria to reduce inappropriate prescribing in the elderly has proved useful in identifying potential drug related problems [167]. For instance, falls in elderly outpatients were significantly reduced in one study which discontinued or reduced doses for fall-risk-increasing drugs e.g. anxiolytics, antihypertensives and opioids [168]. Improvements in monitoring drug treatment are also likely to reduce the ADR burden [169]. The presence of a pharmacist on ward rounds in intensive care units and in general medical wards has been shown to reduce ADEs [170, 171] and increased clinical pharmacy staffing has been associated with lower ADR rates in US hospitals [172]. Improvements in care and attention to teaching of prescribing and prescribing environments have been recommended to reduce prescribing errors [173]. In turn, improvements in these areas may reduce the number of ADRs as it would encourage the prescriber to consider the full clinical status of the patient, including factors such as age and renal function, when prescribing medicines.

1.18 Pharmacogenomics

Pharmacogenomics is the study of pharmacologically relevant genes, their variation, how these variations interact to produce phenotypes, and how these phenotypes affect drug response [174]. For example, the more active S-enantiomer of warfarin is metabolised mainly by the P450 isoform CYP2C9. Patients with variable CYP2C9 alleles are poor metabolisers of the drug and are at greater risk of bleeding [175-177]. The study of pharmacogenomics will hopefully increase the predictability of drug response in individual patients, thereby reducing ADRs. It may also help in improving effectiveness as response rates with most drugs are between 25 and 60% [178]. The ultimate aim of pharmacogenomics is to go largely from the 'one-size fits all' paradigm of drug prescription, to tailored medicines regimens based on a patient's genetic characteristics. Thus, ADRs that were previously considered to be non-preventable may now be preventable

through modification of drug selection and/or dosage in patients based on their genotype [179, 180].

1.19 Conclusions

Extensive work has been undertaken to develop the methodology surrounding ADR research, providing interesting choices for the researcher looking for methods and tools to conduct epidemiological ADR research. Standardisation of terms used in ADR research would be useful to allow greater collaboration between research groups and improve international comparisons of data. The range of methodology, sample sizes and locations of ADR studies leads to difficult comparisons, though it is clear that the burden of ADRs in healthcare is significant, particularly in the elderly population and has changed little in recent decades. Strategies for prevention need to be developed to improve patient outcomes. Despite the presence of multiple studies looking at various aspects of ADR incidences worldwide, no studies of the ADR burden in UK hospital inpatients were identified. There is a need to assess this burden and to identify strategies to reduce this sizeable contribution to morbidity and mortality.

1.20 Aims of Thesis

- To assess the burden of adverse drug reactions (ADRs) in hospital inpatients.

The objectives of the thesis can be summarised as follows:

- To quantify the burden of ADRs in UK hospital inpatients
- To identify key areas for intervention to reduce the impact of ADRs
- To explore possible interventions to reduce ADRs in inpatients
- To critically evaluate the methodology used when studying ADRs in hospital inpatients

In order to fulfil the aims and objectives, a step-wise process was undertaken with the development of methodology at the initiation of the project, with the lessons learnt from this being incorporated into the main inpatient study. This also led to

further investigation of other areas, for example, readmissions, the usefulness of causality assessment tools that have been developed and how contradictory definitions available via Government agencies can lead to confusion in ADR interpretation and impact. Finally, specific areas that require intervention to reduce the ADR burden were identified, and one area was chosen to look at possible avenues for intervention and the difficulties likely to be encountered in the implementation of prevention strategies.

Chapter 2: Adverse Drug Reactions in Hospital Inpatients: a pilot study

2.1 Introduction

ADRs are a common problem, which affect patients in the hospital and community setting. A prospective study demonstrated that 6.5% of patients admitted to hospital were experiencing an ADR, and that these ADRs directly led to admission in 80% of cases [18]. Clearly, ADRs can also occur after admission to hospital. In a meta-analysis, Lazarou *et al* showed that the total incidence of serious ADRs causing admission and those occurring after admission was 6.7%, of which 4.7% caused admission and 2.1% occurred following admission, with an overall fatality rate of 0.32%, placing ADRs as the 4-6th most common cause of death in the USA [89]. This meta-analysis proved controversial [90], though recent research from Sweden has implicated ADRs as the 7th most common cause of death [91].

There are no recent data on the burden of ADRs in hospital inpatients in the UK in terms of impact on length of stay, interventions required and costs. Most of the literature is pre-1990 and usually non-UK based. Furthermore, the studies have varied in design with differences in the methodology, terminology and populations studied. This has resulted in widely varying estimates of the prevalence, from 0.86% in one Australian study [96], to 37% in a Dutch study of elderly patients [98]. In a systematic review, Wiffen *et al* estimated that the frequency of ADRs in inpatients may range from 3.5% to 7.3%, and "best guess" estimate of the overall burden on the NHS was 1.6 million bed days and 13.6 400-bed hospital equivalents [92]. Given the widely varying estimates of the ADR burden on inpatients, it was necessary to conduct a pilot study to establish a practical and robust methodology, and assess the feasibility of conducting a large prospective study. A prospective study was considered necessary to provide a better estimate of the burden of adverse drug reactions on inpatients than is currently available. An article based on this pilot study was published in the Journal of Clinical Pharmacy and Therapeutics in August 2006 [181] (Appendix 2).

2.2 Aim

The aim of this pilot study was to establish practical and robust methodology, which could be used to conduct a large prospective study, in order to assess the impact of adverse drug reactions on inpatients in a UK university hospital.

2.3 Objectives

1) To determine the incidence of ADRs on the wards studied
2) To determine the causality, severity and avoidability of each ADR
3) To classify the mechanism of each ADR
4) To determine the (additional) length of stay (LoS) for patients with ADRs
5) To determine the drugs most frequently associated with ADRs
6) To evaluate the feasibility of expanding the study to conduct a large prospective study of ADRs in inpatients.

2.4 Methods

2.4.1 Subjects and Settings

The pilot study was carried out on five wards (general surgery, endocrinology, gastroenterology, care of the elderly, and rheumatology) of the Royal Liverpool University Hospital. Patients admitted to these wards over a two-week period in spring 2005 were assessed for ADRs throughout their period of hospitalisation. The study protocol was assessed and approved by the Liverpool Local Research Ethics Committee and the audit department at the hospital.

2.4.2 Patient identification and assessment

An adverse drug reaction was defined according to the definition of Edwards and Aronson [16], and in accordance with the adverse effects listed for each drug in their Summary of Product Characteristics [182] and the British National Formulary [183]. ADRs were defined as 'inpatient ADRs' if they fitted one of the three scenarios described in Table 2.1.

Table 2.1: Definitions used to categorise an adverse drug reaction as occurring in a hospital in-patient

• Drug initiated in hospital during current admission, with the adverse reaction occurring during the stay in hospital.
• Drug initiated prior to the current admission, but adverse reaction was not present on admission, and occurred during the patient's stay in hospital.
• Drug initiated prior to the hospital admission, and patient develops an adverse reaction that was either not detected or addressed at admission (and was not the cause of admission), but required treatment during the hospital stay.

Patients were assessed for ADRs during a daily ward visit by the investigator (research pharmacist) in which all medicines and changes in medicines were recorded on the Drug Usage Form (Appendix 3). Changes in medicines acted as a trigger to ascertain the occurrence of an adverse effect. In addition to this, all the study wards were informed of the study and asked to contact the pharmacist via a 'telephone pager' or notification report cards (Appendix 4) in the event of an ADR. In addition, the wards were also routinely attended by the ward pharmacists, who were requested to notify the research pharmacist of suspected ADRs. The hospital dispensary had been provided with an ADR alert drug list for recording any potential ADRs. This list included medicines that might be prescribed to treat the adverse effects of other drugs, for example procyclidine for oculogyric crisis, or oral vancomycin or metronidazole for antibiotic related diarrhoea.

For all patients, the medical and nursing notes were reviewed, and any new symptoms discussed with staff and patients, where appropriate, to determine whether these were due to an ADR. An ADR Assessment Form (Appendix 5) was developed with the Royal Liverpool Hospital Audit Department. Suspected ADRs were recorded on the ADR Assessment Form and analysed for causality using the Naranjo algorithm (Table 1.3) [63]. Severity was assessed using an adapted Hartwig scale [83], as described in Table 2.2. Avoidability was determined using the criteria outlined by Hallas *et al* (Figure 1.2) [88], and the suitability for yellow

card reporting using the criteria set out by the Medicines and Healthcare Regulatory Authority (MHRA) [85].

Table 2.2: Adapted Hartwig Severity Scale

Severity Level	***Description***
1	An ADR occurred but no change in treatment with suspected drug
2	The ADR required that required treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in length of stay
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment required. No increase in length of stay
4	Any Level 3 ADR which increases length of stay by at least one day OR the ADR was the reason for admission
5	Any level 4 ADR which requires intensive medical care
6	The adverse reaction caused permanent harm to the patient
7	The adverse reaction either directly or indirectly led to the death of the patient. For the purposes of this study, adapted as:
7a	The ADR indirectly linked to death of patient
7b	The ADR directly linked to death of patient

The ADRs were also classified as either a Type A reaction i.e. predictable from the drug's pharmacology, or Type B reaction, that is, not predictable from the known pharmacology of the drug [20]. Whether or not the patient's stay was extended due to an ADR was determined by the investigator through chart review, medical case note review and discussion with relevant staff. When an ADR was identified, drugs co-administered as prophylaxis against that ADR were recorded, for example, proton pump inhibitors (PPIs) to protect against non-steroidal anti-inflammatory drug (NSAID) induced gastrointestinal bleeds. All ADRs were initially assessed by the research pharmacist (ED), and subsequently by two senior investigators. A consensus was agreed between all the investigators as to the appropriate final scoring for the ADRs. All drugs administered to each patient

during the admission were recorded, along with these drugs implicated in ADRs. Statistical analysis was performed by χ^2 analysis and Z-test, as appropriate, accepting $p<0.05$ as being significant.

2.5 Results

Over a two-week period, 125 patients (61 female, 64 male) were assessed for ADRs on the study wards. Initially, 30 suspected ADRs were found in 26 patients. After discussion between the investigators, three of these suspected ADRs were excluded for reasons described in Table 2.3.

Table 2.3: Excluded ADRs

Suspected Drug	Summary of ADR	Why excluded
Co-amoxiclav	Patient developed *Clostridium difficile* diarrhoea, following prescription of co-amoxiclav during a previous admission	Readmission occurred due to ADR, but drug not initiated, and ADR did not occur during this admission.
Atorvastatin	Patient admitted due to abdominal pain and distension. Subsided somewhat on atorvastatin discontinuation. Multiple investigations required.	Likely to be reason for or have contributed to admission, and problem addressed on admission.
Clopidogrel	Patient experiencing microcytic anaemia with a haemoglobin level of 11.7g/dl on admission, falling to 11.1g/dl the next day. No further blood levels were available. Clopidogrel was initiated before admission and stopped on discharge (4 day stay).	Difference in haemoglobin level minimal. Most likely to be laboratory variation.

Following these exclusions, it was found that 24 patients (19.2%, 95% confidence interval 12 - 26%) experienced one or more ADRs. A total of 27 adverse reactions

were identified in the 24 patients (1.1 ADRs/patient). More females (n=15) than males (n=9) experienced ADRs, although this was not statistically significant (χ^2 = 2.23, p=NS). The median age of patients who experienced an ADR was 69.5 years (inter-quartile range 52-79 years), compared with 61 years (inter-quartile range 45-78 years) for those who did not experience an ADR (z=1.25, p=NS). The median length of stay for ADR patients was significantly longer at 14.5 days (inter-quartile range 10-21 days), compared with eight days (3-12 days) for those who did not experience ADRs (z= 3.49, p<0.05). A summary of the ADRs identified is shown in Table 2. 4. The most frequent ADR encountered was constipation largely due to the use of opioids.

Table 2.4: Summary of ADRs and their causative drugs

ADR	Frequency	Drugs Implicated
Constipation	9	Co-codamol, fentanyl, morphine, tramadol, fluoxetine, atorvastatin
Hypokalaemia	3	Bendroflumethazide, furosemide, 5-fluorouracil/cisplatin
Gastrointestinal disturbance	3	Ibuprofen, diclofenac, 5-FU, cisplatin, iloprost, co-codamol, morphine
Decreased renal function	2	Furosemide, spironolactone
Gastrointestinal / per rectum bleed	2	Clopidogrel
Angioedema	1	Perindopril
Tremor	1	Salbutamol
Rash	1	Cefalexin
Increased anti factor Xa levels	1	Enoxaparin
Clostridium difficile infection	1	Ciprofloxacin
Dry mouth	1	Dosulepin
Hypotension	1	Atenolol, ramipril
Myoclonic jerks, hallucinations	1	Fentanyl, morphine, oxycodone

The ADRs were assessed using the algorithms described above by three investigators. The ADRs were initially assessed independently by three investigators (ED, CG, MP), before a decision was made through consensus (Table 2.5).

Using the classifications from consensus agreement, CSM/MHRA Yellow Cards were required to be written for 10 (37%) of the ADRs in this study. Type A reactions, accounted for 25 (93%) of the ADRs and 2 (8%) were type B reactions [20]. Using the Naranjo algorithm [63], 17 (63%) of the ADRs were defined as 'possibly' related, 9 (33%) were 'probably' related and 1 (4%) ADR was classified as definitely related to the drug. In terms of prevention [88], 13 (48%) of reactions were classified as 'possibly' avoidable, 3 (11%) were 'definitely' avoidable, and 11 (41%) were recognised to be 'unavoidable'. Adverse drug reactions occurred despite prophylactic medicines in four cases. In three of these cases, constipation was the ADR, with laxatives being used as prophylaxis. In the fourth case, constipation may have been a factor in the GI disturbance the patient experienced, and a laxative was ineffective in its prevention.

According to the Hartwig criteria [83], (Table 2.2), most (n=18) reactions required intervention but did not increase the length of stay (i.e. level 3). However, through assessment of notes and discussion with other healthcare professionals, 7 reactions (26%) were felt to have had an impact on the length of stay, and were thus classified at level 4. The duration of each increase in length of stay was not documented during this pilot study due to difficulty in quantifying the increased stay in hospital with regard to the increased morbidity related to the ADR.

Table 2.5: Summary of ADR classifications

	Evaluator			
	ED (Research Pharmacist)	CG (Senior Investigator)	MP (Senior Investigator)	Consensus
	N° ADRs (%) n=27*	N° ADRs (%) n=26*	N° ADRs (%) n=26*	N° ADRs (%) n=27*
Causality				
Definite	1 (4)	2 (8)	0 (0)	1 (4)
Probable	15 (56)	18 (69)	6 (23)	9 (33)
Possible	11 (41)	6 (23)	20 (77)	17 (63)
Severity				
Level				
2	3 (11)	0 (0)	0 (0)	0 (0)
3	12 (44)	21 (81)	20 (77)	18 (67)
4	9 (33)	0 (0)	4 (15)	7 (26)
5	0 (0)	2 (8)	0 (0)	0 (0)
7A	2 (7)	2 (8)	2 (8)	2 (7)
7B	1 (4)	1 (4)	0 (0)	0 (0)
Avoidability				
Definitely avoidable	4 (15)	3 (12)	2 (8)	2 (7)
Possibly avoidable	16 (59)	15 (58)	11 (42)	14 (52)
Unavoidable	7 (26)	8 (31)	13 (50)	11 (41)
Yellow cards	13 (48)	6 (23)	6 (23)	10 (37)
Mechanism				
A	25 (93)	23 (89)	24 (92)	25 (93)
B	2 (7)	3 (12)	2 (8)	2 (7)

*ED assessed all ADRs independently; CG and MP each assessed 26 of 27 ADRs, and the investigation team discussed all 27 ADRs.

Eight (6%) patients died during their admission, three (2%) of whom had experienced an ADR. Two of those deaths were indirectly related to the adverse drug reaction that occurred during admission and were therefore classified as Level 7a on the adapted Hartwig scale [83], (Table 2.2). Both of these ADRs were classified as 'possibly' preventable. The first of these deaths was indirectly linked to *Clostridium difficile* infection following ciprofloxacin administration. The patient had multiple co-morbidities and his cause of death was given as a respiratory infection, with underlying metastatic rectal cancer. The ADR was classified as 7a as the treatment of the chest infection was delayed due to *Clostridium difficile* concerns. If the infection had been treated promptly without this complication, the patient may have survived this episode. However, co-morbidity was high and he may have succumbed to infection with or without intervention.

The second ADR related to the death of a patient was an upper GI bleed potentially linked to clopidogrel administration prior to, and during, admission for a respiratory tract infection. The patient developed a GI bleed during admission which was then treated. The patient improved initially and then deteriorated rapidly following development of abdominal pain which was not investigated but suspected as a bowel obstruction, or perforation. The patient subsequently died. The cause of death was recorded as a gastro-intestinal haemorrhage.

A total of 225 drugs were administered in the patients admitted during the study. Of these, 24 (11%) were implicated in the ADRs detected. In 17 cases, a single drug was responsible for the ADR and in 10 cases, two or more drugs were involved and could be deemed to be drug interactions. The drugs implicated in ADRs and the frequency of their use in this study is shown in Table 2.6. Opioid analgesia most commonly caused adverse reactions, with co-codamol being the drug most frequently linked with ADRs, followed by fentanyl and morphine. The research pharmacist found that visiting five wards daily was manageable. Once an ADR was identified 10-30 minutes were required to write up that adverse drug reaction. Recording all medicines for each patient was very time-consuming and it would be difficult to incorporate such extensive data collection on a larger scale using similar methods.

Table 2.6: Drugs implicated in ADRs

Drug	*N° of ADRs related to the drug*	*N° of patients in study taking drug*	*Percentage of prescriptions resulting in ADRs*
Co-codamol	8	29	30
Fentanyl	4	5	80
Morphine	4	26	15
Furosemide	3	19	16
Bendroflumethazide	2	7	29
Clopidogrel	2	7	29
Atenolol	1	12	8
Ramipril	1	5	20
Ibuprofen	1	6	17
Perindopril	1	5	20
Salbutamol	1	24	4
Cefalexin	1	2	50
5-Fluorouracil	1	1	100
Cisplatin	1	1	100
Tramadol	1	14	7
Enoxaparin	1	4	25
Ciprofloxacin	1	14	7
Oxycodone	1	2	50
Iloprost	1	2	50
Diclofenac	1	11	9
Dosulepin	1	2	50
Spironolactone	1	5	20
Fluoxetine	1	4	25
Atorvastatin	1	7	14

2.6 Discussion

Despite being extensively studied, there is no doubt that ADRs still represent a significant clinical problem. There is therefore a need to obtain more recent, accurate data on the burden of ADRs on NHS hospital inpatients. This is also important because there have been huge changes in medical practice and NHS operational procedures over the last two decades.

This study was intended to inform the design of a larger study to fully investigate the burden of ADRs in hospital inpatients. The pilot study allowed us to assess the feasibility of conducting a larger study, and to develop operational procedures that enabled intensive monitoring of all patients. The methodology comprises the use of a research pharmacist dedicated to the project, the use of expertise of ward-based pharmacists, and informing medical and nursing personnel on the wards of the study, and securing their co-operation. Importantly, the patients were assessed during their admission, and ADRs recorded prospectively, not retrospectively since data relating to ADRs are often poorly documented in the notes [29] and may not actually be recognised as such by the attending healthcare professionals. This was the case in this pilot, and hence the need to intensively monitor the patients to obtain an accurate record of the burden of ADRs in hospital inpatients.

Despite the fact that this is a pilot, and therefore its findings should be treated with caution, this study shows that ADRs occurred in 19.2% of patients. This figure is consistent with the range of results from 1960s studies which showed ADRs occurred in 10-20% of inpatients [8, 94, 95] but almost three times higher than the estimate of a systematic review [92]. The contradictory figures are likely to be a reflection of the different methodologies used in the different studies, including those used in the systematic review [92].

Although 19% of patients suffered an ADR, fortunately the majority were mild and did not lengthen hospital stay, although most needed some intervention, for example, prescription of laxatives or change in dose. Nevertheless, such ADRs still result in discomfort for the patients, and should therefore be avoided if possible. Given that most of the ADRs were type A reactions, which are

predictable from the known pharmacology of the compound [20], it should be possible to develop strategies to prevent these ADRs. Furthermore, consistent with previous literature [13, 139], almost 60% of the adverse reactions were classified as being either definitely or possibly avoidable. A typical example here is the occurrence of constipation with opioid analgesics, which was the commonest ADR identified. Previous literature has also shown that opioids frequently cause adverse drug reactions [12, 41]. It has been stated that patients receiving opioid therapy should start laxative therapy concurrently to reduce the incidence of constipation [184]. However, it is also important to note that some ADRs occurred despite the use of prophylaxis, indicating either that some ADRs are inevitable and thus unavoidable, or that we need to develop better strategies for prevention of ADRs, including the use of different prophylactic drugs and different doses. The frequency of an ADR relative to frequency of drug-use is also important. For example, although co-codamol was most frequently linked with ADRs, it was also the most-commonly prescribed drug, with an ADR occurring in less than 30% of patients taking the drug. Fentanyl was linked with ADRs in 80% of patients who were prescribed this drug during the study period. In a larger study, assessing the frequency of ADRs in relation to the frequency of drug use will be useful in identifying strategies to reduce the burden of ADRs by targeting specific drug classes. In addition, targeting certain groups of patients for preventing ADRs may be important – for instance, although this study was not powered to detect this, the elderly and females seem to be over-represented in the ADR groups, which is consistent with previous literature [115, 185]. A larger study will be needed to identify relevant risk factors and patients to target for preventive strategies.

More serious ADRs, for example those that prolong hospitalisation or contribute to the death of the patient, represented 33% of the ADRs identified. Such ADRs fit the CSM/MHRA reporting criteria [85] – suggesting that reportable ADRs may be occurring in 9% of hospital inpatients (11 out of the 125 patients assessed in the study) further underlining the fact that most ADRs in hospitals are not reported.

The methodology chosen for this study allowed the investigators to identify and assess ADRs successfully. Assessment methods obtained from the ADR literature were used to assess causality, avoidability and severity of adverse drug reactions.

Table 2.3 shows that there was considerable variability in interpretation of the use of these scales initially by the investigation team. This variability was addressed during a meeting of the investigators where issues with interpretation of the scales were discussed and a consensus of opinion achieved. This will support more uniform interpretation of ADRs using these scales in future studies.

An issue to consider in terms of the severity of the ADRs is the difficult in assessing whether the ADRs prolonged hospitalisation or led to death. There are many aspects of patient care that affect time to discharge, for example the severity of illness, and need for rehabilitation or social care in the community, but it is usually possible to determine whether or not an ADR has been a factor in increasing length of stay. In this pilot, we have attempted to determine whether length of stay was affected by ADRs through review of case-notes and discussion with the attending staff. A criticism of this approach is that it involves a degree of subjective assessment, and because of this, the data should be interpreted with caution, and needs replication in a larger study. Nevertheless, a previous study by Classen *et al* has shown that ADRs can prolong hospitalisation by an average of 2 days [12]. They used matched case-controls identified by a detailed hospital information system employing variables including diagnosis, sex, age, and patient acuity score to determine the effect of an ADR on length of stay [12]. Whilst this method may provide more objective data, it would be difficult and impractical to attempt to use a similar model in the UK, with the limited information technology system used by the study hospital. However, the pilot study provided us with valuable insights into methodology to be used in a larger study. More proactive discussion with nursing and medical staff, will ideally lead to quantification of the increased length of stay. Clearly, caution regarding subjective assessment also applies to the two ADR-related deaths reported in this pilot study.

2.7 Conclusion

This pilot study of ADRs in hospital inpatients has shown that almost one fifth of patients suffered an ADR, with the majority of ADRs being predictable from their pharmacology and potentially avoidable. It is therefore plausible that the impact of ADRs on hospital inpatients can be reduced. The methodology piloted was largely successful although improvements in length of stay assessment would be necessary for the extended prospective study. Analysis of a larger patient population using similar methods will identify risk factors and vulnerable patient groups aiding in development of interventions to reduce the impact of ADRs in hospital inpatients.

