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Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU)

PREVALENCE AND ECONOMIC BURDEN OF MEDICATION ERRORS IN THE NHS IN ENGLAND

Rapid evidence synthesis and economic analysis of the prevalence and burden of medication error in the UK

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Date completed: 22nd February 2018

ACKNOWLEDGEMENTS

This research was funded by the UK Department of Health Policy Research Programme through its Policy Research Unit in Economic Evaluation of Health & Care Interventions (EEPRU). EEPRU is a collaboration between researchers from two institutions (Centre for Health Economics, University of York and School of Health and Related Studies, University of Sheffield). This research involves a collaboration with colleagues at the University of Manchester.

This research was also funded by PREPARE - Partnership for Responsive Policy Analysis and Research. PREPARE is a collaboration between the University of York and the King's Fund funded by the Department of Health Policy Research Programme.

The views expressed in this report are those of the authors and not necessarily those of the Department of Health. Any errors are the responsibility of the authors.

Thanks to Professor Bryony Dean Franklin and Professor Tony Avery for contributing their expertise to this report.

CONTRIBUTION OF AUTHORS

FC, MMSJ, EK and RW designed, conducted, and drafted the systematic reviews.

RAE, EC, DJ, MJS and RF designed, conducted and drafted the economic analysis. RAE, DJ, MJS, and RF led on the analysis on the prevalence of medication error. RAE and EC led on the analysis on the economic burden of medication error.

All authors reviewed and approved the final manuscript.

SUMMARY

1. A medication error is a preventable event that may lead to inappropriate medication use or patient harm.
2. We found 36 studies reported error rates in primary care, care homes and secondary care, and at the various stages of the medication pathway, ranging from 0.2% to 90.6%. Errors were more likely in older people, or in the presence of co-morbidity and polypharmacy.
3. We found four UK studies on the cost of medication errors in specific settings, with a wide range of estimates for costs from €67.93 per intercepted error for inhaler medication to €6,927,078.96 for litigation claims associated with anaesthetic error.
4. We estimated that 237 million medication errors occur at some point in the medication process in England per year. This is a large number, but 72% have little/no potential for harm. It is likely that many errors are picked up before they reach the patient, but we do not know how many.
5. We estimated that 66 million potentially clinically significant errors occur per year, 71.0% of these in primary care. This is where most medicines in the NHS are prescribed and dispensed. Prescribing in primary care accounts for 33.9% of all potentially clinically significant errors.
6. Error rates in the UK are similar to those in other comparable health settings such as the US and other countries in the EU.
7. There is little evidence about how medication errors lead to patient harm. We had to estimate burden using studies that measured harm from adverse drug reactions (ADRs). The estimated NHS costs of definitely avoidable ADRs are £98.5 million per year, consuming 181,626 bed-days, causing 712 deaths, and *contributing* to 1,708 deaths. This can be divided into:
    - Primary care ADRs leading to a hospital admission (£83.7 million; causing 627 deaths);
    - Secondary care ADRs leading to a longer hospital stay (£14.8 million; causing 85 deaths and contributing to 1,081 deaths).
8. Non-steroidal anti-inflammatory drugs, anticoagulants and antiplatelets cause over a third of admissions due to avoidable ADRs. Gastrointestinal (GI) bleeds are implicated in half of the deaths from primary care ADRs. Older people are more likely to suffer avoidable ADRs.
9. These estimates are based on studies at least 10 years old so may not reflect current patient populations or practice. This may be an underestimate of burden as only short-term costs and patient outcomes are included, and we had no data about the burden of errors in care homes.
10. Future work should focus on improving routine collection of information about errors and patient harm, and supporting implementation of evidence-based interventions to reduce errors.

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1. EXECUTIVE SUMMARY

1.1. BACKGROUND

Medication errors are a common cause of harm to patients and can include prescribing, dispensing, administration and monitoring errors. Medication error can result in adverse drug reactions (ADRs), drug-drug interactions, lack of efficacy, suboptimal patient adherence and poor quality of life and patient experience. In turn, these may have significant health and economic consequences, including the increased use of health services, preventable medication-related hospital admissions and death. It has been estimated that in some countries approximately 6-7% of hospital admissions appear to be medication related, with over two-thirds of these considered avoidable and therefore due to errors.

Errors can be minor, leading to no harm, ranging through to major errors causing serious harm and death, and associated healthcare and wider costs. Estimating the prevalence of medication error presents challenges due to varying definitions and classification systems. The evidence linking errors to patient harm and/or costs is sparse with studies using varying methods and having variable quality.

1.2. AIM OF THIS REPORT

This report presents two interlinked elements of work:

1. A rapid review of the literature: a) to identify literature about the incidence and prevalence of medication errors in the UK (Review 1); b) to identify the literature on the costs and health burden associated with medication errors in the UK (Review 2);
2. Modelling to provide national annual estimates of error prevalence and error burden in the NHS in England informed by the literature obtained in Reviews 1 and 2, but drawing on other evidence as appropriate.

1.3. RAPID LITERATURE REVIEWS

1.3.1. Methods

For Review 1, observational studies reporting the prevalence of medication error in the UK post 2007 in primary, secondary, transitional care and care homes were included. For Review 2, Walsh et al. (1) served as the starting point and additional studies meeting the inclusion criteria outlined in Walsh were also included. Data extracted were combined in a narrative synthesis.

1.3.2. Results

The search identified 1821 citations that were screened and considered for inclusion. 36 studies (38 citations) were included in the review. We categorised the studies according to the setting in which the studies were carried out: primary care, care homes, secondary care and studies that looked at medication errors that arose during transition from one care setting to another.

Primary care studies. Seven studies met the inclusion criteria, all of which sought to estimate prescribing and monitoring errors in general practice. Two studies assessed prescribing and monitoring errors, and five assessed potentially inappropriate prescribing (PIP). Across the studies in adult population, prescribing errors of 4.1% and 5.26%, and monitoring errors of 0.9% and 11.8% were observed. PIP rates ranged from 21.1% in middle-aged adults to a PIP rate of 64.4% in people with dementia. Only one study measured the severity of medication errors, of which 11/302 (3.6%) were categorised as severe (though none resulted in a hospital admission or death).

Care homes. Six studies were included. Four of the included studies measured potential inappropriate medication (PIM). One study measured prescribing, monitoring, dispensing and administration errors, while one measured administration errors. In those studies reporting PIMs, prescribing error rates ranged from 37.1%[1] to 90.6% of patients with at least one PIM. In the study measuring medication errors, prescribing errors were 39.1%, monitoring 18.4%, dispensing 36.7% and administration 22.3%. Finally, the study of administration errors, reported an error rate of 30.8% and 57.3% for those without and with dysphagia, respectively.

Secondary care. Nineteen studies were included. Eleven studies assessed prescribing errors, two assessed administration errors, one study assessed prescribing and administration errors, one study assessed serious clinical incidents associated with administration, one study assessed medication incidents associated with antimicrobials, one study assessed medication discrepancies, one study assessed potentially inappropriate medications, and one study assessed dispensing errors.

Across the studies in paediatric populations, prescribing errors of 13% and 13.2%, and administration errors of 19.1% were observed. Unintentional drug discrepancies affecting 41% of patients classified as harmful were observed by one study. Serious clinical incidents associated with analgesia in paediatrics were observed in 0.43% of opioid infusions (one resulting in cardiac arrest) by one study.

Across the studies in children and adult mental health, prescribing errors of 3.3% (of which 11% (15/139) could have had potentially serious clinical consequences) and 10.7% were observed. One study in elderly mental health observed medication administration errors of 25.9%.

One study in elderly patients with chronic kidney disease observed 56% potentially inappropriate medications and one study in elderly patients observed administration errors of 38.4%.

Across the studies in mixed hospital populations, prescribing error rates of 8.8% per 100 medication orders (7.3% serious) were observed amongst 1st-year post-graduate doctors, senior doctors and non-medical prescribers, and 7.5% amongst newly qualified doctors. Prescribing error rates of 43.8% (of which 0.30% were potentially life-threatening) were observed across different grades of doctors in one study, and prescribing error rates of 10.5% (of which 1.6% (n=54) were potentially severe or fatal) were observed amongst doctors (grade not reported) by one study.

Transitional care. Four studies were included, one study in patients on insulin in a large foundation hospital trust, one in patients being discharged from mental health hospitals, one in patients ≤65 years admitted to a Specialist Health and Ageing Unit, and one in patients being discharged from hospital.

Two studies evaluated prescribing errors at discharge, one study evaluated PIPs at admission and discharge, and one evaluated pharmacist-written discharge medication orders.

In one study, 43% of patients were identified as having an error or discrepancy relating to insulin on their discharge summary, with two out of three patients who were readmitted having a discrepancy identified on discharge. In one study a prescribing error rate of 20.8% was observed at discharge of which 4 (5.4%) were associated with potentially serious harm. In one study a potentially inappropriate medication rate of 26.7% at admission and 22.6% at discharge was observed, and in one study a prescription error rate of 0.2% at discharge.

In Review 2, four studies presenting costs associated with medication error in the UK were identified. It is difficult to draw comparisons between the studies due to the different study designs and lack of consistency in measuring medication error. Costs reported in the study ranged from €67.93 per intercepted error for inhaler medication to €6,927,078.96 measured for litigation claims associated with anaesthetic error.

1.3.3. Conclusions from rapid reviews

Review 1 (incidence and prevalence of medication errors in the UK): Error prevalence rates range widely across the included studies from 0.2% to 90.6%, reflecting differences in the type of medication error, measurement methods, data sources, different settings, population groups, professional groups and drug types. Nonetheless, there appeared to be some consistency in the prevalence rates identified that are supported in the wider literature. The elderly are a population for whom error rates are higher, in care home settings, primary and secondary care and during transitional care. This appears to be compounded when there is evidence of co-morbidity, such as dysphagia, kidney disease or dementia. This may be due to multiple risk factors which include polypharmacy. The severity of medication errors was often not reported and so the evidence identified to support the impact of the error rates was limited. In primary care, 3.6% of errors were categorised as severe, in secondary care rates of severe and potentially life-threatening errors were 0.30% and 1.6%, respectively.

Review 2 (evidence for the costs and health burden associated with medication errors in the UK): There is a lack of good quality studies measuring the economic burden of medication errors in the UK.

1.4. ESTIMATING BURDEN OF MEDICATION ERROR IN THE NHS IN ENGLAND

1.4.1. Background

The rapid reviews were intended to inform estimation of burden of medication error in the NHS in England. Review 1 provided estimates of error rates at different stages of the medicines use process in most settings. As no national estimates of prevalence were available, we derived these estimates from published case studies.

Very few data were found on economic burden in Review 2. Very few, or no data were found that indicated direct links between errors and harm, or what proportion of errors occurring at different stages of the medicines use process reached patients, and what proportion of those errors reaching patients caused actual harm.

This required us to develop estimates of burden of medication errors using published work around adverse drug reactions (ADRs) and adverse drug events (ADEs), where these include preventable reactions/events. These studies involved retrospective judgement that harm/burden was due to an ADR/ADE, rather than using data that explicitly or prospectively linked errors to harm. Throughout the report, the term ADR or ADE is used *as per* in the source study.

1.4.2. Objectives

The objectives of this element of work were:

- To use published error rates to estimate numbers of medication errors occurring across primary care, care home and secondary care settings in England.
- To understand what proportion of these errors have the potential to cause harm.
- To develop estimates of burden of medication errors, in terms of costs incurred to the health system and health outcomes.

1.4.3. Methods

We used data preferentially from studies identified in the rapid reviews reporting medication error rates in the UK to determine the prevalence of errors for each stage of the medication use process, in each setting and their sources. The error rates reported in the studies were extrapolated to estimate the prevalence of errors in England as a whole. The extrapolation methods were determined by data availability. The proportions of errors that were judged in studies to have the potential to cause mild, moderate and severe harm were extracted to allow assessment of severity of errors.

The rapid review on costs and health losses from medication error concluded that the evidence directly linking error rates to patient harm and/or costs is sparse. This meant that the prevalence of potentially harmful errors could not be used to estimate the burden associated with medication errors. Therefore, it was necessary to utilise other sources of data to allow us to derive estimates of burden. The primary approach used was to identify available UK-based case studies of estimates of burden, and to extrapolate to estimate impact for England per annum. Due to the lack of data we used estimates of burden of avoidable ADEs, rather than medication errors *per se*. Data from non-UK case studies were used to supplement this evidence where UK studies were not available. The identified literature reported the burden on healthcare resources (inpatient admissions, inpatient stay, accident and emergency (A&E) visits) and deaths associated with medication errors.

1.4.4. Results

Summary of results on prevalence of errors

We estimated that 237,396,371 medication errors occur at some point in the medication use process in England per annum. This is the sum of the errors occurring at all stages of medication use: prescribing

(21.3%), transition (1.4%), dispensing (15.9%), administration (54.4%) and monitoring (6.9%), and in all settings: primary care (38.3%), care homes (41.7%), and secondary care (20.0%).

Overall errors

Error rates per patient in primary care are the lowest but the burden of errors is the second highest due to the size of the sector. Care homes cover fewer patients than the other sectors, but have the highest error rates per patient, leading to a disproportionately high overall number of errors. In summary, the proportion of errors occurring at each stage of the medicines use process is:

- Primary care: 47.9% prescribing, 36.1% dispensing, and 15.9% monitoring.
- Care homes: 3.0% prescribing, 3.6% dispensing, 92.8% administration, and 0.6% monitoring.
- Secondary care: 8.5% prescribing, 7.1% transition, 2.9% dispensing, 78.6% administration, and 2.9% monitoring.

Errors with potential for harm

Of the 237 million medication errors, 72.1% are classed as minor with little or no potential for clinical harm, while 25.8% and 2.0% of errors have the potential to cause moderate and severe harm, respectively. In summary:

- Prescribing errors constitute 21.3% of errors, 49.9% and 2.1% having potential to cause moderate or severe harm, respectively.
- Transition errors constitute 1.4% of errors overall, and 51.6% and 7.3% of these have potential to cause moderate or severe harm, respectively.
- Dispensing errors constitute 15.9% of errors overall, only 34.1% and 1.1% of these have potential to cause moderate or severe harm, respectively.
- Although administration errors constitute 54.4% of errors overall, 92.4% of these errors are classed as minor with little or no potential for clinical harm.
- Monitoring errors constitute 6.9% of errors overall, only 72.7% and 16.4% of these have potential to cause moderate or severe harm, respectively.

We estimate that 61.4 million and 4.8 million errors occur in England per annum that have potential to cause moderate or severe harm, respectively. This constitutes 27.8% of overall errors. Of these 66.2 million clinically significant errors, 47.0 million (71.0%) occur in primary care, of which 22.5 million (33.9%) in prescribing; 11.6 million (17.5%) in dispensing and 12.9 million (19.5%) in monitoring.

Prescribing and monitoring errors are most likely to have the potential to lead to moderate and severe harm, respectively.

Summary of results on burden of errors

The base-case analysis uses only UK-based data on hospitalisations linked to definitely avoidable primary care ADRs (median length of stay (LOS) 5 days) and ADRs during hospital admissions. The estimated costs to the NHS are £98.5 million per annum, consuming 181,626 bed-days, causing 712 deaths, and contributing to 1708 deaths during hospitalisation. Incorporating primary care costs (author estimate), A&E attendances for ADEs (German data) and ICU admissions related to ADEs (French data) provide a higher estimate, with estimated costs to the NHS of £188.4 million per annum, consuming 185,814 bed-days and contributing to 1,855 deaths. Including probably avoidable ADRs across these different settings and a 14.25 day length of stay for primary care error results in a highest cost scenario with estimated costs to the NHS of £1.6 billion consuming 3.8 million bed-days and contributing to 22,303 deaths.

1.4.5. Comparison of the UK setting with other countries

Using systematic reviews as our source, the studies suggest that error rates in the UK are comparable with those in the US, other EU countries and other comparable settings, although the variation in prescribing and dispensing and study design limits comparison.

1.4.6. Limitations of methods

Due to the lack of data, we have had to make assumptions which necessarily lead to a level of uncertainty around the estimates presented. Whilst reported error rates record an error at that stage in the process, an unknown proportion actually reach the patient, and we do not have data to quantify this. The presence of an error does not necessarily lead to patient harm, but increases the probability of harm. The relationship between errors and risk of harm is variably understood, depending on the error, but generally the data here are very sparse.

There is considerable uncertainty in the estimates of burden since the calculations assumed that definitely avoidable ADR/ADEs constitute errors and were extrapolated from studies in one or two centres to the whole NHS. This may be an underestimate of burden as only short-term costs and patient outcomes are included, and we had no data about the burden of errors managed in care homes. It may be an overestimate if the prevalence and burden of definitely avoidable ADR/ADEs are greater than that of medication errors.

1.4.7. Conclusions

Using published error rates, we estimated that 237 million medication errors occur at some point in the medication process in England in one year. Although this is a large number, 72.1% are minor with little or no potential for clinical harm. We estimated that 66.1 million potentially clinically significant errors occur, of which 47.0 million (71.0%) occurs in primary care. Prescribing in primary care accounts for 33.9% of all potentially clinically significant errors. Whether the summed total of 237 million is a useful statistic is debatable. Apart from the uncertainty around this estimate, it is likely that some of these errors are picked up later in the medication use process and never actually reach the patient, but we do not know how many.

The estimated burden of definitely avoidable ADRs was estimated to be £98.5 million NHS costs per annum, consuming 181,626 bed-days, causing 712 deaths, and contributing to 1081 deaths during the index hospitalisation. We used UK-based data on hospitalisations linked to avoidable primary care ADR and avoidable ADRs in hospital to estimate burden due to the lack of evidence linking errors to harm and limited data on the cost and burden of medication errors. There is a high level of uncertainty around this estimate of burden due to the assumption that avoidable ADRs correspond to medication errors. Additionally, these estimates are based on studies involving 1-2 centres, assumed generalisable to the whole of the NHS in England. This estimate does not include any longer term health or cost impact of the error beyond the initial hospitalisation.

The two key recommendations arising from this work are, firstly, to facilitate routine data collection of clinically important errors, and link these to outcome data to allow identification of priority areas for targeting interventions. Secondly, to support implementation of evidence-based interventions that work in the real world, particularly in primary care prescribing.

2. BACKGROUND

Medicines constitute the mainstay of care for most long-term conditions and are associated with substantial evidence to support their use in key disease areas such as cardiovascular, metabolic and respiratory medicine. However, medicines use is also associated with risks, due to side effects, patient co-morbidities and drug-drug interactions, and selection of medicines is often based on careful balancing of perceived benefits versus potential harms. Harm caused by medication is referred to as an adverse drug event (ADE). ADEs in England have previously been estimated to be responsible for 850,000 inpatient episodes, costing £2 billion in additional bed-days, and increased mortality.(2, 3) ADEs can occur even when the medicine is prescribed appropriately, (e.g. due to overdose, adverse drug reactions (ADRs) or allergies), but if there are questions about whether the prescription was appropriate, any resultant harm can be considered "preventable".

The medicines use process is quite complex, starting with prescribing, but also including dispensing, administration and monitoring, involving different health care professionals and other key players at each stage, moving through multiple geographical locations and each of these stages can introduce errors. If an error occurs at any one of these stages and reaches the patient, the harm incurred is considered preventable. In 2007, the National Patient Safety Agency estimated that preventable harm from medication could cost more than £750 million each year in England.(4)

Most health systems are attempting to improve patient safety.(5) Medication errors are considered an important cause of avoidable morbidity and mortality.(2, 6) A study by Cranshaw *et al.* revealed that drug-related medical errors in anaesthesia alone cost the NHS Trusts in England £5 million from 1995 to 2007 in terms of litigation costs.(7) Errors can occur at all stages of the medication use process. Errors can be minor, leading to no harm, ranging through to major errors causing serious harm and death, and associated healthcare and wider costs.

2.1. DEFINING MEDICATION ERRORS

There is no consensus about the definition of a medication error. A systematic review found 26 different terminologies employed for a medication error.(8)

The United States National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as:

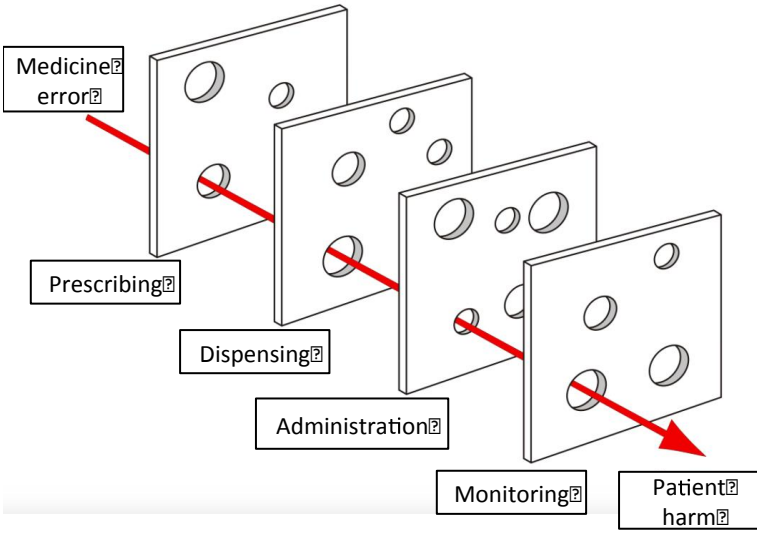
'*Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures and systems including prescribing, order communication, product labelling packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use'*.

This definition is broad and suggests that errors are preventable at different levels. There are a number of different approaches to classifying medication errors. One approach is to base the classification on the stage in the sequence of medication use process, such as prescribing, transcribing, dispensing, administration or monitoring. Another approach is to consider the types of errors occurring, such as wrong medication, dose, frequency, administration route or patient. A further approach classifies errors according to whether they occur from mistakes made when planning actions (knowledge-based or rule-based mistakes), or errors in the execution of appropriately planned actions (action-based errors).

2.2. THE SWISS CHEESE MODEL AND ITS APPLICATION TO MEDICATION ERRORS

To explain the complex and layered healthcare system and how healthcare workers could potentially prevent (and cause) medication errors, James Reason proposed the Swiss Cheese Model.(9) According to this model, a series of barriers are in place to prevent hazards from causing harm to patients. However, each barrier, such as system alarms, administrative controls, pharmacists, nurses, etc., has its unintended and random weaknesses, or holes, just like Swiss cheese. The presence of holes in one of the slices does not normally lead to a bad outcome; but when by chance all holes are aligned, the hazard reaches the patient and causes harm (Figure 1).

Figure 1. Reason's Swiss Cheese model to describe how errors can occur in the medication use process (Swiss Cheese part of diagram from Wikipedia.com)



In reality, medication errors can be initiated at all four stages in the process in the diagram (prescribing, dispensing, administration and monitoring), and can also be detected and eradicated at all four stages. However, some errors, wherever they are initiated will reach the patient, at which point they have the potential to cause harm.

2.3. ASSESSING THE BURDEN OF MEDICATION ERRORS

Medication errors are considered to be a "bad" thing that need to be avoided, with the often implicit assumption that they lead to patient harm and/or costs. However, the evidence directly linking errors to patient harm and/or costs is sparse, with studies using varying methods and having variable quality.(1) Due to methodological and measurement complexity, ethical considerations and the need for impractically large sample sizes and long follow-up times, studies tend to report error rates but not actual impact (patient harm or cost) arising from them. The key ethical issue is that once an error has been detected at any point in the medication use process in a research study, it cannot be left uncorrected to reach the patient, as following an error through the medication use process to see if it causes harm is considered unethical. An early study in the area, a US hospital-based study, estimated the link between errors and harm in1995.(10) They reported that 5 of 530 medication errors (0.9%) resulted in ADEs. The literature tends to examine error rates at each stage of the medication use process. However, an unknown proportion will actually reach the patient. Therefore its value is limited

as an outcome measure. Nonetheless, knowing these error rates has intrinsic value in that they identify where in the medication use process errors occur most commonly, allowing better targeting and testing of interventions to reduce those errors.

2.3.1. Assessment of severity

To deal with this evidence gap between the medication error and the harm caused, many studies have used the concept of ranking errors by some subjective judgment of severity. Many systems have been used. One system developed by Dean and Barber (11) divides errors into "minor", "moderate", or "severe". Thirty health care professionals from four U.K. hospitals scored 50 medication errors in terms of potential patient outcomes on a scale of 0 to 10, where 0 represented a case with no potential effect and 10 a case that would result in death. Limitations of this approach lie with the intrinsic subjectivity of the method, and the fact that many studies develop their own severity assessment system, limiting the comparability of results from different studies.

2.3.2. Assessment of causality and preventability

Whether the adverse event has been caused by a medicine is not always clear. These outcomes may or may not be associated with errors in prescribing, dispensing, administration or monitoring. Not all errors occurring earlier in the medication use process end up reaching the patient and if they do, they may not lead to harm. If harm does occur, the error may be only one of a number of factors leading to a poor outcome. Furthermore, not all ADEs are preventable. Given that many ADEs are caused by drugs such as aspirin, warfarin or diuretics which have potentially significant long-term benefits to patients, are recommended in guidelines due to an evidence base for effect and involve finely balanced decisions about the benefits versus the risks in some categories of patients (e.g. those with multi-morbidity), it can often be difficult when retrospectively reviewing prescribing decisions to make a judgement as to the preventability of the harm. Many ADE studies tend to include large numbers of possibly avoidable ADEs, which are likely to include many cases where hindsight bias might suggest the prescribing decision was wrong, when it had been based on careful balancing of benefits versus harms taking into account evidence-based guidelines and patient preferences.

Many studies have dealt with issues of causality and preventability, generally using the concept of ranking errors by some subjective judgment. In a UK study of the reasons for preventable drug-related admissions to a medical admissions unit,(12) reviewers used criteria for causality,(13) preventability,(14) contribution to the admission and classification of the underlying cause of the drug-related morbidity.(14)

Limitations of this approach lie with the intrinsic subjectivity of the method, the underlying problem of hindsight bias, and the fact that many studies develop their own causality preventability assessment system, limiting the comparability of results from different studies.

2.3.3. Assessment of burden

Very few studies link medication errors directly to patient harm and cost.(1) More studies link ADEs to patient harm and cost, and then assess retrospectively whether the ADE was preventable (that is, caused by a medication error). Different approaches have been used for assessing burden, all with methodological limitations.

The first approach has been to assess the impact of ADEs on healthcare resource use, such as hospitalisations, hospital length of stay and primary care resource use. Studies have investigated hospitalisations from medication errors occurring outside hospital leading to an ADE requiring hospitalisation,(15, 16) and harm from medication-related ADEs occurring in hospital.(17, 18) A US study suggested that the occurrence of an ADE was associated with increased length of stay of 1.91 days and an increased cost of $2262 (P<.001) with an increased risk of death among patients experiencing an ADE of 1.88 (95% confidence interval (CI), 1.54-2.22; P<.001). Bates et al. undertook a case control costing study that defined two sets of cases as patients with an ADE, and patients with a preventable ADE.(19) Controls were selected as patients on the same unit as the case with the most similar pre-event length of stay (LoS). Differences were greatest for patients with preventable ADEs compared with controls: length of stay was 4.6 days longer for patients (P = 0.03), total charges were $11 524 higher for patients (P = 0.06), and total costs were $5857 higher for patients (P = 0.07). Based on a retrospective chart review, Schneider et al. estimated the cost of medication errors requiring extra laboratory tests or treatment without an increased length of stay to be $95 to $227, of errors resulting in a prolonged length of stay to be $2596, and of errors resulting in near-death experience to be $2640.(20) Another US study has attempted to assess the total primary and secondary care costs of primary care ADEs.(21) Key limitations of this approach are poor coding of admissions and longer term health and cost effects after the index hospitalisation are not considered.

The second approach has been to model the estimated costs and harm associated with specific types of errors, that is, estimates based on the aggregation of particular harms. This approach was used to estimate the QALY decrement and cost associated with six common and clinically significant primary care prescribing and monitoring errors targeted in an error-reducing intervention.(22) One of the

limitations of this approach is that it is virtually impossible to generate models to cover the huge variety of errors, and very little data to populate these models once specified.

The third approach has been to attach some general QALY and cost decrement to error rates to estimate impact.(23) In this study, Karnon et al. (23) used a previously published medication errors model which they adapted to describe the pathway of errors occurring at hospital admission through to the occurrence of preventable ADEs. The baseline model was populated using literature-based values, and then calibrated to observed outputs. Costs were taken from published literature. Hypothetical QALY decrements for errors were derived from discussions within the research team and a retrospective study that estimated that 43% (95% CI, 35%-51%) of patients who died following an error defined as definitely or probably preventable would have left the hospital alive given optimal care.(24) One of the limitations of this approach is the high level of uncertainty around any estimates generated due to the elicitation methods and large numbers of assumptions used.

2.4. RATIONALE FOR THIS REPORT

Estimating the prevalence of medication errors is difficult due to the varying definitions and classification systems employed. Rates can vary depending on the denominator used (e.g. patient, prescription or a specific medication). The challenge is compounded by variations in the availability and use of incident reporting systems(25).

Medication error can result in adverse drug reactions, drug-drug interactions, lack of efficacy, suboptimal patient adherence and poor quality of life and patient experience. In turn, these may have significant health and economic consequences, including the increased use of health services, preventable medication-related hospital admissions and death(26). It has been estimated that in some countries approximately 6-7% of hospital admissions appear to be medication related, with over two-thirds of these considered avoidable and therefore due to errors (27-29).