Chapter 3: Adverse Drug Reactions (ADRs) in Hospital Inpatients: A Prospective Analysis of 3695 Patient-Episodes

3.1 Introduction

Adverse drug reactions (ADRs) in hospitalised patients can be divided into two broad categories: those that *cause* admission to hospital, and those that occur in inpatients *after* hospital admission. In a meta-analysis, Lazarou *et al* [89] showed that the total incidence of both categories of serious ADRs was 6.7%, of which 4.7% were responsible for admission and 2.1% occurred after admission, with an overall fatality rate of 0.32%. In a Liverpool study of almost 19000 admissions, it was shown that 6.5% of patient admissions to two NHS hospitals were related to an ADR [18]. This incidence figure is broadly compatible with pooled data from older studies [89, 92], and with more recent studies [93, 186].

There are little data on adverse drug reactions following admission. Lazarou *et al* suggested that 10.9% of patients experienced ADRs of all severities following admission [89]. Differences in methodology and study populations have led to widely varying estimates in individual studies [96-98]. There are no recent large studies on ADR incidence in UK inpatients, although a systematic review from Wiffen estimated that in the NHS in England, 1.6 million bed-days, equivalent to 13.6 (400-bed) hospital equivalents annually are due to ADRs [92]. Much of the data in Wiffen's review relate to studies which are dated. With the changing demographics in the UK, the predisposition of the elderly to ADRs, and the changes in medical practice over recent decades, there is a need for current data on the ADR burden in hospital inpatients.

A pilot study was undertaken to establish the methodology for determining the burden of adverse drug reactions in hospital inpatients and is reported in Chapter 2. The pilot study involved 125 patients and showed that 19% of inpatients suffered ADRs during their hospital admission episode, with patients experiencing an ADR spending 6.5 days longer in hospital than those without ADRs [181]. Minor adaptations were made to the study methodology from the pilot, including improvements in data collection forms, and more pro-active collection of data

relating to increased length of stay. The methodology adapted from the pilot study was then used to undertake a large prospective study to further explore the impact of ADRs on NHS hospital inpatients in terms of incidence, length of stay, costs involved, and factors that predispose patients to ADRs.

3.2 Aim

The aim of the study was to assess the burden of adverse drug reactions on inpatients in a UK university hospital.

3.3 Objectives

1) To determine the incidence of ADRs in the study hospital
2) To determine the causality, severity and avoidability of each ADR
3) To classify the mechanism of the reaction (A/B)
4) To determine the additional length of stay (LoS) for individual patients with ADRs
5) To determine the difference in average length of stay in ADR patients compared with those without ADRs
6) To determine the drugs most frequently associated with ADRs
7) To examine the number of ADRs which occur despite prescription of ADR prophylaxis.
8) To calculate the costs associated with ADRs for all patients

3.4 Methods

The study was conducted on 12 wards (9 medical and 3 surgical) at the Royal Liverpool University Hospital (RLUH) over a six-month period between June and December 2005. The RLUH is a teaching hospital which serves a population of about 0.5 million with a total annual activity of around 90,000 admissions. The study protocol was assessed and approved by the Liverpool Local Research Ethics Committee and the audit department at the RLUH, and the Research Ethics Committee at Liverpool John Moores University.

For the purposes of this study, an ADR was defined according to the definition of Edwards and Aronson [16]. ADRs were identified on the basis that they were well

recognised as evidenced by their inclusion in either the Summary of Product Characteristics [182] or the British National Formulary [183]. Only ADRs that occurred during admission as a result of drugs initiated or continued in hospital were included, while community acquired longstanding ADRs that were treated during the hospital stay were excluded (n=17, 2.3% of all ADRs detected). ADRs that manifested no clinical signs, for example, suspected drug-induced abnormalities in blood test results were included, though differentiated from those which caused clinical symptoms.

The study wards were a convenience sample representative of the medical to surgical ward ratio at the study hospital. Intensive and critical care units, and more specialist units such as the renal dialysis unit were excluded as the focus of this study was on wards that are found in most general hospitals. There are no paediatric, psychiatric or obstetrics and gynaecology wards at the study hospital and thus the results from this study exclude those patient groups. Patients admitted to the study wards during the data collection period were identified daily (Monday to Friday) by the research pharmacist (ED) using the hospital Patient Administration System (PAS). Patients whose admission did not include a weekday were therefore excluded, as were patients recorded on the PAS system following the daily check of ward lists, and discharged within one day prior to the next morning. Study wards were visited daily by ED, and patients' drug charts, medical and nursing notes were reviewed for evidence of an ADR. Details of suspected ADRs were recorded on the ADR Assessment Form (Appendix 6) and manually entered into a study database developed using Microsoft Access. Objective markers of ADRs, e.g. laboratory results were identifiable from the patient notes and the hospital computer system, while subjective markers of ADRs, for example headache, nausea and rash were identified through patient notes, discussion with the ward team and, where appropriate, discussion with the affected patient. Clinical staff were informed that the study was taking place and could also refer directly either in person or through notification cards (Appendix 4) that were made available on the wards. The clinical ward pharmacists were consulted regularly regarding the possibility of ADRs on their designated wards. Following completion of the ward based data-collection period, retrospective case note analysis was performed to assess patient outcomes and to ensure that all available details regarding the ADR had been collected.

Suspected ADRs were classified in terms of causality [63] and avoidability [88] according to validated algorithms and were assessed for seriousness according to criteria for Yellow Card Reporting to the Commission on Human Medicines and to the Medicines and Healthcare products Regulatory Agency (CHM/MHRA) [85]. ADRs were also classified as either type A or type B according to the system introduced by Rawlins and Thompson in 1977 [16]. This classification was chosen instead of the more recent DoTS classification [25] so that the resultant data could be compared with previous studies. Severity of ADRs was recorded according to the Hartwig severity scale [83], which was adapted for the pilot study [181], to include two level 7 ADRs in order to differentiate between ADRs which directly, and those which indirectly, cause death.

Analysis for causality, avoidability, severity and seriousness was done independently by two investigators, the research pharmacist (ED) and Senior Investigator (CG). Discrepancies in scoring were discussed before consensus was achieved through discussion between ED and CG in conjunction with a Professor of Clinical Pharmacology (MP). The overall incidence of inpatient ADRs was defined as the total number of inpatient episodes which resulted in ADRs in relation to the total number of inpatient episodes in the study wards during the study period.

The length of stay for each patient was recorded using data from the hospital Patient Administration System (PAS), enabling comparisons between patients with and without ADRs. Analysis of whether the ADR directly increased the length of stay, and the duration of this increase, was made following an assessment of the clinical features of the underlying disease and ADR, and after discussion with the ward team including the ward pharmacist and medical staff, and assessment of relevant case-notes. Clinical judgment was used to assess the additional length of stay attributable to the ADR. Thus, for example, if a patient had an ADR whilst waiting for nursing home placement, e.g. antibiotic-related *C. difficile* diarrhoea and the wait for placement independently exceeded the duration of the ADR, no additional length of stay was attributed to the reaction. Conversely, if a patient was ready for discharge, but an ADR occurred which required the patient to stay in hospital, the additional length of stay until recovery from the ADR was attributed to

the reaction. All drugs including the causative drug(s) were recorded for all patients with ADRs on the ADR Assessment Form (Appendix 6). In addition, all medicines taken by a random control sample of 1 in 10 inpatients on the same study wards were also recorded using the Drug Usage Form (Appendix 7).

ADRs which occurred despite specific prophylaxis against the ADR were recorded. The potential effect of polypharmacy on ADRs was measured by comparing the number of regular medicines taken by ADR patients on the first day of ADR with the number of medicines taken for the control sample (1 in 10 patients), assessed on the day of the inpatient stay where the patient received the maximum number of medicines. The most frequent ADRs relative to usage were calculated by using data of all drugs administered to one tenth of patients admitted. The frequency of the drug group causing a suspected ADR was divided by the number of times a drug in that class was administered in the sample of patients (if greater than, or equal to, 1). The resulting ratio allowed drug groups to be further ranked by frequency of ADRs relative to drug use. The costs to the NHS were estimated using number of bed-days for additional length of stay based on the standard daily costs of NHS hospital episodes (£228) [187], consistent with the estimates used in a prospective study of hospital admissions [18].

3.4.1 Statistical methods for analysis

Statistical analysis was undertaken with the assistance of Professor Paula Williamson and Mr Stephen Taylor from the University of Liverpool Centre for Medical Statistics and Health Evaluation (CMSHE).

The data were hierarchically structured, in that multiple ADR episodes can occur both within patients and within a particular patient admission (where a patient had >1 admission to hospital), hence the study had patient/admission/episode levels. To compare ADR incidence between hospital wards, a generalised estimating equation (GEE) [188] model with compound symmetry was used to account for within-patient correlation. This was considered more appropriate than a random-effects model when there are small numbers of observations within patients [188].

For all other analyses, where a patient had multiple admissions and/or multiple ADRs, patient's first ADR episode was used and analysed at the patient level only. The first ADR episode was used to simply assess the affected patient population and the risk factors assessed (age, gender, number of medicines and placement on a medical or surgical ward) were identical or assumed to be broadly similar for patients who had multiple admissions. Comparisons between groups using proportions/percentages were assessed using the chi-square statistic for assessing significance. Comparisons between groups using continuous measures used the mean (SD) for describing normally distributed data, and median (IQR) for non-normally distributed data, using the t-test or the Mann-Whitney U-test for assessment of statistical significance, as appropriate. The 5% level was used for assessing significance.

The risk factors for ADRs were identified by analysing data for age, gender, number of drugs prescribed and placement on a medical or surgical ward, in a time to event analysis. Kaplan-Meier curves with log-rank test were used for univariable analysis of categorical factors. Regression analysis was undertaken via the Cox proportional hazards model. Results are given in terms of the hazard ratio (HR) with accompanying 95% confidence interval (95% CI). The 5% significance level was used when assessing factors for model inclusion. The risk factor 'number of drugs prescribed' had data available for 10% of the total sample (n = 374), and therefore multivariable analysis was carried out on this sample. Those risk factors for which data were available for the whole sample (gender, ward type, age) were analysed using the whole sample and results compared to the 10% sample.

3.5 Results

Over six months, there were a total of 3695 patient episodes assessed for ADRs involving 3322 patients. Out of these patient episodes, 545 (14.7%, 95% CI 13.6-15.9%) resulted in one or more ADRs. Initially, 742 ADRs were identified. Nine ADRs (1.2%) were excluded by the investigation team on the basis that the event was unlikely to be drug-related according to the Naranjo algorithm [88], resulting in a total of 733 ADRs for further analysis. At the patient level, using first recorded ADR, women experienced significantly more ADRs (n=308, 17.8%) than men

(n=216, 13.5%; χ^2 =11.6, df=1, p<0.001). The median age was significantly higher in the ADR group at 72 years (Q1-Q3 56-81 years) compared with 61 years in the non-ADR group (Q1-Q3 41-77 years; U=109, p<0.0001). More medical (n=389, 17.2%) than surgical (n=135, 12.8%) patients experienced ADRs (χ^2=10.5, df=1, p<0.01). The incidence of ADR episodes varied further according to the specialty of the wards studied as shown in Table 3.1

Table 3.1: Odds of experiencing an adverse drug reaction by ward type

Medical/Surgical Specialty	Odds ratio (95%CI) in relation to breast/general surgical ward* (n = 555)	N° patients
Respiratory	3.65 (2.37 to 5.61)	298
Cardiology	3.34 (2.13 to 5.25)	256
Endocrine	3.19 (2.02 to 5.06)	242
Elderly medicine (Two wards)	3.06 (2.07 to 4.55)	544
Orthopaedic surgery (Two wards)	2.65 (1.81 to 3.90)	711
Rheumatology	2.55 (1.27 to 5.13)	76
Gastrointestinal/ Liver	2.43 (1.58 to 3.73)	390
Pharmacology	1.53 (0.95 to 2.47)	356
Infectious diseases	1.28 (0.75 to 2.20)	267

*ORs adjusted for multilevel structure

The median length of stay for patient episodes resulting in ADRs was 20 days (Q1-Q3 12-35 days) compared to 8 days (Q1-Q3 5-14 days; U=143, p<0.0001) for those episodes without ADRs. Within the group of patients experiencing an ADR , the mortality was higher, (n=58, 10.7%), compared with 3.9% (n=126) of patients who did not experience an ADR (χ^2 =42.4, df =1, p<0.0001). ADRs contributed to 14 out of the 184 deaths (0.4% of patients admitted, 8.2% of all deaths), with one (0.03% of patients admitted, 0.5% of all deaths) death being directly attributable to the ADR, specifically GI bleed with diclofenac and dalteparin (see Table 3. 2). Of the 733 ADRs identified, Type A ADRs accounted for 690 (94.1%) of the ADRs

while 232 (30.1%) ADRs fulfilled the requirements for reporting to the UK regulatory agency. The majority (n=602, 82.1%) of the ADRs occurred as a result of initiation of the causative drug in hospital, of which 390 (65%) showed clinical signs. Of the cases where the drug had been initiated prior to hospital admission (n=121, 17.9%), with the ADR occurring during admission, 81 of the patients (67%) showed clinical signs.

Table 3.2: Deaths associated with adverse drug reactions

Adverse drug reaction	N° associated patient deaths	Drugs (N° of deaths)	Avoidability (definite, possible, unavoidable)
Renal failure	7*	Gentamicin (1), bumetanide, valsartan (1), bumetanide, furosemide, spironolactone, ramipril (1), allopurinol, ceftriaxone, furosemide (1), diclofenac (1), furosemide, spironolactone (1), bumetanide, metolazone, perindopril, spironolactone, trimethoprim, potassium and calcium supplements (sando K, sandocal) (1, included hypercalcemia and hyperkalemia)	1 definite, 2 possible, 4 unavoidable
Clostridium difficile infection	5*	Ceftriaxone and ciprofloxacin and gentamicin (1), ceftriaxone, ciprofloxacin, lansoprazole (1), amoxicillin, cefuroxime, ciprofloxacin (plus lactulose and senna contributing to diarrhoea) (1), ceftriaxone, erythromycin, clarithromycin, co-amoxiclav (1), ceftriaxone, lansoprazole, trimethoprim (1)	3 possible, 2 unavoidable
GI Bleed	2	Dalteparin, diclofenac (1), aspirin, dalteparin, dipyridamole, enoxaparin (1)	1 definite, 1 possible
Ischemic bowel	1	Glypressin (1)	1 possible

*In one patient both renal failure and *C.difficile* infection contributed to death

Drug-drug interactions were linked to 433 (59.1%) of the ADRs, and these interactions are described Table 3.3.

Table 3.3: Drug-drug Interactions contributing to ADRs

Mechanism of Drug-Drug Interaction	N° of Interactions (n=433)	Example (s)
Pharmacodynamic (PD)	397 (91.7%)	▪ Bleeding with dalteparin and warfarin; Candidal infection after administration of prednisolone, inhaled beclomethasone, amoxicillin and erythromycin ▪ Renal impairment following diclofenac, furosemide, lisinopril and spironolactone administration ▪ Sedation with lorazepam and oxazepam ▪ Gout with bumetanide, furosemide and metolazone
Pharmacokinetic (PK)	23 (5.3%)	▪ Bradycardia with amiodarone and digoxin co-administration ▪ Opioid withdrawal following concomitant methadone and rifampicin administration ▪ Increased INR with erythromycin and warfarin
Mixed mechanisms (PK/PD)	13 (3.0%)	▪ Bleeding following co-administration of amiodarone and warfarin (PK); plus clopidogrel and dalteparin (PD)

All patients with ADRs required some form of intervention which consisted of dose adjustment, change of therapy, replacement therapy or increased monitoring while one (0.1%) patient required intensive care. Tables 3.4 and 3.5 show detailed results of causality, severity and avoidability assessments, with corresponding inter-rater reliability (weighted Kappa (κ^w)) scores from the initial assessments of the ADRs by two investigators (ED and CG).

Table 3.4: The adapted Hartwig severity scale and corresponding adverse drug reaction (ADR) frequency

Severity Level	*Description*	*Frequency of the ADR at each severity level; n (%)**
1	An ADR occurred but no change in treatment with suspected drug	0 (0.0)
2	The ADR required that required treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in length of stay	152 (20.7)
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment required. No increase in length of stay	413 (56.3)
4	Any Level 3 ADR which increases length of stay by at least one day OR the ADR was the reason for admission	152 (20.7)
5	Any level 4 ADR which requires intensive medical care	1 (0.1)
6	The adverse reaction caused permanent harm to the patient	0 (0.0)
7	The adverse reaction led to the death of the patient. For the purposes of this study, adapted as:	
7a	The ADR indirectly linked to death of patient	14 (1.9);
7b	The ADR directly linked to death of patient	1 (0.1)

Initial inter-rater agreement (weighted Kappa (κ^w) score) = 0.64, 95% CI (0.59-0.69)

*The denominator used was the total number of ADRs (n=733).

Table 3.5: Causality and avoidability assessments of ADRs

Assessment	Categories and corresponding frequencies of the ADRs (n; %)*			% Total agreement	Initial inter-rater agreement κ^{W} (95% CI)
Causality	Definite	Probable	Possible		
	23 (3.1)	487 (66.5)	223 (30.4)	60.2%	0.23 (0.17-0.30)
Avoidability	Definite	Possible	Unavoidable		
	47 (6.4)	344 (46.9)	342 (46.7)	61.1%	0.35 (0.29-0.41)

*Denominator used was the total number of ADRs, n=733.

'Definitely' or 'possibly' avoidable 'serious' ADRs were further examined. Causative drug groups for avoidable ADRs were assessed and the reasons for their avoidability were recorded. The contribution of preventable ADRs to length of stay and seriousness of ADR, determined by their need for 'yellow card' reporting to the CHM/MHRA were also assessed. As described in Table 3.5, 391 (53.3%) of all ADRs were classified as definitely or possibly avoidable. Almost one third (n = 225, 30.7%) of ADRs were serious, with 132 (58.7%) of serious ADRs judged to be definitely (n=10), or possibly (n=122), avoidable. The drug groups which most frequently caused serious, definitely or possibly avoidable ADRs were loop diuretics, anticoagulants, opioids and heparins. Electrolyte disturbances, bleeding and renal failure were the most common serious, definitely or possibly avoidable ADRs. Table 3.6 shows all serious and potentially avoidable ADRs, highlighting how frequently the ADR was serious in relation to the frequency the ADR occurred. A median of 2 (IQ range 0-5) additional bed days per patient were attributable to serious, potentially avoidable ADRs. Based on analysis of individual cases, inadequate monitoring and poor prescribing decisions were frequent reasons for avoidability.

Table 3.6 Serious and avoidable ADRS

Description of ADR	Frequency ADR occurred in study	N° ADRs which were serious, and definitely or possibly avoidable (N=132) (%)
Electrolyte disturbances	169	22 (13.0%)
Constipation	100	17 (17.0%)
Increased INR	54	9 (16.7%)
Bleeding	53	20 (37.7%)
Renal failure	45	19 (42.2%)
Hypotension	35	5 (14.3%)
Hypoglycaemia	31	8 (25.8%)
Nausea	29	3 (10.3%)
Clostridium difficile	25	10 (40.0%)
Diarrhoea	16	1 (6.3%)
Opioid toxicity	12	3 (25.0%)
Sedation	7	1 (14.3%)
Hallucinations	6	2 (33.3%)
Anaemia; Digoxin toxicity; opioid withdrawal; urinary retention	4	1 (25.0%)
Digoxin toxicity	4	1 (25.0%)
Opioid withdrawal	4	1 (25.0%)
Urinary retention	4	1 (25.0%)
Psychosis	2	1 (50.0%)
Fall	2	1 (50.0%)
Ileus	2	1 (50.0%)
Benzodiazepine withdrawal	1	1 (100.0%)
Fracture	1	1 (100.0%)
Ischaemic bowel	1	1 (100.0%)
Lithium toxicity	1	1 (100.0%)
Seizure	1	1 (100.0%)

In patient episodes associated with an ADR, the number of medicines taken was significantly higher (median of 9 regular medicines (Q1-Q3 6-13), in comparison to the control sample of patient episodes (median of 6 regular medicines Q1-Q3 4-10 (U=92644; $p<0.0001$)). The drug groups most frequently implicated in the ADRs, and causative drugs relative to usage in the study population are shown in Table 3.7.

Table 3.7: Drugs most frequently implicated in causing ADRS

Drug group	N° (%) ADRs †	Rank: Frequency drug in class contributed to ADR	Rank by frequency of use of drugs	Drugs (N° of ADRs for each causative drug)‡	Adverse drug reactions
Opioids	118 (16.1)	1	1	Morphine (88), tramadol (53), Dihydrocodeine(10), fentanyl (8), codeine(8), oxycodone (7), pethidine (2)	Confusion, constipation, sedation, dizziness, respiratory depression, hallucinations ileus, hypotension, itching, nausea, rash, dependence
Loop diuretics	151 (20.6)	2	14	Furosemide (123), bumetanide (40)	Electrolyte disturbances, gout, hypotension, ileus, nausea, renal failure
Systemic cortico-steroid	87 (11.9)	3	18	Prednisolone (67), dexamethasone (14), hydrocortisone (11), methylprednisolone (1), fludrocortisone (1)	Electrolyte disturbances, increased INR, bleeding, hallucination, hyperglycemia, fracture, hypertension, neutropenia, candidal infection
Beta-agonists (inhaled)	85 (11.4)	4	=12	Salbutamol (85), terbutaline (4), salmeterol (3)	Electrolyte disturbances, nausea, tachycardia
Penicillins	66 (9.0)	5	=6	co-amoxiclav (34), Amoxicillin (24), flucloxacillin (15), benzylpenicillin (7), penicillin v (1), ampicillin (1)	CDT, bleeding, rash, nausea, diarrhoea, increased INR, candidal infection
Oral anticoagulant	72 (9.8)	6	52	Warfarin (72)	Increased INR, bleeding
Cefalo-sporins	67 (9.1)	7	10	Ceftriaxone (40), cefuroxime (24), cefradine (3), cefaclor (2), Cefalexin (1), ceftazidime (1)	CDT, bleeding, increased INR, rash, nausea, neutropenia, candidal infection, worsening renal function
Compound analgesics (with opioid)	64 (8.7)	8	8	Co-codamol (58), co-dydramol (7)	Confusion, constipation, hypotension, sedation
Macrolide antibiotics	50 (6.8)	9	29	Erythromycin (34), clarithromycin (27)	CDT, bleeding, renal failure, deranged LFTs, diarrhoea, increased INR, rash, candidal infection, nausea
Low MWH	50 (6.8)	10	=6	Dalteparin (41), Enoxaparin (12)	Bleeding, heparin induced thrombocytopenia, electrolyte disturbances

Abbreviations: CDT – *Clostridium difficile* toxin disease; LFTs – liver function tests; INR – international normalised ratio; MWH – molecular weight heparins; † -Often greater than one causative drug group per ADR; ‡ - Often greater than one causative drug from group per ADR

The most frequent causative drugs relative to usage were anticoagulants (warfarin), fibrinolytics (streptokinase) (4 ADRs), unfractionated heparin (3 ADRs), loop diuretics and allopurinol (5 ADRs). Drugs which caused ADRs which were not prescribed in the sample of non-ADR patients were metyrapone, linezolid, procyclidine, atovaquone and daunorubicin (all 1 ADR). Warfarin was the most common causative drug relative for use and therefore in-depth analysis of ADRs involving this drug are detailed in Figure 3.1.

Clostridium difficile infection is a common ADR, resolution of which is currently a high priority for the NHS, particularly since the Healthcare Commission report regarding C. d*ifficile* deaths at Maidstone and Tunbridge Wells NHS Trust [189], and constipation is among the most frequent ADRs and therefore further details of these ADRs are described below:

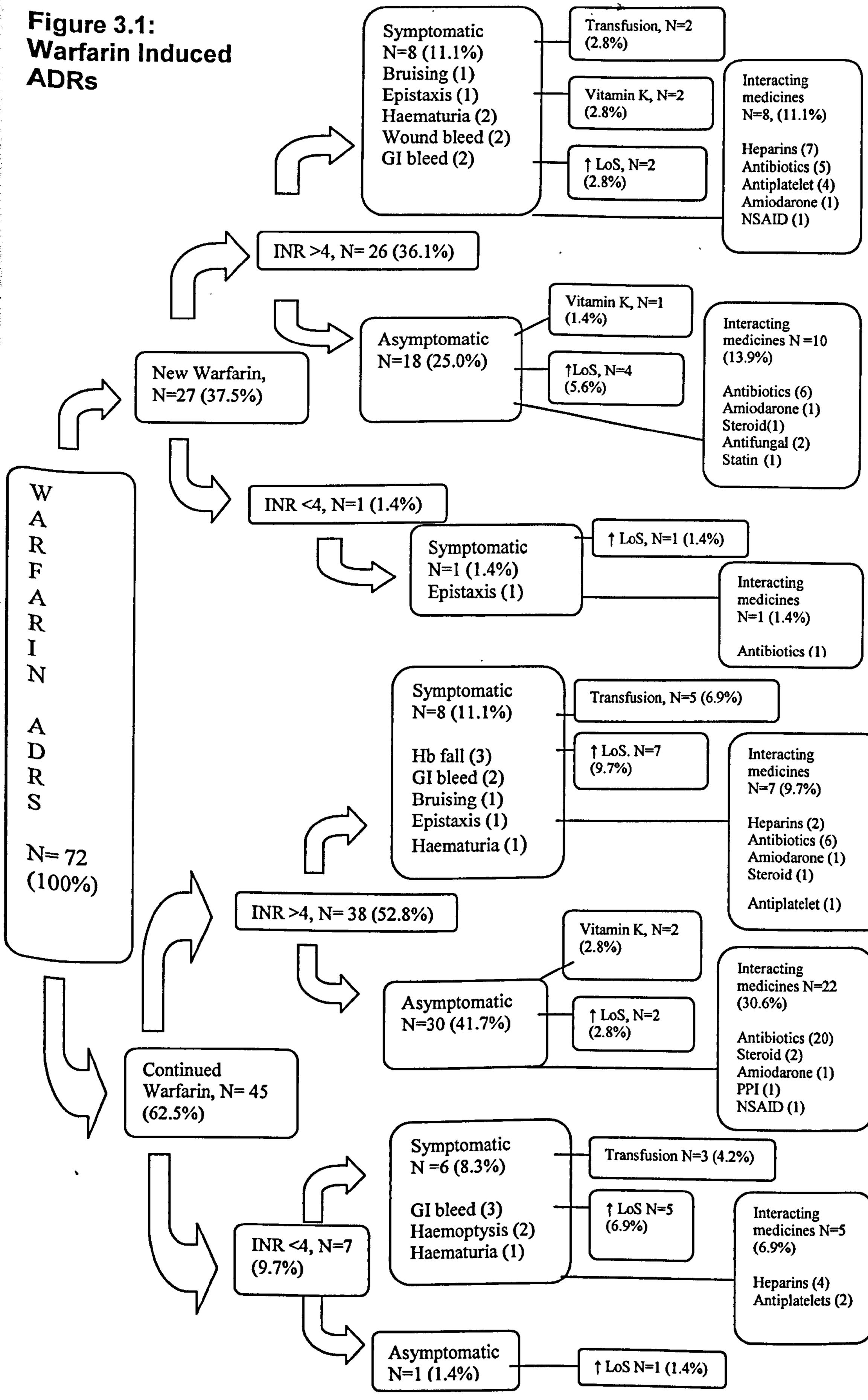
3.5.1 Focus on *Clostridium difficile*

There were 25 cases of *C. difficile* classified as an ADR in this study. Of these, 5 (20%) were linked to death and 13 (52%) directly increased the length of stay, resulting in a total of 174 additional days in hospital attributable to *C. difficile* ADRs. Approximately half (12, 48%) of these ADRs were possibly avoidable. Of the possibly avoidable ADRs 11 involved broad-spectrum cefalosporins. One patient received antibiotics from 5 classes (cefalosporin, macrolide, quinolones trimethoprim, penicillin) plus a proton-pump inhibitor during a lengthy admission with a necrotic heel ulcer. In a separate case, a patient admitted with community acquired pneumonia received a cefalosporin, macrolides and broad spectrum penicillin within the first 6 days of the admission. The patient's length of stay was extended due to diarrhoea, and subsequent dehydration led to acute renal failure. This was treated but diarrhoea persisted despite metronidazole and the admission continued; the patient died due to ruptured abdominal aortic aneurysm (AAA) on day 26 of admission. The AAA was the cause of death, but the patient had been in hospital as a result of problems related to *C.difficile* for 21 days prior to this event.

3.5.2 Focus on constipation

Constipation was the second most common ADR (N=100) in the study population. Constipation was defined as "failure of the bowel to open for three consecutive days" [190]. Most ADRs relating to constipation were minor, with 83 (83%) having no effect on length of stay. Length of stay was increased due to drug-induced constipation in 17 (17%) episodes, contributing a total of 68 additional bed days to these patient episodes. Opioid analgesia contributed to the majority (N=93, 93%) of these ADRs, with morphine the most frequently implicated drug, contributing to half (N=50, 50%) of these ADRs. Prophylactic laxative prescription was prescribed, but ineffective in 30 (30%) of patients with constipation.

Figure 3.1: Warfarin Induced ADRs



ADRs occurred despite prophylaxis in 67 (9.1%) cases involving 10 types of ADR (constipation (35), electrolyte disturbances (10), renal failure (8), bleeding (5), raised INR (3), nausea (2), opioid withdrawal, opioid dependence, oral Candida infection, and diarrhoea (all 1)). ADRs (n=156) directly increased length of stay in 147 (26.8%) patients with an ADR (See Table 3.8), equating to 4.1% of all inpatients and accounting for 934 out of 50145 (1.9%) bed days or 0.25 days/patient admission episode.

Table 3.8: ADRs and length of stay (LoS)

Additional LoS due to ADR (days)	N° ADRs (N=156)	Detail of ADRs
1-3	68	Electrolyte disturbances (13); Bleeding, renal failure (9); constipation (8); Nausea (4); hypoglycaemia, hypotension, increased INR (3); anaemia, bradycardia, opioid toxicity, rash (2); anaphylaxis, *C. difficile*, diarrhoea, gout, hyperglycaemia, sedation, neutropenia, urinary retention (1)
4-7	56	*C. difficile*, constipation (7); hypoglycaemia, increased INR (6); Bleeding (5); deranged LFTs, electrolyte disturbances, hypotension, renal failure (3); diarrhoea (2); benzodiazepine withdrawal, confusion, extra-pyramidal reaction, fracture, gout, hyperglycaemia, nausea, opioid toxicity, rash, seizures, urinary retention (1)
8-15	20	Bleeding (5); Renal failure (4); C.*difficile*, constipation, electrolyte disturbances (2); confusion, deranged LFTs, diarrhoea, digoxin toxicity, urinary retention (1)
16-30	10	*C. difficile* (3); Hypoglycaemia, renal failure (2); Bleeding, ileus, Lithium toxicity (1)
31+	2	Bleeding, *C. difficile* (1)

Multivariable statistical analysis was used to assess the ADR and non-ADR groups for probable risk factors for ADRs. Univariable Kaplan-Meier analyses for the two categorical risk factors, gender and ward type, using the 10% sample, showed that neither was a significant predictor of time to the ADR episode (log-rank p = 0.86 and 0.48, respectively). Age was also a non-significant predictor (HR 1.00). The only significant predictor from univariable analyses was the number of medicines (p < 0.0001; HR 1.14; 95% CI 1.09, 1.20). Multivariable Cox regression confirmed these results (Table 3.9), with the number of medicines as the only significant predictor. Therefore, on average, each additional medicine increases the hazard of an ADR episode by 1.14. There may be a power issue in using the 10% sample, since the full dataset showed that both gender and age were significant risk factors for the ADR episode (p = 0.001 for both factors; respective HR (95% CI) of 1.33 (1.12, 1.59) and 1.01 (1.0, 1.01)). Comparing these with the 10% sample showed that the mean values from the full dataset were contained within the 95% confidence intervals of the 10% sample.

Table 3.9: Risk factors for adverse drug reaction assessed by multivariable analysis

Factor	*N*	*Parameter Estimate*	*Standard Error*	*Chi-sq (df)*	*Pr >Chi Square*	*Hazard Ratio*
Gender (F v M)	374	-0.026	0.240	0.012 (1)	0.9125	0.974
Ward Type (medical v surgical)	374	0.101	0.279	0.131 (1)	0.7178	1.106
Age	374	-0.002	0.007	0.060 (1)	0.8070	0.998
Number of medicines	374	0.130	0.025	26.617 (1)	<.0001	1.138

3.6 Discussion

This is the largest prospective study of adverse drug reactions in UK hospital inpatients. The data collated suggest that at least 1 in 7 inpatient episodes is complicated by an adverse drug reaction. The incidence figure of 14.7% is consistent with the pilot study (Chapter 2) [181] and with studies from the 1960s which showed that ADRs occurred in 10-20% of inpatients [8, 94, 95]. However, this figure is higher than the 3.5-7.3% incidence suggested in a systematic review [92]; this may be explained by the fact that pooling data from ADR studies with different designs can be problematical [5, 90] as illustrated by the widely differing estimates of ADR incidence determined in different studies (from 0.86% [96], to 37% [98]). In order to improve the accuracy of these assessments, individual causality assessments were undertaken using the Naranjo causality assessment tool [63]. Causality assessments are difficult, and inter-rater agreement varies enormously [52], but the use of published algorithms enabled the investigating team to apply consistent criteria to the assessment of cases. The prospective nature of this study, and the intensive nature of data collection and follow-up, similar in nature to two major recent studies of ADRs causing admission [18, 93] has aimed to provide an accurate assessment of ADRs in adult hospital inpatients.

3.6.1 Impact of ADRs on the NHS

A clear limitation of this study is that it was conducted in one hospital and there is likely to be a variation between hospitals due to the differences in the local population characteristics and specialties within the hospitals. The patients included were from study wards selected as a convenience sample representative of the medical and surgical ward ratio in the study hospital, and representative of clinical specialties commonly found in most UK NHS acute hospitals (see Table 3.1). The age distribution of the patients was comparable to figures for all inpatient admissions in England in 2006-07 [191] and by including a large sample size which was thoroughly assessed, it is thought that the results from this study are broadly transferable to the inpatient population as a whole. Intensive care units are known to have a higher rate of ADRs [192]. Therefore, specialist units such as intensive and critical care units, and the kidney transplant unit were excluded to increase the relevance of the results to most UK general hospitals. Hospital episode statistics from the Department of Health state that in 2006-7 there were

9,133,758 adult admission episodes to NHS hospitals (excluding maternity admissions) [191]. There are 126,976 NHS beds in England, with 108, 370 occupied at 85.3% capacity [193]. In this study, 935/50145 (1.9%) bed days were due to an ADR. Therefore, using actual bed day data, it can be estimated that 2059 bed days are due to an ADR at any one time, which is equivalent to roughly three 800-bed NHS hospitals at 85% capacity. If this is added to the estimate that the equivalent of seven 800-bed hospitals are filled with patients admitted with ADRs [18], the combination of ADR-related admissions and ADRs occurring as inpatients, lead to the occupancy of ten 800-bed NHS hospitals. The estimate of additional bed days is in keeping with the medium to high estimates given by Wiffen *et al* in their systematic review [92]. An accurate assessment of the financial cost of these ADRs is difficult, but a crude estimate based on an average cost of a bed day in the NHS suggests that the total costs are likely to exceed £171 million annually. This is however likely to be an underestimate since the direct and indirect costs to patients such as loss of earnings due to extended stay or increased morbidity have not been measured, and neither were the costs which could be attributed to treating ADRs such as the prescribing of more medicines and investigations, and involvement of clinical teams external to the specialty to which the patient was admitted, all of which add to the overall ADR burden. Taken together with the figure of £466 million for ADR-related admissions [18], it is estimated that ADRs cost the NHS in excess of £637 million annually. However, the figures provided here need to be interpreted cautiously as they represent an extrapolation from one hospital to the NHS without an assessment of the causative fractions for the implicated drugs, which is difficult at an individual patient level.

3.6.2 Implicated drugs and severity of reactions

The most frequently implicated drugs were opioid analgesics, diuretics, systemic corticosteroids, anticoagulants and antibiotics. This is in accordance with several other studies of hospital inpatients [10, 12, 144]. When adjusted for the frequency of prescription, warfarin, fibrinolytics and unfractionated heparin were the top three causes of ADRs. It is worrying to note that the same drugs, warfarin, loop diuretics and opioids, are being consistently implicated in different studies of ADRs; this may partly reflect their high usage, but nevertheless suggest that lessons have not been learnt from previous studies, and relevant preventive

strategies have not been put in place. Figure 3.1 shows us that ADRs caused by warfarin administration can be complex, with serious clinical symptoms, and often require blood transfusions or vitamin K administration. Interacting medicines are frequently involved. It also highlights that ADRs can occur even when the INR is in range highlighting the need for close monitoring of patients with warfarin and better prescribing with regard to interacting medicines and the prescription of new drugs. It is clear that current work by the NPSA and in the research community to manage warfarin more appropriately is necessary.

Constipation is a frequently occurring ADR with laxative prescription being a commonly accepted method of prophylaxis [184]. The majority (70%) of constipated patients had received no prophylaxis and subsequently suffered constipation. However, a significant minority of those constipated had received prophylactic laxative treatment unsuccessfully, leading us to question the value of laxatives as prophylactic treatment against constipation, and the choice and dosage of prophylactic therapy given (see Chapter 7).

Approximately three quarters of adverse drug reactions were scored at level 3 or below on the Hartwig scale (Table 3.3) and were therefore relatively minor, although all required intervention. These interventions ranged from stopping the causative medicine(s) to administration of specific antidotes, for example, naloxone for opioid-induced respiratory depression. The remaining ADRs were sufficiently serious to result in an increase in length of stay or admission to intensive care, and in some cases, death. The assessment of the cause of death and in particular whether it is due to the underlying disease or due to an ADR, can be extremely difficult; in our study, careful assessment showed that one fatality was due to an ADR (classified as definitely avoidable), and resulted from a gastro-intestinal (GI) bleed involving prescription of the combination of diclofenac and dalteparin.

Reducing ADR burden on length of stay is an important consideration for the patient and their carers, and also for the hospital in the current UK political climate. The impact of ADRs on length of stay is shown in Table 3.8. Interestingly, the 32 ADRs that increased patient stay by 8 days or more were responsible for more bed days than the 124 ADRs responsible for up to an additional week in hospital.

Bleeding, renal failure and *C. difficile* were responsible for more than half of these high impact ADRs suggesting that focussing on reducing these three types of ADR may be a logical start to attempt to reduce the ADR burden.

3.6.3 Prevention of adverse drug reactions

In this study, just over half of the ADRs were deemed avoidable, slightly less than the 60-70% suggested in the literature [13, 18, 93, 139]. Given the considerable burden of ADRs, there is a need to put into place preventive strategies. Given the wide variety of drugs implicated, and the huge array of ADRs that were identified affecting almost every organ system in the body, prevention is likely to require complex multi-faceted intervention strategies. Identification of risk factors may allow targeting of these interventions to certain high risk groups. In our study, increasing age, admission to a medical ward, female gender, and number of regular medicines were identified as risk factors. Univariable and multivariable analysis showed that the only significant risk factor was the number of medicines the patient was taking, which may in itself be a reflection of age, gender and status as a medical patient. This is consistent with a number of previous studies [110, 194, 195]. Given the increasing age of the population, the high number of potential drug-drug interactions demonstrated in this study, and the trend towards polypharmacy, even in younger patients, the problem of ADRs is likely to remain a significant, if not increasing burden on our hospitals.

Computerised prescribing and monitoring systems [11, 159, 160], the presence of pharmacists on ward rounds [170, 171], the need for better monitoring [169], and enhanced education of prescribing, leading to error reduction [173], are amongst the possible intervention strategies that have been suggested to be important in reducing the burden of ADRs. There is however a need for further research in this area, not only for the development of a robust evidence based to allow for prevention of ADRs, but also in the implementation of these strategies into hospital healthcare systems. Although it would be prudent to initially focus on the more serious ADRs, it is important to remember that even so-called non-serious ADRs, for example constipation from using opioids, can have a significant impact on the patient's quality of life, and also require the development of preventive strategies.

The design has clear limitations. Deciding if a patient has experienced an ADR or not is often difficult as ADRs can mimic disease, and vice versa, and a patient's condition can change rapidly as an inpatient. In order to ensure those ADRs identified could be accurately attributed to the drug two assessors examined each report independently and disputed decisions were discussed with a Professor of Clinical Pharmacology. The initial inter-rater agreement between ED and CG for use of the Naranjo causality algorithm was fair [196]. This agreement is lower than expected from the results achieved in the paper detailing algorithm design [63], but the discrepancies may be explained by the fact that this study used reports generated from the observational study as opposed to published case reports, although this warrants further investigation.

Patients were included once they reached the ward, thereby limiting the study to those patients who required transfer beyond the hospital assessment units. This may have resulted in a sample bias towards the more unwell patients in the hospital. Also, those admitted and discharged over a weekend would be excluded and day cases may have been omitted due to unavailability of patient details on the administration system when records were checked once daily during data collection. All medicines for one tenth of patients admitted was a practical quantity of data which could be could be recorded within the time and personnel restraints of this study. This was due to the need to manually check handwritten patient charts for all medicines and record the data. If electronic prescribing/administration systems had been in place, it would have been possible to record all medicines prescribed to all patients enabling more comprehensive background data to be compiled.

3.7 Conclusion

To conclude, this study shows that ADRs are a significant problem in hospital inpatients, contributing to morbidity and mortality and resulting in considerable financial burden. Over half are definitely or potentially avoidable, and steps should be taken to introduce strategies to reduce their impact.

Chapter 4: Interpreting adverse drug reaction (ADR) reports as hospital patient safety incidents

4.1 Introduction

The National Patient Safety Agency (NPSA) is a Special Health Authority in the National Health Service (NHS) and was set up in 2001 in response to two reports on patient safety in the NHS: *An Organisation with a Memory* [197] and *Building a Safer NHS for Patients* [198]. The role of the NPSA is to collect, analyse and respond to adverse events in the NHS, identifying risks and providing solutions to improve patient safety in the organisation [199, 200]. Variations in taxonomy between countries, organisations and individuals result in different estimates of incidence of hospital patient safety incidents [201]. However, a commonly-quoted estimate from the UK suggests that approximately 11% of patients experience an adverse event in hospital [199, 202], similar to the figure shown in a more recent US study [203].

The NPSA includes adverse drug reactions (ADRs) as a reporting category in medicines-related patient safety incidents [204, 205] although a recent NPSA document, *Safety in doses: medication safety incidents in the NHS* [206], states that:

"*Where medicine has caused harm to a patient but no error took place, the incident is judged to be 'non-preventable' and is usually called an adverse drug reaction (ADR). For example, a patient experiencing a side effect to a medicine for the first time, which could not have been predicted. Data on ADRs are not collected by the NPSA, but these should be reported to the MHRA Pharmacovigilance 'Yellow Card' System.*"

The above definition of an ADR contrasts with ones from the ADR literature which include preventable and non-preventable ADRs [9, 16], although the same NPSA report also prominently uses data from the Liverpool ADR studies to emphasise the scale of medicines-related patient safety incidents [18, 181, 206]. Using ADR data in this way may considerably alter estimates of hospital incidents such as those described by Vincent *et al* [202]. These inconsistencies may potentially

have a negative impact on reporting of ADRs due to the confusion surrounding which organisation ADRs should be reported to, depending on whether or not the incident was regarded as avoidable. Reporting of ADRs via Yellow Cards to the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK has been encouraged since 1964 although under-reporting remains a long-standing problem. For example, the Liverpool ADR admission study generated approximately 980 yellow cards from two hospitals in six months. These were reported to the MHRA, and of these, over 70% were categorised as being either definitely or possibly avoidable [18]. It is also not clear from the NPSA definition whether the ADRs classified as being possibly avoidable should be in the same category as those that are definitely avoidable.

However, since many ADRs are considered to be preventable and are in effect patient safety incidents, the issues raised in the NPSA alert offer another opportunity to review adverse drug reactions, and for organisations, an opportunity to look at the burden of ADRs in manner that fits with their more commonly used reporting systems and allows comparison to other patient safety incidents. Thus, the purpose of this study was to take a cohort of patients who had experienced an ADR, and categorise the incidents in line with the methods suggested by the NPSA and those commonly used by NHS trusts in the UK.

4.2 Aim

To classify adverse drug reactions already identified through a large prospective study according to NPSA Incident grading systems [15, 16] and to discuss the suitability of the system for grading and reporting ADRs.

4.3 Objectives

1. To assess each ADR for its impact on individuals and the organisation according to the NPSA grading system.
2. Compare the incident gradings in the context of ADR avoidability.

4.4 Methods

All 733 adverse drug reactions identified in a six-month prospective study of 3695 inpatient episodes (Chapter 3) at the Royal Liverpool University Hospital were included in this analysis. These ADRs were assessed according to causality, severity and avoidability algorithms from the ADR literature [63, 83, 88] as well as eligibility for reporting to the MHRA [85]. The adverse drug reactions were reclassified by a research pharmacist (ED) according to their impact on the patient and their impact on the organisation, and recorded on the readmissions study assessment form (Appendix 8). Data were then manually entered into a Microsoft Access database.

- The impact of the ADR on the patient was classified according to the grading system determined in the National Patient Safety agency document '*Seven steps to patient safety*' (Table 4.1) [207] ; and
- the organisational impact was determined using the framework defined in the Department of Health document '*Doing Less Harm*' (Table 4.2) [208].

The organisational impact risk matrix employs a four-level traffic light system based on the likelihood of recurrence and potential impact on the organisation if the incident recurs. The draft document '*Doing Less Harm*' [208] has been superseded by the 'Seven steps to patient safety' guidance [207], and the NPSA do not require the impact on the organisation to be reported to them. However, many organisations continue to use the risk matrix grading systems, and follow the same principles as the 'Doing Less Harm' guidance. Therefore this study will assess the ADRs for impact on the organisation according to the published matrix system.

Table 4.1: NPSA terms and definitions for grading patient safety incidents [207]

Table 4.2: Potential future risk to patients and the Organisation [208]

4.5 Results

All inpatient adverse drug reactions (733, 100%) identified in a six-month prospective study of 3695 inpatient episodes at the Royal Liverpool University Hospital were assessed. Data from this study showed that 545 (14.7%) patient-episodes resulted in ADRs, that 391 (53.3%) ADRs were definitely or possibly avoidable, and that 226 (30.1%) of the ADRs were suitable for Yellow Card reporting to the MHRA [85].

The impact on the patient according to the "Seven steps to patient safety" document criteria [207] is shown in Table 4.3.

Table 4.3: Impact of ADRs on the patient

Impact on patient	N° of ADRs (n=733)	N° of Yellow Cards (n=226)
Low (minor treatment)	537 (73.3%)	53 (23.5%)
Moderate (moderate increase in treatment, no permanent harm)	181 (24.7%)	158 (69.9%)
Severe (permanent harm)	14 (1.91%)	14 (6.2%)
Catastrophic (direct cause of death)	1 (0.14%)	1 (0.4%)

Of the 14 'severe' ADRs, one was a case of Type 2 diabetes mellitus resulting from prednisolone use. A further 13 cases were linked to deaths, with drug-induced renal impairment (n=7), *Clostridium difficile* infection (n=5), and ischaemic bowel (n=1) as contributory factors to death, although these ADRs were not judged to be the direct causes of death. In the 'catastrophic' ADR, the patient death was directly related to a drug-induced gastro-intestinal bleed. According to NPSA guidance for 'low' and 'moderate' impact incidents, organisations should record data, investigate demographics and contributory factors when possible, and conduct root-cause analysis where themes emerge. For 'severe' and 'catastrophic' incidents, root-cause analysis including involvement of the patient or carer should be conducted [207].

The results of the assessment of ADRs on the organisation are shown in Table 4.4.

Table 4.4: Impact of ADRs on the organisation [208]

According to the definition of ADR used for the prospective study [16], there were no ADRs that caused 'no harm' since all had an adverse effect. In addition, all ADRs included in this study were recognised from the BNF [183] or Summary of Product Characteristics [182] for each product. This indicates that all ADRs are likely to recur in the hospital. Consequently, no ADRs were classified as 'green' or 'very low risk'.

The ten most frequent ADRs and their organisational impact are shown in Table 4.5.