Errors may also be classified according to their level of severity. These approaches are not mutually exclusive and there is no strong evidence to support particular methods of defining or classifying errors.

With substantial and increasing medication use there is also a growing risk of harm. This is compounded by the need to prescribe for an aging population with increasingly complex medical needs and the introduction of many new medications. There are preventable problems that are likely to

increase. The problem is more pronounced in the elderly, in part due to multiple risk factors, one of which is polypharmacy.

A substantial amount of literature about medication errors is based in the hospital setting, but there are differences in the type of clinical problems encountered, classes of medications used and the organization of services in primary care. This means that the risk posed in primary care and the solutions required may differ from those in hospital settings. Therefore for this review we have separated studies into those that explore error rates in different settings; grouping studies as: primary, care homes, secondary care and transitional care.

This report presents two interlinked elements of work:

1. A rapid review of the literature:
    a. to identify evidence around the incidence and prevalence of medication errors in the UK (Review 1);
    b. to identify the evidence for the costs and health burden associated with medication errors in the UK (Review 2);
2. Modelling to provide national annual estimates of error prevalence at different stages of the medication use process and in different sectors, and error burden in the NHS in England using the evidence obtained in Reviews 1 and 2.

3. Review 1: Rapid Review of the Prevalence of Medication Error in the NHS in England

3.1. Methods Review 1

3.1.1. Identifying Studies

A systematic search for studies was undertaken. The search approach involved the following:

- Contact with experts in the field
- Searching of electronic databases and the grey literature
- Checking of bibliographies and citation searching of retrieved papers

Four major electronic databases were searched from 2007 until present:

1. PubMed: US National Library of Medicine National Institutes of Health 1946 to present
2. EMBASE: Ovid. 1974 to 2017
3. Cochrane Library: Wiley Online (Cochrane Database of Systematic Reviews. 1996-2017; Database of Abstracts of Reviews of Effects. 1995-2015; Cochrane Central Register of Controlled Trials. 1898-2017; Health Technology Assessment Database. 1995-2016; NHS Economic Evaluation Database. 1995-2015)
4. CINAHL: EBSCO. 1974-2017

The strategy comprised keywords for 'medication errors' obtained from a recently published review Walsh et al. (1) combined with 'incidence/prevalence'. The search was limited to literature published in the last 10 years (from 2007 onwards), English language and UK (30) studies by applying a geographical search filter. References were managed using Endnote X8.

A targeted grey literature searching of the UK was carried out in the following sources:

1. NHS England https://www.england.nhs.uk/
2. Department of Health https://www.gov.uk/
3. NICE https://www.nice.org.uk/
4. National Patient Safety Agency http://www.npsa.nhs.uk/
5. The King's Fund https://www.kingsfund.org.uk/
6. The Health Foundation http://www.health.org.uk/
7. CEA registry http://healtheconomics.tuftsmedicalcenter.org/

Expert recommended publications were cross-checked against the database search and reasons for exclusion from the search results were investigated.

3.1.2. Criteria for considering studies for this review

Types of studies

We included observational studies, including prospective and retrospective designs. We included studies that aimed to estimate prevalence of medication errors. We only included studies that were carried out in the UK. We excluded studies that were only available as conference abstracts. We did not exclude any studies on the basis of quality. We excluded intervention studies seeking to reduce medication error rates.

Types of participants/settings

We included studies that were carried out in any health care setting, including primary care, secondary care, care homes, and studies that measured medication error rates occurring at admission and discharge (transition studies). We included studies examining prevalence of medication in any patient population.

Types of medication error

We included studies that explored any type of medication error involving health care professionals, including those occurring at prescription, dispensing, monitoring, and administration. We excluded studies that measured errors in over the counter medication or were related to patient adherence.

Types of outcomes

We included studies that reported the prevalence of medication errors and/or severity of those errors in terms of clinical impact.

3.1.3. Data Extraction

Study selection

Due to the time constraints for this review and the uncertainty about the available relevant literature, an iterative approach to study selection was used. Initially any good quality, relevant systematic reviews reporting UK based data, published between (2007-2017) were included as well as relevant

key publications meeting the inclusion criteria identified by our expert advisory board. When no good quality systematic reviews were identified, we included quantitative observational studies (prospective and retrospective) reporting medication error rates in the UK, published between 2007-2017. When considering the inclusion of observational studies we took into account both the data sources used to gather medication error rates and the study's generalisability to the UK setting. We included data from both primary and secondary care settings and also those reporting error rates during transition. Where appropriate, we included grey literature that reports medication error rates in the UK, where the data were gathered from high quality sources, for example, national registers.

For the purposes of this review we included errors that occurred at the following stages:

- Prescribing (this can be a doctor, nurse or pharmacist)
- Transcribing (referring to when patients move settings)
- Dispensing (usually a pharmacy error)
- Administration (usually nurses or care home workers, or may be by the patient themselves in primary care)
- Monitoring (usually doctors but can be any health care professional, depending on setting)

Exclusion criteria: non-English publications, non-UK. Studies that were concerned with rates of adherence were excluded.

Quality assessment

Quality assessment of included studies was undertaken using a modified version of the National Heart, Lung and Blood Institute, Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.(31)

Data extraction

Data to be extracted included details of authors, type of medication error, definition of medical error, method of extracting errors, study setting, study population, time frame, incidence or prevalence data reported and data source.

Data synthesis

A narrative synthesis was undertaken. A statistical synthesis of the data was not undertaken. However, where there is sufficient homogenous data, further analysis in our reporting of 'implications for research' is recommended.

3.2. RESULTS REVIEW 1

The electronic searches identified 2,125 citations. Forty-seven additional citations were provided by clinical experts and 41 additional citations were identified from references lists of systematic reviews identified by the search.

Following deduplication, there were 1,821 citations of which the titles and abstracts were scrutinised for relevance. Of these, 1,770 were excluded based on title or abstract. Fifty-one articles were obtained as full-text. Of these, 13 full-texts were excluded.(32-42) Six were intervention studies.(32, 35-37, 42, 43) Four did not report an error denominator (e.g. total number of charts, prescriptions, patients, etc.).(33, 34, 40, 41) Two were studies not undertaken in the UK.(38, 44). One was a letter to the Editor.(39) Details of the studies excluded at full-text are presented in Appendix 3.

Thirty-six studies (38 citations) were included in the review. Six studies (7 citations) were undertaken in care homes,(45-51) seven studies (8 citations) were undertaken in primary care,(52-59) 19 studies were undertaken in secondary care,(60-77) and four studies were undertaken in transitional care.(78-81)

The study selection process as a PRISMA flow diagram is presented in Figure 2.

Figure 2 PRISMA Flow Diagram for Review 1

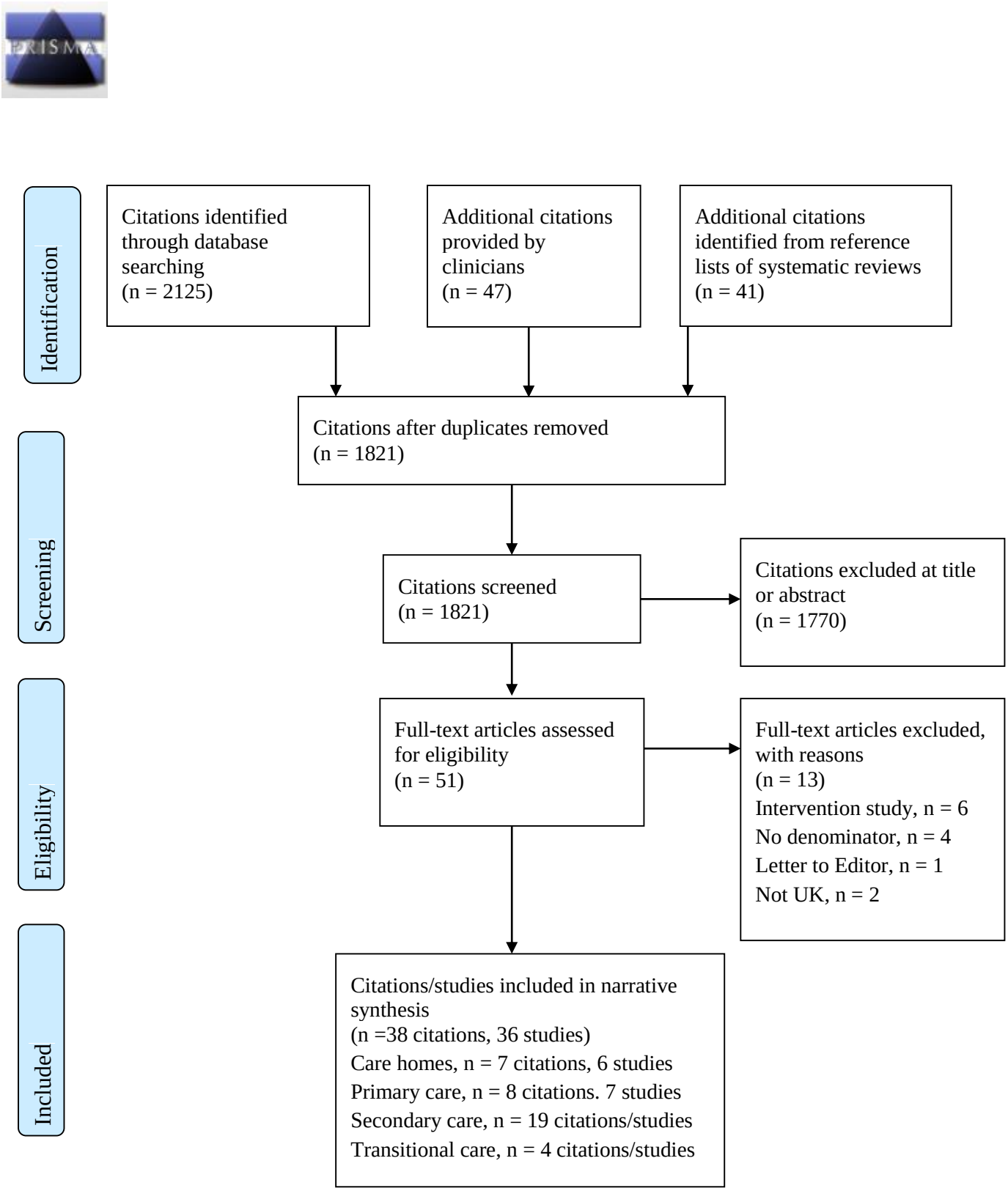


Table 1: Summary of Error Prevalence Rates

	PIP/PIM/PPO	**Prescribing error**	**Monitoring error**	**Administration error**	**Other**
Primary Care					
All	4.9% (52, 53)	4.1% (3.6 to 4.6%) (52, 53)	0.9% (0.7% to 1.1%) (52, 53)		
>18 y		5.26% (59)	11.9% (59)		
45-64 y	21.1 % (57)				
≥ 70 y	33% (55) 29% (56)				
100 y	32% (58)				
People with dementia	64.4% (54)				
Care Homes					
Adults with Type 2 diabetes	90.6% (46)				
Adults with and without dysphagia				30.8% for those without dysphagia and 57.3% for those patients with dysphagia (51)	
Adults with dementia	40.9% and 46.2% (50)				
Adults	PIM 37.1% (48) 71.6% at admission (49) 73.3% at discharge (49) PPO 69.8% at admission (49) 50% at discharge (49)	39.1% (45)	18.4% (45)	22.3% (45)	*Dispensing* 36.7% (45)

	PIP/PIM/PPO	Prescribing error	Monitoring error	Administration error	Other
Transitional care					
Patients prescribed insulin	43% on discharge summary (78)				
Discharge prescriptions	20.8% (79)				
Older people admitted and discharged from a UK hospital	26.7% at admission 22.6% at discharge (80)				
Pharmacist written discharge medication orders	0.2% (81)				
Secondary Care					
Paediatrics		13% (62) 13.2% (67)		19.1% (67)	Unintended medication discrepancies, 45% patients (69) Serious clinical incident 0.43% (73)
Mental health – children and adults		3.3% (63) Admission, 10.7%; in-stay, 6.5%; discharge, 6.5% (72)			
Mental health - elderly				25.9% (68)	
Elderly with kidney disease	PIM - 56% (71)				
Elderly with and without dysphagia				38.4% (77)	

	PIP/PIM/PPO	Prescribing error	Monitoring error	Administration error	Other
Hospital mixed populations – doctors prescribing		8.8 % per 100 scripts (60) 36% charts and 7.5% items (74) 43.8% (75) 10.5% (82)			
Hospital mixed populations – pharmacists prescribing		0.3% (61) 9.2% (65)			
Hospital mixed populations – pharmacists and nurses prescribing		14.7% (66)			
Hospital mixed populations –prescribing of opioids		27.2% (64)			
Hospital mixed populations –dispensing errors					0.016% un-prevented and 0.131% prevented dispensing incidents (70)
Hospital mixed populations – incidents related to antimicrobials		25.4% (83)	5.5% (83)	50.0% (83)	

PIP: potentially inappropriate prescribing; PIN: potentially inappropriate medicines; PPOs: potential prescribing omissions.

3.2.1. Primary care Studies

The searches identified 8 citations and 7 studies that met the inclusion criteria.(52-59) All of the included studies sought to estimate prescribing and monitoring errors made in general practice. There were differences between the studies in terms of the population being investigated, data sources used for indication of error, differences in how an error was defined and in measurement of error severity.

Setting and patient population

Details of the setting and patient group from whom data regarding error rates were collected are shown in Table 2. Three studies examined data from across the UK,(56, 58, 59) one examined data from fifteen general practices across three primary care trusts in England. (52, 53) and three data from Northern Ireland.(54, 55, 57) Three studies focused on error rates in an elderly population,(55, 56, 58) one on patients with dementia,(54) one on middle aged adults (aged 45 to 64 years),(57) and one had no age limits imposed.(52, 53) The numbers of patients in the included studies ranged from n=1771 to n=1,019,491.

Table 2: Setting and patient population included in primary care studies

Study	Country	Patients	Denominator
Avery et al. (53, 84)	E	Patients registered with a GP in three PCTs. 2% random sample of patients within each general practice	n= 6048 prescriptions (1777 patients)
Barry et al. (54)	NI	People with dementia	n= 6826 patients.
Bradley et al. (55)	NI	≥ 70 y registered with a GP	n= 166,108 patients
Bradley et al. (56)	UK	≥ 70 y registered with a GP	n= 1,019,491 patients
Cooper et al. (57)	NI	Middle aged adults (45-64 years)	n= 441,925 patients (EPD database)
Hazra et al. (58)	UK	reached 100 y	n= 7907 patients
Stocks et al. (59)	UK	Adult patients registered with a GP in 526 general practices	n= 949,552 patients

NI: Northern Ireland, UK: United Kingdom, E: England, GP: General Practitioner, EPD: Enhanced Prescribing Database, HSE-PCRS: Datalink Health Services Executive Primary Care Reimbursement Service database, CPRD: Clinical Practice Research

Study design and study duration of studies in primary care

Details of the study design and study duration are presented in Table 3. All of the included studies estimating drug errors in primary care used a retrospective study design. This involved the retrospective review of data, which in 5 studies included a review of the data source in the 12 months

prior to the date of data collection.(52-57) In one study data was collected from the CPRD up to the audit date, (59) and in another study using a retrospective cohort design, the number of inappropriate prescriptions in individuals reaching the age of 100 between 1990 to 2013 was evaluated.(58)

Table 3: Study design and duration in primary care studies

Study	Study design	Duration
Avery et al. (53, 84)	Retrospective case note review of unique medication items to identify prescribing and monitoring errors	1 year (2010/2011)
Barry et al. (54)	Retrospective, cross sectional study to estimate PIP in people with dementia	1 year (2013)
Bradley et al. (55)	Retrospective, cross sectional study to estimate the prevalence of PIP among older people	1 year (2009/2010)
Bradley et al. (56)	Retrospective, cross sectional study to estimate the prevalence of PIP among older people	1 year (2007)
Cooper et al. (57)	Retrospective, cross sectional study to estimate the prevalence of PIP in socioeconomically different populations	1 year (2012)
Hazra et al. (58)	Retrospective cohort study to evaluate inappropriate prescribing in centenarians	23 years (1990/2013)
Stocks et al. (59)	Retrospective, cross sectional study to estimate prescribing and monitoring errors in the adult population	Up to 1 April 2013

PIP: potentially inappropriate prescribing

Source of error data, definition of medication error and severity

Five included studies sought to estimate the prevalence of PIP (potentially inappropriate prescription), defined as; the use of medicines that introduce a risk of adverse drug-related events, which lack evidence based indications, are not cost effective and where a safer, as effective alternative is available to treat the same condition. (54-58) However, there will always be an exception where the prescription is justified for clinical reasons. Four of these studies used a modification of the STOPP screening tool to determine if a PIP had occurred.(54-57) The Screening Tool of Older Person potentially inappropriate Prescriptions (STOPP) provides an explicit process measure of potentially inappropriate prescribing and is validated for use in European countries. It is a physiological system-based screening tool comprising 65 clinically significant criteria which take drug-drug and drug-disease interactions, drug doses and duration of treatment into consideration. It considers clinical effectiveness and the removal of any potentially unnecessary drugs as well as drug duplication. Only subsets of the STOPP criteria could be used as the data sources used in some of the studies did not contain clinical

information. Bradley et al. (55) used the EPD prescription files for study participants. As the EPD does not contain clinical information on diagnoses, 28 of the 65 indicators in the STOPP criteria were considered applicable for this study. Barry et al. (54) used 36 of the 80 criteria in the updated STOPP, and used the EPD as a source of data. Bradley et al. (56) used the CPRD database and was able to access anonymised clinical data. This study used 52 of the STOPP criteria. Hazra et al. (58) looked at PIPs in centenarians; those reaching 100 years of age during the specified time period. This study used electronic health records (EHRs) as a resourced to evaluate inappropriate prescribing. This was determined using the American Geriatrics Society Beers Criteria. Avery et al. (52, 53) and Stocks et al. (59) looked at prescribing and monitoring errors.

Prescribing and monitoring errors were defined by using validated indicators, developed through consensus among GPs and used in the PINCER trial.(85) Avery et al. (52, 53) used this definition of a prescribing error, as one which occurs when as a result of a prescribing decision or prescription writing process, there is an unintentional, significant…reduction in the probability of treatment being timely an effective or…increase in the risk of harm when compared to generally accepted practice'.. The definition was accompanied by a list of examples of what should and should not be included as an error. A monitoring error was defined, based on the consensus definition as one that occurs when a prescribed medicine is not monitored in the way which would be considered acceptable in routine general practice. It includes the absence of tests being carried out at the required frequency. For the purposes of the study, a list of medications requiring blood-test monitoring was used along with recommended monitoring intervals. Cooper et al. (57) used the PROMPT (Prescribing Optimally in Middle-aged People's Treatments). This represents a set of 22 explicit prescribing criteria, organised according to physiological system, which have been developed specifically for middle-aged adults. (57) This set of criteria may be applied to administrative datasets, or drug lists along (i.e. in the absence of clinical information), to determine the prevalence of PIP in middle-aged people. The criteria are similar to the Screening Tool for Older Persons' Prescription (STOPP) in mainly specifying circumstances in which a medicine may be inappropriate (co-morbidities, dosage, duration of use) rather than stating drugs to avoid in all cases, as is more common in the Beers criteria.

Data collection methods in primary care studies

Details of data collection methods in the included studies of primary care are presented in Table 4.

In four studies, the data was collected by a research team,(54-57) and in one by a team of pharmacists.(52, 53) The coding and determination of potential errors was further discussed and confirmed in two studies.(52, 53, 56)

Three studies used the EPD (Enhanced Prescribing Database) as a data source.(54, 55, 57) This database securely holds information on drugs prescribed and subsequently dispensed to patients in primary care. Once prescriptions have been dispensed by community pharmacies, they are forwarded to the Health and Social Care Business Services Organisation at the end of each month for reimbursement. Computer-generated prescriptions link to a patient's Health and Social Care Number with details of their prescribed medication and prescriber. This is held in the EPD. As the dataset lacks clinical or diagnostic information some indicator tools used in the studies could only be partially operationalised due to the absence of data on biochemical monitoring, so could not be included.

Barry et al. (54) and Bradley et al. (55) extracted data from the EPD on drug use using the dispensed drug item and BNF codes. Patients were identified who received a STOPP criteria drug or drug combination from the drug used using the BNF (British National Formulary) codes. Patients were categorised into those who received a STOPP criteria drug or drug combination from the criteria applied in the respective studies. Barry et al. (54) used 36, and Bradley et al. (55) used 28 of the 65 available STOPP indicators.

Cooper et al. (57) also used the EPD database as a source of data, and patients were categorised as having received or not having received any of the PIPs listed in the 22 PROMPT criteria.

Avery et al. (52, 53) gathered data from unique prescription items and the pharmacists trained by the research team to identify potential errors from GP records were able to identify potential prescribing or monitoring errors having taken account of detailed information in patients' medical records relating to patient characteristics, comorbidities, other medications, allergies and the need for monitoring. This data source will have allowed a more comprehensive assessment of medication error as access to clinical information was possible.

Three studies (56, 58, 59) used the CPRD (Clinical Practice Research Datalink) as a data source. It is one of the largest computerised databases on anonymized patient records from primary and secondary care. It provides a complete record of clinical and prescribing data, meaning that a more comprehensive set of criteria can be applied with may more accurately reflect PIP prevalence. The CPRD collects data from approximately 660 general practices in the UK and covers about 8.5% of the population and is broadly representative in terms of age, sex and geography. Exposure status was based on prescription and clinical data in the database. Data on drug use were extracted using Multilex codes

whilst clinical diagnoses were identified from Read codes. Patients who triggered the indicator by receiving a potentially unsafe prescription or having no record of the required monitoring during the time period leading up to the audit data counted as an error.

Table 4: Error type, method of collecting data and definition of error and its severity in primary care studies

Study	Error type	Source of data	Method of collecting data	Method of determining error	Defining of severity
Avery et al. (53, 84)	Prescribing and monitoring	Prescription items	Pharmacists Details of potential errors were discussed by a panel to decide whether they fitted the error definition.	Prescribing errors definition was accompanied by a list of examples of what should and should not be included as an error. Monitoring error was defined, together with a list of medications that need blood test monitoring and its frequency	Severity of each error was identified using a validated 0-10 scale: errors with scores of <3 were considered minor, 3-7 moderate, and >7 severe.
Barry et al. (54)	PIP	EPD	Research team. Anonymised data.	36 of the 80 updated STOPP criteria	Not measured
Bradley et al. (55)	PIP	EPD	Research team Anonymised data.	28 of the 65 STOPP indicators	Not measured
Bradley et al. (56)	PIP	CPRD	Research team, Anonymised data. All codes were manually reviewed and confirmed by MB and an experienced primary care physician.	52 of the 65 STOPP criteria applied	Not measured
Cooper et al. (57)	PIP	EPD	Research team Anonymised data.	22 PROMPT criteria	Not measured
Hazra et al. (58)	PIP	CPRD	Not reported.	2012 American Geriatrics Society Beers Criteria.	Not measured

Study	Error type	Source of data	Method of collecting data	Method of determining error	Defining of severity
Stocks et al. (59)	Prescribing and monitoring	CPRD	Not reported.Anonymised data	Indicators developed through consensus among GPs and used in the PINCER trial	Not measured

EPD: Enhanced Prescribing Database, HSE-PCRS: Datalink Health Services Executive Primary Care Reimbursement Service database, CPRD: Clinical Practice Research, PIP: potentially inappropriate prescription, PROMPT: Prescribing Optimallly in Middle-aged People's Treatments, BNF: British National Formulary, STOPP Screening Tool of Older

Person potentially inappropriate Prescriptions.

Results of studies in primary care

Details of the study population, the denominator, numerator and the reported error rate and severity are presented in Table 5. The table is also ordered by population with subheadings as follows: adult population, middle aged adult population, elderly population, patients with dementia.

The studies by Avery et al. (52, 53) and Stocks et al. (59) both examined prescribing and monitoring errors in patients registered with the participating general practices. Stocks et al. (59) was a larger study, with N= 949,552 patients at risk. Avery et al. (52, 53) included n=6048 prescriptions for 1777 patients. The studies drew data from different sources. Avery et al. (52, 53) used patients records and Stocks et al. (59) used the CPRD database. The study by Avery et al. (52, 53), though smaller, ensured access to greater clinical detail and therefore potentially is more accurate in its identification of prescribing and monitoring errors. Avery et al. (52, 53) found a prevalence of 4.1% (247/6048; 95% CI: 3.6% to 4.6%) errors in the 6048 prescription items reviewed. Both studies (52, 53, 59) found similar rates of prescribing error (4.1% (247/6048; 95% CI: 3.6% to 4.6% and 5.26% (95% CI: 5.21% to 5.30%)) respectively. They reported greater difference in the prevalence of monitoring errors 0.9% (95% CI: 0.7% to 1.1%)(52, 53) and 11.8% (95% CI: 11.6% to 11.9%)(59). This difference may, in part, reflect different approaches to the assessment of monitoring errors and the indicators used to measure this outcome. It may also indicate the differences between practices. It may be possible that those practices taking a more active role in accuracy in prescribing and monitoring medicines were more willing to participate in the Avery et al. (52, 53) study.

Cooper et al. (57) estimated PIPs in prescriptions for middle aged adults (45-64 years). They found PIPs in 93,319/441,925 patients 21.1% (95%: 21.0% to 21.2%) estimated from data from the EPD database.

Two studies (55, 56) estimated PIPs in prescriptions for patients aged 70 years and over, registered with a GP, and showed similarity in prevalence rates. The PIPS identified were: 53,423/166,108 with a prevalence of 33% (confidence interval not reported) (55) and 295,653/1,019,491 with a prevalence of 29% (95% CI: 28 % to 29%)(56). One study (58) measured prevalence of PIPs in patients reaching 100 years, which were estimated to be 2517/7907; 32% (confidence interval not reported). The higher prevalence rates in the elderly populations in the studies included in this review would also support studies that have shown a greater chance of medication errors occurring in the elderly and where patients may be on a number of medications (polypharmacy).

One study (54) looked at the prevalence of errors rates in people with dementia. This group experienced the highest prevalence of PIPs, 4393/6826; with a rate of 64.4% (95% CI: 63.2 % to 65.5%).

Overall, it seems that the proportion of serious medication errors in primary care may be reasonably low. However, given the sheer number of prescriptions issued in primary care, there is still the potential to cause considerable harm in absolute terms.

Only one study (53, 84) measured the severity of medication errors. The severity of each error was identified using a validated 0-10 scale (0 = no risk of harm; 10 = death) was assessed by two GPs, two pharmacists and one clinical pharmacologist. According to this method, the mean score across all five judges was used as the severity score, where errors with scores of <3 were considered minor, 3-7 moderate, and >7 severe. Of the errors identified 128/302 (42.4%) were described as minor, 163/302 (54%) as moderate and 11/302 (3.6%) as severe. No patients were hospitalised or died as a result of the errors.

Table 5: Results of primary care studies

Study	Error type	Patients	Total order/ admissions/ patients/ prescriptions (denominator)	Number of errors (numerator)	Prevalence	Severity
Adult population						
Avery et al. (53, 84)	P and M	Patients registered with a GP in three PCTs.	n= 6048 prescriptions (for 1777 patients prescribed over a 12 month period)	n= 296 prescribing or monitoring errors. n= 247 prescribing errors n= 55 monitoring errors	P and M:4.9% (4.4% to 5.5%) P:4.1% (3.6% to 4.6%) M: 0.9% (0.7% to 1.1%)	Minor: 128/302 (42.4%) Moderate: 163/302 (54%) Severe: 11/302 (3.6%) No patients were hospitalised or died
Stocks et al. (59)	P and M	Adult patients registered with a GP in 526 general practices	n= 949,552 patients at risk	Prescribing error n= 49 927 Monitoring error: n= 21 501	P: 5.26% (5.21% to 5.30%) M: 11.8% (11.6% to 11.9%)	Not measured
Middle aged adults						
Cooper et al. (57)	PIP	Middle aged adults (45-64 years)	n= 441,925 patients .	n= 93,319	21.1% (21.0% to 21.2%)	Not measured
Elderly population						
Bradley et al. (55)	PIP	≥70 y registered	n= 166,108 patients	n= 53,423	33%	Not reported

Study	Error type	Patients	Total order/ admissions/ patients/ prescriptions (denominator)	Number of errors (numerator)	Prevalence	Severity
Bradley et al. (56)	PIP	≥ 70 y registered	n= 1,019,491 persons eligible for inclusion	n=295,653	29% (28 % to 29%)	Not reported
Hazra et al. (58)	PIP	reached 100 y	n= 7907 patients from total sample with at least one prescription during the year of turning 100 years old	n= 2517	32%	Not reported
Patients with dementia						
Barry et al. (54)	PIP	People with dementia	n=6826 patients.	n=4393	64.4% (63.2 % to 65.5%)	Not reported

P: prescribing, M: monitoring

Study quality of studies in primary care

The results of the quality assessment of studies undertaken in primary care are presented in Table 6.

Across all seven of the included studies in primary care (52-59) the research question or objective was clearly stated, and the setting and patient population was clearly specified and defined.