Table 4.5: Most frequent ADRs and organisational impact

ADR	Impact on Organisation			
	Insignificant	**Minor**	**Moderate**	**Major**
Electrolyte disturbances (n=168)	147 (87.5%)	19 (11.3%)	2 (1.2%)	0 (0.0%)
Constipation (n=100)	79 (79.0%)	19 (19.0%)	2 (2.0%)	0 (0.0%)
Increased INR (n=54)	40 (74.1%)	14 (25.9%)	0 (0.0%)	0 (0.0%)
Bleeding (n=53)	21 (39.6%)	22 (41.5%)	8 (15.1%)	2 (3.8%)
Renal impairment (n=45)	21 (46.7%)	18 (40.0%)	4 (8.9%)	2 (4.4%)
Hypotension (n=35)	29 (82.9%)	6 (17.1%)	0 (0.0%)	0 (0.0%)
Candidal infection (n=33)	32 (97.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)
Hypoglycaemia (n=32)	18 (56.3%)	12 (37.5%)	0 (0.0%)	2 (6.2%)
Nausea (n=29)	23 (79.3%)	6 (20.7%)	0 (0.0%)	0 (0.0%)
Clostridium difficile infection (n=25)	0 (0.0%)	18 (72.0%)	3 (12.0%)	4 (16.0%)

From the results, it is clear that the ADRs that cause incidents of greater significance relate to bleeding, renal impairment and *Clostridium difficile* infection. Tables 4.6 and 4.7 describe the avoidability of the ADRs according to the Hallas avoidability criteria [88] in terms of the impact on the patient (Table 4.6) and in terms of the impact on the organisation (Table 4.7). It can be seen that only 47 of the adverse reactions would fall into the category of medication errors according to the NPSA definition if the correlation was restricted to those cases where the ADR was definitely avoidable.

Table 4.6: Impact on patient and avoidability

	Definitely Avoidable n=47 (%)	*Possibly Avoidable n=344 (%)*	*Unavoidable n=342 (%)*
Catastrophic	1 (2.1%)	0 (0.0%)	0 (0.0%)
Severe	1 (2.1%)	9 (2.6%)	4 (1.2%)
Moderate	9 (19.1%)	92 (26.7%)	80 (23.4%)
Low	36 (76.6%)	243 (70.6%)	258 (75.4%)
None	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4.7: Impact on organisation and avoidability

	Definitely Avoidable n=47 (%)	*Possibly Avoidable n=344 (%)*	*Unavoidable n=342 (%)*
Catastrophic	0 (0.0%)	0 (0%)	0 (0.0%)
Major	0 (0.0%)	7 (2.0%)	5 (1.5%)
Moderate	1 (2.1%)	11 (3.2%)	13 (3.8%)
Minor	14 (29.8%)	103 (29.9%)	71 (20.8%)
Insignificant	32 (86.5%)	223 (64.8%)	253 (34.5%)

Table 4.8 describes the frequency and nature of each ADR in terms of both patient and organisational impact.

Table 4.8: Impact of ADR on both patient and organisation

Patient Impact	Organisation impact	N^{o} of reactions (%)	Adverse drug reactions n = 733
Low	Insignificant	489 (66.7%)	Electrolyte disturbances (142); constipation (78); increased INR (40); candidal infection (32); hypotension (30); nausea (22); rash (23); hypoglycaemia, renal impairment (18); bleeding (15); diarrhoea (11); deranged LFTs (9); opioid toxicity, sedation (5); hallucination, itching (4); confusion, tachycardia, toxic drug level (3); anaemia, chest discomfort, dizziness, headache, heparin induced thrombocytopenia, opioid withdrawal (2); bone marrow suppression, bradycardia, chest pain, cough, digoxin toxicity, dyspepsia, ECG changes, heartburn, hypertension prolonged prothrombin time, urinary retention, wheeze (1)
Low	Minor	48 (6.5%)	*Clostridium difficile* (6); increased INR, opioid toxicity (4); abdominal pain, digoxin toxicity, fall, hallucination, hyperglycaemia, hypoglycaemia, opioid withdrawal (2); bleeding, constipation, electrolyte disturbances, renal impairment (3); candidal infection , confusion, diarrhoea, ischaemic foot, nausea, rash, sedation (1)
Moderate	Insignificant	118 (16.1%)	Electrolyte disturbances (22); constipation (15); bleeding (14); renal impairment (12); increased INR (9); hypoglycaemia (8); deranged LFTs (7); hypotension, nausea (5); diarrhoea, urinary retention (3); anemia, bradycardia, *Clostridium difficile* (2); arthralgia, confusion, gout, neutropenia, rash, sedation, seizures, swollen lips (1)
Moderate	Minor	51 (7.0%)	Bleeding (15); *Clostridium difficile* (10); renal impairment (4); opioid toxicity (3); hypoglycaemia (2); constipation; confusion, diarrhoea, digoxin toxicity, electrolyte disturbances, extra-pyramidal reaction, fluid retention, fracture, gout, hyperglycaemia, ileus, increased INR, nausea, psychosis(1)
Moderate	Moderate	2 (0.3%)	Psychosis, bleeding (1)
Moderate	Major	10 (1.4%)	Bleeding, *Clostridium difficile*, hypoglycaemia, renal impairment (2); ileus, lithium toxicity (1)
Severe	Insignificant	3 (0.4%)	Renal impairment (3)
Severe	Minor	6 (0.8%)	*Clostridium difficile*, renal impairment (2); hyperglycaemia, ischaemic bowel (1)
Severe/	Moderate	3 (0.4%)	Bleeding, *Clostridium difficile*, renal impairment (1)
Severe	Major	2 (0.3%)	*Clostridium difficile* (2)
Catastrophic	Moderate	1 (0.1%)	Bleeding (1)

4.6 Discussion

Spontaneous ADR reporting rates are low [29] and this limits the ability to accurately assess the burden of ADRs and their impact. It is interesting to note that there is a core list of medicines which most commonly cause ADRs of all severities [143]. Despite this, however, little has changed to improve the prescribing and monitoring of these drugs and thereby reduce the incidence of ADRs [18].

It was possible to classify all ADRs included in this study according to NPSA guidance and with the organisational risk matrix used by many Trusts. From the data available on individual yellow cards, it is often not possible to undertake a detailed assessment of the individual circumstances surrounding ADRs, which may be possible at a local level where incidents are collected and reviewed. Theoretically, if large numbers of ADRs were analysed using techniques such as root cause analysis to evaluate systems and processes, new interventions to prevent serious and in some cases, fatal ADRs could be identified. This approach may also give organisations new insight into the potential burden of ADRs shown in Chapters 2 and 3 of this thesis [18, 181], and encourage them to take a more robust approach to introducing proactive interventions to prevent or react to the occurrence of ADRs and importantly, in a manner that is relevant to their own organisation. However, the results of this study suggest that root-cause analysis would be unnecessary for the vast majority of ADRs and thus, the value of using a patient-safety incident reporting system over and above that of the Yellow Card Scheme for ADRs is not likely to be great. Nevertheless, the NPSA recommendation that severe or catastrophic incidents should be analysed using root cause analysis [207] usually involves senior managers within organisations, and this may be a method by which to raise the profile of ADR reporting in NHS Trusts.

Although ADRs are a common occurrence, affecting approximately 15% of inpatient episodes (Chapter 3) and causing 6.5% of admissions [18], the majority of ADRs had little impact on the patient or the organisation according to the categorisation recommended by the NPSA. This is a clear limitation of this classification as it ignores the patient perspective, especially effects on quality of life. It is however important to note that 25% of ADRs increased the length of stay

or level of care. Thus, for NHS Trusts, an estimated 2.5% of their patient population will have an ADR which falls in this category. All hospitals are paid for their activity, and this percentage represents a significant expenditure according to payment by results. In addition, given the incidence of hospital acquired infections and the publicity surrounding this, it is noteworthy that *C. difficile* infection provided the highest number of incidents with a major impact on organisations. This is in line with the recent Maidstone and Tunbridge Wells reports which received a significant level of publicity both in the medical and general media [189, 209]. Many hospitals are conducting investigations into *C. difficile* infections to reduce their frequency, but this is more related to adverse publicity surrounding hospital acquired infections, rather than in an effort to reduce ADRs.

Consistency between hospitals in using the "*Doing Less Harm*" system [208] for grading the impact of events on organisations was reported as being difficult to achieve. The revised guidance from the NPSA in "*Seven steps to patient safety*" [207] does not require a patient safety incident to be graded for potential impact, likelihood of recurrence, and impact on organisations. This is reasonable since the consistency of the reporters' interpretations would not be guaranteed and assessing the likelihood of recurrence can only be based on local demographics and knowledge, which would be meaningless nationally [207]. Thus, many NHS organisations still collect these data locally which is why this study assessed the organisational impact of the ADRs studied. In the context of this, when initially identified, each ADR was assessed by at least two investigators (Chapter 3). However, for this study only one investigator re-assessed the ADRs according to the NPSA systems. This is a limitation of the study as interpretation of events by a sole investigator is open to scrutiny, and it has been suggested that multiple methods of data collection are necessary to detect actual and potential adverse events [210, 211].

Incident reporting within organisations is also variable [210] and inconsistencies in reporting are also likely for the impact of incidents on the individual although national data are still collected regarding these aspects of patient safety incidents. A study of intra-hospital variations in incident reporting supported previous findings that doctors are more committed to 'closed' peer-group collegial forms of quality improvement, which exclude non-medical staff, showing that participation in

reporting was greater when reporting was based within rather than outside the medical department [210]. This would suggest that doctors are less likely to report ADRs to a hospital management-led risk management. Research regarding ADR reporting has shown that between 85 and 98% of doctors, depending on the country, never report an adverse event to their national authority [29]. The perception of hospital incident reporting systems are also strongly linked with nurse-reporting of incidents such as 'needle-stick' injuries and falls [210] and a cultural change in reporting would be required to ensure consistent reporting of patient safety-incidents such as those involving ADRs which may lead to in-depth discussion of clinical-decision making.

ADR definitions are inconsistent between the MHRA and the NPSA, with the NPSA asserting that ADRs are not preventable [206], leaving approximately 50% of the ADRs from this study classifiable by the NPSA as medication errors and not ADRs. However, it is also unclear from the NPSA criteria as to whether possibly and definitely avoidable ADRs should be treated in the same manner. This study reports that relatively few ADRs are classified as 'definitely avoidable', although almost half are 'possibly' avoidable. From the ADR data collected, only two ADRs had a major or catastrophic effect on the patient and were 'definitely avoidable', and thus would be certain to require investigation by root-cause analysis according to the NPSA specifications. Even when using published guidance, such as the Hallas criteria [88], the judgement of whether an ADR is 'definitely', 'possibly' avoidable, or indeed unavoidable, is open to interpretation. Overall, the different definitions used by the two Government organisations is likely to lead to confusion. Indeed, this is acknowledged by the NPSA, and the importance of the NPSA and MHRA working together to share ADR data has been highlighted [206]. Collation of data of ADRs currently perceived as unavoidable ADRs is also important, as assessment of trends in the types of patients experiencing these ADRs may, in the future, contribute to a method for avoiding these ADRs. Definitions of patient safety incidents can have profound implications for a hospital's capacity to gather information about patient safety [212]. Healthcare professionals are unlikely to report a large number of incidents, but even less likely to report the same incident via two separate mechanisms, and confusion regarding ADR definitions and the use of ADR data is a barrier to progress in this important area. Clear guidance from the NPSA and MHRA is needed to ensure that healthcare professionals have

a coherent message as to the appropriate actions to be taken in response to the occurrence of an ADR.

4.7 Conclusion

Classification of ADRs according to NPSA guidance offers a different way of viewing the impact of ADRs on patients and on organisations, and root-cause analysis of ADRs may provide useful new strategies for reducing the number of ADRs and responding to serious ADRs for example, rapid referral or closer monitoring. A consistent message however needs to be sent out to prospective reporters of the burden caused by ADRs, the need for reporting using established systems (e.g. Yellow Cards) and the need for continued vigilance in prescribing rationally, and preventing and detecting ADRs. Whether the NPSA can provide something that the MHRA cannot requires some clarity and promotion of dual methods for this purpose may undermine reporting through the established Yellow Card system. Clearly, any change in the manner in which ADRs are dealt with in regulatory terms would be subject to some political debate and collaboration between the NPSA and the MHRA.

Chapter 5: Emergency readmissions to hospital due to adverse drug reactions: A retrospective study

5.1 Introduction

Adverse drug reactions are a burden to hospital patients; a Liverpool study showed that 6.5% of hospital admissions are due to ADRs [18], while the inpatient study demonstrated that almost 15% of patients experience an ADR during their admission (Chapter 3). There has however, been little research conducted into readmissions to hospital due to ADRs. This is particularly important in the UK as NHS organisations are assessed for their readmission rates as part of their performance indicators. A German study from 2004 found that 37% of admissions to internal medicine wards were readmitted, most within six weeks of discharge, but ADR occurrence in previous admissions did not increase risk of ADR in subsequent admissions [150]. Importantly, Dormann *et al* noted that due to the high turnover of inpatients, ADRs caused by in-house therapy are not entirely distinct from community acquired ADRs [150]. Recurrent ADRs causing multiple admissions for the same patient were found to be increasing in an Australian study, and were responsible for one third of ADR-related admissions [101]. Nausea and vomiting, haemorrhage with anticoagulants, drug-induced osteoporosis, and 'poisoning' by cardiovascular agents, were the most common ADRs causing readmission [101].

Possible problems that might result in ADR-related readmissions might include failure to optimally titrate drugs, failure to adequately monitor biochemical or haematological markers following changes in, or additions to drug therapy, and the possibility of interactions which may not become manifest until the patient has been discharged.

With the importance of readmission rates primarily in terms of patient care, but also in achieving governmental targets, it is important to identify strategies to reduce the incidence of readmission to hospital. This study will assess the rate of emergency readmission to hospital within one year to hospital due to drugs prescribed in the initial (index) admission. The one-year time period enabled the identification of ADRs which may not be immediately apparent following

commencement of new medicines. As 28-day readmission is an NHS Performance Indicator [213], this time period was also examined. This study aimed to distinguish ADRs that originated in hospital from those originating elsewhere, and potentially identify which of these ADRs, and subsequent admissions, are preventable in secondary care.

5.2 Aim

To evaluate the contribution of adverse drug reactions (ADRs) to readmission rates in hospital.

5.3 Objectives

1. To assess the incidence of readmission within 1 year for 1000 patients admitted to RLBUHT.
2. To assess the incidence of readmission within 28 days for 1000 patients admitted to RLBUHT.
3. To assess the number of readmitted patients, which were readmitted due to ADRs for both the 1 year and 28 day time-periods.
4. To assess the whether prescription of the causative drugs for readmission ADRs originated in the index admission
5. To conduct a causality, severity and avoidability assessment for each reaction
6. To classify the mechanism (A/B) of each reaction
7. To identify the causative drugs for ADRs
8. To propose risk factors for readmission due to ADRs
9. To suggest possible methods of prevention of readmission due to ADRs

5.4 Methods

The first 1000 patients initially admitted to 12 (9 medical, 3 surgical) wards from 27th June 2005 were included in the study. If they were readmitted within 12 months of discharge from their initial (index) admission, the cause of their readmission was assessed. As a secondary analysis, the readmission rate within 28 days of discharge was also calculated. These patients were part of a large

study of adverse drug reactions in hospital inpatients (Chapter 3). Data on whether or not the patients had an ADR during their index admission was obtained from Chapter 3. Admission and discharge data were extracted from the hospital PAS system with the assistance of the RLBUHT Audit Department using InfoCom and Microsoft Access. A research pharmacist (ED) conducted a retrospective casenote review examining the clinical information available for evidence of ADRs relating to readmission. Data was collected manually using the 'Readmission Assessment Form' (Appendix 8) and transferred to a Microsoft Access database. An adverse drug reaction was defined according to the definition of Edwards and Aronson [16]. This definition includes all doses prescribed clinically, but is intended to exclude accidental or deliberate overdose. An ADR related re-admission was defined as: An ADR, which is the reason for, or contributes to the admission to hospital of a patient in the defined cohort. Adverse drug reactions corresponded with those listed for each drug in their Summary of Product Characteristics [182] and the British National Formulary [183].

The reasons for index admission and subsequent readmission(s) were recorded and the readmissions were coded according to the rationale given in Table 5.1.

Table 5.1 Reasons for index admission and subsequent readmission(s)

Category	Reason for readmission
A	Manifestation of same disease state as index admission
B	Manifestation of different disease state to index admission
C	Social Issues
D	Other (e.g. rehabilitation)

The causative drug for the ADR was then classified, depending on the origin of its prescription, according to the criteria in Table 5.2.

Table 5.2: Classification of Readmission ADR

Category	*Description*
A	Causative drug was initiated during the index admission
B	Causative drug had dose changed during the index admission
C	Causative drug continued unchanged during the index admission
D	Causative drug prescribed/ dose changed elsewhere since the index admission

Suspected ADRs were analysed for causality using the Naranjo algorithm [63], while severity was assessed using an adapted Hartwig scale [83] as used in previous chapters. Avoidability was determined using the criteria outlined by Hallas *et al* [88], and suitability for yellow card reporting using the criteria set out by the Medicines and Healthcare Regulatory Authority (MHRA) [85]. All ADRs were initially assessed by the research pharmacist (ED), and a co-investigator (a Director of Pharmacy at an NHS Trust with previous experience of using this methodology); consensus was agreed between the investigators as to the appropriate final scoring for the ADRs. The ADRs were also classified as either a Type A reaction, i.e. predictable from the drug's pharmacology, or Type B reaction, that is, not predictable from the known pharmacology of the drug [20].

Approval for the study was obtained from the Trust Audit Department; Ethics Committee approval was sought but was not required. Statistical analysis was performed using StatsDirect version 2.6.2 and P values of <0.05 were interpreted as statistically significant.

5.5 Results

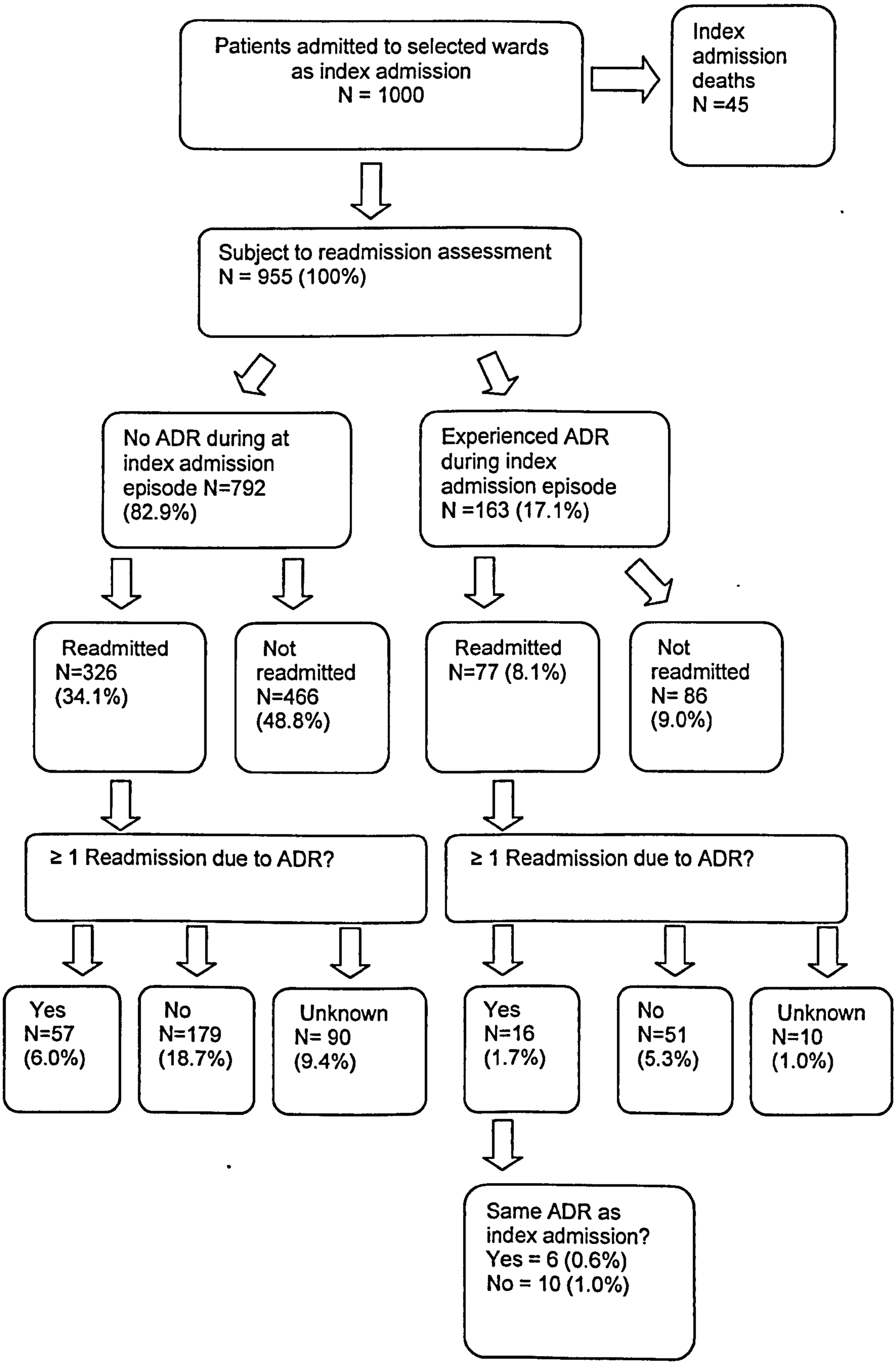
Of the 1000 patients included in the study, 955 (95.5%) were assessed for readmission (45 (4.5%) died during their index admission). Of these, 403 patients (40.3%) were readmitted to the hospital in the year following the index admission. The patients' demographic details are shown in Table 5.3.

Table 5.3: Demographic data – Readmitted vs. Not readmitted patients

Variable	Overall (N= 955)	Readmitted (N=403)	Not Readmitted (N=552)	P Value (Readmitted vs Not Readmitted)
Age (Median, (Q1-Q3))	62 years (42-76)	68 years (47-79)	56 years (39-74)	<0.0001
Sex (% Male)	453 (47.4%)	199 (49.3%)	254 (46.1%)	>0.3
Type of patient (medical or surgical) at index admission (% medical)	679 (71.1%)	316 (78.4%)	363 (65.8%)	<0.0001

Figure 5.1 shows ADR prevalence at admission and at readmission for the 955 patients who were discharged from their index admission. Using this data, 73 patients of the 403 readmitted (18.1%), had at least one ADR related readmission. However, the outcome was unknown for 100 patients. If the patients with unknown outcomes are excluded, 73 of 303 (24.1%) patients had one or more ADR related readmissions within a year of discharge from the index admission.

Figure 5.1: Flow chart showing numbers of patients with ADRs during index admission and those readmitted within one year of discharge from index admission (Patient Level Data)



Patients who experienced ADRs during their index admission did not have a significantly increased risk of being readmitted to hospital than those who did not experience an ADR during their index admission (77/163 (47.2%) vs 326/792 (41.2%) χ^2 = 2.05, P= 0.15). Similarly, there was no significant difference for readmission ADR rate for patients who experienced an ADR and those who did not during the index admission (16/163 (10.5%) vs 57/792 (7.2%), χ^2 = 1.31, P= 0.25). Adjusting the results for patients with unknown outcomes produced similar results.

It is possible to calculate the incidence of readmissions using another approach. Figure 5.2 shows the incidence of readmissions for the 1000 patients included in the study at index admission, and details the prevalence of missing data for retrospective follow-up. A total of 950 readmissions were identified in the 403 patients who were readmitted to hospital. The median time to the first readmission was 65 days (Q1-Q3 22-154 days). The number of readmissions for individual patients ranged from 1 to 28, (median 1 (Q1-Q3 1-3 readmissions)). Using the data from Figure 5.2, it is shown that of the 403 patients readmitted to the RLUH within one year, there were 290 (72.0%) patients for whom all ADR related readmission data were available. Of these, 60 (20.8%) patients had one or more readmissions relating to an ADR within one year of discharge.

There are therefore a number of ways to estimate incidence with this data, each giving slightly different incidence figures. However, from these data it can be concluded that approximately one in five readmitted patients are readmitted due to ADRs.

Within 28 days of the index discharge, 121 patients (12.7%) were readmitted. Complete data for these admissions was available for 100 (83%) patients, and 23 (23.0%) of these patients experienced an ADR- related readmission in this time-period.

Figure 5.2: ADR related readmissions and missing data (Patient and Readmission level)

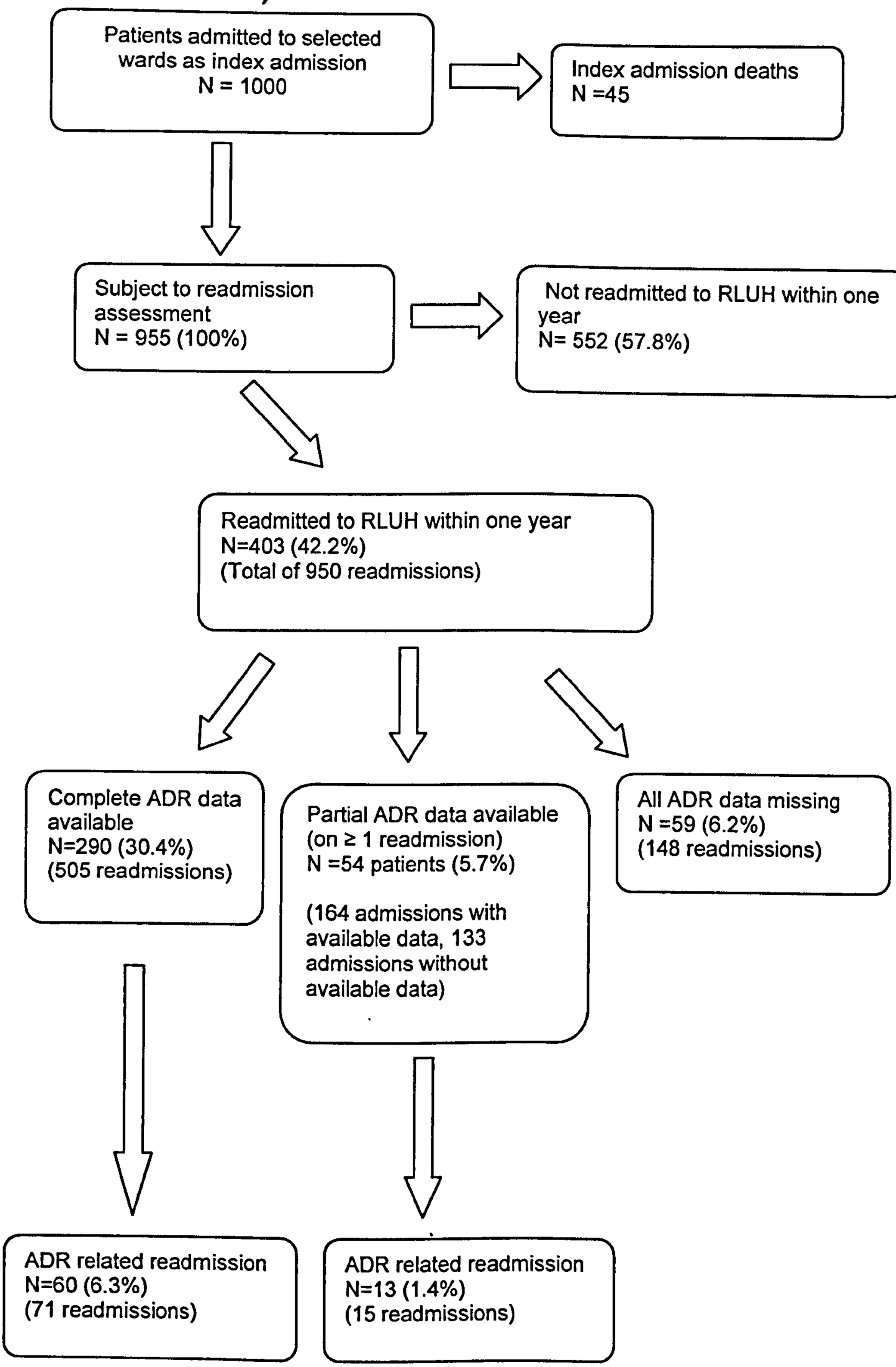


Figure 5.2 shows that there were 669 readmissions which were assessable for ADR data. The reason for readmission and number of ADRs identified for these readmissions are shown in Table 5.4.

Table 5.4: Reasons for readmission and ADRs

Readmission Code	Reason for readmission	N° of readmissions (N=669)	ADR related readmission (N=86)
A	Manifestation of same disease state as index admission	312 (46.6%)	25 (29.1%)
B	Manifestation of different disease state to index admission	333 (49.8%)	58 (67.4%)
C	Social Issues	4 (0.6%)	1 (1.2%)
D	Other (e.g. rehabilitation)	1 (0.1%)	0 (0.0%)
U	Unknown reason for index admission	19 (2.8%)	2 (2.3%)

From available data (Figure 5.2), patients readmitted due to ADRs had a median age of 74 years (Q1-Q3, 61-82 years). A total of 30 of 403 males (7.4%), and 43 of 451 (9.5%) females were readmitted due to ADRs, (χ^2 = 1.17, P>0.1). Median length of stay for index admission was not significantly different between those readmitted due to ADRs (10 days, Q1-Q3, 8-16 days) and those not readmitted due to ADRs (9 days, Q1-Q3, 5-16 days).

A total of 91 ADRs were identified in 73 patients, in 86 readmissions. ADRs were directly responsible for admission in 67 of 669 assessable readmissions (10.0%), and contributed to readmission in 19 (2.8%) cases.

Of the 403 patients readmitted during the year following the index admission, 56 (13.9%) died following a readmission to hospital. Of the 344 patients for whom data on at least one readmission are available (See Figure 5.2), 13 (3.8%) died

following an ADR related readmission. The median length of stay for readmissions directly resulting from ADRs was 8 days (Q1-Q3, 3-14days).

The majority of ADRs (N= 88, 97%) were Type A ADRs [20]; ADRs occurred despite prophylactic treatment in 19 (20%) of cases. These ADRs were bleeding (10), constipation (3), gastritis (2), *C. difficile* infection (1), fractures (1), gastric ulcer (1), and seizure (1). Drug-drug interactions contributed to 38 (42%) ADRs, of which 36 (95%) were pharmacodynamic drug-drug interactions. The two pharmacokinetic interactions involved warfarin and amiodarone causing an increase in International Normalised Ratio (INR), and warfarin and erythromycin causing epistaxis (also with increased INR).

Table 5.5 shows the Adapted Hartwig Scale [83] and describes the results of the severity assessment for the 91 ADRs identified and the inter-rater reliability between initial scoring of ADRs by the research pharmacist and co-investigator. A total of 78 (86%) ADRs were eligible for reporting to the CHM/MHRA Yellow Card Scheme [85].

Table 5.5: Adapted Hartwig severity scale and results

Severity Level	Description	Frequency of the ADR at each severity level; n (%)*
1	An ADR occurred but no change in treatment with suspected drug	0 (0)
2	The ADR required that required treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in length of stay	1 (1)
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment required. No increase in length of stay	18 (20)
4	Any Level 3 ADR which increases length of stay by at least one day OR the ADR was the reason for admission	63 (69)
5	Any level 4 ADR which requires intensive medical care	0 (0)
6	The adverse reaction caused permanent harm to the patient	0 (0)
7	The adverse reaction led to the death of the patient. For the purposes of this study, adapted as:	
7a	The ADR indirectly linked to death of patient	7 (8)
7b	The ADR directly linked to death of patient	1 (1.1)

Initial inter-rater agreement): % Initial total agreement = 89%, Weighted Kappa (κ^w) (95% CI)= 0.78 (0.63-0.93)

*The denominator used was the total number of ADRs (n=91).

Table 5.6 shows detailed results of causality and avoidability assessments, with corresponding inter-rater reliability (weighted Kappa (κ^w)) scores from the initial assessments of the ADRs by the research pharmacist and co-investigator.

Table 5.6: Causality and avoidability assessments of ADRs

Assessment	Categories and corresponding frequencies of the ADRs (n; %)*			% Initial total agreement	Initial inter-rater agreement κ^w (95% CI)
Causality	Definite	Probable	Possible		
	1 (1.1)	52 (57.1)	38 (41.8)	76.9	0.59 (0.44-0.74)
Avoidability	Definite	Possible	Unavoidable		
	13 (14.3)	39 (42.9)	39 (42.9)	58.2	0.43 (0.28-0.58)

*The denominator used was the total number of ADRs (n=91).

As can be seen from Table 5.5, eight ADRs contributed to the death of the affected patient and these deaths are described in Table 5.7.

Table 5.7: ADRs linked with deaths

Adverse drug reaction	N° associated patient deaths (n=8)	Drugs (number of deaths)	Avoidability (definite, possible, unavoidable)
Renal impairment	4	Amiloride (1), atenolol (1), bumetanide (2), enalapril (1), furosemide (2), ramipril (2), spironolactone (1)	1 definite 2 possible 1 unavoidable
Gastro-intestinal bleeding	3	Aspirin (2), clopidogrel (1)	3 unavoidable
Torsades de Pointes	1	Chlorpromazine (1), quetiapine (1)	1 unavoidable

A detailed description of the ADRs and their causative drugs is shown in Table 5.8. Anti-platelets and loop diuretics were the most common causative drug groups, with bleeding and renal impairment the most frequent ADRs.

Table 5.8: Adverse drug reactions within one year of index discharge and causative drugs

Description of reaction	N° of reactions n=91, (N° patients)	Causative drug (number of ADRs)
Bleeding	17 (13)	Aspirin (7); clopidogrel (5); warfarin (3); diclofenac, citalopram (2); alendronate, dalteparin, erythromycin, prednisolone (1)
Renal impairment	11 (8)	Furosemide, spironolactone (6); bumetanide, ramipril (5); digoxin (2); amiloride, atenolol, diclofenac, enalapril, metformin, telmisartan (1)
Constipation	8 (7)	Iron supplements (4); amitriptyline (3); phenytoin (2); citalopram, hyoscine butylbromide, morphine, tramadol (1)
Electrolyte disturbances	8 (7)	Calcitriol, furosemide (2); bumetanide, calcium supplements, citalopram, fludrocortisone, potassium supplements (1)
Hypoglycaemia	5 (4)	Biphasic isophane insulin (5)
C. difficile infection	4 (2)	Amoxicillin, lansoprazole (3); ceftriaxone, ciprofoxacin, clarithromycin, omeprazole (1)
Fall	4 (4)	Perindopril (2); amisulpiride, atenolol, bisoprolol, carbamazepine, co-amilofruse, furosemide, lamotrigine (1)
Fracture	4 (4)	Prednisolone (4); fluticasone (3)
Seizures	3 (1)	Citalopram (3)
Anaemia	2 (2)	Aspirin, clopidogrel, diclofenac, prednisolone (1)
Gastritis	2 (2)	Asprin, citalopram, prednisolone (1)
Increased INR	2 (2)	Warfarin (2); amiodarone (1)
Convulsive reaction	2 (1)	Trimethoprim (2)
Abdominal Pain	1 (1)	Aspirin, diclofenac (1)
Anaphylaxis	1 (1)	Flucloxacillin (1)
Bradycardia	1 (1)	Bisoprolol (1)
Candidal infection	1 (1)	Mycofenolate, prednisolone(1)
Diarrhoea	1 (1)	Amoxicillin, cefalexin, ciprofloxacin (1)
Elevated LFTs	1 (1)	Atorvastatin (1)
Erythema Nodosum	1 (1)	Azathioprine (1)
Flushing	1 (1)	Sulfasalazine (1)
Gastric ulcer	1 (1)	Aspirin, diclofenac (1)
Gout	1 (1)	Furosemide (1)
Hyperglycaemia	1 (1)	Olanzapine (1)
Hyperpyrexia	1 (1)	Trifluoperazine (1)
Neutropenic sepsis	1 (1)	Cancer chemotherapy agents (1)
Opioid dependence	1 (1)	Pethidine (1)
Rash	1 (1)	Flucloxacillin (1)

A total of 64 different drugs, and 148 prescriptions contributed to ADRs. The data were analysed to identify the whether the prescription for the causative drug had been commenced or changed during the index admission, or whether the prescription had been initiated since the index admission (see Table 5.2). Table 5.9 shows the results from this analysis.

Table 5.9: Relation of prescription of causative drug to index admission

Category	Description	*ADR Readmission*	
		Within 28 days: N° of causative drug prescriptions n=37, (%)	**Within one year: N° of causative drug prescriptions n=148, (%)**
A	Causative drug was initiated during the index admission	11 (29.7)	33 (22.3)
B	Causative drug had dose changed during the index admission	2 (5.4)	3 (2.0)
C	Causative drug continued unchanged during the index admission	19 (51.4)	68 (45.9)
D	Causative drug prescribed elsewhere/dose changed since the index admission	5 (13.5)	37 (25.0)
U	Unknown – Data regarding medicines use missing from patient case-notes for index admission.	0 (0)	7 (4.7)

5.6 Discussion

This study has shown that one fifth of those patients readmitted to hospital within one year of discharge from their index episode are readmitted due to an adverse drug reaction, and that approximately half of these ADRs are definitely or possibly avoidable. Different studies of readmissions use varying time-periods for readmission, and different definitions for drug-related problems including ADRs, but have commonly found that drug-related problems are a significant, and often avoidable, factor in readmission [101, 150, 214, 215].

The measurement of the rate of emergency readmission to hospital within 28 days of discharge from hospital is a NHS Performance Indicator, with previous data suggesting that approximately 5% of patients discharged from NHS hospitals are readmitted as an emergency within 28 days [213]. Data from our study showed that 13% of patients were readmitted to the study hospital within the 28-day time period. This study has shown that approximately 23% of these readmissions were related to ADRs.

This study has shown a 28-day readmission rate from the Royal Liverpool Hospital which appears to be considerably higher than the national estimate of 5% [213]. This may be due to several factors including the acknowledged variation between hospitals for readmissions figures [213]. The patients included in this study were sufficiently ill during their index admission to be admitted to a hospital ward. They were therefore likely to have greater morbidity than patients who would have remained on the admissions unit for a relatively short hospital stay. This increased patient morbidity suggests that readmissions may be more likely in this cohort, hence the high readmission incidence demonstrated here.

In common with an Australian study of ADR related hospitalisations [101] increasing age was a significant factor in readmissions overall, and particularly in readmissions due to ADRs. Interestingly, no differences were found in readmission or ADR rates with gender. Gender differences may have been expected in this study as previous work in the study hospital (see Chapters 2 and 3) [18, 185] and in the ADR literature [10, 97, 108] have suggested that the ADR rate is higher in females, although overall, evidence in the literature is not conclusive [110, 123].

Status as a medical patient, rather than a surgical patient, increased the risk of readmission. This may be a reflection of the increased number of medicines and co-morbidities associated with medical patients. Duration of length of stay during the index admission did not affect whether or not the patient experienced an ADR. In agreement with Dormann *et al* [150], the presence of an ADR during the index admission did not increase risk of readmission overall, or readmission due to ADRs.

Approximately 14% of readmitted patients died in hospital within one year of their index admission. Of the eight deaths specifically linked to ADRs, the majority were unavoidable. Potentially avoidable deaths were associated with renal impairment with diuretics and anti-hypertensive medicines. The need for strategies to improve diuretic management was identified in an earlier study of hospital inpatients (Chapter 3) as a key area for reducing ADR-related deaths and this is reiterated in this readmissions study. As the majority of ADRs resulted directly in hospital readmission, most ADRs were serious and therefore fitted CHM/MHRA Yellow Card reporting criteria.

In common with the Liverpool ADR admissions study [18], bleeding was the most common ADR, with antiplatelets (aspirin and clopidogrel) amongst the most common causative drugs. Diuretics and anti-hypertensives also resulted in many ADRs. These findings match those of Zhang *et al*, who found cardiovascular drugs to be those most frequently responsible for repeat ADR admissions [101].

Over 22% of drugs causing readmission were newly prescribed for the patient during the index admission, with the figure for 28-day readmissions rising to almost one third of prescriptions. This suggests that more needs to be done to ensure adequate follow-up of patients commenced on new medicines in hospital. For both readmission periods, the majority of drugs causing the readmission ADR had been initiated prior to the index admission, and remained unchanged throughout the admission. This data may suggest that the drug and dose were appropriate for the patient during the index admission, and problems developed following discharge, resulting in the subsequent ADR-related readmission. It may also suggest that the drug prescription was not sufficiently reviewed for appropriateness during the index admission. In order to decrease readmission

rates, prescription review in hospital needs to be improved to optimise patient care. In addition, liaison between primary and secondary care and the individual patient is essential to ensure that medicines are continually reviewed for suitability in the patient's home environment [151, 216].

Despite this being the largest study of ADR related readmissions in the UK, the limitations of this study are clear. The admission to hospital used as the 'index admission' in this study is unlikely to have been the first ever hospital admission for many of the patients in this study, and it therefore serves as an arbitrary baseline assessment. This study identified similar characteristics to the Liverpool admissions study in terms of types of ADR, drugs causing ADR, length of stay resulting from ADR related admission and ADR rate increasing with age [18]. In contrast, this readmissions study shows no increased incidence of ADR related readmission with female gender, and estimated a lower rate of avoidability than the Liverpool admissions study. As previously discussed, retrospective studies rely on the accuracy of the data recorded in the patient case-notes [31]. In the study hospital, casenotes are paper-based, often in several volumes, making case-note tracking difficult and resulting in frequently missing data. Extrapolations made to generate incidence rates for readmissions in this study were made with caution in the knowledge that the majority of data was available for analysis, and statistical advice was sought to confirm the study findings.

Readmission within one year was chosen as the primary outcome measure in this study to enable ADRs which were not immediately apparent following commencement of to be identified. The 28-day rates are given for comparison as these formed the basis of the NHS Performance Indicators. Emergency readmissions to the study hospital alone were assessed. It is possible that the patients may have been readmitted to another hospital, which would have resulted in a higher readmission and possibly a higher ADR rate. The absence of data on morbidity and mortality for patients not readmitted to the study hospital also limits outcome comparison.

The readmissions study was planned in the knowledge that ADRs which may occur days or weeks after hospital discharge, or those that only occur after chronic administration, may not be identified in a study of hospital inpatients. For example,

amiodarone toxicity with insidious onset. More recently, an increased risk of heart failure with rosiglitazone has been demonstrated [217]. Although an ADR such as this is unlikely to manifest itself during a short hospitalisation, it may become more apparent with studies of readmissions. In reality, a trend towards the emergence of such ADRs was not demonstrated in this study.

A valid criticism of studies, and political targets, which assess readmission as a health-related outcome, is that they fail to consider that avoiding readmission is not a direct objective of hospital care and that some readmissions are planned and some are unavoidable [218]. This study ensured that only emergency readmissions were assessed, and that each ADR was assessed for avoidability in order to maintain objectivity when assessing the impact of ADRs on hospital readmission.

Future work in this area would encompass a large study examining admissions related to ADRs and readmissions simultaneously to discover if ADRs causing first admission and those causing readmission were significantly different in the study population. In common with of many studies of ADRs, the elderly are the most vulnerable. Focusing on improving prescribing new drugs and monitoring longer term medicines may help to reduce the readmission rate due to ADRs. Increasing communication with the patient and the multi-disciplinary team at the primary-secondary care interface may help to identify potential ADRs and prevent readmissions to hospital.

5.7 Conclusion

One fifth of patients readmitted to hospital within one year of discharge from their index admission are readmitted due in part to an adverse drug reaction. There are consequently significant burdens on NHS resources due to avoidable ADRs. In common with general admissions studies, aspirin and diuretics are among the most frequent causative drugs, and the elderly are the most at risk. This study further highlights the need to effectively review patients' medicines both during the inpatient stay, and in primary care.

Chapter 6: An investigation of the reliability of causality assessment of adverse drug reactions (ADRs)

6.1 Introduction

Methods to aid identification and assess causality of ADRs have been in existence since the 1970s. They vary considerably with different levels of complexity and standardisation, and include

- unstructured assessments based solely on the evaluator's opinion;
- semi-structured assessments where categorisation follows broad guidelines;
- structured algorithms which lead to categorical causality assessment; and
- in-depth Bayesian approaches to the assessment of ADRs [53, 56].

There is a body of literature which compares these different methods of assessment [54, 56, 57, 64, 65, 74, 219, 220]. However, there is limited data surrounding inter-assessor reliability for the same algorithm, particularly with regard to different professions assessing ADRs independently. This is especially important now given that different healthcare professionals are able to act as independent prescribers.

Causality assessment of ADRs is inherently flawed as absolute certainty that a drug has caused an ADR is currently impossible to obtain, and causality assessment does not eliminate or quantify uncertainty; at best, it categorises it in a semi-quantitative way [221]. When assessing 733 ADRs for a large epidemiological study of ADRs (Chapter 3) using the Naranjo algorithm [63] two independent assessors showed statistically low inter-assessor agreement (κ^w 0.23, percentage agreement, 60%), which is comparable with Arimone *et al*'s assessment of comparability of expert judgement using global introspection [56]. However, this was much less than the original inter-assessor agreement found on algorithm validation [63]. The sample size in the original paper was small and used published cases as opposed to those generated in an epidemiological study which may confound the comparison.

Sample sizes for algorithm validation and comparison vary considerably, with some [57, 65, 74, 219] studies being relatively small given the literature that surrounds the statistics of inter and intra-assessor agreement [222, 223]. The types of ADRs assessed ranged from those collected spontaneously [54, 56, 57, 219, 220] to case reports reported in the medical literature [64, 65]. Undertaking causality assessment of ADRs is accepted practice in assessment of spontaneous ADR reports in some regulatory agencies, for example in France. It has also been utilised in ADR epidemiological studies, but this may potentially be without value if the inter-assessor reproducibility is consistently poor. Furthermore, whether individuals with different backgrounds have even more differences in causality assessments is unclear – evaluation of this may provide useful insights into problems of causality assessments, and with the possibility of developing better tools for the future.

6.2 Aim

Using three assessment methods, this study aims to compare inter-assessor agreement of causality assessments of ADRs generated via an epidemiological study between individuals and healthcare professions, and also to look at intra-assessor agreement between algorithms.

6.3 Objectives

1. To assess each ADR for causality according to 3 recognised methods
2. To compare the results for each assessor individually for each algorithm (inter-assessor reliability).
3. To compare results of each assessor across algorithms (intra-assessor reliability).
4. To make judgements regarding suitability of algorithms for assessment of ADRs in epidemiological studies and for assessing spontaneous reports.

6.4 Methods

Six assessors (two pharmacists, two physicians and two nurses), were given 200 adverse drug reaction (ADR) reports to assess for causality using 2 algorithmic scales [63, 70] and the global introspection criteria set out by WHO [60]. The ADRs were selected at random from 733 adverse drug reaction reports generated during an epidemiological study of ADRs (Chapter 3). These reports contained anonomised demographic data for the affected patient, details of suspected and concurrent medication, brief past medical history, and a description of the adverse reaction, treatment and outcome. The assessors recorded their assessment results on the 'ADR Assessment Scales' reporting form (Appendix 9). The professional training of the assessors varied. Both pharmacists were senior pharmacists in hospital and academic settings with experience of identifying and reporting ADRs in epidemiological studies and/or daily practice. Both physicians were specialist registrars in clinical pharmacology. Both nurses are experienced specialist practising clinicians although from outside of pharmacology-based settings. The sample size for each profession was too small to make generalisations about the suitability of members of each profession to assess ADRs for causality, but the relevant experience of the individual assessors may reflect on their differences of opinion. The assessors were not given training on the use of the algorithms, in order to reflect the concept that these scales are adopted for unrelated studies worldwide without standardised training.

The Naranjo ADR Probability Scale [63] is shown in Chapter One, Table 1.3. It utilises the answers to ten questions regarding the ADR and provides a subsequent assessment of causality.

The World Health Organisation (WHO) causality term assessment criteria [60] are shown in Chapter One, Table 1.2. This provides guidance to assessors as to how to judge an ADR but provides no guidance on to how the evidence should be weighted with regard to classifying the ADR. It provides two categories 'Conditional / Unclassified' and 'Unassessable/Unclassifiable' which allow for the assessor to agree that an ADR may have occurred but that there is not enough data to provide an assessment of causality. ADRs assessed according to these two categories were excluded from the final results of this study.

Table 6.1 shows the three-part Venulet algorithm [70]. It attempts to draw on the ADR itself, prior knowledge of the patient and the experience of the assessors. The causality is attributed using a numerical scoring system [70], and is dependent on the assessment of the category of the ADR (i.e. dose-related, Type I allergic etc). The numerical scores can then be translated into categorical classifications (Definite, probable, possible and unlikely/unrelated).