In two studies (52-54) there may be some limitations in the representativeness of the study sample to the patient population of interest. The Avery et al. (52) study invited 97 general practices from three English primary care trusts (PCTs) with differing characteristics. Thirty replied and 20 expressed an interest in taking part, 15 were then purposefully selected to obtain a wide spread of different types of practice. However, it is possible that the recruited practices had relatively high levels of interest in prescribing and a greater openness to external scrutiny which could have caused the study to underestimate the true rate of prescribing errors. In the Barry et al. study (54) patients with dementia were identified by use of four drugs prescribed in the management of dementia, however, this may have excluded some with dementia of different aetiologies or those with severe cases in whom the medication had been stopped.

The selection of subjects were from similar population and the inclusion and exclusion criteria for being in the study was pre-specified and applied uniformly to all patient populations, setting and medication errors. Medication errors and the tools to determine if an error had occurred were clearly defined. However, only two studies (52, 53, 56) described checking identified errors and seeking a consensus.

Some limitations arose in the reliability of the data source used in six of the studies (54-59). Three studies (54, 55, 57) used the EPD database to estimate prevalence of error rates. The lack of clinical data within the EPD only allows the application of a subset of the STOPP criteria and some diagnoses were determined using drug proxies. Therefore some instances of PIP identified within these studies may not be clinically relevant and prescribing decisions are also based upon clinical and personal knowledge of each patient. Other limitations of using drug dispensing data is that patient adherence to medication is assumed. Over the counter (OTC) medications are not accounted for, which may underestimate or overestimate PIP prevalence and use of anticholinergic/antimuscarinic medications in particular. For example, PIP may be overestimated if a patient on a strong opioid has purchased an over-the-counter laxative, or alternatively may be underestimated if a patient is taking over-the-counter omeprazole while on clopidogrel.

Four studies used the CPRD database as a data source for error rates. This too has limitations. The identification of Read codes for clinical diagnoses could be ambiguous. This could lead to over or under-estimation of the prevalence of some errors. Therapeutic duplication was difficult to accurately assess using medication records or prescription database and may be misrepresented. It is possible that therapeutic duplication may be overestimated. Some patients may have belonged to practices that were inactive or had transferred out of the CPRD resulting in some data loss during the study period. This could have potentially led to a slight under-estimation of PIP. Such comparisons would require access to routinely collected patient data (even CPRD might be missing some data; for example, INR tests).

One study (58) used the Beers criteria to identify errors. The Beers Criteria has limitations, as some drugs used in the UK are not captured by it. The STOPP/START criteria has addressed some of these limitations, however frequencies of PIP should be interpreted cautiously because each person's risk benefit ratio for a drug will depend on his or her physiological and clinical status.

It is possible across all of the studies that the pharmacists and research teams varied in their ability to detect potential prescribing and monitoring errors. Little information was given to determine the process of training and validating the data extraction and classification process.

Table 6: Study quality of studies in primary care

Reference	Was the research question or objective in this paper clearly stated?	Was the setting and patient population clearly specified and defined?	Is the patient population representative of a general population?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all patient populations, settings, and medication errors?	Was a sample size justification, power description, or variance and effect estimates provided?	Were medication errors clearly defined, in accordance with recognised criteria?	Were medication errors assessed consistently across all study participants?	Were the observers blinded to the subjects they were assessing?	Is the method for collecting data (medication errors) reliable?
Avery et al. (52, 53)	Y	Y	SL	Y	Y	Y	Y	Y	N	Y
Barry et al. (54)	Y	Y	SL	Y	Y	Y	Y	CD	Y	SL
Bradley et al. (55)	Y	Y	Y	Y	Y	N	Y	CD	Y	SL
Bradley et al. (56)	Y	Y	Y	Y	Y	Y	Y	Y	Y	SL
Cooper et al. (57)	Y	Y	Y	Y	Y	Y	Y	CD	Y	SL
Hazra et al. (58)	Y	Y	Y	Y	Y	N	Y	CD	Y	SL
Stocks et al. (59)	Y	Y	Y	Y	Y	Y	Y	CD	Y	SL

CD, cannot determine (unclear); N, no; NR, not reported; Y, yes; SL: some limitations

Summary of studies undertaken in primary care

The searches identified 8 citations from 7 studies that met the inclusion criteria (52-59). All of the included studies sought to estimate prescribing and monitoring errors made in General Practice. All were retrospective design.

One study was in patients registered with a GP in three PCTs,(53, 84) one was in adult patients registered with a GP in 526 general practices,(59) one was in middle-aged (45-64 years) patients,(57) two were in patients aged ≥70 years,(55, 56) one was in patients who had reached 100 years,(58)and one was in patients with dementia.(54)

Two studies assessed prescribing and monitoring errors,(53, 59, 84) and five assessed potentially inappropriate prescribing (PIP).(54-58) Across the studies assessing PIP,(54-58) was defined as the use of medicines that introduce a risk of adverse drug-related events, which lack evidence based indications, are not cost effective and where a safer, as effective alternative is available to treat the same condition. Four (54-57) of these studies used a modification of the STOPP screening tool to determine if a PIP had occurred.

Across the studies in adult population, prescribing errors of 4.1%(53, 84) and 5.26%,(59) and monitoring errors of 0.9%(53, 84) and 11.8%(59) were observed. One study reported that 3.6% of prescribing and monitoring errors were serious, but that no patients were hospitalised or died.(53, 84)

In the study in middle-aged adults a PIP rate of 21.1% was observed.(57) Across the studies in elderly populations, PIP rates of 33%(55) and 29%(56) were observed. One study in people with dementia observed a PIP rate of 64.4%.(54)

Study quality was variable across the studies in primary care. Whilst the research question/study objectives were clearly stated for all studies and errors were assessed in a consistent manner within studies, there was great variability in study reporting of data collection methods and generalisability of findings. Most studies in primary care had some limitations in the way data were collected.

3.2.2. Transitional Studies

The searches identified 4 studies in examining medication errors occurring during patient transition.(78-81) Although transition can occur at a number of interfaces, the included studies all focused on errors in discharge medication prescriptions.

Setting and patient characteristics

Details of the study setting and patient population are presented in Table 7. All of the included studies were undertaken in England but in different settings. Two studies examined prescription errors for patients at discharge from hospital, one focused on insulin prescriptions. (78) (81) One study was

undertaken in mental health settings at three NHS mental health trusts (79) and one in a specialist Health and Ageing Unit (HAU) within an acute hospital trust (80).

Table 7: Setting and patient population in transitional studies

Study	country	Setting	Patients
Bain et al. (78)	England	Large foundation trust hospital in the North of England	Patients being treated with insulin and were included in the 2016 National Inpatient Diabetes Audit (NaDIA)
Keers et al. (79)	England	Mental health settings at 3 NHS mental health trusts.	Patients being discharged from mental health hospitals
Onatade et al. (80)	England	Specialist Health and Ageing Unit (HAU) of a 950-bed acute hospital trust in England, UK	Aged C65 years admitted to the HAU in June and July 2011.
Onatade et al. (81)	England	A London hospital	Patients being discharged

Study design and study duration in transitional care studies

Details of the study design and study duration are presented in Table 8. One of the included studies of transitional care was a prospective design (79) and three were retrospective design (78, 80, 81).

In the prospective study (79), data were collected over 6 weeks, from 9am to 5pm on weekdays. Trained pharmacy teams reviewed all newly written discharge prescriptions recoding the number of prescribing errors, clerical errors and errors involving lack of communication about medicines stopped during hospital admission. All prescribing errors were reviewed and validated by a multidisciplinary panel.

In the retrospective studies, the duration of time in which the error rates were measured and the data source varied. Bain et al. (78) undertook a retrospective analysis of all patients with insulin-treated diabetes who were receiving care as inpatients at the study hospital during one day (29th September 2016), were eligible for inclusion in the National Diabetes Inpatient Audit (NaDIA) and whose data was collected for the NaDIA. Patients who were excluded from the NaDIA (paediatric patients, patients on mental health wards, in the emergency department, day case wards, short-stay units or palliative care units) or whose data was unable to be retrieved during the NaDIA) were not included in the study.

Onatade et al. (80) used the hospital's electronic patient record (EPR) system to identify all patients discharged from the HAU over a 2-month period in 2011. Patients were included if they were 65 years of age or above on admission and if their clinical information and medical records were available electronically.

Onatade et al. (81) aimed to quantify errors in pharmacist written discharge medication orders. Data collection occurred on convenient days (determined by researcher availability) over a 15 month period (October 2013 to January 2014). The discharge prescription was examined for prescription error (omission, commission/addition, duplication, administration frequency, dosage form, route) and all errors were also rated independently for their potential clinical impact by one senior physician and one senior clinical pharmacist. The raters were given descriptions of the errors and asked to use their clinical and professional judgment to categorise each error according to a validated adaptation of the National Coordinating Council for Medication Error Prevention (NCCMERP) index and descriptors for potential harm.

Table 8: Study design and duration

Study	Study design	Duration
Bain et al. (78)	Retrospective study investigating insulin-related prescribing errors at discharge from hospital	1 day
Keers et al. (79)	Prospective study of discharge prescriptions written at mental health hospitals	6 week Data collected 9am-5pm on weekdays
Onatade et al. (80)	Retrospective study determining prevalence of PIPs in older people discharged from a specialist Health and Ageing Unit	8 week
Onatade et al. (81)	Retrospective study investigating the extent and clinical significance of errors in pharmacist-written discharge medication orders.	22 days on convenient days over 15 months

R: retrospective, P: prospective, CS: cross sectional

Sources of data, methods of data collection and defining error in transitional studies

Details of sources of data, methods of data collection and defining error in transitional studies are presented in Table 9.

The sources of data included discharge prescriptions, inpatient clinical records, discharge summaries, and electronic patient records. The focus of one study was on prevalence of errors in pharmacist written discharge prescriptions;(81) and another focused on insulin based prescriptions.(78)

In two studies,(79, 81) trained pharmacists reviewed the discharge prescriptions and medication history, inpatient chart, patient records and discharge summary to identify errors. The errors were validated further to determine whether a genuine prescribing error had occurred and to categorise the error type. In one study,(78) a single reviewer used a data collection sheet to capture discrepancies or errors relating to insulin information and prescription as well as the extent of adherence to medication related discharge recommendations. Ambiguities could be discussed with a clinical pharmacist. In another study,(80) the method of data collection was not reported.

Bain et al. (78) categorised as errors any erroneous or incomplete documentation of insulin preparation, device, route, dose (number of units) or frequency transcribed onto the discharge summary when compared with the inpatient prescription on the day of discharge. A discrepancy was defined as a failure to communicate any changes made to insulin therapy in the designated medication 'medication changes' section of the discharge prescription. They also measured the severity of errors by recording hospital readmission within 30 days of discharge.

Keers et al. (79) defined a prescribing error as an error resulting from a prescribing decision or in the prescription-writing process, with an unintentional significant reduction in the probability of treatment being timely and effective, or an increase in the risk of harm when compared with generally accepted practice. This definition was extended in scope to include mental health specific scenarios. Clerical errors were defined operationally to include incorrect entries or omitted patient NHS numbers; patient full names, dates of admission to a discharge from hospital; drug allergies and intolerances; patient DOB and details of whether GPs or hospital services were required to continue prescribing individual medication items post-discharge.

Onatade et al. (80) used the STOPP criteria to identify medication and medication –disease combinations that indicated a PIM (potentially inappropriate medication).(80)

Onatade et al. (81) categorized errors according to type: omission, commission, duplication, administration, dosage, route) and each error was assigned a potential clinical significance rating based on the NCCMERP scale by a physician and an independent senior clinical pharmacist working separately.

Table 9: Source of error, method of collecting data defining error in transitional studies

Study	Source of data	Method of collecting data	Method of determining error	Definition of error	Defining of severity
Bain et al. (78)	Analysis of discharge summaries. In patient medical notes, including prescriptions, retrospectively uploaded to an electronic patient record after discharge.	Patients medical records were examined by a single reviewer for the entire inpatient episode that included the NaDIA collection data (29th Sept 2016). This included admission documentation, prescription charges and electronic discharge summaries.	Data collection sheet was designed to capture in free-form any noted discrepancies or errors relating to insulin information and prescription as well as the extent of adherence to medication related discharge recommendations. Ambiguities in interpretation of information contained in medical records arose, a single clinical pharmacist was consulted to clarify and confirm information at the point of data collection.	Erroneous or incomplete documentation of insulin preparation, device, route, dose (number of units) or frequency transcribed onto the discharge summary when compared with the inpatient prescription on the day of discharge. A discrepancy was defined as a failure to communicate any changes made to insulin therapy in the designated medication 'medication changes' section of the discharge prescription.	Hospital readmission within 30 days of discharge.
Keers et al. (79)	Inpatient's paper-based prescription charts, paper-based leave prescriptions and paper or electronically generated discharge prescriptions on weekdays.	Trained pharmacists reviewed all newly written discharge prescriptions over a 6 week period, recording the number of prescribing errors, clerical errors and errors involving lack of communication about medicines stopped during hospital admission. All prescribing errors were reviewed and validated by a multidisciplinary panel.	A multidisciplinary panel validated each recorded PE to determine whether a genuine prescribing error had occurred, to categorize the error type and its potential severity.	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription-writing process, there is an unintentional significant reduction in the probability of treatment being timely and effective, or an increase in the risk of harm when compared with generally accepted practice. This definition was extended in scope to include mental health specific scenarios. Clerical errors were defined operationally to include either incorrect (e.g. incorrect entries or omitted patient NHS numbers; patient	Not measured

Study	Source of data	Method of collecting data	Method of determining error	Definition of error	Defining of severity
				full names, dates of admission to an discharge from hospital; drug allergies and intolerances; patient DOB and details of whether GPs or hospital services were required to continue prescribing individual medication items post-discharge.	
Onatade et al. (80)	Clinical data were abstracted from the EPR and the Electronic Prescribing and Medication Administration (EPMA) systems. Admission and discharge medication lists were reviewed for any medication and medication-disease combination according to the STOPP criteria. Any documentation in individual patient records regarding possible issues with the use of PIPs was noted. Medication records from	Not reported	Relevant clinical data were abstracted from the EPR and the Electronic Prescribing and Medication Administration (EPMA) systems, including past medical history, history of falls, reason for admission, full medication history (‘gold standard’ as confirmed and documented by a pharmacist)on admission, discharge medication list, and any documented monitoring, follow-up or review plans for discharge medication. Regular and as required medication were included. Over-the-counter medication not prescribed on admission or in discharge orders was excluded. Admission and discharge medication lists were reviewed for any medication and medication–disease combinations that appear in	STOPP criteria	Not measured

Study	Source of data	Method of collecting data	Method of determining error	Definition of error	Defining of severity
	previous admissions were checked.		the STOPP criteria. In addition, any documentation in individual patient records regarding possible issues with the use of a PIM was noted.		
Onatade et al. (81)	Pharmacist written discharge medication orders, medication history, inpatient drug charges, and electronic patient records.	Pre-registration pharmacists reviewed all discharge medication orders written by pharmacists and identified discrepancies between the medication history, inpatient chart, patient records and discharge summary.	A senior clinical pharmacist confirmed the presence of an error	Errors were categorised according to type: omission, commission, duplication, administration, dosage, route)	Each error was assigned a potential clinical significance rating based on the NCCMERP scale by a physician and an independent senior clinical pharmacist working separately.

3.2.3. Results of transition studies

Details of the error type, denominator and numerator, the reported error rate and severity are presented in Table 10. The prevalence of errors ranged from 0.2% to 81%, to some extent representing the broad definition of medication error used in some of the studies. Keers et al. (79) found that 222/274; 81% (95% CI 76% to 85.2%) of discharge prescriptions for patients being discharged from mental health hospitals were affected by at least one prescribing error (PE), clerical error (CE), or an error regarding a medicine stopped during admission (MSA). However, when limited to only prescribing errors the prevalence was more consistent with other study findings: 54/259 (20.8% (95% CI:15.9% to 25.8%)) of eligible discharge prescriptions. Onatade et al. (81) found that the prevalence of prescribing errors in discharge prescription in older people leaving a specialist aging unit was 51/195, 22.6% (95% CI: 16.7%–28.5%). Bain et al. (78) also used a broad definition of what would constitute a medication error in insulin related discharge prescriptions.(78) It found a prevalence of 18/ 42, 43% (confidence interval not reported).

The clinical relevance and severity of the medication error was assessed in three studies.(78, 79, 81) In one study,(78) this was done by measuring hospital readmission within 30 days of discharge. In this small study (n=42), two of the three patients with discrepancies in their discharge medication prescription were readmitted to hospital within 30 days of discharge. In Keers et al. (79) severity was determined by a multidisciplinary panel. They found that n=54 errors (73%) were potentially clinically relevant for patients, with 4 (5.4%) associated with potentially serious harm. In the Onatade et al. (81) study, errors were assigned a potential clinical significance rating based on the NCCMERP scale by a physician and an independent senior clinical pharmacist working separately. This study was exploring the error rates of pharmacist written prescriptions, which they found to be 0.2%, and of these n=1 (0.02%) had potential to cause temporary harm.

Table 10: Study results in transitional studies

Study	Error type	Total order/ admissions/ patients/ prescriptions (denominator)	Number of errors (numerator)	Prevalence	Severity
Bain et al. (78)	Insulin related error or discrepancy discharge summary	N= 42	N=18 patients were identified as having an error or discrepancy relating to insulin on their discharge summary.	43%	N=2 (of 3 patients readmitted for diabetes related reasons) had a discrepancy identified on the discharge
Keers et al. (79)	Errors in discharge prescriptions written at mental health hospitals	N= 274 discharge prescriptions, 259 contained newly written or omitted prescription items	N= 222 discharges were affected by at least one PE, CE and/or MSA (medicines stopped during admission) N= 54 PEs	PEs, CEs and MSA: 81% (76-85.2%) PE only: 54/259 20.8% (15.9% to 25.8%) of eligible discharge prescriptions CE only: 197/274 71.9% (66.5–77.3%) MSA data 44/64 (68.8%	N=54 (73%) were potentially clinically relevant for patients, with 4 (5.4%) associated with potentially serious harm

Study	Error type	Total order/ admissions/ patients/ prescriptions (denominator)	Number of errors (numerator)	Prevalence	Severity
Onatade et al. (80)	Prevalence and types of PIMs in older people admitted to and discharged from a UK hospital	N= 195 patients medication lists	Admission: N= 52 patients had PIMs Discharge: N=51 patients had PIMs	Admission PIM prevalence was 26.7 % (95 % CI 20.5–32.9; 52 patients, 74 PIMs). Discharge PIM prevalence was 22.6 % (95 % CI 16.7–	Not reported
Onatade et al. (81)	Pharmacist written discharge medication orders	N= 509 prescriptions	N=10 prescriptions contained errors	0.2%	N=1 (0.02%) had potential to cause temporary harm.

PE; prescribing error, CE: clerical error, MSA: medicines stopped during administration

Quality assessment of transition studies

The results of the quality assessment of studies undertaken exploring errors that occur during transition are presented in Table 11.

All four of the included transition studies clearly stated the research question or objective, setting and patient population.(78-81)

Two studies were at risk of bias as the patient population was not representative of a general population.(78, 80) In one study,(78) there was a small sample size and a large proportion of patients were not included on account of unavailable patient medical records at the time of data collection. Another study,(80) was limited in its representativeness, as it was a single-centre study conducted in a specialist older people's unit of a large urban teaching hospital.

In another study,(81) the prospective design may have introduced a potential Hawthorne effect, with the assessment of errors influencing practice. Further potential bias was introduced as there was a lack of randomisation in the data collection which occurred on conveniently selected days. Some discharge prescriptions were also excluded due to unavailable records.

The methods of assessing error were not consistently applied in three of the studies (78-80). It was not clear to what extent the individuals extracting data on error rates were doing so consistently, and nor was it clear how this was verified.

The inclusion and exclusion criteria was pre-specified and applied uniformly to all patient populations and settings in all four of the included studies.(78-81) Two studies did not report variance of effect estimates.(78, 81)

One study used the STOPP criteria to measure prevalence of potentially inappropriate prescriptions.(80) A limitation that potentially led to underestimating PIP prevalence was the inability to check primary care records for those drugs that are inappropriate when prescribed long term. This is a common limitation in retrospective studies. The STOPP criteria itself had limitations when applied to the patient population. Potentially inappropriate opiates featured commonly in the admission and discharge medication. Most of these were combination analgesics with weak opiates; however, STOPP does not distinguish between weak and strong opiates in patients at risk of falls.

Table 11: Quality assessment of transitional studies

	Was the research question or objective in this paper clearly stated?	Was the setting and patient population clearly specified and defined?	Is the patient population representative of a general population?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all patient populations, settings, and medication errors?	Was a sample size justification, power description, or variance and effect estimates provided?	Were medication errors clearly defined, in accordance with recognised criteria?	Were medication errors assessed consistently across all study participants?	Were the observers blinded to the subjects they were assessing?	Is the method for collecting data (medication errors) reliable?
Bain et al. (78)	Y	Y	N	Y	Y	N	U	N	N	Y
Keers et al. (79)	Y	Y	Y	Y	Y	Y	U	N	N	Y
Onatade et al. (80)	Y	Y	N	Y	Y	Y	U	N	N	Y
Onatade et al. (81)	Y	Y	Y	Y	Y	N	Y	Y	N	N

Summary of studies measuring medication error that occurs during transition

The searches identified 4 studies in examining medication errors in transitional care that met the inclusion criteria.(78-81) Three of these were retrospective design,(78, 80, 81) and one was prospective.(79)

One study was in patients being treated with insulin within a large foundation hospital trust,(78) one was in patients being discharged from mental health hospitals,(79) one was in patients ≤65 years

admitted to a Specialist Health and Ageing Unit,(80) and one was in patients being discharged from hospital.(81)

Two studies evaluated prescribing errors at discharge,(78, 79) one study evaluated PIPs at admission and discharge,(80) and one evaluated pharmacist-written discharge medication orders.(81).

Across the studies, a variety of error definitions were applied. In one study, 43% of patients were identified as having an error or discrepancy relating to insulin on their discharge summary, with two out of three patients who were readmitted having a discrepancy identified on discharge.(78) In one study, a prescribing error rate of 20.8% was observed at discharge, of which 4 (5.4%) were associated with potentially serious harm.(79) In one study, a potentially inappropriate medication rate of 26.7% at admission and 22.6% at discharge was observed,(80) In one study, a prescription error rate of 0.2% at discharge with one instance (0.02%) having the potential to cause temporary harm.(81)

Study quality was variable across the studies in transitional care. Whilst the research question/study objectives were clearly stated for all studies, there it was often unclear how errors were assessed and there was variability in study reporting regarding generalisability of findings.

3.2.4. Care home Studies

Six studies meeting the inclusion criteria were identified from the searches.(45, 46, 48-51) One study was reported in two publications.(45, 47)

Setting patients and treatment administration routes

Details of the care setting and patient population are presented in Table 12 below. Four studies took place in England,(45, 46, 50, 51) one in Scotland,(48) and one in Northern Ireland.(49) Three took place in care homes,(45, 46, 51), while one took place in intermediate care facilities,(49) one in residential homes,(50) and one was an analysis of Health Informatic Centre data of care home residents.(48)

All studies were in adult patients, with all studies apart from one,(51) reporting a mean or median age of over 80 years. Three studies were undertaken in specific patient populations, one (46) in adults with Type 2 diabetes, one in adults with dementia,(50) and one in adults with dysphagia.(51) Study sizes ranged from 3 care facilities(49) to 55 care homes.(45) The Barnett et al. study (48) did not report the number of care homes. No studies reported specific treatment administration route, so it was assumed that all routes of treatment administration were included.

Table 12: Study setting, patients and treatment administration route for care home studies

Study	Setting	Patients	Treatment administration route[a]
Alldred et al. (45) & Barber et al. (47)	55 care homes in 3 areas of England	Adult (mean age 85)	All
Andreassen et al. (46)	30 care homes in East Anglia	Adults with Type 2 diabetes (median age: 86)	All
Barnett et al. (48)	Health Informatics Centre data for 400,000 individuals in 74 GP practices, Scotland	4557 care home residents (mean age 84.5 ± 7.5)	All
Millar et al. (49)	3 intermediate care facilities, Northern Ireland	Adult ≥ 65 years (mean age 83.5±7.4 years)	All
Parsons et al. (50)	6 residential homes in Southeast England	Adults with dementia (mean age: 86.8 ±6.7)	All
Santos et al. (51)	6 care homes in North Yorkshire	Adults with and without dysphagia	All

[a]If the article did not specify whether all or particular route(s) were studied, it was assumed that medication administered via all routes was observed

Study design and study duration in care home studies

Details of the study design and duration for the included care home studies are presented in Table 13. One study looked at prescribing, monitoring, dispensing and administration of medications.(45) One study looked at administration,(51) while the other four looked at prescribing. Five of the six included care home studies using retrospective analyses of patient records for information on medication, although not all were labelled as retrospective studies by the authors. Santos, in contrast, was the only study to use direct observation of drug rounds.(51) Study duration was unclear in most of the studies, although Millar et al. (49) did state that the study was undertaken over an eight week period, and Parsons et al. (50) over a 16 week period.

Table 13: Study design and study duration for care home studies

Study	Design	Duration
Alldred et al. (45) & Barber (47)	Prescribing, monitoring, dispensing and administration. Mixed methods: observation, interviews, checking records. Patients randomly chosen	Unclear 2006-7
Andreassen et al. (46)	Prescribing. Retrospective sub-analysis of data from an RCT to determine potential for de-prescribing	March 2011-March 2013
Barnett et al. (48)	Prescribing. Cohort study stratified by place of residence; examination of prescribing records.	2005-2006
Millar et al. (49)	Prescribing. Observational; use of screening tools (STOPP/START version 2) applied to medical records	8 weeks (Aug-Oct 2014)
Parsons et al. (50)	Prescribing. Retrospective analysis of medication administration records; care homes were in previous prospective longitudinal study.	2 time points 16 weeks apart
Santos et al. (51)	Administration. Observational study of medicine administration	13 drug rounds

Definition of medication errors and severity in care home studies

Information on the definition of medication errors and their severity in the care home studies are presented in Table 14. All six studies presented information on the definition of medication errors used in the studies. However, the level of detail reported varied considerably. Alldred et al. presented definitions for prescribing, monitoring, dispensing and administration errors.(45, 47) One study used NHS PrescQIPP tool to identify PIP,(46) one study used the Beers Criteria,(48) one study used either the STOPP,(50) one study used STOPP/Screening Tool to Alert doctors to Right Treatment (START) version 2,(49) while one study presented 14 definitions for different types of administration errors.(51)

Only two studies provided information on the severity of medication errors. Alldred et al. reported the use of a panel to determine severity.(45, 47) All errors reported in this study were assessed by the panel to be of low severity. The second study reporting information on severity reported only that some drug classes had either a high or low severity rating, based on the Beers Criteria.(48)

Table 14: Definition and severity of medication error in care home studies

Study	Definition of medication errors	Severity of medication error
Alldred et al. (45) & Barber et al. (47)	*Prescription error*: A prescribing decision or prescription-writing process that results in an unintentional, significant: 1. Reduction in the probability of treatment being timely and effective, or 2. Increase in the risk of harm, when compared to generally accepted practice. *Monitoring error*: occurs when a prescribed medicine is not monitored in the way which would be considered acceptable in routine general practice. It includes the absence of tests being carried out at the frequency listed in the criteria, with tolerance of +50%. *Dispensing error*: One or more deviations from an interpretable written prescription or medication order, including written modifications to the prescription made by a pharmacist following contact with the prescriber. *Administration error*: Any deviation between the medication prescribed and that administered.	Severity not reported. No harms observed; likely harm assessed by panel and rated "low".
Andreassen et al. (46)	NHS PrescQIPP used to identify PIP (an evidence based, pragmatic medicines optimisation tool)	Not reported
Barnett et al. (48)	PIM as identified using the updated Beers Criteria.	Some specific PIMs given a "high" severity rating.
Millar (49)	PIP (PIM and PPO) using STOPP/START version 2	Not reported
Parsons et al. (50)	PIP defined using STOPP	Not reported
Santos et al. (51)	Definitions for 14 medicine administration errors presented.	Not reported

Data collection methods and observers

Details of data collection methods and observers for the care home studies are reported in

Table 15. Observation was used in only two studies: Alldred et al. (45, 47) for administration of medications, although it is unclear who was being observed; and Santos et al. (51) for administration of medication by nurses. In most cases the observer, or the individual collecting the data, was a pharmacist. The identity of the observed was unclear in two studies.(48, 50)

Table 15: Data collection methods and observers for care home studies

Study	Observation method	Observer
Alldred et al. (45) & Barber et al. (47)	Dispensing: visual check of medication and records; Prescribing & monitoring: clinical medication review Administration: observation of 2 drug rounds	3 research pharmacists
Andreassen et al. (46)	Retrospective analysis of records	3 pharmacists with checking by physician
Barnett et al. (48)	Retrospective analysis of records	Study authors (no further info provided)
Millar et al. (49)	Screening of medical notes and prescription charts	1 pharmacist
Parsons et al. (50)	Analysis of records	Unclear
Santos et al. (51)	Observation (undisguised)	1 pharmacist

Results of care home studies

Table 16 shows the number of patients included in each study (denominator) and the total number of errors (numerator) as well as the reported error rate. The number of patients included in the care home studies ranged from 74(49) to 4557.(48) Four studies measured potential inappropriate medication (PIM).(46, 48-50) Alldred measured prescribing, monitoring, dispensing and administration errors.(45, 47) Santos et al. (51) measured administration errors.