Table 6.1: The Venulet algorithm [70]

Category of ADR: Circle at least one

A – DOSE RELATED

B – DOSE UNRELATED

C – TYPE I ALLERGIC

D - AT SITE OF APPLICATION

E – INTERACTION

F – DRUG DEPENDENCE

G – IRREVERSIBLE

H – WITHDRAWAL SYMPTOMS

I – FOETAL MALFORMATION

Z – UNCLASSIFIED

6.4.1 Statistical analysis

Inter- and intra- assessor reliability between the assessors and algorithms was compared using weighted kappa (κ^w), and the observed proportion of overall agreement between assessors (P_o (w)). Although the use of weighted kappa has - recently been questioned in describing inter-assessor reliability [224] a literature review failed to identify a suitable alternative. Kappa values will be interpreted according to the guidance from Landis and Koch [225], shown in Table 6.2.

Table 6.2: Interpretation of kappa statistic [225]

The results between assessors and algorithms were compared with the emphasis on inter-assessor reliability and the implications of this for the quality of causality assessment, the feasibility of using the algorithms and recognition of ADRs between individuals and professions.

6.5 Results

Each assessor received 200 reports, although there were some missing or illegible assessments, resulting in a sample size of <200 for most assessor comparisons. Tables 6.3, 6.4 and 6.5 show the frequency of ADR assessment in each causality category for the Naranjo [63], WHO [60] and Venulet [70] methods respectively.

Table 6.3: Distribution of causality categorisation using the Naranjo algorithm (n=200 for all assessors)

	Definite	*Probable*	*Possible*	*Doubtful*	*Missing data*
Pharmacist 1	8 (4.0%)	98 (49.0%)	87 (43.5%)	3 (1.5%)	4 (2.0%)
Pharmacist 2	21 (10.5%)	101 (50.5%)	76 (38.0%)	2 (1.0%)	0 (0.0%)
Physician 1	21 (10.5%)	98 (49.0%)	76 (38.0%)	2 (1.0%)	3 (1.5%)
Physician 2	31 (15.5%)	107 (53.5%)	54 (27.0%)	0 (0.0%)	8 (4.0%)
Nurse 1	1 (0.5%)	48 (24.0%)	141 (70.5%)	3 (1.5%)	7 (3.5%)
Nurse 2	5 (2.5%)	105 (52.5%)	83 (41.5%)	6 (3.0%)	1 (0.5%)

For the Naranjo algorithm (Table 6.3), the majority of assessments were either 'probable' or 'possible' for all assessors. The pharmacists and physicians appeared more likely to attribute a 'definite' causality assessment to the ADR than the nurses.

Table 6.4: Distribution of causality categorisation using the WHO criteria (n=200 for all assessors)

	Certain	*Probable*	*Possible*	*Unlikely*	*Conditional/ Unassess-able*	*Missing data*
Pharmacist 1	12 (6.0%)	81 (40.5%)	102 (51.0%)	2 (1.0%)	0 (0.0%)	3 (1.5%)
Pharmacist 2	63 (31.5%)	43 (21.5%)	62 (31.0%)	7 (3.5%)	25 (12.5%)	0 (0.0%)
Physician 1	37 (18.5%)	95 (47.5%)	57 (28.5%)	7 (3.5%)	2 (1.0%)	2 (1.0%)
Physician 2	44 (22.0%)	127 (63.5%)	20 (10.0%)	1 (0.5%)	0 (0.0%)	8 (4.0%)
Nurse 1	2 (1.0%)	37 (18.5%)	141 (70.5%)	11 (5.5%)	2 (1.0%)	7 (3.5%)
Nurse 2	9 (4.5%)	68 (34.0%)	78 (39.0%)	25 (12.5%)	17 (8.5%)	3 (1.5%)

Using the WHO 'global introspection' criteria, the pharmacist and physician assessors attributed 'certain' causality assessments more than the nurses; however most assessments for all assessors were again 'probable' or 'possible'. Pharmacist 2 and Nurse 2 were unable to make a full assessment for 25 and 17 ADRs respectively, citing that further information was required.

Table 6.5: Distribution of causality categorisation using the Venulet algorithm (n=200 for all assessors)

	Definite	*Probable*	*Possible*	*Unlikely/ Unrelated*	*Missing data*
Pharmacist 1	12 (6.0%)	63 (31.5%)	95 (47.5%)	27 (13.5%)	3 (1.5%)
Pharmacist 2	20 (10.0%)	45 (22.5%)	114 (57.0%)	21 (10.5%)	0 (0.0%)
Physician 1	19 (9.5%)	58 (29.5%)	92 (46.0%)	29 (14.5%)	2 (1.0%)
Physician 2	15 (7.5%)	58 (29.0%)	112 (56.0%)	9 (4.5%)	6 (3.0%)
Nurse 1	1 (0.5%)	23 (11.5%)	88 (44.0%)	81 (40.5%)	7 (3.5%)
Nurse 2	1 (0.5%)	9 (4.5%)	69 (34.5%)	120 (60.0%)	1 (0.5%)

When assessments were made using the Venulet algorithm, both nurses attributed many more 'unlikely' or 'unrelated' scores than either the physicians or pharmacists. For pharmacists and physicians, the majority of results were again probable or possible, but there was a higher frequency of 'unlikely' ratings when using the Venulet algorithm compared with equivalent assessment levels from the other methods of causality determination.

The results of inter-assessor agreement between algorithms are shown in Table 6.6. The sample size is also shown. For the WHO criteria, assessments scored as 'unassessable' or 'conditional' were excluded.

Table 6.6: Inter-assessor agreement between algorithms

	Algorithm								
	Naranjo			WHO			Venulet		
Assessors*	n	P_o (w)	κ^w	n	Po(w)	κ^w	n	P_o (w)	κ^w
P1 v P2	196	0.837	0.253	172	0.740	0.150	196	0.789	0.229
P1 v D1	193	0.827	0.212	193	0.788	0.175	195	0.722	0.035
P1 v D2	189	0.819	0.208	190	0.786	0.200	192	0.802	0.231
P1 v N1	189	0.833	0.162	188	0.823	0.134	190	0.739	0.143
P1 v N2	195	0.840	0.203	178	0.785	0.142	196	0.668	0.038
P2 v D1	197	0.838	0.288	172	0.756	0.223	198	0.751	0.128
P2 v D2	192	0.840	0.306	167	0.781	0.250	194	0.825	0.315
P2 v N1	193	0.810	0.178	168	0.655	0.005	193	0.731	0.124
P2 v N2	199	0.806	0.107	159	0.690	0.095	199	0.663	0.019
D1 v D2	189	0.817	0.219	188	0.796	0.177	192	0.752	0.079
D1 v N1	190	0.798	0.134	187	0.724	0.068	191	0.686	0.007
D1 v N2	196	0.793	0.050	177	0.688	-0.024	197	0.626	-0.043
D2 v N1	185	0.771	0.131	183	0.671	0.032	187	0.726	0.108
D2 v N2	191	0.801	0.140	172	0.702	0.077	193	0.660	0.045
N1 v N2	192	0.816	0.091	172	0.762	-0.100	192	0.780	0.040
Mean values	192	0.816	0.179	178	0.743	0.107	194	0.674	0.100

Kappa Agreement [20]: < 0, Less than chance agreement; 0.01 - 0.2 Slight agreement; 0.21 – 0.4 Fair agreement; 0.41 – 0.6 Moderate agreement; 0.61 – 0.8 Substantial agreement; 0.81 – 0.99 Almost perfect agreement

*P = Pharmacist, D = Physician, N = Nurse

Interpretation of the results from this study show that inter-assessor agreement was no greater than 'fair' for any comparison of two assessors according to the commonly accepted interpretation of the kappa scale described in table 6.2 [225]. For three comparisons, inter-assessor agreement was less than that expected by chance. Conversely, the proportion of observed agreement (P_o (w)) was good (>0.6) for all assessments.

Table 6.7: Intra-assessor agreement between algorithms

	Algorithms for comparison								
Assessor	Naranjo v WHO			Naranjo v Venulet			WHO v Venulet		
	n	P_o (w)	κ^w	n	P_o (w)	κ^w	n	P_o (w)	κ^w
Pharmacist 1	196	0.918	0.608	196	0.866	0.467	197	0.856	0.427
Pharmacist 2	175	0.795	0.323	200	0.835	0.408	175	0.743	0.274
Physician 1	195	0.898	0.598	197	0.777	0.222	196	0.737	0.176
Physician 2	192	0.873	0.416	192	0.813	0.309	192	0.735	0.131
Nurse 1	191	0.913	0.403	193	0.798	0.189	191	0.805	0.183
Nurse 2	180	0.856	0.417	199	0.643	0.042	180	0.689	0.109
Mean values	188	0.876	0.461	196	0.789	0.273	189	0.761	0.235

Kappa Agreement [20]: < 0, Less than chance agreement; 0.01 - 0.2 Slight agreement; 0.21 – 0.4 Fair agreement; 0.41 – 0.6 Moderate agreement; 0.61 – 0.8 Substantial agreement; 0.81 – 0.99 Almost perfect agreement

Table 6.7 shows that intra-assessor agreement between scales was highest for the Naranjo algorithm versus the WHO algorithm, with 'substantial' agreement between assessments made by Pharmacist 1. The lowest level of agreement within assessors came from Nurse 2 when comparing the Naranjo and Venulet algorithms, where agreement was 'slight'.

6.6 Discussion

To decide whether a drug has caused an adverse reaction is a difficult process which requires taking into account many different variables. In the large majority of cases, due to the lack of available data or specific tests, absolute certainty of causality is not possible. Estimation of the likelihood that an adverse reaction was caused by a drug based on the study of the available facts surrounding each case is therefore the only alternative. However, the literature shows that such causality assessments are problematic. A recent systematic review of the methods used for causality assessments found 34 different methods, from global introspection to the use of Bayesian statistics [52]. It concluded that no method has proved consistent and reproducible in its assessment of ADR causality, and none is universally accepted [52]. The findings of this study are largely consistent with this conclusion.

Research by the investigators has applied the Naranjo algorithm [63] to assess causality in four studies (Chapter 2, 3, 5 and 7), reporting low levels of inter-assessor agreement (κ^w) where assessed. Anecdotal reports from the investigators have also indicated frustration with the assessment instrument, with subjective judgement between assessors in key questions such as Question 5: "Are there alternative causes (other than the drug) that could on their own have caused the reaction?" [63], becoming the subject of contention, particularly where patients have multiple co-morbidities. The need to explore the use of other methods of causality assessment, and their interpretation was therefore identified. Sample sizes were often small in algorithm validation, using case reports from the literature, which may question the algorithm validity when applied to reports from a prospective study. The authors of the Naranjo algorithm questioned whether the high reproducibility of their results using the algorithm were due to the use of published case reports, where only three causality categories were used 'possible', 'probable' and 'definite', generating spurious reproducibility [63]. Similarly, whilst published case-reports were not assessed in this study, all 200 reports distributed to the assessors were identified as ADRs in a prospective study (Chapter 3) and subsequently had previously been assessed by two investigators according to the Naranjo algorithm as either 'possible', 'probable' or 'definite' in order to enable their inclusion in the prospective study. This minimised the likelihood of 'doubtful' causality assessments by subsequent assessors in this

study, particularly when using the Naranjo algorithm, and may have produced bias in these results which show the highest overall levels of agreement with the Naranjo algorithm.

The key elements to any causality assessment involve questions regarding the temporal relationship between drug administration and adverse event, the effects of de-challenge, possible re-challenge, and alternative causes for the clinical condition which arises. In order to score, and suggest a 'definite' or 'certain' ADR, a re-challenge is often required, which is not ethically possible in many cases. There are usually few 'doubtful' ADRs as it is difficult to disprove an association between a drug and a recognised adverse event. Consequently, most ADRs are logically graded as 'probable' or 'possible' and this is reflected in the results from this study. Exceptionally, there is a high frequency of 'unlikely' and 'unrelated' among the results of Nurse 1 and Nurse 2 for the Venulet algorithm (Table 6.5). This appears to be due to Part III of the Venulet algorithm involving the experience of the assessor. Both nurses may have placed greater emphasis on alternative causes of the reaction, above that of the potential drug reaction, giving lower overall scores and negative outcomes using the Venulet algorithm. Across all assessors however, an 'unlikely' rating were much more frequent with the Venulet algorithm than with WHO or Naranjo. With short individual reports, there is little scope for assessment of the patient's past adverse reaction history, leaving Part II of the Venulet Scale largely redundant. The weighting therefore falls heavily on the concepts of re-challenge, de-challenge and alternative causes for the ADR in Parts I and III. Due to the more detailed questioning of the reaction in the Venulet algorithm, multiple confounding factors are assessed and may contribute to a lower score. This is in contrast to the Naranjo algorithm, where a single question regarding alternate causes forms only a small, though essential, part of the weighting scheme, and with the WHO criteria, where the assessor decides upon the weighting.

Agreement between assessors using the weighted kappa statistic (κ^w) was 'fair' at best, although the proportion of agreement between observers P_o (w) was relatively high for all assessments, probably due to the intrinsically high rate of 'probable and 'possible' ratings. This paradox of low kappa, but high P_o has been discussed in several statistical papers [226-228] and is related to the 'skewness' of

the data. A high level of weighted kappa agreement is unlikely with the assessments of reported ADRs as the results will typically be skewed away from 'doubtful/unlikely' ADRs, as events unlikely to be ADRs will rarely be reported in a prospective study, or to regulatory authorities, although this did not prove to be the case for all assessors using the Venulet algorithm. The highest levels of agreement between the assessors was with the Naranjo scale, perhaps due to its relatively simple application, and the difficulty of achieving a 'definite' or 'doubtful' result. Poorer levels of agreement were found with the WHO criteria and the Venulet algorithm. This may be due to the need to apply personal experience and greater subjectivity to both scales. The varying experience of the assessors may have led them to apply the criteria or answer the algorithm questions differently, resulting in more profound differences in results.

Agreement between methods for the same assessor (intra-assessor agreement) was highest between the Naranjo and WHO methods, which showed at least moderate agreement for the majority of assessors reflecting some comparability between methods. Agreement was again lower for comparisons involving the Venulet algorithm, perhaps, as before, reflecting its complexity and the differences in the experience of the assessors. The methodology for this study required the assessors to record their results on a single report form (Appendix 9). On this form both the final categorical results for the WHO and Naranjo methods are visible to the assessor, but the results for the Venulet algorithm are not. This may have influenced the assessors, particularly in view of the increased correlation between the Naranjo and WHO methods compared to either of those methods with Venulet. In future studies, extended time periods between application of the three methods may be necessary to minimise this potential bias.

This study has shown a low level of comparability between algorithms in common with other studies which compare ADR causality assessment procedures, [57, 74, 220, 229]. This is in contrast to the original validation of the Naranjo algorithm which showed high levels of inter-assessor reliability, although all assessors were attending physicians in the same hospital and the sample size was small (63 cases) using published case reports which must contain evidence of cause and effect to justify publication [63, 229]. Low inter-assessor reliability was found when applying the Naranjo algorithm to adverse drug reactions in the intensive-care unit,

perhaps again reflecting the difficulty in applying the algorithm to everyday situations [67].

Louik *et al* concluded that the usefulness of algorithms in drug surveillance programs was limited due to the poor reliability of the results [229]. Our results are in accordance with these conclusions which were made over two decades ago, as none of the methods assessed in this study showed high levels of inter-assessor reliability. The value in such assessments lies in their ability to lead the assessor through a logical process for assessing the ADR, serving as an 'aide-memoire' for a systemic analysis for the case [53].

Attempts have been made to improve on causality assessment procedures involving the incorporation of Bayesian statistics [76, 77]. However, the complexity of the instrument means that it is unsuitable for routine use in clinical practice and epidemiological studies such as those assessed in this study. Comparison of Naranjo and BARDI instruments showed significant correlation between the two instruments [54] which suggests that Naranjo is the 'best' method for assessing adverse drug reactions in routine practice.

6.7 Conclusions

True validation of causality assessments is currently impossible [221]. This study shows that comparability between assessors is 'fair' or less for the ADR causality assessment methods examined in this study. The most consistent results were produced by the application of the Naranjo algorithm, and the least consistent with the Venulet algorithm. The experiences of the assessor appear to have implications on how the assessment methods are applied. Low levels of agreement shown in this study question the value of causality assessments overall, and also highlight the need to be cautious when interpreting studies of ADRs. Despite many studies now showing that causality assessment tools are imperfect, it is surprising that better more reliable tools have not been developed. Perhaps, this is never going to be possible, or alternatively we need to be developing different assessment tools for different situations.

Chapter 7: The use of opioids and laxatives, and incidence of constipation, in patients requiring neck of femur (NOF) surgery

7.1 Introduction

Constipation is one of the most frequent adverse drug reactions (ADRs) occurring in hospital inpatients as shown in Chapters 2 and 3 of this thesis [181]. Whilst the effects on the patient are often relatively minor, prolonged bowel dysfunction can cause severe pain and/or have other serious consequences including faecal impaction, exacerbation of post-operative ileus, intestinal obstruction and urinary retention [230]. Constipation may theoretically be preventable with appropriate laxative prescribing which is relatively inexpensive in comparison to other therapeutic areas. Recommendations for laxative use with opioids in post-operative care however are usually taken from oncology and palliative care [184, 231]; there does not seem to be an evidence base to demonstrate that laxatives should be routinely prescribed with opioids post-operatively in patients undergoing surgery. Reflecting this, a point prevalence audit of opioid prescribing in 40 orthopaedic inpatients at the Royal Liverpool University Hospital showed that regular laxatives were not initiated as prophylaxis against constipation at the same time as opioid therapy was initiated, on any occasion [232]. In order to reduce the heterogeneity caused by different forms of surgery, patients admitted as emergencies for neck-of-femur (NOF) surgery were selected. A research paper based on the results from this study was accepted for publication by the Journal of Clinical Pharmacy and Therapeutics in June 2008 (Appendix 10) [233].

7.2 Aim

The aim of the study was to determine the current nature of opioid and laxative prescribing in patients who require emergency surgery, and the corresponding incidence and impact of constipation in these patients.

7.3 Objectives

1. To assess how many patients undergoing neck of femur surgery were given opioid analgesia
2. To assess how many patients were given laxative therapy and whether laxative therapy was used as prophylaxis against constipation, or as treatment for constipation.
3. To assess how many patients became constipated during their stay
4. To compare characteristics of patients who experienced constipation in comparison to those who did not, in terms of. age, sex, opioid dose received, laxative use, previous bowel disorders, cognitive impairment, nutritional status and mobility.
5. To assess the effect of constipation on length of stay in hospital
6. To quantify the cost of laxative intervention
7. To assess the patient for side-effects of laxative therapy
8. To draw conclusions regarding the appropriate use of opioids and laxatives in the study population

7.4 Methods

Patients admitted to the orthopaedic wards for emergency surgery for fractured NOF in the Royal Liverpool Hospital over an eight week period in Spring 2007 were included in the study. A research pharmacist (ED) reviewed prescription charts daily for the duration of the patient stay on the acute orthopaedic wards. The cause of admission, all medicines taken during admission, time to mobilisation, date of surgery, and length of stay were recorded on the Opioid Intervention Form (Appendix 11). Constipation was defined as "failure of the bowel to open for three consecutive days" [190]. Constipation was then determined by asking nursing staff and patients, and by examining patient case-notes for information regarding frequency of bowel movements.

Adverse effects of laxative prescribing and the cost of laxative therapy were recorded. Time to mobilisation was documented as the number of days required to begin post-operative mobilisation exercises out of bed or chair. Nutritional status was documented as 'poor' if clerking indicated poor nutritional status on hospital

admission, if nutritional supplements were prescribed during admission or if a need for better nutrition was documented in the case notes during the patient's admission. Cognitive impairment was determined by an Abbreviated Mental Test (AMT) score of ≤ 8/10, [234] or in the absence of an AMT, if dementia or chronic confusion were documented in the case-notes. A patient was documented as having previous 'bowel problems' if they were prescribed laxatives prior to admission.

Trust approval for the study was obtained from the Trust Audit Department; Ethics Committee approval was not required. Statistical analysis was performed using StatsDirect version 2.6.2 and P values of <0.05 were interpreted as statistically significant.

7.5 Results

During an eight-week period, 46 patients were admitted to the orthopaedic wards for emergency treatment of a NOF fracture. The median age of the patients was 81 years (IQR 75-87 years), with 29 (63%) being female. The median day of surgery for patients was day 3 (IQR 2-3 days) after admission, while patients stayed for a median of 15 days (IQR 10-27 days). The most common type of surgery was a dynamic hip screw (DHS) operation for 12 (26%) of patients, but a number of other surgical interventions to repair fractured NOF were also undertaken.

Overall, 33 (72%) patients became constipated, and this occurred post-operatively in 32 (70%) patients, 15 (47%) experienced clinical symptoms such as bloating, abdominal pain and discomfort. In two patients, this discomfort warranted an abdominal x-ray for investigation of pain. One patient was constipated pre-operatively, although this patient had an extended time to surgery (9 days) due to investigations for underlying disease. Of the 13 (28%) patients who did not meet our definition for constipation, two patients were described as having 'stubborn' bowels and one was diagnosed with overflow diarrhoea, secondary to constipation.

The demographic details and characteristics of the patients with and without constipation during their admission are described in Table 7.1. There were statistically significant differences only for age and nutritional status between the two groups. The length of stay was not directly extended due to constipation in any of the patients in this study. The range of length of stay overall and post-operatively was increased in constipated patients when compared with non-constipated patients, but this difference was not statistically significant. There were no significant differences in time to mobilisation or in numbers of patients who did not mobilise at all during the admission. Most patients with constipation (30, 91%), and all of those without constipation were taking other medicines, in addition to opioids, which include constipation in their side-effect profile.

Table 7. 1: Demographics and characteristics of constipated and non-constipated patients

Variable	All patients (n=46)	Patients not constipated (n=13)	Constipated Patients (n=33)	P values
Age (median, range))	81 (52-97)	76 years (52-86)	86 years (53-97)	P=0.007
Male Gender (n, %)	17, 37%	4, 31%	13, 39%	P=0.42
LoS* post-op (median, range))	13 days (3-70)	12 days (4-28)	13 days (3-70)	P=0.25
LoS* overall (median, range))	15 days (5-72)	13 days (17-30)	16 days (5-72)	P=0.26
Did not mobilise during admission	12	2	10	P=0.63
Previous bowel problems	11	3	8	P=0.63
Poor nutrition	18	2	16	P=0.04
Cognitive impairment	17	2	15	P=0.06

*LoS – length of stay

The majority of patients (43, 93%) received opioids pre- and post-operatively, with 2 (4%) and 1 (2%) receiving doses pre- and post operatively only, respectively. Figure 7.1 shows the number of patients remaining in the hospital following admission up to 27 days post-operatively, and the mean daily dose of opioids (expressed as equivalents of parenteral morphine [235, 236]).