In those studies reporting PIMs, prescribing error rates ranged from 37.1 %(48) to 90.6% (46) of patients with at least one PIM. In the study measuring medication errors,(45, 47) prescribing errors were 39.1%, monitoring 18.4%, dispensing 367% and administration 22.3%. The study of administration errors reported an error rate of 30.8% for those without dysphagia and 57.3% for those with dysphagia.(51)

Table 16: Number of patients, total number of errors and error rate for care home studies

Study	Number of patients (denominator)	Total number of errors (numerator)	Error rate
Alldred et al. (45) & Barber, et al. (47)	Total number of patients: 256 patients recruited	Prescribing: 100 residents had one or more error; total 153 prescribing errors Monitoring: 27 (out of 147 patients requiring monitoring) Dispensing: 94 residents had a total of 187 dispensing errors Administration: 57 residents had a total of 116 administration errors	178 (69.5%) of residents had at least one medication error Prescribing: 39.1% (8.3% opportunity for error); Monitoring: 18.4% (14.7% of prescribed items requiring monitoring); Dispensing: 36.7% (9.8% opportunity for error); Administration: 22.3% (8.4% opportunity for error)
Andreassen, et al. (46)	106 with type 2 diabetes (total of 826 patients)	346 PIMs	96 patients (90.6%) had at least one PIM, 39% endorsed by physician for de-prescribing.
Barnett et al. (48)	4557 patients	1 PIM: 2336 (27.1%) 2 PIMs: 364 (8%) 3 PIMs 76 (1.7%) 4+ PIMs: 14 (0.3%)	1690 (37.1%) of patients in care homes received a PIM during the 2 year observation period.
Millar et al. (49)	74 patients	147 PIMs in 53 patients at admission; 95 PPOs in 45 patients at admission At discharge: 54 PIMs amongst 22 patients and 34 PPOs in 15 patients.	Admission: PIM: 71.6% PPO: 69.8% Discharge: PIM: 73.3% PPO: 50.0%
Parsons et al. (50)	133 patients recruited	68 PIMs at time point 1 57 PIMs at time point 2	Time point 1: 55 (46.2%) residents had one or more PIM, 11 (9.2%) had 2 or more and 2 (1.7%) had 3 PIMs. Time point 2: 45 (40.9%) residents had 1 or more PIM; 10 (9.1%) had 2 or more and 1 (0.9%) had 3.
Santos et al. (51)	166 patients, 38 with dysphagia (22.9%)	738 total administrations observed; 300 administration errors within 100 residents	30.8% for those without dysphagia and 57.3% for those patients with dysphagia

Study quality of care home studies

The quality of the included studies is assessed in Table 17. Ten questions were used to assess study quality. All of the studies had clearly defined research questions and the setting and patient populations were clearly specified and defined. However, it was difficult to determine whether the patient populations in the studies were representative of the general population in all of the studies apart from one.(48) The study inclusion and exclusion criteria were clear in all studies, apart from one.(46) Sample size justification was presented in only two of the studies.(45, 51) Medication errors were clearly defined and assessed consistently in all studies. There was no blinding of observers in any of the included studies. In three of the studies,(46, 49, 50) it was impossible to determine whether or not the methods for collecting data were reliable.

Table 17: Quality assessment of care home studies

Reference	Was the research question or objective in this paper clearly stated?	Was the setting and patient population clearly specified and defined?	Is the patient population representative of a general population?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all patient populations, settings, and medication errors?	Was a sample size justification, power description, or variance and effect estimates provided?	Were medication errors clearly defined, in accordance with recognised criteria?	Were medication errors assessed consistently across all study participants?	Were the observers blinded to the subjects they were assessing?	Is the method for collecting data (medication errors) reliable?
Alldred et al. (45) & Barber et al. (47)	Y	Y	CD*	CD**	Y	Y	Y	Y	N	Y
Andreassen et al. (46)	Y	Y	CD	Y	CD	N	Y	Y	N	CD
Barnett et al. (48)	Y	Y	Y	Y	Y	N	Y	Y	N	Y
Millar te al. (49)	Y	Y	CD	Y	Y	N	Y	Y	N	CD
Parsons et al. (50)	Y	Y	CD	Y	Y	N	Y	Y	N	CD
Santos et al. (51)	Y	Y	CD	Y	Y	Y	Y	Y	N	Y

CD, cannot determine (unclear); N, no; NR, not reported; Y, yes; *appears to be representative of care homes in England; **time period of recruitment unclear

Summary of studies undertaken in care homes

Six studies were included in this review of medication errors in care home settings. Four took place in England,(45, 46, 50, 51) one in Scotland,(48) and one in Northern Ireland.(49) The number of patients in the study ranged from 74(86) to 4557.(48) Only one of the studies used direct observation to

determine the prevalence of medication error,(51) while the other studies undertook a retrospective analysis of medical records.

Four studies measured potential inappropriate medication (PIM).(46, 48-50) Alldred et al. (45, 47) measured prescribing, monitoring, dispensing and administration errors. Santos et al. (51) measured administration errors. In those studies reporting PIMs, prescribing error rates ranged from 37.1% (48) to 90.6% (46) of patients with at least one PIM. In the study measuring medication errors,(45, 47) prescribing errors were 39.1%, monitoring 18.4%, dispensing 367% and administration 22.3%. The study of administration errors, (51) reported an error rate of 30.8% for those without dysphagia and 57.3% for those with dysphagia.

The studies were of moderate quality although time periods were not always clearly described and it was not clear the identity of the prescriber. The four studies measuring PIM may not be directly comparable to the others as PIM may not be a direct proxy for medication error. Very little information was provided in the studies on severity of the medication errors. From the information reported in the studies, it is not clear whether or not the results are generalisable.

3.2.5. Secondary care Studies

The searches identified 19 studies in secondary care that met the inclusion criteria.(60-77, 83)

Hospital setting, patients and treatment administration routes of studies in secondary care

Details of the hospital setting and patient population and treatment administration routes are presented in Table 18.

Where reported, the number of hospital sites ranged from one (62, 64, 65, 68, 71, 76) to 20 sites.(60) Fifteen studies were undertaken in hospitals in England,(60-69, 71, 72, 75-77) one study was undertaken in district hospitals in Wales,(70) one study was undertaken in acute paediatric pain teams across the UK and Eire,(73) one study was undertaken in teaching and district general hospitals in Scotland,(74) and one study was undertaken across hospitals in a regional area of Scotland. (83)

Four studies were in paediatric populations only.(62, 67, 69, 73) One study included child and adolescent mental health services in addition to acute adult mental health services,(63) one study included one of five hospitals that was a children's teaching hospital,(67) and one study included specialist centres for paediatrics in addition to teaching hospitals, general hospitals, and women's health and mental health hospitals.(75) Three studies were undertaken in mental health hospitals only.(63, 68, 72) One study was undertaken in a care-of-the elderly ward and a stroke unit.(77)

Patient characteristics and stage of hospital stay (admission, inpatient, discharge) varied greatly across the 17 secondary care studies. Four studies reported that the population included inpatients,(60, 61, 72, 76) with two of these reporting that patients were those at admission, during stay and at discharge.(60, 75) One study reported that patients were both inpatients and patients at discharge,(76) and one study reported on paediatric patients at admission and during patient stay.(69)

Across the three studies in paediatric populations,(62, 69, 73) one focused on children admitted under the under the care of oral/maxillofacial surgery,(62) one focused on children who were admitted and prescribed at least one long-term medication,(69) and one focused on patients aged 0–18 years in the acute pain setting.(73)

Across the four studies that included populations in mental health, one study included patients from acute adult mental health services, forensic mental health services, long-term mental health care of older people services, adult psychiatric intensive care services, and child and adolescent mental health services;(63) one study included elderly long-stay wards in a psychiatric hospital,(68) one study recruited mental health inpatient wards,(72) and one study included teaching hospitals, district hospitals and specialist services for paediatrics, women and mental health.(75)

Across the other studies, one study included most adult medical and surgical specialities,(64) one study included at least one medical admissions ward and at least one surgical ward,(66) and one study included a wide variety of specialities across a regional area.(83)

The patient population consisted of patients over 70 years of age with chronic kidney disease in one study,(71) and elderly patients with and without dysphagia in another study.(77) The patient population or speciality was unclear for three studies.(65, 70, 74)

Only two studies provided details regarding the route of treatment administration. One study reporting that opioid infusions used for sedation in the intensive care setting were excluded,(64) and one study reporting that intravenous fluid charts were not included.(71) Across the remaining studies, if the article did not specify whether all or particular route(s) were studied, it was assumed that medication administered via all routes was observed.

Table 18: Details of the hospital setting, patient population and treatment administration routes in studies undertaken in secondary care

Study	Setting	Patients	Treatment administration route[a]
Ashcroft et al. (60)	20 National Health Service (NHS) hospitals located across the north-west of England.	Hospital patients on admission, during stay and at discharge.	All
Baqir et al. (61)	3 National Health Service (NHS) hospitals located across the north-west of England.	Inpatients across all wards.	All
Bolt et al. (62)	Children's hospital in England.	Children admitted under the under the care of oral/maxillofacial surgery.	All
Cottney and Innes (63)	National Health Service (NHS) Foundation Trust mental health hospitals in England.	Acute adult mental health services (15 wards), forensic mental health services (15 wards), MHCOP services (7 wards), adult psychiatric intensive care services (4 wards), and child and adolescent mental health services (2 wards).	All
Covvey et al. (83)	A regional area of hospitals in National Health Service Scotland.	General medical services: cardiology, endocrinology, gastroenterology, respiratory medicine, rheumatology, dermatology and accident & emergency; medical specialty services: plastics, nephrology, neurosurgery/neurology and haematology/oncology; rehabilitation, geriatric medicine and palliative care.	All
Denison Davies et al. (64)	Adult medical and surgical specialities in a large multi-speciality teaching hospital in England.	Most adult medical and surgical specialities.	Excluded opioid infusions used for sedation in the intensive care setting
Franklin et al. (65)	One clinical directorate in a London teaching trust comprising two hospitals.	The directorate is comprised of ten specialities (not described).	All
Franklin et al. (66)	At least one medical admissions ward and at least one surgical ward in each of three hospitals in England.	At least one medical admissions ward and at least one surgical ward.	All

Study	Setting	Patients	Treatment administration route[a]
Ghaleb et al. (67)	11 paediatric wards (prescribing errors) and 10 paediatric wards (medication administration errors) across five hospitals (one specialist children's teaching hospital, one nonteaching hospital and three teaching hospitals) in the London area.	The five hospitals selected were one specialist children's teaching hospital (hospital A), three general teaching hospitals (hospitals B to D) and one non-teaching general hospital (hospital E).	All
Haw et al. (68)	Two elderly long-stay wards in an independent UK psychiatric hospital in England.	Patients with a wide range of mental health problems.	All
Huynh et al. (69)	Paediatric hospital wards in four English hospitals providing secondary and tertiary care.	Children that were admitted over a 5-month study period, and prescribed at least one long-term medication at admission.	All
James et al. (70)	Five district general hospitals across Wales.	Not reported.	All
Jones and Bhandari (71)	Medical admissions unit of a University Teaching Hospital (Hull Royal Infirmary).	100 patients over 70 years of age with chronic kidney disease stages 3–5 based on the medical records and previous biochemistry.	Intravenous fluid charts were not analysed in this study
Keers et al. (72)	Three National Health Service (NHS) mental health hospitals in the North West of England.	50 mental health inpatient wards. Prescription items were screened at hospital admission and during patient stay.	All
Kelly et al. (77)	One care-of-the-elderly ward and one stroke unit at each of four acute hospitals in the East of England.	625 patients with and without dysphagia - 214 (34.2%) had swallowing difficulties.	All
Morton Errera (73)	Eighteen acute paediatric pain teams in the United Kingdom and Eire.	Patients aged 0–18.	All
Ryan et al. (74)	Eight hospitals in Scotland.	Not reported but paediatric and obstetric units were excluded.	All
Seden et al. (75)	Nine diverse National Health Service hospitals in North West England.	Teaching hospitals, general hospitals, specialist centres for paediatrics, women's health and mental health at admission and discharge.	All

Study	Setting	Patients	Treatment administration route[a]
Tully et al. (76)	880-bed university teaching hospital in England.	Hospital admission, inpatients and discharge.	All

[a]If the article did not specify whether all or particular route(s) were studied, it was assumed that medication administered via all routes was observed

Study design and study duration of studies in secondary care

Details of the study design and study duration are presented in Table 19.

Fourteen of the included studies in secondary care were prospective design,(60, 61, 63, 65-69, 72-77) and five were retrospective design.(62, 64, 70, 71, 83)

Across the prospective studies, study duration ranged from two weeks (61, 67) to 18 months.(76) Three of the prospective studies did not report on study duration.(63, 68, 75) Study duration across the retrospective studies ranged from one day (64) to 12 months.(62)

Of the prospective studies, nine evaluated prescribing errors.(60, 61, 65, 66, 69, 72, 74-76) Two of these reported on prescribing errors made by newly qualified doctors,(60, 74) one reported on prescribing errors made by newly qualified and junior doctors, mid-grade and senior doctors, nurses and pharmacists;(75) one reported on medication order errors made by hospital doctors (grade not specified),(76) one reported on prescribing errors made by pharmacists,(61) three prospective studies evaluating prescribing errors did not report who the prescribers were.(65, 66, 72)

One prospective study evaluated prescribing errors made by doctors and administration errors made by nurses,(67) two evaluated medication administration errors made by nurses,(68, 77) and one reported on prescribing errors made by nurses.(63)

One prospective study evaluated serious clinical incidents associated with continuous opioid infusion, patient-controlled analgesia administration, and nurse-controlled analgesia administration.(73)

Of the retrospective studies, one evaluated prescribing errors made by doctors from paediatric maxillofacial and anaesthetic teams,(62) one evaluated prescribing errors across adult medical and surgical specialities wards (prescriber not reported),(64) one evaluated hospital dispensing errors, e.g., wrong strength on label (label error) or wrong strength dispensed (drug error),(70), one evaluated potentially inappropriate medication prescribing (contraindicated or prescribed at an inappropriate dose for the level of renal function) in elderly patients with chronic kidney disease,(71) and one evaluated incident reports involving antimicrobials reported on an electronic reporting system.(83)

Table 19: Details of the study design and study duration in studies undertaken in secondary care

Study	Design	Duration
Ashcroft et al. (60)	Prospective study of prescribing errors made by first-year post-graduate doctors, senior doctors and non-medical prescribers.	Seven selected weekdays, each approximately one month apart.
Baqir et al. (61)	Prospective study of prescribing errors made by pharmacists.	10 days (Monday to Friday) over two consecutive weeks.
Bolt et al. (62)	Retrospective study of prescribing errors made by doctors from paediatric maxillofacial and anaesthetic teams.	1 January 2010 to 1 January 2011.
Cottney and Innes (63)	Prospective study of medication administration errors made by nurses.	Not reported - each of the four daily medication rounds on each of the inpatient wards was observed.
Covvey et al. (83)	Retrospective analysis of Datix* incident reports involving antimicrobials.	April 2010 to December 2013.
Denison Davies et al. (64)	Retrospective study of opioid prescribing errors across adult medical and surgical specialities wards (prescriber not reported).	One day in December 2009.
Franklin et al. (65)	Prospective study of prescribing errors across a directorate comprising ten specialities (prescriber not reported).	One day each fortnight between February and May 2005.
Franklin et al. (66)	Prospective study of prescribing errors identified by ward pharmacists (prescriber not reported).	One day each fortnight between February and May 2005.
Ghaleb et al. (67)	Prospective study of prescribing errors made by doctors and administration errors made by nurses.	Data were collected every week day for two consecutive weeks in each of the 11 wards at the five hospitals during 2004/2005.
Haw et al. (68)	Prospective study of medication administration errors made by nurses.	Not reported.
Huynh et al. (69)	Prospective study of prescribing errors (medication order) made by hospital doctors at admission .	Five-month study period.
James et al. (70)	Retrospective study of hospital dispensing errors.	September 2005 to December 2005.
Jones and Bhandari (71)	Retrospective study of potentially inappropriate medication prescribing in elderly patients with CKD.	January 2008 to June 2008.
Keers et al. (72)	Prospective study of prescribing errors at admission and during patient stay (prescriber not reported).	10 data collection days individually selected between January–April 2013.
Kelly et al. (77)	Prospective study of medication administration errors made by nurses.	Each ward was visited twice a month between 1 March and 30 June 2008.

Study	Design	Duration
Morton and Errera (73)	Prospective study to determine serious clinical incidents (SCIs) associated with the techniques of continuous opioid infusion, patient-controlled analgesia, and nurse-controlled analgesia in patients aged 0–18.	17 months.
Ryan et al. (74)	Prospective study of prescribing errors amongst foundation doctors.	14 months.
Seden et al. (75)	Prospective study of prescribing errors (different grades of prescriber).	Not reported.
Tully et al. (76)	Prospective study of prescribing errors identified by pharmacists in hospital amongst doctors (grade not reported).	March 2003 to August 2004.

CKD =chronic kidney disease, *Datix is a web-based software tool used for the collection, analysis and dissemination of information related to patient safety and risk management in the NHS

Details of definitions of medication errors and their severity reported by the included studies in secondary care are presented in Table 20.

Across the studies in secondary care a variety of definitions of medication error were applied. Six of the included studies (60, 66, 72, 74-76) defined errors according to the definition by Dean et al.(87) and one used definitions by Dean et al.(87) and the Department of Health.(88) One study (63) defined errors according to the definition by Barker at al. (89) and one study (68) defined errors according to the definitions by Barker et al. (89) and O'Shea (90) One study (77) categorised administration errors according to Dean (91) but as the study was concerned with administration via nasogastric or percutaneous endoscopic gastrostomy tubes, where preparation and administration technique are particularly relevant and inter-related, these categories were combined, and together with time errors, and 'others' were added to Dean's classification to give an 11-point classification system The study that evaluated potentially inappropriate medication prescribing in elderly patients with chronic kidney disease(71) used the modified Beers criteria.(92)

Various error definitions were used across four studies in hospital inpatient populations.(61, 64, 67, 70) One study (61) classified errors according to the EQUIP study,(93) one classified prescribing errors according to work by Ghaleb et al.,(94) one study(64) applied local,(95, 96) national,(97) and international guidelines(98, 99) to create a pool of potential prescribing errors; and one study(70) used an established system for reporting standardised dispensing error data in accordance with the UK National Patient Safety Agency guidance to ensure consistency with the UK National Reporting and Learning System.(100-102)

One study of prescribing errors made by doctors from paediatric maxillofacial and anaesthetic teams(62) defined errors as the difference between prescribed and calculated doses and one study evaluating serious clinical incidents (SCIs) associated with the techniques of continuous opioid infusion, patient-controlled analgesia, and nurse-controlled analgesia;(73) defined SCIs as according to eight categories identified in advance by an expert panel. One study reporting on prescribing, administration, and monitoring errors associated with antimicrobials did not provide definitions.(83)

Severity of errors was assessed by eight of the included studies in secondary care.(60, 63, 64, 68, 69, 72, 75, 76) Across these studies the categorisations of severity varied. Two studies(72, 75) used criteria (minor, serious or potentially life-threatening) from the EQUIP study.(93) One study used criteria (minor clinical severity, negligible clinical severity, potentially serious clinical consequences, potentially life threatening) defined by Haw et al.(68) Two studies(60, 76) used the severity categorisations (problem orders, potentially significant, potentially serious and potentially severe or fatal) of Lesar et al.(103) One study(68) used categorisations (errors or omissions: of doubtful or negligible importance, likely to result in minor adverse effects or worsening condition, likely to result in serious effects or relapse, likely to result in fatality, unrateable) by Stubbs et al.(104) One study(69) classifiable unintentional medication discrepancies into the 'harm' classification by Terry et al.(105) One study(64) categorised prescribing errors as potentially lethal, serious, significant, or minor (classification system not reported). One study defined incident severity medication related incident reports for antimicrobials as minor clinical severity, negligible clinical severity, potentially serious clinical consequences, and potentially life threatening (classification system not reported).(83)

Table 20: Details of definitions of medication errors and severity in studies undertaken in secondary care

Study	Definition of error	Error severity definition
Ashcroft et al. (60)	Error was one which occurs when, as a result of a prescribing decision or prescription writing process, there is an unintended, significant reduction in the probability of treatment being timely and effective, or increase in the risk of harm when compared with generally accepted practice.(87)	Severity categories included minor, significant, serious, or potentially lethal errors and were based on rating scales used in previous medication error research(103, 106)
Baqir et al. (61)	Any intervention the clinical pharmacist had to make to ensure that the prescribing was clinically correct and legal. Errors were classified according to the EQUIP study.(93)	Severity not assessed.
Bolt et al. (62)	Difference between prescribed and calculated doses.	Severity not assessed.
Cottney and Innes (63)	A dose administered differently than as prescribed on the patient's medication chart. An opportunity for error was defined as a dose that was either observed being given or omitted.(89)	Severity of error was categorized according to a previously reported system.(68) Minor clinical severity, negligible clinical severity, potentially serious clinical consequences, potentially life threatening.
Covvey et al. (83)	Prescribing, administration and monitoring errors associated with antimicrobials.	Incident severity: Negligible, Minor, Moderate, Major, Severe.
Denison Davies et al. (64)	The study authors created a pool of potential prescribing errors based on a series of quality statements based on local,(95, 96) national,(97) and international guidelines.(98, 99)	Potentially Lethal (Category A) Serious (Category B) Significant (Category C) Minor (Category D) Severity categories not defined
Franklin et al. (65)	A prescribing error was defined as a prescribing decision or prescription-writing process that results in an unintentional, significant: (i) reduction in the probability of treatment being timely and effective or (ii) increase in the risk of harm, when compared to generally accepted practice.(87, 88)	Study authors chose not to assess severity or type of errors.
Franklin, et al. (66)	A practitioner-led definition of a prescribing error.(87)	Severity not assessed.
Ghaleb et al. (67)	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant: (1) Reduction in the probability of treatment being timely and effective or (2) Increase in the risk of harm when compared with generally accepted practice(94)	Study authors report that the severity of these medication errors remains to be explored.

Study	Definition of error	Error severity definition
Haw et al. (68)	A deviation from a prescriber's valid prescription or the hospital's policy in relation to drug administration, including failure to correctly record the administration of a medication.(89, 90)	Medication administration errors defined as follows(104): Grade 1: errors or omissions of doubtful or negligible importance. Grade 2: errors or omissions likely to result in minor adverse effects or worsening condition. Grade 3: errors or omissions likely to result in serious effects or relapse. Grade 4: errors or omissions likely to result in fatality. Grade X: unrateable.
Huynh et al. (69)	A discrepancy was defined as a difference between the patient's pre-admission medication (PAM) compared with the initial admission medication orders (AMO) written by the hospital doctor. The discrepancies were classified into intentional and unintentional discrepancies. The unintentional discrepancies were assessed for potential clinical harm.	Unintentional discrepancies were classifiable into the 'harm' classification.(105)
James et al. (70)	UKDEAS - an established system for reporting standardised dispensing error data, classified in accordance with the UK National Patient Safety Agency guidance to ensure consistency with the UK National Reporting and Learning System.(100-102)	Severity not assessed.
Jones and Bhandari (71)	PIMs were defined by using the modified Beers' criteria(92) as any medication deemed inappropriate by the authors if it was contraindicated or prescribed at an inappropriate dose for the level of renal function.	Severity not assessed.
Keers et al. (72)	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription-writing process, there is an unintentional significant reduction in the probability of treatment being timely and effective, or an increase in the risk of harm when compared with generally accepted practice.(87) Scope extended to include prescribing a drug without first registering a patient with the appropriate monitoring service and prescribing a drug to treat mental health illness without authorisation from a Mental Health Act form.	Prescribing error classification: (93) Not clinically relevant: Minor. Clinically relevant prescribing errors: Significant, Serious, Life-threatening.

Study	Definition of error	Error severity definition
Kelly et al. (77)	Using the British National Formulary (British Medical Association and Royal Pharmaceutical Society of Great Britain 2006), British Association of Parenteral Nutrition guidelines (British Association of Parenteral and Enteral Nutrition 2004) and White and Bradnam's (2006) guidelines appropriateness of administration was evaluated. The results were then categorized using Dean's (91) adapted American Society of Hospital Pharmacists (ASHP) classification (American Society of Hospital Pharmacists 1993). Time errors, and 'others' were added to Dean's classification to give an 11-point classification system.	Severity not assessed.
Morton and Errera (73)	Eight categories of SCI were identified in advance by an expert panel including drug error (not defined).	Severity not assessed.
Ryan et al. (74)	One which occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant reduction in the probability of treatment being timely and effective or an increase in the risk of harm when compared with generally accepted practice.(87)	Severity not assessed.
Seden et al. (75)	A clinically meaningful prescribing error occurs when, as a result of a prescribing decision or prescription writing process, there is an unintentional significant: (1) reduction in the probability of treatment being timely and effective or (2) increase in the risk of harm when compared with generally accepted practice.(87)	A modified EQUIP study criteria(93) was used for error categorisation and severity (minor, serious or potentially life-threatening).
Tully et al. (76)	Pharmacists judged whether a prescribing error had occurred and categorised it, using the definition and typology of Dean et al.(87)	Severity was defined using the categorization of Lesar et al.(103) (problem orders, potentially significant, potentially serious and potentially severe or fatal)

UKDEAS = UK Dispensing Error Analysis Scheme; PIM = potentially inappropriate medication; SCIs = serious clinical incidents

Data collection methods and observers in studies in secondary care

Details of data collection methods and observers reported by the included studies in secondary care are presented in

Table 21.

There were three prospective studies in secondary care in paediatric populations.(67, 69, 73) In one study, pharmacists reviewed medication orders made by doctors on drug charts for prescribing errors and nurses were observed during drug administration for administration errors.(67) In one study, a team of healthcare professionals compared medication records from the GP against the admission medication order written by hospital doctors in children who were admitted and prescribed long-term medication at admission.(69) In one study, serious clinical incidents associated with the techniques of continuous opioid infusion, patient-controlled analgesia, and nurse-controlled analgesia were recorded and reviewed by an expert panel.(73)

There were three prospective studies in populations with mental health problems.(63, 68, 72) In one study, pharmacists checked medication orders written by nurses in acute mental health.(63) In one study, pharmacists identified prescribing errors for all newly prescribed/written or omitted items across mental health inpatients.(72) In one study, a pharmacist observed medication administration by nurses of regular and as required drugs.(68)

There were eight prospective studies in mixed populations. In one study pharmacists identified errors made by first-year post-graduate doctors, senior doctors and non-medical prescribers.(60) In one study, pharmacists identified errors made by newly qualified doctors.(74) In one study, ward-based pharmacists checked inpatient medication orders written by pharmacists for errors.(61) In one study, pharmacists identified errors made by prescribers of different grades.(75) In one study, a nurse experienced in observing medicine rounds observed nurses administering medicines to patients.(77) In three studies where the prescriber was not reported, pharmacists recorded data on prescribing errors.(65, 66, 76)

There were four retrospective studies in secondary care. In one study in children admitted under the care of oral/maxillofacial surgery, drug charts were retrieved and checked for adequate and appropriate drug prescribing.(62) In one study in elderly patients with chronic kidney disease, case notes were analysed and the number of patients receiving at least one potentially inappropriate medication (PIM) and the number of PIMs out of all medications prescribed were analysed.(71) In one study in medical and surgical specialities, drug charts were retrieved for most adult medical and surgical specialities and were checked by doctors.(64) In one study across district general hospitals, details of non-prevented and prevented dispensing incidents were self-reported by pharmacy staff on standardised UK Dispensing Error Analysis Scheme dispensing error forms that were reviewed by dispensary

managers.(70) In one study in hospitals in one regional area, data were extracted from an electronic incident reporting system (Datix[1]).(83)

[1] Datix is a web-based software tool used for the collection, analysis and dissemination of information related to patient safety and risk management in the NHS

Table 21: Data collection in studies undertaken in secondary care

Reference	Observation method	Observer
Ashcroft et al. (60)	All newly prescribed or rewritten inpatient medication orders were screened for prescribing errors.	Hospital Pharmacists.
Baqir et al. (61)	All prescribing was assessed for safety and accuracy.	Ward-based clinical pharmacists, who were not prescribers.
Bolt et al. (62)	The appropriate drug chart was retrieved and checked to ensure that it had been completed for adequate and appropriate drug prescribing.	Not reported.
Cottney et al. (63)	Each of the four daily medication rounds on each of the inpatient wards was observed.	15 pharmacists and 7 pharmacy technicians.
Covvey et al. (83)	Data columns of interest included hospital directorate (a coordinated group of related clinical specialties), medication administered, and incident date, subcategory, stage, description, action taken, result and severity, were extracted from Datix*.	Not reported.
Denison Davies et al. (64)	Review of all drug charts across the hospital wards.	A team of five doctors (four anaesthetic specialist registrars and one palliative care specialist registrar).
Franklin et al. (65)	Pharmacists providing ward pharmacy services to the twenty wards within the selected directorate were asked to record data on any prescribing errors identified on newly prescribed regular, when required and discharge medication.	Pharmacists.
Franklin et al. (66)	Pharmacists documented details of any prescribing errors identified, the number of doses administered (or omitted) before the error was corrected, whether or not they made an intervention to correct the error and the number of occupied beds on the ward.	Pharmacists.
Ghaleb et al. (67)	Data collectors accompanied the pharmacists who were experienced in paediatrics and documented any errors identified and nurses were observed during drug administration.	There were five data collectors (including the principal) The data collectors were given training and advice from the principal investigator on the methods used and what information to collect.
Haw et al. (68)	The head pharmacist observed medication administration of regular and as required drugs given at each of the four routine daily drug rounds.	Head pharmacist.