Figure 7.1: Opioid dose and length of stay

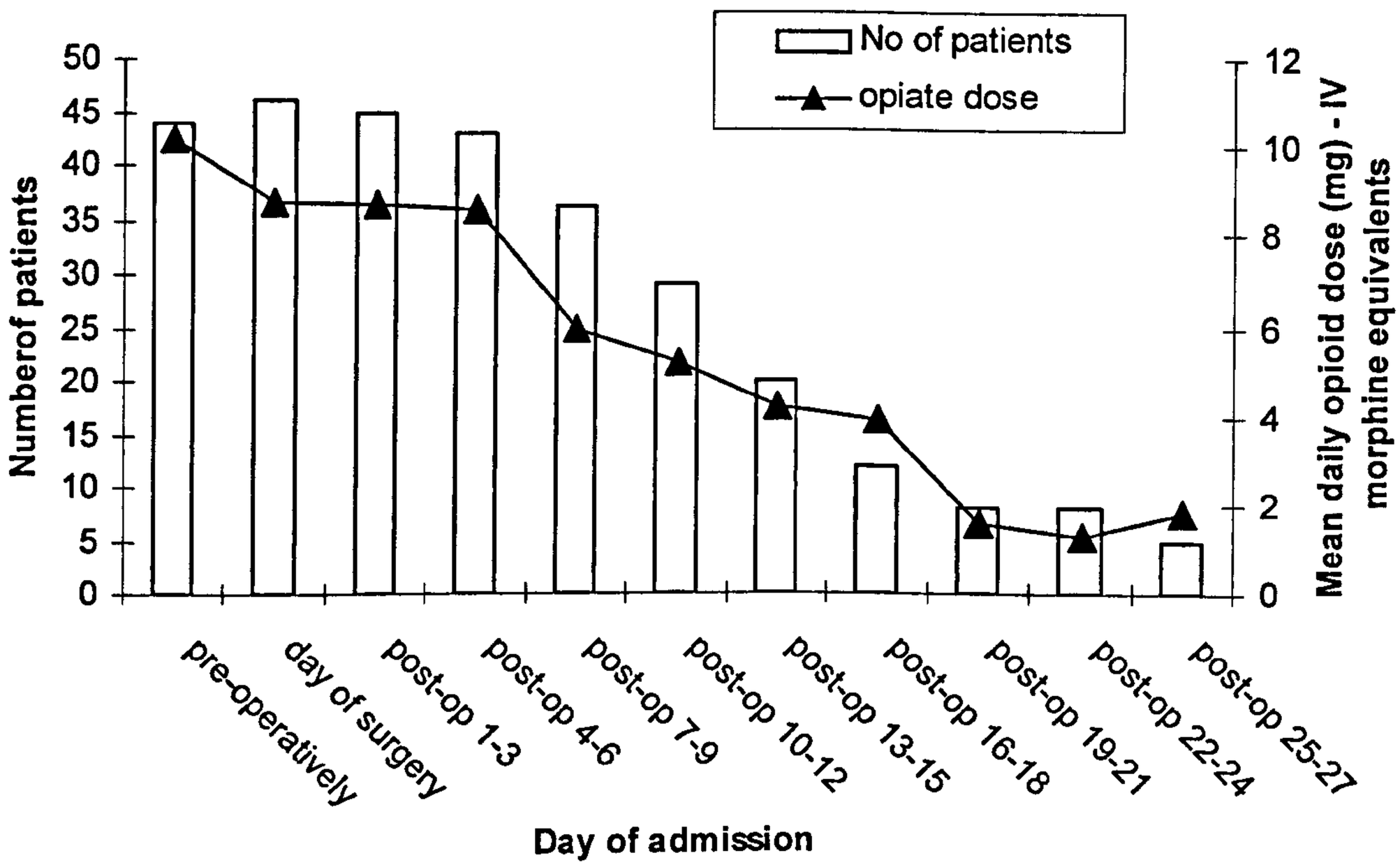
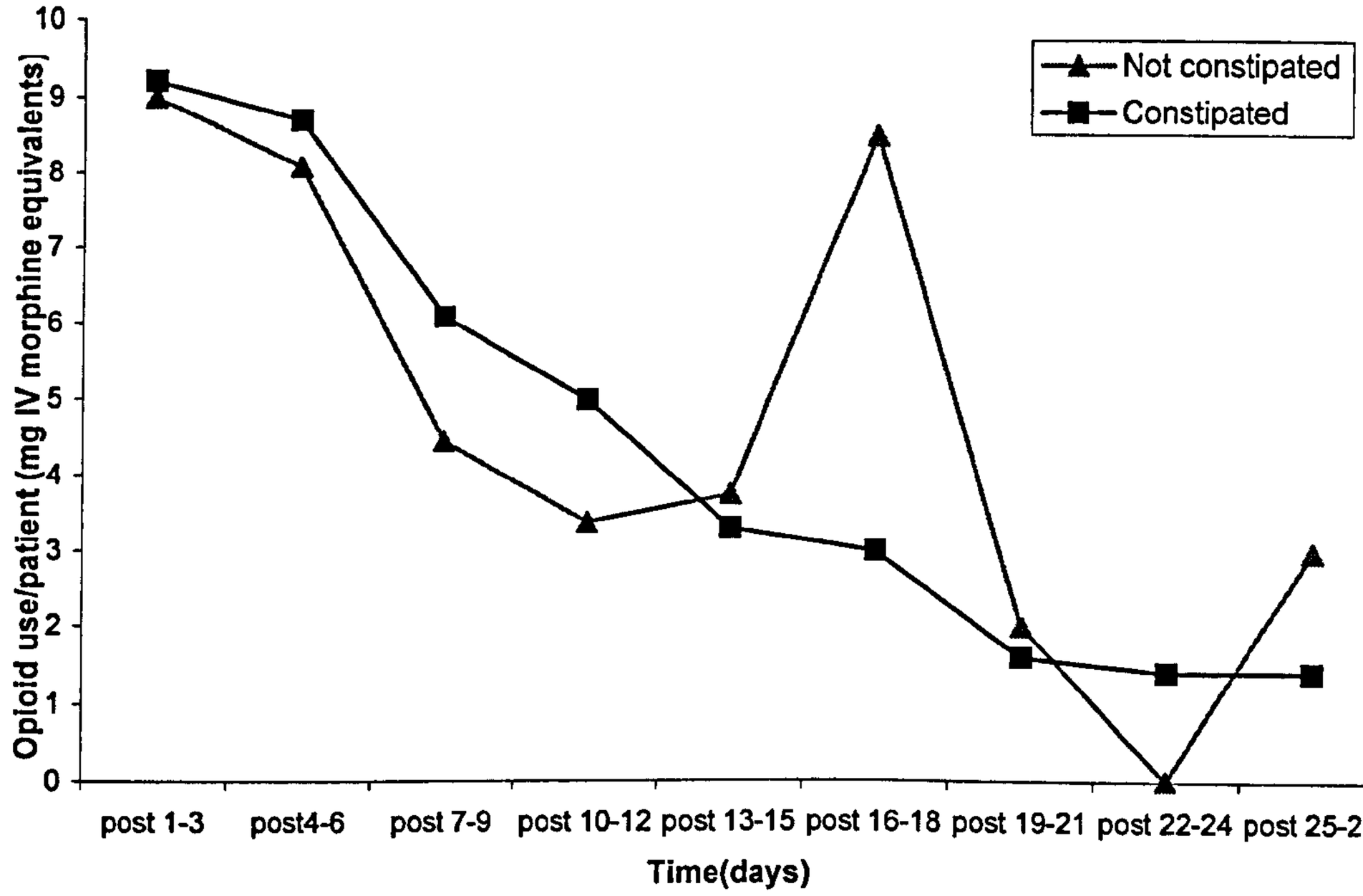


Figure 7.2 shows the mean daily post-operative opioid use (in equivalents of IV morphine) in patients who were constipated compared with those who were not. As length of stay increased, the number of patients remaining in hospital decreased and the results therefore became more sensitive to the differences in dosing between individuals. There were no significant differences in opioid dose between constipated and non-constipated patients, although initially post-operatively opioid doses in constipated patients appeared higher.

Figure 7. 2: Opioid use post-operatively in constipated patients and non-constipated patients



The choice of opioids prescribed is described in Table 7.2. Morphine was the most commonly prescribed analgesic on admission, and immediately post-operatively. Patients were prescribed 1-4 different opioids during their stay. Morphine, followed by regular analgesic preparations such as co-codamol and or tramadol were the most common combinations, although there were no clear patterns in prescribing.

Table 7.2: Opioid choice and constipation incidence in patients following admission for emergency NOF surgery

Opioid choice	Constipated (n=33 (%))	Not constipated (n=13 (%))
Morphine	28 (85%)	10 (77%)
Co-codamol/ Co-dydramol	21 (64%)	8 (62%)
Tramadol	14 (42%)	7 (54%)
Fentanyl	1 (3%)	0 (0%)
Codeine	9 (27%)	3 (23%)
Dihydrocodeine	1 (3%)	0 (0%)
Diamorphine	1 (3%)	0 (0%)

Laxatives were prescribed in 33 (72%) patients requiring emergency NOF surgery. Of these, 20 (44%) patients received laxatives to prevent constipation but despite this, 12 (60%) subsequently developed constipation. Of the 26 patients not prescribed prophylactic laxatives, 21 (80%) developed constipation. This failed to achieve statistical significance (Z test, P=0.1, 95% CI for the difference -0.5 to 0.06).

Senna and lactulose in combination were the most frequent laxatives used for prophylaxis in both patient groups (14/20 patients (70%), 8 (57%) of whom developed constipation). Lactulose alone was used as prophylaxis in 5 patients (4 (80%) of whom became constipated) with lactulose and Movicol used together in one patient who did not develop constipation. Multiple combinations of laxatives were used to treat constipation. For those already on prophylactic laxatives, treatment involved the addition of macrogols (4 patients), an enema (4 patients), or senna (1 patient), with a maximum of two additional laxative agents. If no prophylaxis was used, up to 5 laxative agents were used in a single patient.

A summary of interventions in response to constipation is shown in Table 7.3. The majority of interventions involved the use of laxatives, while two patients required abdominal x-ray. Using cost estimates of laxatives from the British National Formulary [183], the cost of laxative prescribing in this study was £1.67 per patient/per admission. This cost estimate relies solely on the cost of pharmacological intervention as support from the multi-disciplinary team members such as physiotherapists and nutritionists was not documented in this study. The cost per abdominal x-ray within the trust is given as £18 internally (excluding overhead costs) and £29 to external trusts [237].

Table 7.3: Pharmacological and non-pharmacological interventions directly related to constipation

Pharmacological Intervention	**N° of patients (n=33, %)**
Initiate laxatives	12 (36%)
None	7 (21%)
Continue prophylactic laxatives	6 (18%)
Additional laxatives added to prophylaxis	6 (18%)
Reduce opioid dose	1 (3%)
Stop opioids and add laxatives	1 (3%)
Direct non-pharmacological Intervention	
Abdominal X-ray	2 (6%)

Laxative therapy has recognised side-effects, the most frequent of which is diarrhoea. Diarrhoea occurred in 9 (27%) patients taking laxatives. Using a validated causality assessment scale [63], four instances of diarrhoea were judged as being 'possibly' due to laxatives, while five were 'probably' due to laxative therapy.

7.6 Discussion

This study has examined the relationship between opioids, laxatives and constipation in patients following emergency NOF surgery. No previous studies examining the incidence of constipation in patients following treatment for fractured neck of femur were identified in the literature. Although our sample size is small and therefore the data need to be interpreted with caution, the study raises some interesting issues which need to be explored in future studies.

The majority (72%) of patients in this study experienced constipation during their stay. Studies of the elderly population in the community suggest that constipation prevalence is around 20% [238-240]. Studies of constipation in cancer patients and patients with chronic pain report an incidence of between 52% and 87% [238, 241]. The prevalence of constipation in patients requiring opioids acutely in this study was therefore greater than the incidence in the community, which may be

expected given the reduced mobility due to fracture, and opioid therapy. It is interesting that the incidence of constipation in the study population receiving opioids acutely appears to be similar to that in patients requiring long-term opioids. This suggests that other factors, in addition to opioid therapy may also be influential in the aetiology of constipation in the patient population studied.

There is a need to be aware of the limitations of current definitions of constipation. We used a simple definition developed to assess acutely unwell patients [190] instead of the more complicated definitions of constipation that have been used in some other studies, principally for chronic constipation, where the size, stool form, comfort of stool passage, and frequency of bowel motions are all assessed [242-244]. This made the assessment of constipation less complex, although modification of the definition may be necessary to ensure that all patients who experience pain and discomfort from constipation are included in the incidence figures [245]. Two patients who appeared constipated clinically could not be included in the incidence data as they did not fit the criteria determined by the definition used. Conversely, about half of the patients who were recorded as being constipated in this study did not experience any clinical symptoms.

Constipation is a multi-factorial problem resulting from a number of factors including drug therapy, nutritional intake and mobility, as well as anxiety, depression and decreasing cognitive function [245-248]. More patients with constipation were documented as having cognitive impairment and poor mobility, although the differences were not significant. Significantly more patients with constipation were documented as having nutritional problems in this study, although the methods to assess nutritional status were subjective and further studies would benefit from the use of a validated nutrition assessment score such as the Mini Nutritional Assessment (MNA) [249] or the Malnutrition Universal Screening Tool (MUST) [250].

Increasing dietary fibre and encouraging oral fluids, as well as encouraging exercise, are established interventions to both prevent and treat constipation [183, 251]. Increasing age was a significant factor in our patients with constipation. There is conflicting evidence around age as a risk factor for constipation [252-254]. Ageing does not have major effects on the large bowel, including colonic or

rectosigmoid motility and water transport across the bowel wall; only minor changes in intestinal transit time have been reported and therefore the ageing process itself should have little impact on constipation incidence [253-256]. However, factors such as drug use, concomitant bowel disease, co-morbidities, decreased mobility, poor nutrition and inadequate hydration are factors which cause constipation are more prevalent in the elderly [255], resulting in the increased incidence of constipation with increasing age. The length of stay in our patients with constipation was longer, although this increase was not statistically significant. This may not be causal but may reflect the fact that these patients had a more complex illness and therefore time-course in hospital. In our study of adverse drug reactions in hospital inpatients, 100 instances of constipation were identified, the majority of which were associated with opioid use, with 17 (17%) directly increasing length of stay (Chapter 3). When considering patients admitted as an emergency with fractured NOF, other discharge issues involving social circumstances and rehabilitation placement can act as important confounders in the increased length of stay.

Opioids can cause constipation, mainly by their action at mu opioid receptors in the gastro-intestinal (GI) tract. This reduces GI propulsion, slows the movement of intestinal contents, decreases pancreatic and biliary secretions and increases fluid and electrolyte absorption [257]. Given the pharmacological action of opioids, it is assumed that greater opioid use would result in greater levels of constipation, although this effect may be diminished when taking into account other possible causes of constipation. Opioids are given to patients with co-morbidities which are often also associated with constipation, and thus it can be extremely difficult to assess causality in individual patients. This is consistent with the fact that the choices of opioids were broadly similar in both the constipated and non-constipated groups. There is little convincing clinical data in the literature to indicate that different opioid agents, or different routes of administration, result in less GI adverse effects at equianalgesic doses [258].

Reviews of laxative use in the elderly and patients with cancer and chronic pain have concluded that it is impossible to determine which laxative treatments are the most clinically effective, or cost-effective, because of the lack of evidence [246, 259, 260]. There are also no national guidelines for laxative use to prevent

constipation in surgical patients. The Scottish Intercollegiate Guideline Network (SIGN) has stated that the best prophylactic treatment for preventing opioid-induced constipation in patients with cancer pain is a combination of a stimulant and softening agent [261-263]. In this study, senna, a stimulant laxative, and lactulose, an osmotic laxative, were used in combination as the most commonly prescribed combination for prophylaxis, followed by lactulose alone. However, there was no difference in the incidence of constipation in those patients receiving prophylaxis, although the numbers were small. Treatment for constipation when no prophylactic therapy had been prescribed was haphazard, with the addition of up to five agents to relieve constipation. Taken together, this highlights the need for more studies in this area to improve the evidence base. There also needs to be more pharmacologically diverse agents available for the treatment of constipation. This is evidenced by the fact that, as dehydration is a cause of constipation and opioids can result in more efficient absorption of water and electrolytes [247-251], an osmotic laxative may not be appropriate pharmacologically to treat opioid-induced constipation, although the evidence in the literature is inconclusive [246, 259]. Another issue to consider with laxative use is the possibility of adverse effects. One third of patients in this study experienced diarrhoea linked to their laxative therapy, which is a particularly unwelcome side-effect in immobile patients.

7.7 Conclusion

In conclusion, constipation is an uncomfortable and often embarrassing complaint for patients and reducing its incidence through simple means would improve patient quality of life, and may decrease the patient length of stay. Further work with a larger patient group is necessary to determine if laxatives truly prevent constipation in patients suffering NOF fracture, and those undergoing other types of surgery, and therefore if structured interventions are necessary to improve their prescribing. There is an absence of useful literature in this area and further research is essential to produce recommendations for prevention and treatment of constipation in all conditions including post-operative patients. Laxative therapy is inexpensive, and if length of stay could be reduced by laxative use, it would likely be a cost-effective intervention. However, this must be weighed against the risk of adverse effects from laxatives. Although laxatives represent one option, one

should also remember that prescribing of opioids should be for the shortest time possible (where this is appropriate), and at the lowest effective dose; this is also likely to represent an effective preventive strategy for constipation, even in patients who have other predisposing factors, where opioids are acting as contributory as opposed to sole causal agents.

Chapter 8: Thesis Discussion

The overall aim of this thesis was to assess the burden of adverse drug reactions (ADRs) on hospital inpatients. The pilot study, reported in Chapter 2, examined ADRs in hospital inpatients for a two-week period and reported an incidence of 19.2% (95% confidence interval 12-26%) of patient episodes. Approximately one third of reactions were serious and reportable to the CHM/MHRA. The pilot study tested chosen methodology before a larger study was undertaken, and was largely robust, although quantifying additional length of stay proved a challenge which was addressed for the expanded study with more pro-active co-operation between the investigator and the multi-disciplinary team. The subsequent expanded prospective study of over 3500 patients (Chapter 3) was the largest study of its kind undertaken in the UK. It aimed to quantify the burden of ADRs in hospital inpatients, and identified common adverse drug reactions and key patient groups affected by ADRs. The incidence of ADRs reported for the expanded study of hospital inpatients was 14.7%, which is within the confidence intervals of the pilot study, thus validating the pilot's findings. The incidence figure was considerably greater than that suggested by a previously published systematic review (3.5-7.3%) [92]; this may be explained by the fact that pooling data from ADR studies with different designs can be problematic [90] as illustrated by the widely differing estimates of ADR incidence determined in different studies in different populations [96, 98]. The financial burden of ADRs on the National Health Service (NHS) was estimated to be greater than £171 million annually, and combined with data regarding ADR-related hospital admissions [18], the equivalent of ten 800-bed NHS hospitals are occupied as a result of ADRs at any one time. Using descriptive statistics, factors affecting increased risk of ADRs appeared to be female sex, increasing age, placement on a medical ward, and the number of regular medicines taken, although multivariable analysis showed that the only significant risk factor was number of medicines, with each additional medicine increasing the hazard of an ADR episode by 1.14. This is in common with a study of adverse drug effects (ADEs), encompassing medication errors in addition to ADRs, which found no consistent risk factors for ADEs in hospital inpatients [264].

It is clear that observational research of this nature has many limitations, although efforts were made to minimise these through the chosen methodology. Daily ward

visits were made by one pharmacist observer, and though aided by the multi-disciplinary team, particularly the clinical pharmacists, it is probable that some ADRs were missed. This form of manual data collection is similar to that used in studies from the 1970s and 80s [40-42], Within the study hospital, neither the individual patient record nor the prescription system was electronic, and therefore are not integrated with the on-line laboratory test reporting system, making searching for ADR signals electronically impossible in the current climate. In this electronic age it is likely that methods of detection can be improved upon with integrated information technology (IT) systems. Much work has been carried out internationally to attempt to improve ADR detection and reporting using IT. Computerised systems have been shown to produce many more ADR reports than spontaneous reporting [46, 265], with subsequent research demonstrating that IT systems with drug-databases linked to laboratory systems were able to detect ADRs such as hepatotoxicity, renal disturbances, and falls in haemoglobin (although with many false positives). Intensive surveillance by an observer was required to detect more subjective symptoms such as dyskinesia and increased sedation [44, 47]. Further improvements in specificity and sensitivity of electronic systems will make them increasingly useful [45, 160]. There is an opportunity within the NHS to implement electronic monitoring of ADRs, a form of intensive surveillance, with the likely introduction of the National Programme for Information Technology (NPfIT).

The nine medical and three surgical wards included in the large prospective study (Chapter 3) were a convenience sample chosen to reflect a balance of medical and surgical wards in the study hospital. Highly specialist wards such as the intensive care units, renal transplant unit, and colo-rectal surgery were excluded as our focus was on ADRs occurring in wards that are found in most UK general hospitals. The study hospital does not have psychiatric, paediatric or obstetrics and gynaecology wards, and thus our estimate of the incidence of ADRs excludes such patient groups. This ward choice is likely to affect the estimate of ADR incidence, as medical wards have been reported in the literature as having a higher rate of ADRs than surgical patients [89, 110] and adverse drug events are reportedly twice as frequent in medical intensive care units when compared with surgical intensive care units and general wards [131].

Haematology and oncology wards were also excluded again due to their specialist nature and the desire to ensure that results from our prospective observational study would be transferable to adult general hospitals. However, this is an important area in pharmacovigilance that warrants further study. A previous study examined ADRs in a French cancer institute in 1993 and found a relatively low incidence with ADRs occurring in 5% of patients (171/3429) [266]. This low incidence may be due to the method of detection that relied upon use of diagnosis codes and retrospective follow-up. However, in almost all cases, the drugs involved in serious ADRs were antineoplastic agents, and they primarily concerned patients with incurable cancer. ADRs, both major and minor, can impair the outcomes for cancer patients [266]. An important issue to be addressed with some cancer and HIV drugs is their accelerated licensing due to their emergence in new therapeutic areas and great potential importance. Whilst potentially expediting breakthroughs in the treatment of disease, this means that there are fewer data available regarding safety when the drug is marketed. Between 1996 and 2002, 79% of all cancer or HIV drugs that received accelerated approval in the US were identified as being associated with serious ADRs, compared with 25% of non-accelerated drugs [267].

With regard to other excluded groups, new research projects to quantify and reduce the burden of ADRs in children have commenced in Liverpool as part of the Medicines for Children Research Network, which should, amongst other findings, begin to address the risk of unlicensed and off-label medicines use in children [135, 136]. Anaesthetics is an area largely neglected in pharmacovigilance, and no reliable data regarding the overall incidence of ADRs in the operating theatre is available. Developing pharmacovigilance strategies in this area is important to improve patient safety throughout the inpatient stay in hospital. Recent work which examined CHM/MHRA Yellow Card data for reported anaesthetic adverse drug reactions found that the highest mortality was with inhalational anaesthetics, and the lowest from local anaesthetic agents, with the peak 'at risk' time being at induction of anaesthesia [268]. This analysis of spontaneous reports does not have any reliable denominator data, and thus may not reflect the overall picture of ADRs in anaesthetics [268], highlighting the need for detailed prospective examination of adverse drug reactions in this clinical area.

The methods used in the prospective study are good at detecting short-term adverse reactions, but fail to identify those which may occur days or weeks after hospital discharge, or those that only occur after chronic administration. This leads to a higher rate of ADRs reported for drugs where the adverse effect is apparent soon after initiation, although other drugs may be responsible for many ADRs of insidious onset, which may or may not be clearly distinguished from underlying disease. For example, increased risk of heart failure with rosiglitazone [217], or increased cardiac risk with Cox-II inhibitors [2]. Admittedly, these insidious reactions are more likely to be relevant to studies of hospital admission or readmission, in terms of estimates of ADR prevalence, than inpatient studies. The identification of delayed reactions is however, of great importance in pharmacovigilance. Detection of such adverse effects are more likely to come to prominence through pooled spontaneous report data or longitudinal trial data, than in an observational study, due to the difficulty in detecting the ADR in individuals, given the high prevalence of the underlying disease and a tendency to look at recent changes in condition or prescribing for a trigger for an ADR.

The readmissions study (Chapter 5) attempted to explore the risk of readmission following recent discharge from hospital. In the current NHS climate, patient length of stay is minimised as much as possible. This increases patient turnover, and apparent efficiency, particularly in view of the Payment by Results (PbR) remuneration system. In PbR, additional length of stay beyond that expected for a particular episode or procedure carries financial penalties for the NHS Trust involved, as well as being personally distressing and inconvenient for the patient. The readmissions study (Chapter 5) aimed to explore drug-related reasons for readmission to hospital and examined if drugs prescribed in the first admission were implicated in subsequent admissions, with the expedited discharge of patients possibly proving counter-productive. Results from the readmissions study showed that one in five patients readmitted to hospital within one year of discharge were readmitted due to an ADR. The drugs contributing to the ADR were initiated during the index admission in approximately 20% of cases, with half of the causative drugs continued unchanged throughout the index admission. These results suggest that improving drug monitoring may help to reduce readmissions from ADRs, as continual monitoring of long-term drug therapy is important to minimise adverse effects. For example, an optimal dose of a diuretic or anti-

hypertensive during the index admission may require adjustment in primary care following discharge in light of a patient's fluctuating clinical condition, to prevent readmission due to dehydration or falls. Improved communication between the clinical teams and the patient, and between secondary and primary care may help to improve patient outcomes. In terms of positive interventions in improving post-discharge morbidity, pharmacist counselling of patients at discharge has been shown to reduce the number of drug related problems following hospitalisation [269]. In the community, pharmacist telephone counselling appeared to improve outcomes for patients receiving polypharmacy [270], but home-based medication review by pharmacists have not been shown to reduce hospital admissions in heart failure patients [271], a key group for intervention considering the delicate risk-benefit balance of using diuretics in heart failure.