Reference	Observation method	Observer
Huynh et al. (69)	The patient's medication record from the GP was defined as the patient's PAM list, and this was compared against the initial AMOs written by the hospital doctor prior to pharmacist input. A panel of experts consisting of two paediatric clinical pharmacists, two hospital doctors and a medicines management nurse (the 'Clinical Assessment Panel') met and categorised the discrepancies.	Team of healthcare professionals, which included doctors, pharmacists and nurses.
James et al. (70)	Details of un-prevented and prevented dispensing incidents, defined by the inclusion criteria were self-reported by pharmacy staff on an anonymous, standardised UKDEAS dispensing error form. Pharmacy staff used a standardised matrix to categorise the severity of patient harm for patients who had taken the medicine involved in un-prevented dispensing incidents and potential risk of harm for those who had not received the medication (including prevented dispensing incidents).	As per routine practice, the dispensary managers reviewed each error form for accuracy as they submitted the reports online to UKDEAS via the NHS intranet.
Jones and Bhandari (71)	Case notes were retrospectively analysed. The number of patients receiving at least one PIM (PIM prevalence among patients) and the number of PIMs out of all medications prescribed (PIM prevalence among prescribed medications) were analysed.	Not reported.
Keers et al. (72)	The process of recording inpatient prescribing errors was based on the UK EQUIP study.(93)	Twenty-nine clinical pharmacists employed across the study sites identified prescribing errors for all newly prescribed/written or omitted items as part of their routine clinical practice.
Kelly et al. (77)	Undisguised direct observation of the nurses administering medicines to patients was used. Two detailed standardized proforma (one for oral and one for enteral administration) were used to help reduce observer bias.	All observations were carried out by a nurse experienced in observing medicine rounds.
Morton and Errera (73)	The Document Capture Company was commissioned to design a web-based data reporting form for denominator data and a detailed SCI reporting form.	Reports on all SCIs were sent to the expert panel for review.
Ryan et al. (74)	In each study hospital, data were collected from each participating ward. Ward clinical pharmacists reviewed prescription charts for possible errors and for study purposes, recorded data on: age, sex, allergy status, number of medicines prescribed, grade of prescribing doctor	Ward clinical pharmacists

Reference	Observation method	Observer
Seden et al. (75)	Nominated ward-based clinical pharmacists prospectively documented prescribing errors at the point of checking inpatient or discharge prescriptions, during normal pharmacy working hours.	Nominated ward-based clinical pharmacists.
Tully et al. (76)	Nine pharmacists recorded the prescribing errors they identified during their normal ward visits on that day. All wards visited by pharmacists were included in the study, categorised by speciality.	Hospital pharmacists.

AMO = admission medication orders; PAM = patient's preadmission medication; PIM = potentially inappropriate medication; SCI = serious clinical incident; UKDEAS = UK Dispensing Error Analysis Scheme.

*Datix is a web-based software tool used for the collection, analysis and dissemination of information related to patient safety and risk management in the NHS

Results of studies in secondary care

Details of the study design and prescriber, denominator and numerator, and the reported error rate and severity, are presented in Table 22. The table is also ordered by population with subheadings as follows: paediatrics, adult and children mental health, elderly mental health, elderly with kidney disease, and mixed hospital populations.

Paediatrics

The retrospective study by Bolt et al. (62) in doctors from maxillofacial and anaesthetic teams prescribing in children, reported an overall error rate of 13% (no variance estimate reported) with respect to prescription of medication frequency, with significantly more errors made by the oral/ maxillofacial team than the anaesthetics team. Error severity was not assessed.

The prospective study by Ghaleb et al. (67) in doctors prescribing and nurses administering medications to paediatric patients, reported that there were 13.2% (95% CI 12.0% to 14.5%) prescribing errors and 19.1% (95% CI 17.5% to 20.7%) administration errors.

The prospective study by Huynh et al. (69) assessing unintended medication discrepancies made by hospital doctors at admission in paediatric hospital wards, reported that there were 209 unintentional discrepancies, affecting 109/244 (45%) patients. Of these, 189 unintentional drug discrepancies affecting 100/244 (41%) patients were classifiable into the 'harm' classification of Terry et al.(105)

The prospective study by Morton and Errera (73) assessing serious clinical incidents (SCI) associated with analgesia in paediatrics, reported 46 SCIs out of 10,726 opioid infusion techniques (0.43%), one

resulting in cardiac arrest (0.009%). Of these, 17 (0.16%) were drug errors, of which 9 (0.16%) would have resulted in over-administration of opioid.

Mental health – children and adults

The prospective study by Cottney and Innes (63) in nurses prescribing in acute adult mental health services, reported that there were 139 errors across 4,177 opportunities (3.3%). Of these errors, 98/139 (71%) were of minor clinical severity, and 15/139 (11%) could have had potentially serious clinical consequences according to the criteria of Haw et al.(68) None were reported as life-threatening.

The prospective study by Keers et al.(72) assessing prescribing errors in mental health inpatients, reported that orders prescribed on admission to hospital were associated with the highest prescribing error rate (10.7% (95% CI 8.6% to 12.7%)) when compared to items prescribed during hospital stay (6.5% (5.3% to 7.8%)) or at discharge (6.5% (4.3% to 8.6%)). Of the clinically relevant prescribing errors according to the criteria from the EQUIP study,(93) 142 (49.3%) were significant, 19 (6.6%) were serious and 1 (0.3%) was life-threatening.

Mental health – elderly

The prospective study by Haw et al. (68) assessing nurse medication administration in old-age psychiatry, reported that 369 errors were made across 1,423 administered medication doses (25.9%). Of these, 1 (0.3%) was an error likely to result in minor adverse effects or worsening condition and none were likely to result in fatality according to the criteria by Stubbs et al.(104)

Elderly patients with chronic kidney disease

The retrospective study by Jones and Bhandari (71) assessing potentially inappropriate medications (PIMs) in 100 patients over 70 years of age with chronic kidney disease, reported that 56/100 (56%) had a PIM prescribed and 81/622 (13%) of all medications prescribed were potentially inappropriate. Error severity was not assessed.

Elderly patients with and without dysphagia

The prospective study by Kelly et al. (77) assessing oral and enteral administration errors in elderly patients with and without dysphagia, reported that of the 2129 medicine administrations observed, 817 (38.4%) involved an error, and of these 313 involved patients with dysphagia. Error severity was not assessed.

Hospital mixed populations

The prospective study by Ashcroft et al. (60) of prescribing errors made by first-year post-graduate doctors, senior doctors and non-medical prescribers, reported that the mean prescribing error rate across all prescribers was 8.8% (95% CI 8.6–9.1) errors. The error rate associated with medication orders at the time of hospital admission (13.3%, 95% CI 12.8–13.8) was higher than when newly prescribed medication was initiated during the hospital stay (7.5%, 95% CI 7.1–7.9) or when medication was prescribed on discharge from hospital (6.3%, 95% CI 5.9–6.7). The study authors reported 51.6% of prescribing errors were significant and 7.3% were serious according to the criteria of Lesar et al.(103)

The prospective study by Ryan et al. (74), on prescribing errors by newly qualified doctors, reported that 36% of 4,710 patient charts and 7.5% of items prescribed had errors. Of the 44,726 items prescribed, errors were observed in 1,907 (56.7%) at admissions, 123 (3.7%) at transcription of a new drug chart, 825 (24.5%) during inpatient stay, and 489 (14.5%) at discharge. Severity of errors was not assessed in this study.

The prospective study by Seden et al. (75), on prescribing errors observed across different grades of doctors, reported that of 4238 prescriptions 43.8% contained at least one error. Of these, 1629 (54.1%) were significant, 109 (3.6%) were serious and nine (0.30%) were reported as potentially life threatening according to the criteria of the EQUIP study.(93)

In the prospective study of prescribing errors by Tully et al. (76) where the grade of doctor was not reported, 3,455 errors in 33,012 individual new medication (10.5%) were identified for 2,040 patients. Of these, 197 (5.7%) were reported as potentially serious, and 54 (1.6%) were potentially severe or fatal according to the criteria of Lesar et al.(103)

The prospective studies by Baqir et al. (61) and Franklin et al. (65) both assessed prescribing errors made by pharmacists. Baqir et al. (61) reported that there were four errors in 1,415 pharmacist-prescribed medication orders (0.3% error rate, variance not reported). Franklin et al. (65) reported that there were 462 medication orders containing at least one prescribing error out of 4,995 medication orders written (9.2%; 95% CI 8.5 –10.1%). Neither study assessed error severity.

The prospective study by Franklin et al. (66) evaluated prescribing errors made by pharmacists and nurses. Overall, 1025 prescribing errors were identified in 974 of 6605 medication orders (14.7%, 95% CI 13.8% to 15.6%). Error severity was not assessed.

In the retrospective study of opioid prescribing in hospital patients by Denison Davies et al. (64) a total of 90/330 (27.2%) individual charts with errors were found. Of these, a consensus group identified 26/90 (28.9%) serious errors and 4/90 (4.4%) lethal errors.

In the retrospective study of incident reports involving antimicrobials by et al. (83) 342/1345 (25.4%) prescribing errors, 673/1345 (50.0%) administration errors and 74/1345 (5.5%) monitoring errors were observed. No severe errors were reported.

In the retrospective study of hospital dispensing errors by James et al. (70) out of 221,670 dispensed items, 35 non-prevented dispensing incidents occurred (0.016%) involving 42 types of dispensing error, and 291 prevented dispensing incidents occurred (0.131%) involving 339 types of dispensing error, were reported. Error severity was not assessed.

Table 22: Summary of studies undertaken in secondary care.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Paediatric					
Bolt et al. (62)	Retrospective study of doctors from maxillofacial and anaesthetic teams prescribing in children.	60 patients; 4 had no drug chart. Across 56, 99 doses prescribed (71 anaesthetic team, 28 oral/max surgery).	99 weight-adjusted doses of medications.	An overall error rate of 13% was found with respect to prescription of medication frequency, with significantly more by oral/ maxillofacial than anaesthetic team. The majority of 'errors' in frequency prescribing by the anaesthetic team related to omission of any entry in the drug chart, whereas all oral/maxillofacial errors related to an incorrect entry.	Not assessed.
Ghaleb et al. (67)	Prospective study of doctors prescribing and nurses administering medications to paediatric patients.	A total of 444 paediatric patients with 2955 medication orders and 2249 opportunities for administration error were studied over 22 weeks.	There were 391 prescribing errors. Prescribing error rates varied between 5% (95% CI 2.2% to 7.8%) in one ward and 31.5% (95% CI 24.3 to 38.6) in another. Incomplete prescriptions were the most common type of prescribing error, and dosing errors the third most common. 429 medication administration errors were identified.	13.2% (95% CI 12.0% to 14.5%) prescribing errors. 19.1% (95% CI 17.5% to 20.7%) erroneous administrations.	Study authors report that the severity of these medication errors remains to be explored.
Huynh, 2016(69)	Prospective study of unintended medication	Two hundred and forty-four patients were admitted to the	582 medication discrepancies from the 1004 drug prescriptions (58%) affecting 203 patients	209 unintentional discrepancies, affecting 109/244 (45%) patients	189 drug discrepancies affecting 100 patients were unintentional discrepancies

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
	discrepancies in paediatric hospital wards made by hospital doctors at admission.	study and 1004 individual drug prescriptions were recorded.	(83%). Of the 582 discrepancies, 209 were classified as unintentional, 277 were intentional and 96 were reclassified as trivial.		and were classifiable into the 'harm' classifications The remaining 20 unintentional discrepancies were considered to be clinically beneficial to the patient.
Morton and Errera (73)	Prospective study of serious clinical incidents associated with continuous infusion, patient-controlled analgesia, or nurse-controlled analgesia in paediatrics.	Data on 10,726 children were collected	Forty-six SCIs (cardiac arrest, 1; respiratory depression, 14; less serious adverse effects, 14; drug errors, 17) were reported in 10,726 opioid infusion techniques (0.43%). Of the 17 drug errors 12 were programming errors and five prescribing errors. Out of the 17 drug errors, 9 would have resulted in over-administration of opioid, in one case by a factor of 80, and two of the 17 would have resulted in under-delivery of opioid with resultant inadequate analgesia. Of the 17, 6 were very minor errors, which would have resulted in the correct dose of opioid being administered.	Not reported.	Not assessed.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Mental health – children and adult					
Cottney and Innes (63)	Prospective study of nurses prescribing in acute adult mental health services.	4177 opportunities for error.	139 errors.	3.3% (139/4177) per opportunity with 0.81% (139/172) errors per medication round. At least one error was made on 37% (63/172) of the observed medication rounds.	The majority of errors (71%, 98/139) were of minor clinical severity. Nineteen percent (26/139) were of negligible clinical severity, and the remaining 11% (15/139) could have had potentially serious clinical consequences. None had the potential to be life threatening.
Keers 2014(72)	Prospective study of prescribing errors in mental health inpatients.	4427 newly written or omitted prescription items were assessed by study pharmacists.	After review by the expert panel, 281 newly prescribed or omitted items were found to be affected by 1 or more PEs, giving an error rate of 6.3% (95% CI 5.6 to 7.1%). Seven prescription items were affected by 2 Pes.	Orders prescribed on admission to hospital were associated with the highest PE rate (10.7% (95% CI 8.6% to 12.7%)) when compared to items prescribed during hospital stay (6.5% (5.3% to 7.8%)) or at discharge (6.5% (4.3% to 8.6%)).	Not clinically relevant (Minor): 126 (43.8%). Clinically relevant prescribing errors: Significant: 142 (49.3%). Serious: 19 (6.6%). Life-threatening: 1 (0.3%).

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Mental health – elderly					
Haw et al. (68)	Prospective study of nurse medication administration in old-age psychiatry.	1423 opportunities for errors.	A total of 369 errors were made. For 20 (1.4%) doses, two errors were made. Errors detected by chart review: yhe independent pharmacist who reviewed the medication charts detected 148 administration errors Errors reported using the Hospital's medication error reporting system - none	25.9%.	Medication administration: Grade 1: errors or omissions of doubtful or negligible importance - 255 (69.1%). Grade 2: errors or omissions likely to result in minor adverse effects or worsening condition - 27 (7.3%). Grade 3: errors or omissions likely to result in serious effects or relapse - 1 (0.3%). Grade 4: errors or omissions likely to result in fatality - 0 (0%). Grade X: unrateable - 86 (23.3%).
Elderly with chronic kidney disease					
Jones and Bhandari (71)	Retrospective study of PIMs in patients over 70 years of age with chronic kidney disease.	100 patients.	56 out of the 100 patients had a PIM prescribed. A total of 622 medications were prescribed among the 100 patients with an average six medications per patient (range 1–12).	The prevalence rate of PIMs among patients was 56%. Overall, 13% (81/622) of all medications prescribed were potentially inappropriate.	Not assessed.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Elderly with and without dysphagia					
Kelley et al. (77)	Prospective study of medication administration errors in elderly patients with and without dysphagia.	2129 medicine administrations.	817 involved an error, and of these 313 involved patients with dysphagia.	38.4% Excluding time errors, the normalised frequency of medicine administration errors for patients with dysphagia was 21.1% compared with 5.9% for patients without.	Not assessed.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Hospital – mixed populations					
Ashcroft et al. (60)	Prospective study of prescribing errors made by first-year post-graduate doctors, senior doctors and non-medical prescribers in hospital patients on admission, during stay and at discharge.	26,019 patients and 124,260 medication orders.	10,986 medication orders had prescribing errors, resulting in 11,235 prescribing errors being detected.	The mean prescribing error rate (all prescribers) was 8.8% (95% CI 8.6–9.1) errors per 100 medication orders. The error rate associated with medication orders at the time of hospital admission (13.3%, 95% CI 12.8–13.8) was higher than when newly prescribed medication was initiated during the hospital stay (7.5%, 95% CI 7.1–7.9) or when medication was prescribed on discharge from hospital (6.3%, 95 % CI 5.9–6.7) Foundation doctors (FY1 and FY2) wrote the majority of medication orders (68%) and had the highest prescribing error rates (FY1 8.6%, 95% CI 8.2–8.9; FY2 10.2%, 95% CI 9.7–10.7) in comparison with other types of prescriber.	Severity grading found that 41.1% of prescribing errors were minor, 51.6% were significant and the remaining 7.3% were serious or potentially life threatening. The rate of potentially serious prescribing errors was higher for consultants and nurse prescribers than all other types of prescriber, but not significant.
Baqir et al. (61)	Prospective study of pharmacists prescribing across all wards	1415 pharmacist-prescribed medication orders	Four errors	0.3% error rate.	Not assessed.
Hospital – mixed populations cont.					

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Covvey et al. (83)	Retrospective analysis of Datix* incident reports involving antimicrobials.	1345 Datix reports on incidents related to antimicrobials.	Reports concerning prescribing, medication administration/supply and monitoring errors.	Prescribing, 25.4% (n = 342). Administration/supply 50.0% (n = 673). Monitoring 5.5% (n = 74). 138 reports (10.3%) were classified as 'other'.	The most common incident (all types) severity rating was minor 47.7% (n=642), followed by negligible 32.9% (n=443), moderate 16.6% (n=223) and major 0.6% (n=8). No severe errors were reported, and 29 reports (2.2%) had no severity rating attached.
Denison Davies et al. (64)	Retrospective study of opioid prescribing in hospital patients.	Opioids were prescribed on 353/722 (49%) of charts, 23 were excluded on expert consensus.	On the study day, a total of 74/330 (22.4%) individual charts with errors were found. On further review by the expert consensus group another 16 individual charts with errors were found (4.8%). The total number of charts with errors was therefore 90/330 (27.2%).	27.2%.	The consensus group review established that all Potentially Lethal (Category A) errors (4/90) were picked up on the study day. There were 26/90 Serious (Category B) errors, 22 of which were picked up on the study day; 38/90 Significant (Category C) errors, 29 of which were picked up on the study day and 22/90 Minor (Category D) errors, 19 of which were picked up on the study day Severity categories not defined.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Franklin et al. (65)	Prospective study of pharmacists prescribing across ten specialities.	4,995 medication orders were written.	462 contained at least one prescribing error. The total number of prescribing errors identified was 474.	9.2%; 95% CI 8.5 –10.1%.	Study authors chose not to assess severity or type of errors.
Franklin et al. (66)	Prospective study of pharmacists and nurses prescribing in hospitals.	A total of 6237 newly written medication orders were studied across three organisations and 10 wards; 368 erroneous prescribing omissions were also identified, giving a denominator of 6605.	Overall, 1025 prescribing errors were identified in 974 of 6605 medication orders This corresponds to 58 prescribing errors per 100 patient days. For the 4035 medication orders that were screened by the pharmacist at the same time as checking the patient's medication history, the error rate was 17.3%; for the other 2564 medication orders, the error rate was lower at 12.1% (95% CI for the difference 3.5% to 6.9%).	(14.7%, 95% CI 13.8% to 15.6%).	Not assessed.
James et al. (70)	Retrospective study of dispensing error in hospital.	221,670 dispensed items.	Thirty-five un-prevented dispensing incidents, involving 42 types of dispensing error, and 291 prevented dispensing incidents, involving 339 types of dispensing error, were reported.	Un-prevented 0.016%, prevented 0.131%	Not assessed.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Ryan et al. (74)	Prospective study of prescribing errors amongst newly qualified doctors	4710 patient prescription charts and 44726 items prescribed.	Prescribing errors were found in 1700 patient prescription charts and 3364 items prescribed.	36% of patient prescription charts and 7.5% of items prescribed. Admission, 1907/44726 (56.7%) Transcription of a new drug chart, 123/44726 (3.7%). Inpatient Stay, 825 (24.5%). Discharge, 489/44726 (14.5%). The most commonly encountered error type was medication omitted, 28.6% (963/3364) The majority of errors occurred at time of admission to hospital (1907; 56.7%)	Not assessed.
Seden et al. (75)	Prospective study of prescribing errors observed across different grades of doctors.	A total of 4238 prescriptions were evaluated.	1857 prescriptions contained at least one error. The overall prevalence of prescribing errors (number of prescriptions with one or more error/prescriptions evaluated) ranged from 20% to 60% across the nine hospitals. The rate of errors per prescribed item was 10.9%. A total of 3011 individual errors were observed within the 1857 prescriptions containing an error	43.8% prescriptions contained at least one error.	Of 3011 errors, 1264 (41.9%) were minor, 1629 (54.1%) were significant, 109 (3.6%) were serious and nine (0.30%) were potentially life threatening.

Study	Design and prescriber	Denominator, n	Numerator (and format)	Error Rate %	Error severity
Tully et al. (76)	Prospective study of prescribing errors made by doctors.	33,012 individual new medication orders reviewed for 5,199 patients (6.3/patient).	3,455 errors (in 10.5% of orders) were identified for 2,040 patients.	39.2%; median 1, (range 1–12). Overall, 44.7% of patients (n = 2,324) had at least one error identified in their prescribed medication at the time of admission.	Most were classified as problem orders (1,456, 42.1%) or potentially significant errors (1,748, 50.6%). Less than 6% were potentially serious (197, 5.7%), and 1.6% (n = 54) were potentially severe or fatal.

PE = prescribing error; PIM = potentially inappropriate medicines; SCI = serious clinical incident

*Datix is a web-based software tool used for the collection, analysis and dissemination of information related to patient safety and risk management in the NHS

Format: total number of errors unless stated otherwise

Study quality of studies in secondary care

The results of the quality assessment of studies undertaken in secondary care are presented in Table 23.

Across all 19 of the included studies in secondary care,(60-76, 83) the research question or objective was clearly stated.

In all but two of the studies,(65, 70) the setting and patient population was clearly specified and defined. The study by Franklin et al. (65) reported that the directorate comprised 10 specialities but did not describe what the specialities were and the study by James et al. (70) did not report what the patient population was.

Only eight studies commented on the generalisability of study findings.(61, 64, 66, 67, 69, 72, 74, 76) Denison Davies et al. 2011(64) commented that the study population was a representative sample of patients from both medical and surgical specialities and Ghaleb et al.(67) commented that the study had included different types of hospitals and wards, and the results are therefore likely to be generalisable to other UK clinical environments. Similarly, Huynh 2016(69) commented that as the study was carried out across four geographically different hospital settings with variations in health service delivery, the findings may be generalisable to the paediatric population nationally and internationally**.** Ryan et al. (74) also commented that the generalisabilty of the findings was strengthened by inclusion of a range of ward and hospital types from across Scotland and the use of a mixed approach to questionnaire distribution to maximise response.

In contrast, Baqir 2015(61) commented that the patients were those present on the study weeks, so may not be representative of a standard group of patients and that it is also not known whether the results are generalisable to other hospitals, Franklin et al. (66) commented that further work would be needed to explore the generalisability of findings to other specialties and other NHS organisations, Keers et al. (72) commented that whilst the study was a large study, its findings may not be generalisable to inpatient psychiatric care across the National Health Service, and Tully 2009(76) commented that data in the study were several years old, potentially limiting their generalisability.

In all of the 18 studies(60-76, 83) participants were recruited from the same populations and during the same time period.

Only five of the included studies in secondary care reported the inclusion and exclusion criteria for the study patient population.(64, 66, 69, 72, 74)

Only four studies reported a sample size estimation.(62, 74, 75) Ryan et al. (74) reported that the power calculation was based on an estimated error rate of 15% for 22,400 items and Seden et al. (75) reported that the number of prescriptions audited was empirically determined in order to generate a sample size equivalent to a large study recently undertaken in the UK. Bolt et al. (62) reported that Audit Services provided assistance in the sample size estimation. However, the sample size estimation was not reported. Kelly et al. (77) reported that a sample size calculation identified that 456 medicine dose administration observations to patients without dysphagia were required. Across the remaining studies a sample size estimation was not reported.

Six studies(60, 65, 66, 72, 74-76) defined medication errors according to the criteria of Dean et al.,(87) and one study defined medication errors according to the criteria of Dean et al. and the Department of Health.(87, 88) Across the other studies that reported a standardised description of errors, the standard varied. Baqir 2015(61) defined errors according to the EQUIP study,(61) Ghaleb et al.(67) defined errors according to Ghaleb et al.,(94) Cottney and Innes (63) defined errors according to Barker et al. (89) Haw et al. (68) defined errors according to the criteria of Barker et al. (89) Kelly et al. (77) defined errors according to Dean (91) modified to accommodate nasogastric or percutaneous endoscopic gastrostomy tube administration and time errors, and O'Shea (90) Denison Davies et al. (64) defined errors according to a series of quality statements based on local,(95, 96) national,(97) and international guidelines;(98, 99) Jones and Bhandari (71) defined errors according to Beers et al. (92) and James et al. (70) defined errors according to the UK National Patient Safety Agency guidance to ensure consistency with the UK National Reporting and Learning System.(100-102) The remaining four studies did not report a source for their medication error definition.(62, 69, 73, 83)

Only two studies reported on blinding.(68, 77) The study by Haw et al. (68) reported that a pharmacist undertook a blind retrospective chart review of medication errors. The study by Kelly et al. (77) reported that undisguised direct observation of the nurses administering medicines to patients was undertaken.

The method of data collection was considered reliable for 12 studies.(60-64, 68-70, 72-75, 77) Two studies reported that data collectors had received formal training on standardised data collection methods,(60, 63, 69) eight studies reported the use of standardised data collection forms, proformas or audit forms;(61, 62, 64, 68, 72-74, 77) one study commissioned a document capture company to design a web-based data reporting form;(70) and one study accessed data from the UK Dispensing Error Analysis Scheme (UKDEAS).(75)

Table 23: Quality assessment of studies undertaken in secondary care

Reference	Was the research question or objective in this paper clearly stated?	Was the setting and patient population clearly specified and defined?	Is the patient population representative of a general population?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all patient populations, settings, and medication errors?	Was a sample size justification, power description, or variance and effect estimates provided?	Were medication errors clearly defined, in accordance with recognised criteria?	Were medication errors assessed consistently across all study participants?	Were the observers blinded to the subjects they were assessing?	Is the method for collecting data (medication errors) reliable?
Ashcroft et al. (60)	Y	Y	CD	Y	NR	NR	Y	Y	NR	Y
Baqir et al. (61)	Y	Y	N	Y	NR	NR	N	Y	NR	Y
Bolt et al. (62)	Y	Y	CD	Y	NR	CD	N	Y	NR	Y
Cottney and Innes (63)	Y	Y	CD	Y	NR	NR	Y	Y	NR	Y
Covvey et al. (83)	Y	Y	CD	Y	NR	NR	N	NR	NR	CD
Denison Davies et al. (64)	Y	Y	Y	Y	Y	NR	Y	Y	NR	Y
Franklin et al. (65)	Y	CD	CD	Y	NR	NR	Y	Y	NR	CD
Franklin et al. (66)	Y	Y	N	Y	Y	NR	Y	Y	NR	CD
Ghaleb et al. (67)	Y	Y	Y	Y	NR	NR	Y	Y	NR	CD
Haw et al. (68)	Y	Y	CD	Y	NR	NR	Y	Y	Y	Y
Huynh et al.(69)	Y	Y	Y	Y	Y	NR	N	Y	NR	Y
James et al.(70)	Y	CD	CD	Y	NR	NR	N	Y	NR	Y
Jones and Bhandari (71)	Y	Y	CD	Y	NR	NR	Y	Y	NR	CD
Keers et al. (72)	Y	Y	N	Y	Y	NR	Y	Y	NR	Y
Kelly et al.(77)	Y	Y	CD	Y	NR	Y	Y	Y	No	Y
Morton and Errera (73)	Y	Y	CD	Y	NR	NR	N	Y	NR	Y
Ryan et al. (74)	Y	Y	Y	Y	Y	Y	Y	Y	NR	CD

Reference	Was the research question or objective in this paper clearly stated?	Was the setting and patient population clearly specified and defined?	Is the patient population representative of a general population?	Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all patient populations, settings, and medication errors?	Was a sample size justification, power description, or variance and effect estimates provided?	Were medication errors clearly defined, in accordance with recognised criteria?	Were medication errors assessed consistently across all study participants?	Were the observers blinded to the subjects they were assessing?	Is the method for collecting data (medication errors) reliable?
Seden et al. (75)	Y	Y	CD	Y	NR	Y	Y	Y	NR	Y
Tully et al. (76)	Y	Y	N	Y	NR	NR	Y	Y	NR	CD

Summary of studies undertaken in secondary care

Nineteen studies in secondary care were included.(60-77, 83) Fourteen of these were prospective design,(60, 61, 63, 65-69, 72-77) and five were retrospective design.(62, 64, 70, 71, 83) Four studies were in paediatric populations,(62, 67, 69, 73) two studies were in children and adult mental health,(63, 72) one study was in elderly mental health(68) one study was in elderly patients with chronic kidney disease, (71) one study was in elderly patients with and without dysphagia,(77) and seven studies were in mixed hospital populations.(60, 61, 64-66, 70, 83)

Eleven studies assessed prescribing errors,(60-66, 72, 74-76) two studies assessed administration errors,(68, 77) one study assessed prescribing and administration errors,(67) one study assessed serious clinical incidents associated with administration,(73) one study assessed medication incidents associated with antimicrobials,(83) one study assessed medication discrepancies,(69) one study assessed potentially inappropriate medications,(71) and one study assessed dispensing errors.(70)

Across the studies a variety of error definitions were applied.