Quantifying additional length of stay due to ADRs was a difficult task for the extended prospective study of hospital inpatients (Chapter 3), although much improved on the pilot study, with more pro-active involvement of the clinical team. Factors affecting length of stay included social and rehabilitation issues prior to discharge, fluctuations in underlying disease state and the ADR mimicking underlying disease. In view of the extensive confounding, the investigators were conservative in attributing additional length of stay to the ADR. This difficulty, and others in the assessment of ADRs, was eloquently summarised by Koch-Weser *et al* in 1977; "How, except by educated guesswork can anybody judge for most ADRs the precise morbidity they caused, how much they prolonged hospitalisation or whether they contributed to the death of a patient" [58].

Identification of ADRs and assessment of the relationship between the drug and event (causality assessment) are a particular area of concern among ADR researchers undertaking epidemiological research. This has led to the development of multiple methods of assessment [52], none of which is universally accepted. Four chapters of this thesis (Chapter 2, 3, 5 and 7) used the Naranjo algorithm [63] for causality assessments. Using the same algorithm throughout these studies ensured consistency of approach throughout the thesis, but the agreement between different assessors was much less than that found in the original research describing the development of the Naranjo algorithm [63]. The same two investigators assessed all ADRs for causality according to the Naranjo

algorithm [63] in three of the ADR studies in this thesis. For the first (pilot study), percentage agreement was 39% and weighted Kappa (Kw) was 0.021, meaning agreement between the assessors on initial analysis was barely greater than that expected by chance. Agreement improved for the larger prospective study to a Kw of 0.23 ('fair' agreement [225]) and a percentage agreement of 60%. This low level of agreement and anecdotal dissatisfaction with the difficulty of achieving a 'definite' classification of ADR led to the development of the study described in Chapter 6. Assessment of the ADRs collated for the readmissions study showed a further improvement in Kw of 0.56 (moderate agreement) and a percentage agreement of 77%. Following the initial assessments, for which the statistics above describe, the investigators discussed the ADRs with a view to achieving consensus regarding causality. Improvements in agreement do not necessarily show that they became 'better' at assessing ADRs, but it does show that application of the algorithm became more uniform as this thesis progressed.

Chapter 6 demonstrated that application of three methods of causality assessment [60, 63, 70] was inconsistent. Six assessors (2 doctors, 2 nurses and 2 pharmacists) analysed 200 ADR reports according to the selected methods. Correlation of causality assessment results for different individuals using the same algorithm, and for the same individual using different algorithms, was often poor. This demonstrates one of the problems in comparing different studies of ADRs, and shows that ADR recognition varies from person to person.

To assess severity of ADRs, the studies in this thesis have consistently applied the Hartwig scale [83] adapted for the pilot study (Chapter 2) to include two categories of fatal ADR, category 7a, which suggests an ADR is related to, but not the direct cause of, the patient's death, and 7b, which asserts that the death was directly related to the ADR. Whilst this scale was useful, ADRs at severity level 1 "An ADR occurred but no change in treatment with suspected drug" were not included as these ADRs are excluded, by definition, when using the Edwards and Aronson ADR definition [16]. Few ADRs in any of the studies in this thesis were categorised as severity levels 5, "ADRs which require intensive medical care", or 6, "ADRs which cause permanent harm to the patient", although several were directly or indirectly linked to death (level 7). Future adaptations of the scale may be appropriate to consider adapting, amalgamating, or removing levels which were of

little use in out epidemiological research. Using the CHM/MHRA 'Yellow Card' criteria [85] was a useful way of establishing the number of 'serious' reactions, however, Yellow Card criteria also require all reactions to new (black triangle) drugs to be reported, whether 'serious' or not. In an epidemiological study, this theoretically may have led to an upward estimate of 'serious' reactions. The number of black triangle drugs used in hospitals in inpatients is very small relative to overall drug use, and is likely not to have had a significant impact on the results reported here.

Work from this thesis suggests that approximately 50% of ADRs in inpatients may be avoidable, consistent with the studies from the ADR literature [43, 272]. It is difficult to make judgements as to the preventability of ADRs, even when using guidelines such as the Hallas criteria [88], if the extent of how preventable adverse effects are unknown. This is partly due to the lack of knowledge regarding the effectiveness of drugs used as prophylaxis against ADRs. The lack of evidence surrounding the effectiveness of laxative use and opioid –induced constipation is one example of this, with 30% of those taking laxatives to prevent constipation in a study of patients post neck-of-femur surgery, experiencing laxative-induced diarrhoea (Chapter 7). The Hallas criteria states that an ADR is 'definitely avoidable' when the event was due to a procedure inconsistent with present day knowledge or good medical practice [88]. Long-term NSAID use leading to a gastro-intestinal bleed, without co-prescription of a PPI may therefore be deemed 'definitely avoidable' although there is no data to suggest how effective the PPI protection is in varying age groups in people with multiple co-morbidities and therefore in most patients it could be argued that there is insufficient data to deem this ADR as 'definitely avoidable'.

Decisions regarding the benefit-harm ratio and drug therapy are difficult, especially as most available data from evidence-based medicine comes from randomised controlled trials designed to assess the benefits of new therapies, and not to focus on the harms [30]. Data on the frequency of adverse effects is limited. Clinical trials are relatively short in duration, the populations limited, and access to trial data is often restricted by the manufacturer. Spontaneous reporting is too poorly undertaken in practice to allow ADR incidence to be accurately assessed in the general population. Vandenbroucke argued that pharmacoepidemiologists could

learn from systematic reviews of pooled trial data, and that those conducting trials could adopt some of the best methods of observational pharmacoepidemiology in order to gain a better insight into the associated harms of new drugs, as well as assessing their benefits [273].

Considering ADRs form such a large economic and social burden, the application of prevention strategies to prevent ADRs is of great importance. Clearly, more research is needed into interventions to help reduce the ADR burden in hospital inpatients. Key areas identified in Chapter 3 included reducing warfarin-related ADRs, renal impairment with diuretics, *Clostridium difficile* infection linked with poor antibiotic use, and the high incidence of opioid-induced constipation. Chapter 7 reported a study which examined the use of opioids and laxatives, and the incidence of constipation in patients following emergency admission for a fractured neck of femur (NOF). Commonly accepted practice suggests that opioid-induced constipation is preventable with prophylactic laxative use; however there is no clear evidence to support this suggestion [246]. This study therefore examined the relationship between constipation, opioids and laxatives in a small population, and concluded that constipation is a multi-factorial problem, and questioned the lack of an evidence base surrounding recommendations for laxatives to prevent opioid-induced constipation. Further work surrounding the preventability of ADRs and the true benefit of commonly recommended prevention strategies would be useful. For example, exploring the role and capability of proton-pump inhibitors (PPIs) to prevent non-steroid anti-inflammatory drug (NSAID) -induced gastro-intestinal bleeding outside of the manufacturer's clinical trial environment. Indeed, "the therapeutic challenge lies not in the recognition of new adverse reactions but in having enough data to guide the management of well-established safety concerns" [30].

Improvements in IT systems have long been hailed as potential methods of reducing ADRs [11, 160], with potential for decision-support systems to improve prescribing and reduce adverse events [164, 274, 275]. Pharmacogenomics aims to ultimately produce tailored medicines regimens based on a patient's genetic characteristics. Although the reality of this is decades away for most drugs and conditions, a practical application of pharmacogenomics is available for patients treated with azathioprine. Dose selection based on TPMT (thiopurine

methyltransferase) enzyme testing may minimise the risk of neutropenia, offering the prospect of safer, more effective treatment [276].

Discussion surrounding the conflicting methodology and definitions of ADR when presenting research from Chapters 2 and 3 at research conferences led to the exploration the concept of ADRs as hospital patient safety incidents (Chapter 4). The Patient Safety Division of the National Patient Safety Agency (NPSA) is a part of the NHS for England and Wales and suggests that preventable ADRs should be reported as incidents to the NPSA [206]. Incident reporting analysis methods were successfully applied to ADRs in Chapter 4, and using these methods would introduce the concept of root-cause analysis being applied to ADRs. Root-cause analysis would potentially assist in identifying systems failures which contribute to adverse drug reactions, for example, poor prescribing and insufficient monitoring of medicines. In the absence of a clearly defined intervention group, the reduction of such systems failures have been suggested into be the most likely way of successfully reducing ADEs [264]. Current pooling of data by the Yellow Card scheme does not allow for detailed assessment of the individual circumstances surrounding ADRs, and root-cause analysis may raise the profile of ADRs both clinically and politically. However, due to the large underlying ADR problem identified by the prospective study, it is unlikely that current NHS Trusts would have the resources to conduct root-cause analysis on the scale that would be required. Requiring ADRs to be reported to two organisations (MHRA and NPSA) may cause confusion and undermine the current reporting system (Yellow Card scheme), which is already underused [29]. It is clear that the NPSA, in seeking to improve systems and processes from a patient safety perspective, and the MHRA, seeking to collate data about medicines use and risk may have some overlapping goals, and collaboration between the two organisations could provide new strategies for preventing ADRs.

Chapter 9: Thesis Conclusion

This thesis has demonstrated that ADRs are a significant problem, affecting almost 15% of UK hospital inpatients. Approximately half of these ADRs may be avoidable, and action must be taken to reduce the ADR burden. Action should be multi-faceted, improving the quality of drug prescribing and monitoring. Improvements in the NHS infrastructure, including upgraded IT systems, and analysis of the high-pressure environment in which prescribers work should also be encouraged in order to improve patient safety. Commonly used drugs, causing well-known reactions are the most frequently occurring ADRs in hospital inpatients, suggesting that strategies for their prevention should be identifiable. Warfarin related bleeding, *Clostridium difficile* infection linked to poor antibiotic prescribing, and renal impairment resulting from over-diuresis are the ADRs with the highest impact, increasing patient morbidity and mortality. Pharmacological methods for preventing ADRs are largely unproven. More research into effective methods of ADR prophylaxis is essential to ensure that intervention strategies are safe and evidence-based.

Variations in pharmacovigilance methods, including multiple methods of ADR identification and validation, limit the extrapolation of the work derived from a single research centre. Standardisation of terms and definitions may help to increase the level of comparability of pharmacovigilance studies internationally, despite the inevitable underlying variations in study populations.

In summary, this thesis has provided the most robust estimate of the extent and nature of the burden of ADRs in UK hospital inpatients to date. Clearly the methodology has led to identification of the burden posed by known ADRs. Different types of methodologies need to be used to identify new signals of ADRs. Given the huge burden of ADRs causing admission to hospital, and occurring within hospital, there is an urgent need to develop robust methods for prevention of ADRs in the future.

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APPENDIX 3: Drug Usage Form (Chapter 2: Pilot Study)

ADR INPATIENT STUDY DRUG USAGE FORM

STUDY ID: **ADDRESSOGRAPH:**

DATE OF ADMISSION **To Hosp:**

To Ward:

PC: **DIAGNOSIS:** **PMH:**

Drug	Dose	Freq.Rx	Date		Route	Comment
			Start	Stop		

APPENDIX 4: ADR Alert Cards

ADVERSE DRUG REACTION

PLEASE REPORT ALL SUSPECTED ADRs:
Bleep 979 and complete form

Addressograph: Or patient name, ward and date of birth	
Date of Report:	**Suspect Drug (s):**
Details of reaction:	
Other relevant information:	
Reporter's name:	**Contact/Bleep number:**
Profession:	**Department:**

Any member of staff may complete this form. It will be collected from your nursing station or can be returned by internal mail to Emma Davies, Pharmacy

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Adverse Drug Reactions: The Burden on Hospital Inpatients. A Research Study

ADVERSE DRUG REACTION

PLEASE REPORT ALL SUSPECTED ADRs:
Bleep 979 and complete form

Addressograph: Or patient name, ward and date of birth	
Date of Report:	**Suspect Drug (s):**
Details of reaction:	
Other relevant information:	
Reporter's name:	**Contact/Bleep number:**
Profession:	**Department:**

Any member of staff may complete this form. It will be collected from your nursing station or can be returned by internal mail to Emma Davies, Pharmacy

APPENDIX 5: ADR Assessment Form (Chapter 2: Pilot Study)

Draft

ADR Assessment Form. (Part 1)

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Section 1. Identification Details

Hospital No. | | | | | | | | | | |

(BG or RLH numbers only)

Report I.D: |

Patient Study Number: |

Surname: |

Forenames: |

Date of Admission: | | / | | / | | | | |

D.O.B: | | / | | / | | | | |

Weight: | | Kg

Section 2. Medical Details

Presenting Complaint: |

Diagnosis: |

Past Medical History.

Type 1 Diabetes	☐	Hypertension	☐	
Type 2 Diabetes	☐	Heart Failure	☐	
Asthma	☐	Chronic/Acute Renal Failure	☐	
COPd	☐	Chronic/Acute Hepatic Impairment	☐	
RA	☐	Cancer (Specify)	☐	
OA	☐	Infection (Specify)	☐	
IHD	☐	Other (Specify)	☐	

Comments:

Other Relevant History

Known drug Allergies/Sensitives:

ADR Assessment Form.

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Draft .

Hospital No. | | | | | | | | | | |

(BG or RLH)(numbers only)

Section 3. Details of ADR

1. Suspected Drug

Contra-indicated in patient ☐ Yes ☐ No

Reaction:

BNF Chapter of Drug:

Dosage:

Indication for Drug:

Date Reaction started: / / Date Reaction Stopped / /

Date Drug started: / / Date Drug Stopped: / /

2.

Suspected Drug

Contra-indicated in patient ☐ Yes ☐ No

Reaction:

BNF Chapter of Drug:

Dosage:

Indication for Drug:

Date Reaction started: / / Date Reaction Stopped / /

Date Drug started: / / Date Drug Stopped: / /

Section 4. Concurent Medication

	Name of Drug:	Dosage:	Indication:
1.			

Route ☐ PR ☐ PO ☐ IV ☐ IM ☐ INH

Other:

Date Drug started: / / Date Drug Stopped: / /

Interaction with suspected drug ☐ Yes ☐ No

Interaction with another listed drug ☐ Yes ☐ No

Contrainicated in patient ☐ Yes ☐ No

Draft

ADR Assessment Form.

The Royal Liverpool and NHS
Broadgreen University Hospitals
NHS Trust

Hospital No. ☐☐☐ ☐☐☐☐☐☐☐☐ ☐

(BG or RLH]numbers only)

Section 4. Cont...

2\. Name of Drug: ☐ Dosage: ☐ Indication: ☐

Other: ☐

Route ☐ PR ☐ PO ☐ IV ☐ IM ☐ INH

Date Drug started: ☐☐ / ☐☐ / ☐☐☐☐ Date Drug Stopped: ☐☐ / ☐☐ / ☐☐☐☐

Interaction with suspected drug ☐ Yes ☐ No Interaction with another listed drug ☐ Yes ☐ No

Contrainicated in patient ☐ Yes ☐ No

Name of Drug: ☐ Dosage: ☐ Indication: ☐

Other: ☐

Route ☐ PR ☐ PO ☐ IV ☐ IM ☐ INH

Date Drug started: ☐☐ / ☐☐ / ☐☐☐☐ Date Drug Stopped: ☐☐ / ☐☐ / ☐☐☐☐

Interaction with suspected drug ☐ Yes ☐ No Interaction with another listed drug ☐ Yes ☐ No

Contrainicated in patient ☐ Yes ☐ No

Name of Drug: ☐ Dosage: ☐ Indication: ☐

Other: ☐

Route ☐ PR ☐ PO ☐ IV ☐ IM ☐ INH

Date Drug started: ☐☐ / ☐☐ / ☐☐☐☐ Date Drug Stopped: ☐☐ / ☐☐ / ☐☐☐☐

Interaction with suspected drug ☐ Yes ☐ No Interaction with another listed drug ☐ Yes ☐ No

Contrainicated in patient ☐ Yes ☐ No

Draft

ADR Assessment Form.

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Hospital No. | | | | | | | | | | |

(BG or RLH)(numbers only)

Section 5. Prophylactic Medication

Name of Drug(s):

1. | |

2. | |

Section 6. Relevant Biochemistry

Section 7. Interventions

Section 8. Additional Length of Stay.

Additional length of stay due to ADR :

Actual Length of Stay:

Days

Potential Length of stay:

Days

Section 9. Date of Discharge

/ /

Section 10. Notes

Draft

ADR Assessment Form. (Part 2)

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

Hospital No. ☐☐☐☐☐☐☐☐☐☐

(BG or RLH{numbers only)

Assessment Scores.

Causality:

Score : - 4 to +13

☐

&

☐ Definite ☐ Probable ☐ Possible ☐ Doubtful

Avoidability ☐ Definitley ☐ Probably ☐ Unavoidable

Severity score ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Yellow Card ☐ Yes ☐ No

Classification ☐ A ☐ B

Part 3. Workload Assesment.

Number of visits required to complete data: ☐

Approximate time taken to collect data: ☐

Approximate time taken to complete assessment: ☐

APPENDIX 6: ADR Assessment Form (Chapter 3: Main Study)

ADR Assessment Form

Patient Details

Report ID:	Patient Study Number:
Addressograph:	Date of Admission:
	Date of Discharge:
	Consultant:

Suspected Drugs

Suspected Drug(s)	Dose	Route	Started	Stopped	On At Home?	Indication

Description of reaction (including relevant lab results), date started and stopped

ADR Assessment Form Version 1 – Main Study 06/05

Interventions

Medical History

Presenting Complaint:	Diagnosis:
Past medical history:	Known Drug Allergies/Sensitivities
Other relevant information	

Length of Stay data

Length of Stay (Days)	Days attributed to ADR

Concurrent Medication

Drug	Dose	Route	Started	Stopped	At Home?	Indication

APPENDIX 7: Drug Usage Form (Chapter 3: Main Study)

Drug Usage Form – 1 in 10

Patient Study Number:	Date of Admission:
Addressograph:	Date of Discharge
	Length of stay:
	Consultant:

Medication

Drug	Dose	Route	Started	Stopped	On At Home?	Indication

APPENDIX 8: Readmission Assessment Form

Readmission Assessment Form

Form No	DB No

Version 2 – 04/07

Patient Details

Readmission Study Number:		Emergency readmission no 1,2,3:	
Initials:	DOB:	Date of Admission:	
Unit number		Date of Discharge:	Los:
ADR Y/N		Consultant:	Ward:
Admitted due to ADR Y/Coincidental/N		Reason for admission:	

Suspected Drugs

Suspected Drug(s)	Dose	Route	Started	Stopped	Dose @discharge?	A-D/U/ comment

Description of reaction (including relevant lab results), date started and stopped

Readmission Assessment Form

Version 2 – 04/07

Reason for Index Ad: _____

Re-admission code: _____

Interventions

Medical History

Past medical history:	Known Drug Allergies/Sensitivities
IHD HF HT DM CRF LIV COPD/Asthma	
Other relevant information	

Concurrent Medication

Drug	Dose	Route	Started	Stopped	Dose @discharge?	A-D/U - comment

Notes

APPENDIX 9: Causality Assessments Reporting Form

ADR ASSESSMENT SCALES

REPORT NUMBER _____

ASSESSOR INITIALS _____

1. VENULET – SCORING SYSTEM (See paper for guidance)

All questions refer to the suspected drugs or in cases of interactions to both drugs	Encircle One			
	K	Y	N	U
I. History of present adverse reaction				
1. Dose or duration of treatment exceeded?		Y	N	U
2. Drug given prior to event?		Y	N	U
3. Concomitant or preceding drug therapy?		Y	N	U
4. Reaction at site of application? (inj, supp, subling and top)		Y	N	U
5. ADR immediately follows the drug? (within approx 1 hour)		Y	N	U
6. Dechallenge positive? (if ADR reversible) (without treatment = K; with treatment = Y)	K	Y	N	U
7. Rechallenge positive?		Y	N	U
8. Were concomitant drugs stopped at the same time? (Only if 3=Y)		Y	N	U
II. Patient's past adverse reaction history				
9. Same ADR to this drug before?		Y	N	U
10. Other ADR to this drug before?		Y	N	U
11. Similar symptoms in the past? (not related to drug treatment)		Y	N	U
12. Similar ADR with other drugs in the past?		Y	N	U
III. Monitor's experience				
13. Drug/ADR interval compatible with the event	K	Y	N	U
14. Adverse event of rare spontaneous occurrence? (Y or N only)		Y	N	U
15. Similar events known to occur with the disease treated or concomitant disease(s)?		Y	N	U
16. ADR occurrence facilitated by the disease treated or concomitant disease?		Y	N	U
17. Contributory role of non-drug therapies?		Y	N	U
18. Other contributory factors? (habits, environment etc)		Y	N	U
19. ADR known with suspected drug? (K, Y or N only) (known=K; suspected=N)	K	Y	N	U
20. ADR explainable by the biological properties of the suspected drug? (only if 19=N)		Y	N	U
21. ADR known with pharmacologically-related drugs? (only if 19=N)		Y	N	U
22. ADR known with concomitant or preceding drug therapy (only if 3=Y; if well known =K)	K	Y	N	U
23. Drug interaction as possible cause of ADR? (only if 3=Y)		Y	N	U

Category of ADR: Circle at least one

A – DOSE RELATED

B – DOSE UNRELATED

C – TYPE I ALLERGIC

D - AT SITE OF APPLICATION

E – INTERACTION

F – DRUG DEPENDENCE

G – IRREVERSIBLE

H – WITHDRAWAL SYMPTOMS

I – FOETAL MALFORMATION

Z – UNCLASSIFIED

2. WHO Causality term Assessment Criteria (All points should be reasonably complied with)

Certain
- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

Probable /Likely
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

Possible
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely
- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Conditional / Unclassified
- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

Unassessable/Unclassifiable
- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

CATEGORY DECISION_____

3. Causality –Naranjo

No	Question	Yes	No	Do not Know
1	Are there previous *conclusive* reports on this reaction?	+1	0	0
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or *a specific* antagonist was administered?	+1	0	0
4	Did the adverse reaction reappear after the drug was readministered?	+2	-1	0
5	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6	Did the reaction reappear when a placebo was given?	-1	+1	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0
			Total	

Scoring : Definite ≥ 9; Probable 5- 8; Possible 1-4; Doubtful ≤ 0

APPENDIX 11: Opioid Study Intervention Form

Patient Number:	Sex:	DoB:	Unit Number:	Included Y/N – if N why
Date of admission	Date of discharge	LoS (days):	Ward +cons	Study No

Opiate analgesia

Drug(s)	Dose prescribed inc R/S/P	Route	On at home?	Dose given Day 1 (_/_/_)	Day 2(_/_/_)	Day 3 (_/_/_)	Day4 _/_/_)	Day5 (_/_/_)	Day 6 (_/_/_)	Day7 (_/_/_)
Total daily dose (mg morphine equivalent)										

Laxatives

Drug(s)	Dose presc inc R/S/P	Route	On at home?	Dose given Day 1 (_/_/_)	Day 2(_/_/_)	Day 3 (_/_/_)	Day 4 _/_/_)	Day 5 (_/_/_)	Day 6 _/_/_	Day7 _/_/_

Bowel movements (note when op occurred) – also symptoms of constipation e.g. abdo pain/cramping and/or diarrhoea

Pre-ad habit	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Documented as constipated in notes? Y/N Date _____

General information

Presenting Complaint:	Diagnosis:
Past medical history	Other relevant info
Allergies/sensitivites	

Surgery information

	1	2	3
Type of operation			
Date of operation			

Other medication

Drug	Dose	Rt	Start	Stop	H ?	Reg/prn/Stat	Drug	Dose	Rt	Start	Stop	H?	Reg/prn/Stat

IV Fluids

OT/PT Input e.g. when visited, notes made regarding rehab and mobility

Nutrition team input e.g. when visited, notes made regarding dietary habit/bowels, nutrition status

Mobility status: e.g. 1. mobile and self-caring, 2. help to transfer, 3. Bed bound plus notes if necessary

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7

Cognitive assessment if done – MMT score and date – also remarks in notes regarding cognition

Interventions relating to constipation (not laxatives) - LoS increase Y/N No Days_____

Other relevant info inc side effects of laxatives/incidence of diarrhoea

Opiate Intervention form Version 2 – March 2007