Across the studies in paediatric populations, prescribing errors of 13%(62) and 13.2%,(67) and administration errors of 19.1%(67) were observed. Unintentional drug discrepancies affecting 41% of patients classified as harmful were observed by one study.(69) Serious clinical incidents associated with analgesia in paediatrics were observed in 0.43% of opioid infusions (one resulting in cardiac arrest) by one study.(73)

Across the studies in children and adult mental health, prescribing errors of 3.3% (of which 11% (15/139) could have had potentially serious clinical consequences),(63) and 10.7%(72) were observed. One study in elderly mental health observed medication administration errors of 25.9%.(68)

One study in elderly patients with chronic kidney disease observed 56% potentially inappropriate medications.(71)

One study in elderly patients with and without dysphagia observed 38.4% administration errors, of which 313 involved patients with dysphagia.(77)

Across the studies in mixed hospital populations, prescribing error rates of 8.8% per 100 medication orders (7.3% of which were serious)(60) were observed amongst first-year post-graduate doctors, senior doctors and non-medical prescribers(60) and 7.5% of items prescribed)(74) were observed amongst newly qualified doctors. Prescribing error rates of 43.8% (of which 0.30% were potentially life-threatening) were observed across different grades of doctors in one study,(75) and prescribing

error rates of 10.5% (of which 1.6% (n=54) were potentially severe or fatal) were observed amongst doctors (grade not reported) by one study.(76)

A prescribing error rate of 25.4%, an administration error rate of 50.0%, and a monitoring error rate of 5.5%, associated with antimicrobial administration incidents, was observed by one study.(83)

Prescribing error rates of 0.3%(61) and 9.2%(65) were observed amongst pharmacists. Prescribing error rates of 14.7% were observed amongst pharmacists and nurses by one study.(66)

An opioid prescribing error rate of 27.2% (4/90 (4.4%) were lethal) was observed by one study.(64)

A prevented dispensing error rate of 0.131% and an un un-prevented dispensing error rate of 0.016% was observed by one study.(70)

Study quality was variable across the studies in secondary care. Whilst the research question/study objectives were clearly stated for all studies and errors were assessed in a consistent manner within studies, there was great variability in study reporting of data collection methods and generalisability of findings. Inclusion and exclusion criteria for participants and settings in studies was infrequently reported, as was sample size estimation and the method of data collection. Only one study reported that the assessment of errors (retrospective chart review) was blind.(68)

4. REVIEW 2: RAPID REVIEW OF THE COSTS AND HEALTH BURDEN ASSOCIATED WITH MEDICATION ERRORS IN THE UK

4.1. BACKGROUND TO REVIEW 2

Medication errors are associated with considerable economic burden, which in this context has three constituent parts: the incidence of medication error, the resource use associated with error and the health effects of error. Review 2 aims to answer the question: What is the evidence for the costs and health burden associated with medication errors in the UK?

4.2. METHODS REVIEW 2

4.2.1. Identification of studies

The review by Walsh et al. (1) served as the starting point for Review 2. Additional studies to be included needed to meet the inclusion criteria outlined in Walsh et al. (1). Relevant key publications meeting the inclusion criteria identified by our expert advisory panel were also included.

Exclusion criteria: non-English publication, non-UK data reported

The search approach involved the following:

- Contact with experts in the field
- Update search of a recently published review (Walsh et al. (1))
- Searching of the grey literature
- Checking of bibliographies and citation searching of retrieved papers

Four major electronic databases were searched from 2016 until October 2017:

1: PubMed: US National Library of Medicine National Institutes of Health 1946 to present

2: EMBASE: Ovid. 1974 to 2017

3: Cochrane Library: Wiley Online (Cochrane Database of Systematic Reviews. 1996-2017; Database of Abstracts of Reviews of Effects. 1995-2015; Cochrane Central Register of Controlled Trials. 1898-2017; Health Technology Assessment Database. 1995-2016; NHS Economic Evaluation Database. 1995-2015)

4: CINAHL: EBSCO. 1974-2017

The strategy comprised keywords for 'medication errors' obtained from a recently published review Walsh et al. (1) combined with 'costs/econ' (Appendices 1 and 2). The search was limited to the last two years (from 2016 onwards) and English language. References were managed using Endnote X8.

Targeted grey literature searching of UK websites was carried out in the following sources:

1. NHS England https://www.england.nhs.uk/
2. Department of Health https://www.gov.uk/
3. NICE https://www.nice.org.uk/
4. National Patient Safety Agency http://www.npsa.nhs.uk/
5. The King's Fund https://www.kingsfund.org.uk/
6. The Health Foundation http://www.health.org.uk/
7. CEA registry http://healtheconomics.tuftsmedicalcenter.org/

Expert recommended publications were cross-checked against the database searches and reasons for exclusion of full text studies are presented in Appendix 2.

4.2.2. Quality assessment

Quality assessment of systematic reviews, including Walsh et al. (1) were undertaken using an adaptation of AMSTAR(107). Quality assessment of primary studies was assessed using the seven parameters of quality assessment outlined in Walsh et al. (1).

4.2.3. Data extraction and synthesis

Data extracted included details of authors, type of medication error, definition of medical error, study setting, study population, study sample size, economic method, outcome measures and results. A narrative synthesis was undertaken using the same approach as described in Walsh et al. (1).

4.3. RESULTS REVIEW 2

4.3.1. Walsh review

A recent systematic review, Walsh et al. (1) exploring the economic impact of medication error serves as the basis of this chapter. The review included 16 studies. The mean cost per error per study ranged from €2.58 to €111,727.08. Table 24 presents a quality assessment of the Walsh review using the AMSTAR checklist for systematic reviews.(107) The review scores 8/11 on the AMSTAR checklist, showing that it is a reasonably good quality systematic review.

Table 24: AMSTAR(107) checklist quality assessment of Walsh et al. (1) systematic review

AMSTAR question	Walsh et al. (1)
1. Was an "a priori" design provided?	Yes, the research question and inclusion criteria were established before the review was conducted.
2. Was there duplicate study selection and data extraction?	Yes, there was duplicate study selection at full text stage and duplicate data extraction.
3. Was a comprehensive literature search performed?	Yes, 7 databases were searched and years included. Search terms are provided. Reference lists of eligible studies and systematic reviews were hand searched.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No, grey literature was excluded.
5. Was a list of studies (included and excluded) provided?	No, a list of included studies is presented but there is no list of excluded studies and references for the excluded studies are not provided.
6. Were the characteristics of the included studies provided?	Yes, a table of study characteristics is presented.
7. Was the scientific quality of the included studies assessed and documented?	Yes, appropriate quality assessment was undertaken.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes, study quality is mentioned in the discussion.

9. Were the methods used to combine the findings of studies appropriate?	Yes, narrative synthesis was used which is appropriate.
10. Was the likelihood of publication bias assessed?	No, publication bias was not assessed.
11. Was the conflict of interest included?	Yes, statement included that the authors had no conflicts of interest.

Of the 16 included studies in the Walsh review, two were UK based, Cranshaw (7) and Zaidi.(43) These studies are presented below in Table 26.

4.3.2. Additional cost studies

In order to identify additional cost studies, we updated the searches used in the Walsh review (1). Of the 977 hits, five additional potentially relevant systematic reviews were identified. These were all excluded. Reasons for exclusion are shown in Table 25 below. No relevant primary cost studies, post 2016 were identified. The potentially relevant systematic reviews were examined for possible primary studies for inclusion. One study, Karnon et al. (23) was included in both the Agbabiaka et al. (108) and Ahmed et al. (109) reviews. Details of the Karnon et al. (23) study are shown in Table 26.

Table 25: Excluded systematic reviews and UK primary studies identified

Review	**Reason for exclusion**	**UK studies (post 2007) identified from the review**
Agbabiaka et al. (108)	Health care preventable adverse events	Karnon et al. (23)
Ahmed et al. (109)	Covers cost of intervention: economic impact of electronic prescribing	Karnon et al. (110) (as above)
Hyttinen et al. (111)	Unavailable through University of Sheffield library electronic journals database	N/A
Macfie et al. (112)	No cost data reported	Schulman et al. (113), excluded, no costs reported
Parand et al. (114)	Medical administration errors in domiciliary settings	0

Citation searches of the Cranshaw et al. (7) and Zaidi et al. (43) studies were also undertaken and of the 24 hits identified, none were relevant so all were excluded. In addition, the studies from Review 1

were assessed for cost data. From these, one study was identified for inclusion (55) and details are shown in Table 26.

Table 26: Summary of UK cost studies

First author, year	Title	Study design Methods used to identify medication errors	Study population Study setting	Sample size patients	Sample size errors	Type of medication error. EMA Classification	Economic method	Outcome measure	Results
UK studies from Walsh(1) review									
Cranshaw et al. (7)	Litigation related to drug errors in anaesthesia: an analysis of claims against the NHS in England.	Cross-sectional: retrospective review of NHS litigation authority database of clinical claims made against the NHS from patients alleging harm from drug errors in anaesthesia.	Patients alleging harm from drug errors in anaesthesia in hospital (secondary/tertiary care).	1067	62	Drug administration error (wrong drug, dose, order, route or drug omission) Errors with harm.	Measuring of direct costs.	Cost of clinical claims made against the NHS by patients.	62 errors costed (with harm) €6,927,078.96
Zaidi et al. (43)	Quantifying and reducing inhaler prescription errors in secondary care.	Cross sectional: review of incorrect prescriptions by pharmacists.	Hospital inpatients prescribed an inhaler (secondary/tertiary care).	Not stated.	61	Prescription error (incorrect device, strength or drug) intercepted medication errors.	Measuring of direct cost.	Cost of erroneous medication.	Cost per error (intercepted error) €67.93 (mean)

First author, year	Title	Study design Methods used to identify medication errors	Study population Study setting	Sample size patients	Sample size errors	Type of medication error. EMA Classification	Economic method	Outcome measure	Results
Studies identified outside of Walsh review									
Bradley et al. (55)	Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database	Retrospective cross-sectional population study	People aged ≥ 70 years in 2009-10 in Northern Ireland Primary care	166,108	53,423 (34%)	Prescription error (potentially inappropriate prescribing using STOPP criteria)	Measuring of direct costs	Total gross cost of PIP in 2009-10 in Northern Ireland.	Total gross cost of PIP €6,098,419
Karnon et al. (23)	Modelling the expected net benefits of interventions to reduce the burden of medication errors	Modelling study	Hospital patients 400 bed hospital in UK	162,000 prescription orders/year	Incidence of pADEs: 432 (224-650)	pADEs	Model	Health service costs	£0.6 million/year for a 400 bed acute hospital

pADEs= preventable adverse drug events

Study design, populations and settings

Three of the studies were cross-sectional retrospective reviews: one of a litigation database,(7) one of prescriptions in secondary care,(43) and one of prescribing database.(55) The fourth study was an economic modelling study.(23, 115) With regard to setting, three studies were in hospitals while the fourth was in primary care.(55) Study populations varied with one study of patients claiming anaesthetic drug errors,(7) one of patients prescribed inhalers,(43) one of elderly patients in primary care,(55) and one stating that hospital inpatients were included.(23)

Sample size and types of errors

In one study sample size was not stated,(43) one had a sample size of just over 1000,(7) and two had sample sizes of over 160,000.(55, 115) Type of medication error also varied between the studies, with one study looking at administration error,(7) one prescription error,(43) one potentially inappropriate prescribing,(55) and one at preventable adverse drug events.(23)

Quality assessment of included studies

Quality assessment of the studies is shown in Table 27. Seven criteria as outlined in Walsh et al. (1) were used to assess the quality of the included studies. None of the studies fulfilled all of the quality criteria. The viewpoint was explicitly stated in only one study,(23) although implied in the other three. The study population was clearly stated in all four studies and most described the costs included, apart from Zaidi.(43) None of the studies adjusted costs for differential timing and only one implied that incremental/attributable costs were calculated.(23) No studies reported that sensitivity analyses were performed and all gave a statement of costs pertaining to actual or potential errors.

Table 27: Study quality: quality assessment criteria outlined in Walsh et al. (1)

Quality assessment criteria from Walsh	Cranshaw(7)*	Zaidi*(43)	Bradley(55)	Karnon(23)
1 Viewpoint/perspective (e.g. patient/health service) of the analysis clearly stated and justified.	[+]	[+]	[+]	+
2 Study population clearly stated.	+	+	+	+
3 All relevant medical and/or non-medical costs included and their sources clearly stated.	[+]	0	[+]	[+]
4 All costs adjusted for differential timing, where appropriate: discounting applied to costs if a study was conducted over >1 year.	N/A	N/A	N/A	0

Quality assessment criteria from Walsh	Cranshaw(7)*	Zaidi*(43)	Bradley(55)	Karnon(23)
5 Incremental/attributable costs calculated: calculation of difference in costs incurred by the study population and a non-exposed population.	0	0	0	[+]
6 Sensitivity analysis performed to address uncertainties or methodological controversy.	0	0	0	0
7 Clear statement if reported costs pertained to an actual or potential error and if the error was associated with harm.	+	[+]	+	[+]

+=present; [+]=partly fulfilled; 0=absent; N/A= non-applicable; * quality assessment taken from Walsh (1)

Summary of Results of Review 2

Cranshaw measured cost of litigation claims and of the 62 errors costed, associated costs were €6,927,078.96.(7) Zaidi et al. (43) measured the cost of erroneous inhaler medication and stated that the cost per intercepted error was €67.93. Bradley et al. (55) calculated the cost of PIP in Northern Ireland over a one year period and the total gross cost was €6,098,419. Karnon et al. (23) in the only modelling study identified, estimated £0.6 million/year for a 400 bed acute hospital as the cost of preventable adverse events.

4.3.3. Review 2 Conclusions

Four studies presenting costs associated with medication error in the UK were identified in this review. It is difficult to draw comparisons between the studies due to the different study designs and lack of consistency in measuring medication error. One was a modelling study,(23) and the others were cross sectional retrospective reviews.(7, 43, 55) The studies were of moderate quality. Costs reported in the study ranged from €67.93 per intercepted error for inhaler medication (43) to €6,927,078.96 measured for litigation claims associated with anaesthetic error.(7) More cost studies may have been identified if a full systematic review had been undertaken rather than using the Walsh et al. (1) review as a starting point for this review. There is a lack of good quality studies measuring the economic burden of medication errors in the UK.

4.4. CONCLUSIONS FROM THE RAPID REVIEW

This rapid review had two aims, to determine the incidence and prevalence of medication errors in the UK (Review 1) and to determine the costs and health burden associated with medication errors in the UK (Review 2).

4.4.1. Review 1

For Review 1, studies were identified from primary and secondary care settings, care homes and transitional care.

Primary care

Seven primary care studies met the inclusion criteria, all of which sought to estimate prescribing and monitoring errors in general practice. Two studies assessed prescribing and monitoring errors,(53, 59, 84) and five assessed potentially inappropriate prescribing (PIP).(54-58) Across the studies in the adult population, prescribing errors of 4.1%(53, 84) and 5.26%,(59) and monitoring errors of 0.9%(53, 84) and 11.8%(59) were observed. PIP rates ranged from 21.1% in middle-aged adults (57) to a PIP rate of 64.4% in people with dementia.(54) Only one study (53, 84) measured the severity of medication errors, of which 11/302 (3.6%) were categorised as severe (though none resulted in a hospital admission or death).

Care homes

Six studies were included in this review of medication errors in care home settings. Four of the included studies (46, 48-50) measured potential inappropriate medication (PIM). One study measured prescribing, monitoring, dispensing and administration errors,(45, 47) while another study measured administration errors.(51) In those studies reporting PIMs, prescribing error rates ranged from 37.1%(48) to 90.6% (46) of patients with at least one PIM. In the study measuring medication errors,(45, 47) prescribing errors were 39.1%, monitoring 18.4%, dispensing 36.7% and administration 22.3%. The study of administration errors reported an error rate of 30.8% for those without dysphagia and 57.3% for those with dysphagia.(51)

Secondary care

Nineteen studies in secondary care were included.(60-77, 83) Eleven studies assessed prescribing errors,(60-66, 72, 74-76) two studies assessed administration errors,(68, 77) one study assess prescribing and administration errors,(67) one study assessed serious clinical incidents associated with administration,(73), one study assessed medication incidents associated with antimicrobials,(83) one study assessed medication discrepancies,(69) one study assessed potentially inappropriate medications,(71) and one study assessed dispensing errors.(70)

Across the studies in children and adult mental health, prescribing errors of 3.3% (of which 11% (15/139) could have had potentially serious clinical consequences)(63) and 10.7%(72) were observed. One study in elderly mental health observed medication administration errors of 25.9%.(68)

One study in elderly patients with chronic kidney disease observed 56% potentially inappropriate medications,(71) and one study in elderly patients with and without dysphagia observed medication administration errors of 38.4%.(77)

Across the studies in mixed hospital populations, prescribing error rates of 8.8% per 100 medication orders (7.3% of which were serious) were observed amongst first-year post-graduate doctors, senior doctors and non-medical prescribers(60) and 7.5% of items prescribed were observed amongst newly qualified doctors.(74) Prescribing error rates of 43.8% (of which 0.30% were potentially life-threatening) were observed across different grades of doctors in one study,(75) and prescribing error rates of 10.5% (of which 1.6% (n=54) were potentially severe or fatal) were observed amongst doctors (grade not reported) by one study.(76)

Prescribing error rates of 0.3%(61) and 9.2%(65) were observed amongst pharmacists. Prescribing error rates of 14.7% were observed amongst pharmacists and nurses by one study.(66)

An opioid prescribing error rate of 27.2% (4/90 (4.4%) were lethal) was observed by one study.(64)

A prevented dispensing error rate of 0.131% and an un-prevented dispensing error rate of 0.016% was observed by one study.(70)

A prescribing error rate of 25.4%, an administration error rate of 50.0%, and a monitoring error rate of 5.5% associated with antimicrobial administration incidents was observed by one study.(83)

Transitional care

The searches identified four studies in examining medication errors in transitional care that met the inclusion criteria (78-81). Three of these were retrospective design,(78, 80, 81) and one was prospective.(79)

One study was in patients being treated with insulin within a large foundation hospital trust,(78) one was in patients being discharged from mental health hospitals,(79) one was in patients ≤65 years admitted to a Specialist Health and Ageing Unit,(80) and one was in patients being discharged from hospital.(81)

Two studies evaluated prescribing errors at discharge,(78, 79) one study evaluated PIPs at admission and discharge,(80) and one evaluated pharmacist-written discharge medication orders.(81)

Across the studies a variety of error definitions were applied.

In one study, 43% of patients were identified as having an error or discrepancy relating to insulin on their discharge summary, with two out of three patients who were readmitted having a discrepancy identified on discharge.(78) In one study, a prescribing error rate of 20.8% was observed at discharge of which 4 (5.4%) were associated with potentially serious harm.(79) In one study, a potentially inappropriate medication rate of 26.7% at admission and 22.6% at discharge was observed.(80) In one study, a prescription error rate of 0.2% at discharge with one (0.02%) having the potential to cause temporary harm.(81)

Study quality was variable across the studies in transitional care. Whilst the research question/study objectives were clearly stated for all studies, it was often unclear how errors were assessed and there was variability in study reporting regarding generalisability of findings.

For Review 2, four studies presenting costs associated with medication error in the UK were identified, two of which were found in the Walsh (1) review. Costs reported in the study ranged from € 67.93 per intercepted error for inhaler medication (43) to €6,927,078.96 measured for litigation claims associated with anaesthetic error (7).

4.4.2. Limitations and areas for future research

There are limitations in this review resulting from our use of rapid review methods that were chosen to achieve a synthesis of the evidence in a six-week time frame. We imposed limitations on our inclusion criteria for studies at the protocol stage that may have resulted in the exclusion of relevant data. This included the exclusion of non-UK studies, studies published before 2007 and intervention studies. Intervention studies may include baseline data that could describe prevalence of medication rates. We also excluded studies that reported adverse event data, which may have included avoidable adverse events resulting from medication error.

These are potential limitations that should be considered when interpreting the findings from Reviews 1 and 2. Some differences in the inclusion of studies in modelling and those in Reviews 1 and 2 reflect the fact that the rapid review process was guided by a protocol in which inclusion and exclusion criteria for studies were explicit and were followed. Recommendations for future research include undertaking a systematic review using broader inclusion criteria so that alternative sources of data are included, and also a quantitative synthesis of the data where studies are sufficiently homogenous.

5. ESTIMATING BURDEN OF MEDICATION ERROR IN THE NHS IN ENGLAND

5.1. BACKGROUND

The rapid reviews were intended to inform and underpin the estimation of burden of medication error in the NHS in England. The UK is a dominant presence in research in this area, particularly in primary care errors, so Review 1 provided some fairly robust estimates of error rates at different stages of the medicines use process in most settings, but no national estimates of prevalence. Effective targeting of medication errors requires understanding of where errors cause the most burden, and so this report set out to derive a national estimate of prevalence of errors in different settings and at each stage of the medication use process, and the severity of those errors.

Review 2 found very little data on the burden of errors. Very little, or no data were found that indicated direct links between errors and harm, or what proportion of errors occurring at different stages of the medicines use process reached patients, and what proportion of those errors reaching patients caused actual harm. This required us to develop estimates of burden of medication errors using published work around ADRs or ADEs, depending on what was the outcome used by the study, where a retrospective judgement had been made that harm/burden was due to an ADR or ADE, rather than using data that explicitly or prospectively linked errors to harm. Throughout this section, the terms ADR and ADE are used as per the source study reporting the estimate.

Section 5 of this report details the methods and results of deriving national estimates of error rates and the burden associated with those errors. Limitations of the data available and methods used to generate estimates are presented clearly, with alternative scenarios where the methods used are changed, so that readers are aware of the level of uncertainty around the estimates presented. Comparison with error rates in other comparable health care settings is presented to provide international context. Previous efforts to estimate burden are presented, along with how our methods echo or differ. The section concludes with recommendations around priority areas for action.

5.2. OBJECTIVES

The objectives were to:

- Use published error rates to estimate numbers of medication errors occurring across primary care, care home and secondary care settings in England at each stage of the medication use process.
- To understand the potential of these errors to cause harm.

- To develop national estimates of burden of medication errors.

5.3. METHODS

This section describes the methods used to achieve the three objectives.

5.3.1. Methods for estimating the prevalence of errors

The prevalence of errors was calculated by extracting the rate of errors (number of errors per 100 medication items) reported in the literature to the number of items prescribed, dispensed and administered annually in England. This section provides details of the types of errors included in the analysis, the data sources for error rates and the methods for extrapolating error rates nationally.

Categories of medication errors included

We included errors that occurred at the following stages of the medication use process:

- Prescribing (this can be a doctor, nurse or pharmacist)
- Transcribing (referring to when patients move settings)
- Dispensing (usually a pharmacy error)
- Administration (in secondary care and care homes only as medication are administered by a third party (usually nurses or care home workers). Administration errors by the patient themselves in primary care is usually called non-adherence and is not included here)
- Monitoring (usually doctors but can be any health care professional, depending on setting)

We included medication errors at all these stages occurring across primary care, care home and secondary care settings in England. Care homes include both residential and nursing homes unless stated otherwise. We then extrapolated published error rates to derive a national annual estimate of errors occurring in England.

Data sources for error rates

The error rates were extracted from the studies identified by Review 1 where possible. Where gaps still remained, we have used further studies.(67, 68, 77, 116-119) Where more than one study was identified for the same type of error and setting, their generalisability was assessed based on the demographics of the patient population and the disease area. The most generalisable studies were used to derive the number of errors in England, except for hospital administration errors. The hospital administration error rate was derived by merging the error rates from five UK studies in different

inpatient populations (surgical, paediatrics, geriatric, stroke, dementia) to derive an arithmetic mean (67, 68, 77, 118, 119) identified in a recent systematic review.(116)

Details of how the data sources were selected and the description of each study are provided later in this section.

Summary of published error rates

Table 28 summarises the prevalence of errors for each stage of the medication use process in each setting and their sources. Error rates reported refer to the number of errors per 100 medication items.

Table 28: Published UK error rates for each stage of the medication use process in each setting

Error category	Errors as a percentage of medication items in each health care setting		
	Primary care (%)	**Care homes (%)**	**Secondary care (%)**
Prescribing	4.2 (52)	8.3(45)	9.0(120)
Transitional	No UK data available	No UK data available	5.1(79)
Dispensing	3.1(42)	9.8(45)	Generalised from dispensing errors in primary care[a]
Administration	N/A	8.4[b](45)	18.6[bc]
Monitoring	1.76(52)	1.74(45)	Generalised from monitoring errors in primary care [ad]

[a]there were no UK prospective studies of dispensing errors in secondary care that reflected how many errors would leave the pharmacy. A UK retrospective incident reporting was considered to understimate dispensing errors. (70) Therefore we assumed that secondary care dispensing error rates were equivalent to primary care;

[b]administered doses;

[c]arithmetic mean derived from five UK studies(67, 68, 77, 118, 119);

[d]there were no UK prospective studies of monitoring errors in secondary care. Therefore, we assumed that secondary care monitoring error rates were equivalent to primary care.

5.3.2. Methods for extrapolating published rates of errors to derive a national annual estimate of errors occurring in England

The rates of errors reported in the studies shown in Table 28 was extrapolated to estimate the prevalence of errors in England as a whole. The parameters used to extrapolate the error rates are presented in Table 29.

Table 29. Parameters used to extrapolate error rates in Table 28 to the population of England

	Parameters used to derive the number of errors per year in England	**Value**	**Source**
Care homes	Total number of items dispensed for patients in care homes	35,942,400	416,000 people live in care homes.(121) Patients take mean 7.2 medicines.(45) Each item is dispensed 12 times (assumption to take into account that items are prescribed multiple times).
	Total number of items administered in care homes	151,840,000	416,000 people live in care homes.(121) Patients take mean 7.2 medicines.(45) Assume each prescribed medicine is administered once daily.
Primary care	Total number of items dispensed in primary care (excluding care homes)	1,068,157,600	1,104 million items dispensed in primary care in 2016.(122) 35,942,400 of those are dispensed for patients in care homes.
	Number of acute medicines dispensed in primary care (excluding care homes)	245,676,248	23% of prescribed items are for acute medication.(123)
	Number of repeat medicines dispensed in primary care (excluding care homes)	822,481,352	Total number of items – number of acute items. (see above)
Secondary care	Number of items dispensed to inpatients every year	44,724,144	9,364,860 hospital admissions in the year 2015 to 2016 (16,251,841 admissions including elective, non-elective and day cases - 6,886,981 day cases.(124) 4.78 items prescribed per inpatient.(120)
	Number of patients discharged from hospital every year	16,251,841	Finished admission episodes reported in 2015-16. (124)
	Number of items administered in hospitals every year	200,313,353	131,072 hospital beds are available in England.(125) 47,841,280 bed days per year (131,072*365) The average bed occupancy in the NHS was 87.23%.(125) 4.78 items are prescribed per inpatient.(120) Assume each patient takes each medicine once daily

Extrapolation methods used in primary care, secondary care and care homes are described below.

Primary care errors

Primary care prescribing errors

To estimate prescribing errors in primary care, the prescribing error rate reported in a UK study was extrapolated using national dispensing data because there are no national data for prescribing volume.

National dispensing data

According to NHS Digital information, 1.10 billion items were dispensed in primary care in 2016.(122) It is unlikely that 100% of prescribed items are dispensed. Since we have no equivalent national estimates of prescribing rates, we assumed that the prevalence of errors in prescribed and dispensed items are similar. The estimate 1.10 billion includes items dispensed for patients who live in care homes. In our analysis, the prevalence of errors in care homes was calculated separately, and so the items dispensed for care homes were excluded from the analysis of errors in primary care. We estimated that 35,942,400 items are dispensed for care homes annually (for details see Section "Deriving a national annual estimate for care home errors"). Therefore, we estimate that 1,068,157,600 items were dispensed for ambulatory patients in primary care in 2016.

Acute versus repeat prescribing

In the UK, most NHS patients receive medicines intended for long-term use as "repeat prescriptions". These are prescription items that are generated without the need for a consultation from a list of authorised repeat medicines. Previous work suggests that only 23% of prescribed items are for acute medication (where only one prescription is issued, such as for a course of antibiotics), as the vast majority of prescriptions issued are repeat prescriptions for long-term chronic health conditions.(123) Extrapolating this to the national dispensing data suggests that 245 million of the items dispensed for ambulatory patients are acute, while 822 million are repeats.

Prevalence of errors

The prevalence of errors was derived from the PRACtICe study,(52) the only study of prescribing errors in primary care identified in Review 1 that included a mixed patient population (in terms of demographics and therapeutic areas). In the study, 2% patient records (1777 patients) from 15 general practices were reviewed to identify prescribing and monitoring errors. In total, 6048 unique items prescribed to 1200 patients were reviewed during the 12-month retrospective review of their records. Unique items refer to items that were prescribed at least once. When a medicine was prescribed for the same patient multiple times, only the most recent prescription for that medicine was considered. Of the 6048 items, 2929 were acute prescriptions, while 3119 items were unique repeat prescriptions.

The authors did not report how many prescriptions were issued in total for the 1200 patients. Therefore, we do not know how many times each repeat medicine was prescribed or dispensed. Assuming that the ratio between acute and repeat prescriptions in the practice study were the same as that reported by Petty et al. (123), then the 2929 acute items would comprise 23% of all items, and the total number of items prescribed in the PRACtICe study (when each repeat prescription is counted as a separate item) can be estimated to be 12,734.

In the PRACtICe study, 247 (4.08%) of the 6048 unique items were found to contain at least one prescribing error. The authors did not report the error rates in acute and repeat prescriptions separately, nor whether prescribing errors in repeat items perpetuated through every subsequent repeat.

Number of errors

We applied the 4.08% rate of errors to the number (1.068 billion) of dispensed items to estimate the total number of prescribing errors in primary care, assuming that any prescribing errors that occurred for a chronic treatment perpetuated through every subsequent repeat.

We also explored an alternative assumption, that errors occurred only in unique items, i.e. in acute items and one issue of each repeat, and that all subsequent repeats are free of error. If all such errors were captured in the PRACtICe study and the total number of items prescribed during the study period was 12,734, then the prevalence of errors across all items would be 1.94% (247/12,734). This prevalence was then applied to all dispensed items (1.068 billion) to estimate the total number of prescribing errors under this alternative assumption.

Primary care dispensing errors

To estimate dispensing errors in primary care, the dispensing error rate in primary care reported in a UK-based study was applied to the 1.068 billion items dispensed for ambulatory patients in primary care in 2016, estimated in the previous section.(42)

Review 1 did not identify any studies on the dispensing error rates in primary care. Therefore, the study by Franklin and O'Grady (42) was used on advice from our expert advisory panel (personal communication, Bryony Dean Franklin). Franklin and O'Grady identified dispensing errors by checking 2,859 items that had undergone the dispensing process and were ready to be collected by patients, against corresponding prescriptions. The study conducted in 15 UK pharmacies found that 3.1% of the items were found to contain at least one dispensing error.

Primary care monitoring errors

The prevalence of monitoring errors in primary care was derived from the PRACtICE study.(52) As described in the 'Primary care prescribing errors' section, the study was conducted in 2% of the patient population in 15 general practices in the UK. Medical records of 1777 patients were reviewed retrospectively, and 770 items that required blood monitoring were identified. All 770 items were repeat medication. Fifty-five monitoring errors were identified; this comprised 7.14% of all repeat medication requiring monitoring. However, we had no data regarding the prescribing error rate for the items that require monitoring nationally. We estimated that 7.14% of all repeat medication requiring monitoring would equate to 1.76% of all repeat items and applied this estimate to the 822 million items estimated to be dispensed nationally. By doing this we assumed that each monitoring error perpetuates through each repeat.

Secondary care (hospital) errors

Secondary care prescribing errors

Out of 11 studies on prescribing errors in secondary care, only one study by Ashcroft *et al*. (120) included patients from a range of therapeutic areas and prescribers with different levels of experience. Therefore, it was used to derive the national estimate of the prevalence of errors in secondary care. It was a UK-based study where pharmacists recorded all errors in newly prescribed or written inpatient medication orders. The study was conducted in 20 hospitals, and included 124,260 medication orders prescribed to 26,019 patients over seven prospectively selected days. The authors found that 8.8% of medication orders had at least one prescribing error.

Extrapolating the rate of errors requires an estimate of the annual number of medication orders in secondary care in England. These data are not available. Therefore, we estimate the annual number of medication orders from known annual hospital admission rates and reported numbers of items prescribed per patient admission. In England, there were 9,364,860 hospital admissions (finished admission episodes elective and non-elective, excluding day cases) in the year 2015 to 2016.(126) Using the rate of a mean of 4.78 items prescribed per inpatient,(120) this equates to an estimated 44,724,144 items prescribed annually in secondary care.

Secondary care dispensing errors

Review 1 in this report identified one study reporting dispensing errors in secondary care.(70) The authors reported the proportion of all dispensed items, which patients and health professionals reported to contain an error after they left the pharmacy. The authors reported that 0.016% of the dispensed

items were reported to contain an error. As this is a retrospective incident reporting study, this is likely to be an underestimate of the total prevalence of errors. Therefore, the number of dispensing errors in secondary care was derived by extrapolating the dispensing error rate in primary care to the number of items dispensed in secondary care (personal communication, Bryony Dean Franklin).

The rate of errors in primary care is 3.1% of all dispensed items.(42) The number of medication items dispensed annually in secondary care in England is not known. Therefore, it was assumed to be equivalent to the total number of items prescribed in secondary care, estimated to be 44,724,144 earlier in this section.

Secondary care transitional errors

Transitional errors represent errors due to miscommunication between different settings. There is very little evidence around transitional error rates other than inaccurate prescribing of patients' regular medication on admission to hospital, inaccurate prescriptions on discharge from hospital, and failure of GPs to continue hospital-initiated treatment post-discharge. Therefore, we have only considered transitional errors in the secondary care setting. It is likely that this underestimates the true rate of transitional errors.

Accuracy of hospital prescribing on admission was measured in the study by Ashcroft et al. 2015 (120), therefore these errors are captured in the estimate of prescribing errors in secondary care.

Review 1 identified one study that included a patient population representative of the general population so this study was used to estimate the total number of errors (79). The authors found that 20.8% of 259 discharge prescriptions contained an error.

The total number of errors was calculated by applying this error rate to the total number of patients discharged from hospitals in England. These discharge data are not directly available. In our estimation of errors, we used total number of finished admission estimates to estimate total hospital discharges (16,251,841 FAEs in 2015-16)(126), assuming that all discharged patients had a prescription, of which 20.8% were assumed to contain an error.

Review 1 did not identify any studies that measured errors that occur in primary care due to failure to adopt changes recommended by the hospital. The PRACtICe study reported discrepancies between hospital discharges and subsequent medication prescribed by the GP.(52) They reported that, out of 87 medicines newly prescribed by the hospital, 21 were not continued by the GP; however, it is not clear whether these decisions were errors or intentionally omitted by the prescriber. The findings from the PRACtICe study were thus not included in the analysis.

Secondary care administration errors

On advice from our expert panel, we used a systematic review of medication administration errors in secondary care to estimate the rate of errors.(116) The review reported 87 studies on administration errors published internationally between 1985 and 2015. Five studies in the review were conducted between 2007 and 2015 and set in different inpatient populations (surgical, paediatrics, geriatric, stroke, dementia) in the UK.(67, 68, 77, 118, 119) The five studies were pooled and their mean administration errors rate was 18.64% of administered doses.

Extrapolating the rate of errors requires an estimate of the annual number of administered doses in England. These data are not directly available. We estimated annual number of administered doses from known number of overnight beds and reported numbers of items prescribed per patient admission. In England there are 131,072 hospital beds,(125) which can approximate to 47,841,280 bed days per year (131,072*365). We used NHS England data to estimate the average bed occupancy in NHS hospitals in England. Based on the number of available and occupied beds in each quarter we estimated that the average occupancy was 87.23%(127). From this, we estimated that the number of occupied bed days per year was 41,731,948. Ashcroft et al. (120) reported that 4.78 items are prescribed per inpatient. These data can be used to generate an approximate estimate of 200,313,353 administered doses annually in secondary care. This is likely to be an underestimate of administered doses.

Secondary care monitoring errors

Review 1 did not identify any studies on monitoring errors in secondary care, and so findings from the PRACtICe study (in monitoring in primary care) were used, where 1.76% of medicines for chronic conditions were found to contain a monitoring error.

The rate of 1.76% was extrapolated to 77,614,580 items estimated to be prescribed for inpatients annually. Use of this value to estimate number of secondary care monitoring errors is likely to be associated with high levels of uncertainty. It is difficult to predict whether this value is an under- or over-estimate. The medicines prescribed in secondary care and nature of conditions that require admission mean that the need for monitoring is likely to be higher in secondary care than in primary care, suggesting that this estimate is an underestimate. Conversely, the higher availability of routine monitoring in secondary care suggests that it could be an overestimate.

Errors in care homes

In Review 1, six studies were found to measure the prescribing error rates in care homes.(45-51) One study (CHUMS) included a mixed patient population (as opposed to patients with specific conditions)

and provided estimates of prescribing, dispensing, administration and monitoring errors, both in nursing and residential homes.(45) The estimates from this study were used to estimate the number of errors in care homes in England. The study included 1843 medicines taken by 256 patients (mean: 7.2 medicines per patient) in 55 care homes in the UK. The methods for measuring the rates of errors and extrapolating them are described for each type of error individually.

Care home prescribing errors

In the CHUMS study, 1843 medicines were reviewed and 8.3% of the items were found to contain a prescribing error. The error rate was extrapolated to the items prescribed nationally in care homes every year, derived from the total number of people reported to live in care homes and the average number of medicines taken by care home residents.

ENRICH 2017 cite the results of the Laing and Buisson survey, 2016, that 416,000 people lived in care homes in 2016. If each resident takes 7.2 medicines,(45) this amounts to 2,995,200 items taken by care home residents. Some of these 2,995,200 medicines are repeat medication, and they are prescribed multiple times every year. We did not have an estimate of how many times each item is prescribed annually, and so we assumed that each medicine is prescribed 12 times per year (i.e. monthly). This amounts to 35,942,400 items prescribed and dispensed for care homes annually.

Care home dispensing errors

The authors of the CHUMS study visually inspected the dispensed items against the prescription to identify any medication errors (45). Errors were identified in 9.8% of the items. The total number of dispensing errors in care homes was derived by applying the rate of care home errors (9.8%) to the total number of medicines taken by care home residents (35,942,400) derived in the previous section.

Care home administration errors

In the CHUMS study two medication rounds were observed for each patient in the study and 8.4% of administered doses were found to contain an error (45). This suggests that, if a patient takes one medicine daily, the expected number of administration errors per year would be 31 (8.4% of 365).

We had no data on the number of doses administered to care home residents annually. Therefore, we assumed that each medicine was administered once daily to provide a conservative estimate. If 2,995,200 medicines are administered once daily, the total number of doses administered annually is 1,093,248,000. The total number of errors was derived by applying the rate of errors to this estimate of annually administered doses.

Care home monitoring errors

The monitoring error rate in the CHUMS study was found to be 1.74% (of all medicines).(45) The rate was extrapolated to the derived number of medicines prescribed to care home patients.

Summary of methods for estimating the annual number of medication of errors in England

Table 30 summarises the data sources for error rates, the parameters they were extrapolated to, and any assumptions made in the extrapolation, for each type of error and setting.

Table 30. Summary of methods for estimating the annual number of medication errors

		Source				Extrapolation	
		Study	**Year**	**Sample size**	**Sample and data collection**	**Extrapolated to**	**Assumptions**
Primary care	Prescribing	PRACTICE study(52)	2013	1,777 patients (6048 prescribed items)	2% of patients from 15 General Practices throughout the UK. Patients' medical (GP) notes checked retrospectively. Checked for errors in unique prescription item issued in the 12 months prior to the data collection date.	1.068 billion	The error rate among prescribed items is the same as among dispensed items. The error rate among repeats is the same as among acute items. An alternative scenario was considered where errors were assumed to only occur in one issue of each item.
	Monitoring					822 million	Monitoring errors only occur in repeat medication All monitoring is correctly recorded in GP notes (i.e. no record means the medication usage was not monitored elsewhere).
	Dispensing	Franklin and O'Grady (42)	2007	2,859 dispensed items	11 UK pharmacies located throughout England and Wales Checked for errors in dispensed items that were bagged up and ready for collection.	1.068 billion	All errors identified after medicines were bagged up reach the patient.
Care homes	Prescribing	CHUMS (45)	2009	256 care home residents (1,843	256 patients from 55 care homes in the UK Checked for errors by:	35,942,400	All errors propagate across every repeat.
	Dispensing					35,942,400	All identified errors reach the patient.

		Source				Extrapolation	
		Study	**Year**	**Sample size**	**Sample and data collection**	**Extrapolated to**	**Assumptions**
	Administration			medication items)	- reviewing GP and care home notes, and consultation with residents and/or staff, - physically checking dispensed medication to prescriptions and medication administration record sheets, - physically observing two drug rounds for each patient.	151,840,000	All medicines in care homes are administered to patients. All prescribed medication is administered once daily.
	Monitoring					35,942,400	All monitoring is accurately recorded in patients' notes.
Secondary care	Prescribing	EQUIP study (120)	2014	26,019 patients (124,260 medication orders)	26,019 patients in 20 UK NHS hospitals over 7 days.	77,614,580	
	Dispensing	Franklin and O'Grady (42)	2007	2,859 dispensed items	11 UK pharmacies located throughout England and Wales Checked for errors in dispensed items that were bagged up and ready for collection.	77,614,580	The prevalence of dispensing errors in primary and secondary care are comparable.
	Administration	Conroy et al. (41)	2007	752[1]	Patients in one paediatric hospital in the UK.[2]	200,313,353	All medicines in secondary care are administered to patients. All prescribed medication is administered once daily. All monitoring is accurately recorded in patients' notes.
		Haw et al. (68)	2007	1423[1]	Patients in one dementia unit with challenging behaviour and one elderly care ward with enduring mental illness.[2]		

		Source				Extrapolation	
		Study	**Year**	**Sample size**	**Sample and data collection**	**Extrapolated to**	**Assumptions**
		Franklin and O'Grady (42)	2007	1644[1]	Patients on one general surgery ward.[2]		
		Ghaleb et al.(67)	2009	2249[1]	Patients on 10 paediatric units.[2]		
		Kelly et al.(77)	2011	2129[1]	2 wards of one UK hospital: geriatrics and stroke ward.[2]		
	Monitoring	PRACTICE study(52)	2013	1,777	2% of 20 general practices Population chosen to match the general population in terms of SES, age, gender, etc.	77,614,580	All monitoring is correctly recorded in patients' notes

[1] Number of administered doses observed in the study.

[2] All studies identified errors by physically observing administration of medicines.

5.3.3. Methods for estimating the potential of reported medication errors to cause harm

Some of the studies used to estimate numbers of errors also assessed their potential to cause harm and subsequently scored them as "minor", "moderate", or "severe".(2, 52, 117, 120, 128) The proportions of errors in each study that cause mild, moderate and severe harm are presented in Table 31.

Only one of the five studies used to derive administration error rates in secondary care had assessed their potential to cause harm.(68) This study only examined errors in a very specific patient group, adults with dementia, so may not be representative of the inpatient population. However, in the absence of any other data, the proportions from this study were applied to the overall numbers of administration errors in secondary care to assess their potential to cause harm.

The proportion of medication errors judged to be capable of causing mild, moderate and severe harm in care homes was not available, because data were only reported as the mean score and range for each type of error.(45) Instead, the number of moderate and severe errors in care homes was derived assuming that we could use the same proportions of errors that fall into these categories reported in the studies in primary care (prescribing, dispensing and monitoring) and secondary care (administration). This could potentially lead to an overestimate of potential harm, as in the care home study,(45) unlike in other settings, none of the errors were considered to be severe. It should be noted that these studies did not use the same methods to assess severity of potential harm, limiting comparison between studies. Examples of mild, moderate and severe errors in each study are provided in Table 32.

Table 31: Published estimates of severity of potential harm associated with errors for each stage of the medication use process in each setting

Error category	Percentage of all errors by severity in each health care setting		
	Primary care (%)	**Care homes**	**Secondary care (%)**
Prescribing	Mild: 49.4% Moderate: 49.8% Severe: 0.81%(52)	Mild: 49.4% Moderate: 49.8% Severe: 0.81%(52)[a]	Mild: 41.1% Moderate: 51.6% Severe: 7.3%(120)
Transitioning	No UK data available	No UK data available	Mild: 41.1% Moderate: 51.6% Severe: 7.3%(120)[c]
Dispensing	Mild: 64.8% Moderate: 34.1% Severe: 1.1%(42)	Mild: 64.8% Moderate: 34.1% Severe: 1.1%(42)[a]	Mild: 85.7% Moderate: 8.6% Severe: 5.7%(70)
Administration	N/A	Mild: 92.4% Moderate: 7.3% Severe: 0.3%(68)[b]	Mild: 92.4% Moderate: 7.3% Severe: 0.3%(68)
Monitoring	Mild: 10.9% Moderate: 72.7% Severe: 16.4%(52)	Mild: 10.9% Moderate: 72.7% Severe: 16.4%(52)[a]	Mild: 10.9% Moderate: 72.7% Severe: 16.4%(120)

[a]no data available for care homes, so primary care data used

[b]no data available for care homes, so secondary care data used

[c]no data available for transitional errors, so secondary care data used.

Table 32: Examples of mild moderate and severe errors in each study.

Study	Method for determining the severity of errors	Examples of mild errors	Examples of moderate errors	Examples of severe errors
PRACTICE (52)	A panel of 5 judges assessed each error using a visual analogue scale from zero to 10, then classified errors with scores 0-2 as minor, 3-7 as moderate, 8-10 as severe	1-year old girl prescribed amoxicillin 123mg/ml suspension twice during the same consultation. One was for 2.5ml TDS for one week, and the other for 5ml for one week	64 year old patient was prescribed ibuprofen 400mg to be taken three times daily after a road accident. No concomitant medication was prescribed for gastric protection. Patient also on aspirin for peripheral vascular disease.	62 year old patient with documented allergy to penicillin; prescribed a course of oral flucloxacillin.
Franklin and O'Grady (42)	A panel of four judges (2 GPs and 2 hospital clinical pharmacists with previous experience in community pharmacy) scored errors in the same way as Avery et al. in the PRACTICE study	56 aspirin 75 mg ordered, 57 dispensed	Balneum bath oil dispensed, which had expired three months previously	100 doxycycline 100 mg capsules. One prescribed to be taken each day one week before travel and to continue for four weeks after return. Label stated: 'One capsule a week prior to travel and continue four weeks after return to the UK'
EQUIP (120)	Two validation panels (consisted of hospital clinicians and pharmacists) classified errors as potentially lethal, serious, significant and minor.	Minor: Duplicate therapy prescribed without potential for increased adverse effects	Significant: The dose of the drug with low therapeutic index is too high (half-four times the normal dose)	Serious or potentially lethal: The route of drug administration ordered is inappropriate with the potential of causing the patient to suffer a severe toxic reaction.
Haw et al. (68)	Three researchers classified errors into grades 1-4 (1 - doubtful or negligible importance; 2 - likely to result in minor adverse effects or worsening condition; 3 - likely to result in serious effects or relapse; 4 - likely to result in fatality).	Grade 1: Lactulose 20ml administered – 30ml prescribed.	Grade 2: Sinemet 110 administered at the wrong time	Grades 3 and 4: Insulin omitted but the nurse recorded administration on the medication chart.

The reported proportions of errors that were considered to be mild, moderate and severe (for each type of error and setting) were used to derive the total number of mild, moderate and severe errors that could potentially lead to harm.

5.3.4. Methods for developing estimates of burden of medication errors

It is generally believed that while some medication errors do not lead to harm, others can lead to a range of harms including serious harms and death. Linking numbers of errors directly to burden requires information (or major assumptions when evidence is lacking) about which errors persist through the medication use process, wherever they are initiated, and then the impact they have on patients and costs. Ideally, the data needed to assess impact of all types of errors occurring in all sectors are costs (NHS/PSS/societal perspective, time horizon) sufficient to encompass all effects of error and patient outcomes (intermediate measures such as primary and secondary health care utilization, fatal and non-fatal serious harm outcomes (such as GI bleed, stroke, death rates), health status, life-years gained (LYG)/lost, quality-adjusted life-years (QALYs)). However, from the systematic review, it is clear that the evidence directly linking errors to patient harm and/or costs is sparse. Therefore, it has been necessary to utilise existing sources of data to allow us to derive estimates of burden associated with medication error.

Review 2 found very little data on the burden of errors. Very little, or no data were found that indicated direct links between errors and harm, or what proportion of errors occurring at different stages of the medicines use process reached patients, and what proportion of those errors reaching patients caused actual harm. This required us to develop estimates of burden of medication errors using published work around ADRs or ADEs, depending on what was the outcome used by the study, where a retrospective judgement had been made that harm/burden was due to an ADR or ADE, rather than using data that explicitly or prospectively linked errors to harm. Throughout this section, the terms ADR and ADE are used as per the source study reporting the estimate.

The primary approach used was to identify available UK-based case studies of estimates of burden from ADRs/ADEs and extrapolate to estimate impact for England per annum. Data from non-UK case studies were used to supplement this evidence where UK-studies were not available and were used to inform secondary analyses.

The studies identified through the rapid reviews were screened for relevant estimates of harm and additional studies were identified through consultation with expert researchers in this field. Six key studies were used to generate the estimates in this section. Only one of these studies was included in

one of the rapid systematic reviews reported above.(52) The remaining five were excluded from review 2 for the following reasons:

- non-UK studies (129, 130);
- study title referred to adverse drug reactions (ADRs) rather than medication errors (12, 15, 17);
- study published before 2007. (12, 15)

For our base-case, we considered the number of hospitalisations and deaths associated with ADRs in primary care,(12, 15) and increased length of hospitalisations associated with ADRs in secondary care.(17) The rationale was that the highest number of errors occur in primary and secondary care. The key assumption is that definitely avoidable ADRs approximate to medication errors; hence these studies were considered acceptable.

Applying the quality criteria used in the rapid reviews, the six papers were of a generally high quality, all but one (130) using pre-defined and published criteria to identify errors and all using published criteria to determine preventability. We included these two studies which were published more than ten years ago which may not reflect current prescribing practices but more recent data were not available.

Hospitalisations due to ADRs occurring in primary care

Admissions to hospital

Pirmohamed et al. (15) is a prospective UK study of ADRs leading to hospital admission in two hospitals. It reported that 6.5% of 18,820 admissions over 6 months (adults 16 or over, excluding gynaecological and obstetric admissions) were due to an ADR, with the reaction directly leading to the admission in 80% of these cases.(15) Causality was assessed for each data entry(13), with 20% assumed to be coincidental (i.e. reason for admission coincidental to drug error). Most reactions (72%) were either definitely (9%) or possibly (63%) avoidable, so the avoidable admissions rate directly related to ADRs was estimated to be 0.47% (i.e. 9% of 80% of 6.5%) for definitely avoidable and 3.74% (i.e. 72% of 80% of 6.5%) for definitely or possibly avoidable ADRs.

Howard et al. (12) is an UK study of 4093 patients seen by pharmacists on a medical admissions unit. Of these, 265 (6.5%) admissions were judged to be drug-related and 178 (67%) of these were judged to be preventable. Preventable admissions were mainly due to problems with prescribing (63 cases (35%)), monitoring (46 cases (26%)), and adherence to medication (53 cases (30%)). The drugs most commonly implicated were NSAIDs, antiplatelets, antiepileptics, hypoglycaemics, diuretics, inhaled corticosteroids, cardiac glycosides, and beta-blockers. Potentially (definitely or possibly) preventable

drug-related morbidity was associated with 3.0% of admissions once adherence was excluded as a contributory factor. This study did not identify which of the errors were definitely avoidable.

From these two studies, hospital admissions due to definitely or possibly preventable drug-related morbidity was assumed to account for between 3.0 and 3.74% (midpoint 3.4%) of all non-elective admissions, (excluding paediatrics and obstetrics specialities). The base case estimate included only ADRs which were definitely avoidable which was derived from the first study (15) as 0.47% of non-elective admissions.

Hospital length of stay

The median length of stay of admissions due to preventable drug-related morbidity was 8 days (IQR: 4-18 days) according to Pirmohamed et al.(15) The mean length of stay of admissions due to preventable drug-related morbidity was not reported by the authors, but can be derived from the total number of bed-days reported (17,452) and number of admissions (1,225), to be 14.25 days. However there has been a downward trend in average length of hospital stays which was 5 days in 2015/16.(124) This was used to calculate number of bed-days and costs of hospitalisations. The two values taken from the Pirmohamed et al. study (15) (8 and 14.25 days) were used to calculate alternative estimates of bed-days and costs of hospitalisations.

Admissions to Intensive Care Unit (ICU)

Jolivot et al. (130) is a French observational study which assessed how many adult ICU admissions were caused by ADEs. This study was conducted in a single 18-bed medical ICU unit of a hospital in Paris between February 2013-February 2014. ADEs were defined as "any injury from medical intervention related to a drug". The admissions to ICU were assessed for causality (due to ADE vs for a matter other than ADE) and classified as preventable or unpreventable. ICU admissions due to preventable ADEs included admissions due to non-compliance and self-medication but not self-poisoning.

Among the 743 ICU admissions included during the study period, 173 (23.3 %) were related to ADEs, with 102 (13.7%) classified as preventable by the authors. However, within these 102 admissions, 31 were due to non-adherence and 11 were due to self-medication. These are not classed as medication errors for the purpose of this report. Excluding these 42 errors left 60 preventable errors from 743 ICU admissions (i.e. 8.1% of admissions).

The median length of stay *within* the ICU associated with an ADE was 4 days and 14% of the patients admitted to ICU due to a preventable ADE died on the unit. The authors reported that 58% of these

admissions were directly from home or the emergency department, so at least 58% of these admissions were related to primary care errors.

ICU admissions are not mentioned explicitly in either study examining resource use associated with primary care or secondary care incidents.(15, 17) Therefore it is not clear if we are double counting ICU costs if we include these data. This estimate is not based on UK data, hence these costs were not included in the base case cost estimate for impact of errors. The costs (based on the number of estimated admissions and mean cost per day for adult critical care admissions in England) were included in an alternative scenario analysis and ICU bed days (based on 4 days per ADE) were also estimated.

Deaths associated with ADRs occurring in primary care

In the Pirmohamed et al. study (15), the drugs most commonly implicated in causing these admissions were low dose aspirin, diuretics, warfarin, and non-steroidal anti-inflammatory drugs.(15) Gastrointestinal bleeding was the most common adverse effect, occurring in 157 (72%) of all aspirin related-admissions. Of the 28 deaths which were identified as being a direct result of the ADR (as detailed in either the case notes or on the death certificate), 22 were due to bleeds caused by NSAIDs/aspirin/warfarin. This gave an index hospitalisation death rate of 0.15% due to ADRs (2.3% of ADRs were fatal (1.25% of ADRs led to fatal GI bleeds), which was used to calculate an annual national estimate of deaths. We have assumed that as 9% of the ADRs in the Pirmohamed et al. study (15) were definitely preventable, and that the same proportion of ADR-related deaths were also preventable. No other data were available around impact on mortality or other measures of patient health.

Accident and emergency visits (not resulting in a hospitalisation) due to medication errors in primary care

No UK studies were found that examined accident and emergency (A&E) visits (not resulting in a hospitalisation) due to medication errors occurring in primary care. We identified a German prospective observational study investigating the admissions to A&E related to ADEs (Meier et al).(129) The study was set in a tertiary care hospital, and data was collected in September 2010, April 2011 and November-December 2011 on adult non-trauma A&E admissions. ADEs were classified either as ADRs or medication errors. ADRs were defined as "a noxious and/or unintended response to medication which occurs despite appropriate drug dosage for prophylaxis, diagnosis or therapy of the indicating medical condition". Medication error was defined as "wrong and inadequate use of

medication comprising, for example, ignored contraindications, missing indications, and wrong dosage." ADEs were classified in terms of causality of the admission, predictability, and preventability. There were 2262 adult non-trauma patients attending the A&E evaluated in the study. The reason for attendance in 16.2% (n=366) of cases was related to at least one ADE. In total, there were 400 ADEs, of which 318 (79.5%) were classified as ADRs and 82 (20.5%) as medication errors.(129)

This paper did not report their results separately for admitted and non-admitted attendances so it was necessary to estimate this using national data for England. In 2015/16 in England, 79.8% of A&E attendances did not result in a hospitalisation(131). These values were used to calculate an estimate of preventable A&E attendances and associated costs related to medication errors that did not result in a hospitalisation. No data were available around impact on mortality or other measures of patient health.

Primary care health care resource use due to medication errors occurring in primary care

No UK studies were found that examined primary care resource use (not resulting in an A&E visit or hospitalisation) due to medication errors occurring in primary care. In previous work modelling the impact of six clinically important medication errors, the probability of an event requiring primary care contact in the form of a GP visit was estimated to be between 2.03% and 15.41%.(22) The midway between these two points was 6.0% and this probability was used to provide an estimate of primary care health care resource use due to medication errors occurring in primary care.

Avery et al. (52) estimated that 12% of patients registered at a primary care practice experience an unavoidable prescribing or a monitoring error and that of these errors, 54% and 3.6% of errors could lead to moderate or serious harm, respectively. The number of people registered with a GP practice in England in April 2016 was used to estimate the number of people at risk from these errors.(132) These errors can be considered to be of similar clinical significance to the errors described in the PINCER study.(22) Therefore, we estimated that 6.0% (range 2.03-15.41%) of avoidable moderate or severe errors would result in a GP visit, and generated costs based on this.

This estimate is not based on primary data, so these costs were not included in the base case cost estimate for impact of errors. The costs were included in an alternative scenario analysis. No data were available around impact on mortality or other measures of patient health.

Increased length of hospitalisations due to ADRs occurring in secondary care

Davies et al. (17) is a UK-based study, in which patients admitted to twelve wards (covering both planned and unplanned admissions) over a six month period in 2005 were assessed for ADRs throughout their admission. Out of the 3695 patient episodes assessed for ADRs, 545 (14.7%, 95% CI 13.6–15.9%) experienced one or more ADRs, 53.3% of which were definitely or possibly avoidable (6.4% definitely avoidable, 46.9% possibly avoidable). The drugs most frequently associated with ADRs were diuretics, opioid analgesics, and anticoagulants. ADRs were reported by this study to increase the length of stay by 4 days for 26.8% of patients experiencing an ADR. The data from this study were used to calculate an estimate for the increased length of hospitalisations, and associated costs, due to ADRs occurring in secondary care.

Deaths associated with ADRs occurring in secondary care

The same UK-based study also reported that out of the 3695 patient episodes assessed, there were 14 deaths in which an ADR was a contributing factor, and one of which was as a direct result of the ADR. (17) This gave an index death rate of 0.38% of all admissions due to ADRs in which the ADR was a contributing factor and 0.03% in which the ADR was the direct cause. Assuming that 6.4% of these ADR-related deaths were definitely avoidable and 53.3% were definitely or possibly avoidable, (17) annual national estimates of avoidable deaths in which medication errors occurring in secondary care caused or contributed to were generated. The number of deaths in which an ADR was a contributing factor was used as the base case estimate because of the small number of deaths (one) caused by an ADR observed in the source study. No data were available on impact for other measures of patient health.

Extrapolation to the NHS

Unit costs and other data used in the estimation of total costs are summarised in Table 33. All values are data recorded by the NHS for the year 2015/16. First, the number of admissions and bed days were calculated for the different sources of errors and then multiplied by the relevant unit costs to generate estimates of the cost to the NHS. To estimate the number of hospital admissions due to primary care ADRs, the number of non-elective finished admission episodes (FAEs) excluding obstetrics and paediatrics (to mirror the admissions observed in the Pirmohamed et al. study (15)) was used as the denominator and multiplied by the rate of errors as observed by Pirmohamed et al.(15) The rate of inpatient admissions during which there was an ADR observed by Davies et al. (17) was applied to the

number of elective and non-elective FAEs, excluding paediatrics and obstetrics; day cases were also excluded from the base case estimate as the ADR rate may be different in day compared to overnight admissions. A scenario analysis was conducted in which day cases were included. The proportion of ICU admissions observed to be related to ADRs by Jolivot et al. (130) was applied to the total number of critical care FAE recorded in the NHS in 2015/16. A proportion of all A&E attendances related to medication errors was calculated from the study by Meier et al.(129) This rate was applied to the total number of non-admitted A&E attendances in the NHS. Avery et al. (52) reported the proportion of patients registered at a GP practice who experienced a medication error. To estimate the number of primary care visits due to medication errors, the total number of patients registered at GP practices was used.

Table 33: Unit costs, extrapolation parameters and their sources used in estimations

Parameter	Value	Source
Unit costs		
Excess bed day cost • non-elective • elective • Mean Cost per non-admitted A&E attendance Cost per (adult) critical care (ICU) admission Mean non-elective inpatient stay: 5 days Per additional day	 £298 £362 £330 £140 £1307 £3058 £298	NHS reference costs(126)
GP visit	£36	PSSRU (133)
Number of episodes in England per annum (2015-16)		
Finished admission episodes (FAEs) Elective and non-elective FAEs excluding obstetrics and paediatrics Elective and non-elective FAEs excluding obstetrics, paediatrics, and day cases Non-elective FAEs excluding obstetrics and paediatrics Critical care FAEs	16,251,841 8,464,215 4,443,564 5,821,746 12,926	NHS Digital(124)
A&E attendances % A&E visits leading to admissions If 79.8% non-admitted	20,457,805 20.2% 16,325,328	NHS Digital(131)
People registered at a GP practice	57,631,776	NHS Digital(132)

A&E: accident and emergency; FAE: finished admission episodes, PSSRU: Personal Social Services Research Unit

5.4. RESULTS

5.4.1. Number of errors

The estimated number of errors per annum in England overall and for each stage of the medication use process in each setting are presented in Table 34.

Table 34: Estimated number of errors per annum in England overall and for each stage of the medication use process in each setting

Error category	Number of medication errors per annum in England			
	Primary care	Care homes	Secondary care	Total
Prescribing	43,623,500	2,983,219	4,043,745	50,650,464
Transitioning	No data	No data	3,380,383	3,380,383
Dispensing	32,877,883	3,522,355	1,376,609	37,776,847
Administration	Not applicable	91,832,832	37,258,284	129,091,116
Monitoring	14,503,519	625,398	1,368,644	16,497,561
TOTAL	91,004,902	98,963,804	47,427,665	237,396,371

We have estimated that there are 237,396,371 medication errors in England in one year. Errors occur at all stages of the medicines use process: prescribing (21.3%), transition (1.4%), dispensing (15.9%), administration (54.4%) and monitoring (6.9%), and in all settings: primary care (38.3%), care homes (41.7%), and secondary care (20.0%). Error rates per patient in primary care are the lowest, but the burden of errors is the second highest due to the size of the sector. Care homes cover fewer patients than the other sectors, but have the highest error rates per patient, leading to a disproportionately high overall number of errors.

The proportion of errors occurring at each stage of the medicines use process is:

- Primary care: 47.9% prescribing, 36.1% dispensing, 15.9% monitoring.
- Care homes: 3.0% prescribing, 3.6% dispensing, 92.8% administration, 0.6% monitoring.
- Secondary care: 8.5% prescribing, 7.1% transition, 2.9% dispensing, 78.6% administration, and 2.9% monitoring.

5.4.2. Proportion of errors have the potential to cause harm

The estimated numbers of errors per annum in England that could potentially lead to mild, moderate or severe harm are presented in Table 35.

Table 35: Estimated number of errors per annum in England overall and for each stage of the medication use process in each setting, presented according to potential to cause harm

Error category	Number of medication errors per annum in England			
	Primary care	**Care homes**	**Secondary care**	**Total for all settings**
Prescribing				
Minor	21,170,690	1,447,770	1,663,208	24,281,668
Moderate	21,723,443	1,485,571	2,087,199	25,296,213
Severe	729,367	49,878	293,338	1,072,583
Total	43,623,500	2,983,219	4,043,745	50,650,464
Transitioning				
Minor	No data	No data	1,390,365	1,390,365
Moderate	No data	No data	1,744,801	1,744,801
Severe	No data	No data	245,217	245,217
Total	No data	No data	3,380,383	3,380,383
Dispensing				
Minor	21,295,902	2,281,526	891,667	24,469,095
Moderate	11,208,369	1,200,803	469,298	12,878,470
Severe	373,612	40,027	15,643	429,282
Total	32,877,883	3,522,355	1,376,609	37,776,847
Administration				
Minor	N/A	84,856,111	34,426,654	119,282,765
Moderate	N/A	6,727,552	2,719,855	9,447,407
Severe	N/A	249,169	111,775	360,944
Total	N/A	91,832,832	37,258,284	129,091,116
Monitoring				
Minor	1,582,202	68,225	149,307	1,799,734
Moderate	10,548,013	454,835	995,378	11,998,226
Severe	2,373,303	102,338	223,960	2,699,601
Total	14,503,519	625,398	1,368,644	16,497,561
All medication use errors				

Error category	Number of medication errors per annum in England			
	Primary care	**Care homes**	**Secondary care**	**Total for all settings**
Minor	44,048,794	88,653,632	38,521,201	171,223,627
Moderate	43,479,825	9,868,761	8,016,531	61,365,117
Severe	3,476,282	441,412	889,933	4,807,627
TOTAL	91,004,902	98,963,804	47,427,665	237,396,371

Of the 237.4 million medication errors in England in one year, 72.1% are estimated to have the potential to cause minor harm only. Those errors that are clinically significant, with potential to cause moderate or severe harm, constitute 25.8% and 2.0% of overall errors, respectively.

In summary:

- Prescribing errors constitute 21.3% of errors overall, and 49.9% and 2.1% of these have potential to cause moderate or severe harm, respectively.
- Transition errors constitute 1.4% of errors overall, and 51.6% and 7.3% of these have potential to cause moderate or severe harm, respectively.
- Dispensing errors constitute 15.9% of errors overall, only 34.1% and 1.1% of these have potential to cause moderate or severe harm, respectively.
- Although administration errors constitute 54.4% of errors overall, 92.4% of these errors are classed as minor with little or no potential for clinical harm.
- Monitoring errors constitute 6.9% of errors overall, 72.7% and 16.4% of these have potential to cause moderate or severe harm, respectively.

We estimate that 61.4 million and 4.8 million errors occur in England per annum that have potential to cause moderate or severe harm, respectively. This constitutes 27.8% of overall errors. Of these 66.2 million clinically significant errors, 47.0 million (71.0%) occur in primary care; in particular 22.5 million (33.9%) are prescribing, 11.6 million (17.5%) are dispensing and 12.9 million (19.5%) are monitoring errors.

The majority of moderate and severe errors (70.9% and 72.3% respectively) occur in primary care. In particular, primary care prescribing errors account for 33.9% of moderate and severe errors. Prescribing errors are most likely to cause moderate harm (41.2% of moderate errors), while monitoring errors account for 56.2% of those with potential to cause severe harm.

5.4.3. Estimates of burden of medication errors

Burden of medication errors occurring in primary care

Table 36 summarises the base case estimate and key alternative scenarios of the cost associated with ADRs and medication errors occurring in primary care. The base case estimate includes only the costs associated with the index admission related to definitely avoidable ADRs. Definitely avoidable ADRs cause 27,362 hospitalisations, related with 136,811 bed days, costing £83.7 million.

Table 36: Estimated national annual cost associated with primary care ADRs and medication errors

Scenarios	Cost/£
Base case	
Hospitalisations due to definitely avoidable primary care ADRs (0.47% admission rate, LOS 5 days, costing £3058 per admission (lowest cost scenario)	83,673,627
Alternative scenarios	
Avoidability	
1. Base case + probably avoidable primary care ADRs (3.0% admission rate(12))	534,086,978
2. Base case + probably avoidable primary care ADRs (3.4% admission rate(12) (15))	605,298,575
3. Base case + probably avoidable primary care ADRs (3.74% admission rate (15))	665,828,433
Admission length	
4. Base case + admission length 8 days (£3952 per admission)[a]	108,135,439
5. Base case + admission length 14.25 days (£5815 per admission)[b]	159,097,548
Primary care contacts (12% error rate for all patients registered with a GP resulting in 3,983,508 errors; primary care contact £36)	
6. Base case + cost primary care contacts for 2.03% of errors[c]	86,584,775
7. Base case + cost primary care contacts for 6.0% of errors[d]	92,278,005
8. Base case + cost primary care contacts for 15.41% of errors[e]	105,772,538
Accident and Emergency visits	
9. Base case + cost A&E attendances not leading to a hospitalisation (16.2% of all A&E attendances related to an ADE, 20.5% due to definitely preventable medication errors, 79.8% of A&E attendances do not lead to a hospitalisation); £140 per non-admitted A&E attendance[f]	159,576,609
Highest cost scenario	
10. Scenario 3 + admission length 14.25 days[g] + cost primary care contacts (15.41%) + cost A&E attendances	1,364,012,168

[a]total: 218,898 bed days.

[b]total: 389,911 bed days.

[c]number of GP contacts and cost: 80,865 contacts, costing £2,911,148.

[d]number of GP contacts and cost: 239,011 contacts, costing £8,604,378.

[e]number of GP contacts and cost: 613,859 contacts, costing £22,098,911.

[f]number of non-admitted A&E attendances and cost: 542,164 attendances, costing £75,902,982.

[g]number of admissions, bed days, and cost: 217,733 admissions, occupying 3,102,700 bed days, costing £1,266,010,275.

Burden of medication errors occurring in secondary care

Table 37 summarises the estimated national burden associated with primary and secondary care errors, reporting the base case estimate and alternative scenarios. Based on the combined number of overnight planned and unplanned admissions (FAEs, excluding obstetric and paediatric specialities) in 2015/16 (N=4,443,564), we estimated that a definitely avoidable ADRs occurred during 41,805 inpatient admissions (ADRs in 14.7% of admissions, 6.4% of which were definitely avoidable) across England in one year. Assuming that in 26.8% of inpatient ADRs admission length is increased by 4 days, this totals 44,815 bed days per year and costs the NHS in England £14,788,955 (based on a cost of £330 per additional day which is the mean of the planned and unplanned excess bed day costs in NHS hospitals).

Definitely avoidable inpatient ADRs are estimated to contribute to 1,081 deaths annually (0.38% of all planned and unplanned admissions, assuming that 6.4% were definitely avoidable) and directly cause 85 deaths (0.03% of admissions, assuming 6.4% were definitely avoidable). Primary care ADRs leading to hospitalisation were estimated to directly result in 627 deaths annually, approximately half of which involve a gastrointestinal bleed.

Table 37: Estimated national burden associated with primary and secondary care errors (base case and alternative scenarios)

Base case and higher cost scenarios	Cost (£)	Bed days/year	Deaths
Base case (hospitalisations linked to definitely avoidable primary care ADRs and definitely avoidable ADRs during overnight hospital admissions)			
• Hospitalisations due to primary care ADRs (base case and lowest cost estimate) • 2.3% of ADRs directly result in death • 9% of ADRs definitely avoidable	83,673,627	136,811	627
• ADRs during overnight inpatient admissions (14.7% error rate); 4 days added to length of stay for 26.8% of patients with an inpatient ADR; £330 for each day added to admission; • 0.38% of all admissions result in a death for which an ADR was a **contributing factor** • 0.03% of all admissions result in a death **caused by** an ADR* • 53.36.4% of ADRs definitely avoidable	14,788,955	44,815	1,081 85*
Total (base case)	98,462,582	181,626	1,708[(1)]
Alternative base case scenarios			
Scenario 1a: (base case + probably avoidable ADRs during overnight admissions - 14.7% error rate, 53.3% definitely or probably avoidable)			
• Hospitalisations due to primary care ADRs • ADRs directly resulting in death • 72% of ADRs probably or definitely avoidable	605,298,575	989,697	5,013
• ADRs during overnight inpatient admissions • Deaths for which inpatient ADR was a **contributing factor** • 53.3% of ADRs probably or definitely avoidable	123,164,262	373,225	9,000
Total (Scenario 1a)	728,462,837	1,362,922	14,013
Scenario 1b: (base case + definitely avoidable ADRs during day case admissions)			
• ADRs during all inpatient admissions • Deaths for which inpatient ADR was a **contributing factor** • 6.4% of ADRs definitely avoidable	28,170,381	85,365	2,058
Total (Scenario 1b)	111,844,008	222,176	2,685
Cumulative burden scenarios			

Base case and higher cost scenarios	Cost (£)	Bed days/year	Deaths
Scenario 2: (base case + cost of primary care contacts for 6.0% of primary care errors)			
Total (Scenario 2)	107,066,960	181,626	1,708
Scenario 3: (base case + A&E attendances for primary care medication errors)			
Total (Scenario 3)	174,365,564	181,626	1,708
Scenario 4: (base case + ICU admissions related to ADEs)			
• ICU admissions related to preventable ADEs (8.1% of ICU admissions); length of ICU stay 4 days; £5228 per ICU admission • Death during ICU admission (14% of ICU admissions for preventable ADEs)	5,473,747	4,188	147
Total (Scenario 4)	103,936,329	185,814	1,855
Scenario 5: (base case + primary care costs (6.0% of errors) + A&E attendances for primary care errors + ICU admissions related to ADEs)			
Total (Scenario 5)	188,443,689	185,814	1,855
Scenario 6: (highest cost scenario)			
• definitely or probably avoidable ADRs (3.74% of admissions), admission length 14.25 days, primary care costs for 15.41% of errors, and A&E attendances for primary care medication errors	1,364,012,168	3,102,700	5,013
• definitely or probably avoidable inpatient ADRs (including day cases)	234,606,454	710,929	17,143
• ICU admissions related to ADEs	5,473,747	4,188	147
Total (Scenario 6)	1,604,092,369	3,817,817	22,303

(1)The base case estimate includes deaths in which an ADR was a contributing factor rather than the direct cause.

Summary of results

The base case uses only UK-based data on hospitalisations linked to definitely avoidable primary care ADRs (LOS 5 days) and ADRs during hospital admissions. The estimated costs to the NHS are £98,462,582 per annum, consuming 181,626 bed-days, causing 712 deaths, and contributing to 1,708 deaths during the index hospitalisation. Incorporating primary care costs (author estimate), A&E attendances for primary care ADEs (German data) and ICU admissions related to ADEs (French data)

provide a higher estimate, with estimated costs to the NHS of £188,443,689 per annum, consuming 185,814 bed-days and contributing to 1,855 deaths. Including possibly avoidable ADRs and assuming a 14.25 day admission for primary care errors to this estimate provides the highest cost scenario estimate of £1,604,092,369 per annum, consuming 3,817,817 bed-days, and contributing to 22,303 deaths.

5.5. DISCUSSION

5.5.1. Key findings

We have estimated that there are 237.4 million medication errors in England in one year. This is a high number but it is important to note that, of these, 72.1% are estimated to have the potential to cause minor harm only, and not all these errors would have reached the patient. Those errors that are clinically significant, with potential to cause moderate or severe harm, constitute 25.8% and 2.0% of overall errors, respectively.

Errors occur at all stages of the medicines use process: prescribing (21.3%), transition (1.4%), dispensing (15.9%), administration (54.4%) and monitoring (6.9%), and in all settings: primary care (38.3%), care homes (41.7%), and secondary care (20.0%). The error rate per medication item within a particular setting and the number of medication items in that setting determine the total number of errors. Error rates per item in primary care are the lowest but the total number of errors is the second highest due to the large number of medications used in primary care. Care homes serve fewer patients than the other sectors, but have the highest error rates, leading to a disproportionately high overall number of errors. The highest proportion of errors with potential to cause moderate and severe harm are prescribing and monitoring errors, respectively.

We found no data on the costs and health burden associated with medication errors occurring in the NHS. We found some data on the costs and health burden of definitely avoidable ADRs in primary and secondary care, which we assumed that were a proxy for medication error. The estimated costs to the NHS of definitely avoidable ADRs are £98.5 million (£98,462,582) per annum, consuming 181,626 bed-days, causing 712 deaths, and contributing to 1,708 deaths during the index hospitalisation. These costs and deaths can be divided into ADRs in primary care leading to a hospital admission (£83,673,627; causing 627 deaths) and ADRs in secondary care leading to a longer hospital stay (£14,788,955; causing 85 deaths, and contributing to 1,081 deaths).

In both primary and secondary care studies, patients with ADRs were older than those without. In the Pirmohamed et al. study (15), patients admitted with ADRs (median age 76 years, interquartile range

65-83) were significantly older than patients without ADRs (66 years, 46-79; $p < 0.0001$).(15) In secondary care ADRs, the median age was also significantly higher in the ADR group at 72 years (IQR 56–81 years) compared with 61 years in the non-ADR group (IQR 41–77 years; $p< 0.0001$).(17) In this latter study, more medical patient episodes (n=406, 16.0%) than surgical episodes (n=139, 12.0%) resulted in ADRs ($p < 0.01$).

A systematic review of studies reporting which drugs lead to hospital admissions suggested that the majority (51%) of preventable drug-related admissions involved antiplatelets (16%), diuretics (16%), nonsteroidal anti-inflammatory drugs (NSAIDs) (11%) or anticoagulants (8%).(16) In the Pirmohamed et al. study (15), primary care ADRs leading to hospital admission were most commonly caused by NSAIDs and diuretics. Aspirin was the most common drug, implicated in 18% of admissions, of whom 162 (74%) patients were taking 75 mg daily. Gastrointestinal bleeding was the most common adverse effect, occurring in 157 (72%) of all aspirin related admissions.(15) NSAIDs prescribing without GI protection in people with one or more risk factors, leading to some sort of GI event (not specified) was also the most common reason for admission in the Howard study.(12) Secondary care ADRs were most frequently caused by anticoagulants (warfarin), fibrinolytics (streptokinase), unfractionated heparin, loop diuretics and allopurinol.(17)

5.5.2. Comparison with published estimates of medication error prevalence and burden

We are not aware of another published estimate of numbers of errors. There are limited examples of published estimates of harm, which have all used a similar approach to ours in focusing on costs associated with primary care ADRs/ADEs leading to hospital admissions(15) and costs associated with secondary care admissions leading to longer hospital stays.(4)

We have restricted our primary estimate to definitely avoidable ADRs. For hospital admissions due to ADRs, this gave a rate of 0.47% of admissions (i.e. 9% of 80% of 6.5%) based on observations by Pirmohamed et al. (15), assuming that all ‘definitely’ avoidable ADRs are medication errors. Assuming that both ‘probably’ and ‘definitely’ avoidable ADRs were errors changed the estimate of burden significantly, from 0.47% to 3.4% of all admissions. (134, 135).

Like other researchers in this area, Pirmohamed et al. (15) used a method that requires a degree of clinical judgment to assess avoidability of the error. It is consistent with data from France (136) and the Howard study (12), which suggested that 80% and 67% of ADRs, respectively, were preventable. It is also compatible with a meta-analysis, where the rate of preventable ADRs was 59% (interquartile range 50-73%).(137)

Pirmohamed et al. (15) suggested that admissions related to definitely or possibly avoidable ADRs cost the NHS up to £466m annually in 2004 at 2003 prices (£647m at 2015/16 prices (133)).(15) They suggested that their estimates were comparable with the lower estimates from the United States(18, 19). Using Pirmohamed et al's estimates of 3.74% hospital admissions due to definitely or possibly avoidable ADRs, we estimate a cost to the NHS of £665,828,433 at 2016 prices. With the lower admissions rate derived from merging Howard et al. (12) and Pirmohamed et al. (15) estimates, this provides a base case estimate cost of £605,298,575 to the NHS per annum, not dissimilar to the original Pirmohamed et al cost estimates, especially when changes in the general population are taken into account (that is, a larger number of people and a greater proportion of whom are older adults).

In 2007, the National Patient Safety Agency (NPSA) estimated NHS costs of preventable medication errors to be £774 million, at 2005/6 prices (£954 million at 2015/16 prices).(4, 133) This sum was derived from costs of admissions (£359 million), costs of increased lengths of admissions from errors occurring whilst in hospital (£411 million) and litigation costs (£4 million). They used a hospital admissions rate due to definitely or probably preventable ADRs of 4.68%, derived from the Pirmohamed et al. study (15) admissions rate of 6.5% adjusted for 72% of admissions being preventable, but not accounting for the 20% of admissions judged to be not directly related to the drug as was done in this analysis. Our admissions rate is derived from 72% of 5.0%, not 6.5%, as Pirmohamed et al. (15) judged that 1.5% admissions detected were coincidental, rather than truly linked to an ADE. To estimate hospital costs, the NPSA used a systematic review suggesting that the rate of hospital-based ADEs in the UK and Europe was about 7.0% (although this did not include major areas of error, such as drug administration).(138) In the absence of other evidence on avoidability, the same rate of 72% was applied, leading to an avoidable rate of 5.04%. Wiffen et al. (138) estimated the range of additional days spent in hospital as a result of an ADE to be between two and four, taking three additional days as being representative. In our base case estimate, we used primary observational data from a UK-based study instead of this review-based estimate.(17) Out of the 3695 patient episodes assessed for ADRs, 545 (14.7%, 95% CI 13.6–15.9%) experienced one or more ADRs, 53.3% of which were definitely or possibly avoidable (6.4% definitely avoidable, 46.9% possibly avoidable). ADRs were reported by this study to increase the length of stay by 4 days for 26.8% of patients experiencing an ADR. NHS litigation costs represented around 0.5% of the total cost of errors estimated by NPSA. The NPSA estimate is higher than our estimate, as we included only definitely avoidable ADRs as a proxy medication errors.

5.5.3. Comparison of the UK setting with other settings

The systematic review in this report focused on identifying medication error rates in the UK. Whilst a full systematic review of the evidence around error rates globally is beyond the scope of this report, it is important to examine whether the error rates reported in the UK are different from, or similar to, those reported in other healthcare settings. Where available, published systematic reviews have been used to provide information about error rates in other countries at the different stages of the medication use process. These are summarised below. The dominance of UK research activity in this area is reflected by the high proportion of UK prevalence studies, compared with research from other countries. The US is equally active in research in the secondary care setting, but the UK has produced the vast majority of research around errors in primary care. None of the data found suggests that error rates in the UK are higher than in other comparable health care settings, although the huge variation in study design limits much meaningful comparison.

Prescribing error rates

Primary care

A systematic review of 33 studies of primary care prescribing errors, the majority from the US (n=12) and the UK (n=10), suggested that prescribing error rates were comparable across countries in some instances – Bahrain: 7.7% prescriptions; UK: 7.5% and 5% prescriptions; USA 7.6% and 11% prescriptions; India 6.1% items and Ireland 6.2% prescriptions.(139) One US study reported that over one-third of 651 patients were found to have a prescribing error occurring at hospital admission in the USA.(140) Prescribing errors are also prevalent in primary care, affecting 37% of 9385 prescriptions in the USA, although many of these were due to being illegible, which isn't really an issue in the UK due to the electronic nature of prescribing.(141) A study in the Netherlands evaluating medication omission errors in elderly patients admitted to hospital reported adverse consequences in 21% of 100 patients.(142) A Swedish study found a medication error rate of 42%.(143) However, two-thirds were related to a failure to state the purpose of the treatment on prescriptions and only 1% of errors resulted in an incorrect dose.

Secondary care

A systematic review of 65 studies carried out in 13 countries, the majority from the US (25) and the UK (22), of hospital prescribing errors found that the median reported error rate was 7% (IQR 2–14%).(144) The definition of a prescribing error was extremely varied, with 42% of studies (27/65) developing their own definitions or modifying ones used in previous studies. Reported error rates ranged between 1.9 to 15.4% in the US, 2.4 to 24.2% in the UK and 9.9 to 20.3% in the Netherlands.

Dispensing error rates

Secondary care

A systematic review of 15 studies carried out in four countries of hospital dispensing errors found that reported error rates varied between 0.016% and 33.5%.(145) Reported error rates were very much dependent on the dispensing system and methods used to measure errors, limiting comparison between studies, or countries One US study reported an error rate of 3.6%, but then stated that 79% of these errors were detected by pharmacists before they left the pharmacy, giving an undetected error rate of 0.75%.(146) One French study reported an error rate of 2.4%, but then stated that 86.6% of these errors were detected by pharmacists before they left the pharmacy, giving an undetected error rate of 0.3%.(147) There is no equivalent UK observational study of undetected errors leaving the hospital pharmacy, but a UK study did report similar rates of errors being detected at final check (2.7%)(148) as the US and French studies in this review, suggesting that error rates are probably largely comparable.

Primary care

A systematic review of studies of dispensing errors in community pharmacies found that reported error rates varied widely due to differences in methods.(149) However, dispensing error rates were consistently low across countries. This review reports that, in the four UK studies, prevented dispensing incidents occurred at a rate of 0.22–0.48%. In contrast, the rate of unprevented dispensing incidents varied considerably from 0.04 to 3.32%. In the seven US studies, the rate of prevented dispensing incidents was 1.28% but the rate of unprevented dispensing incidents ranged from 0.08 to 24%. Other studies suggest that dispensing errors are reported to range between 1.7 and 12.5% in the USA. In the USA, Flynn et al. (150) observed four dispensing errors per day per 250 prescriptions in 50 pharmacies, giving an error rate of 77 errors in 4481 dispensed items (1.7%), of which 5 (6.5%) were judged to be clinically important errors. Two US studies report a 12.1% and 12.5% dispensing error rates in a hospital outpatient pharmacy, respectively.(151, 152)

Administration error rates

An extensive review of studies of medication administration errors examined 91 studies from 16 countries, the majority from the US (25) and the UK (22)(116). Despite heterogeneity in methods limiting meaningful comparison between studies, country-level comparisons suggest comparable error rates in the UK, USA, Australia, the Netherlands, France and Canada.

5.5.4. Limitations and areas of uncertainty

Prevalence of errors

The estimates of total number of errors were based on the prevalence of errors reported in the literature for each type of error and setting, combined with the reported medicine use in that sector. Alternatively, medication error can be seen as a stock and flow problem where errors occur but can be resolved in subsequent steps of the process. Estimating the total number of errors as the sum of errors occurring at each step of the process represents an estimate of the total number of errors but not the errors that actually reach and may harm patients, which are arguably those of most concern. Methodological complexity and ethical issues around safety (once an error is detected, it is unethical to leave it uncorrected) make better understanding of this process challenging.

Lack of existing data specific to support all stages of the medicines use process and all settings means that we have had to make assumptions to calculate the total number of errors. These assumptions necessarily lead to a level of uncertainty around the estimates presented. These uncertainties arise from four sources: (1) limited data available, (2) generalisability of primary studies, (3) assumptions required to extrapolate the error rate, and (4) lack of data on the number of errors that actually reach patients. Each are discussed in turn below.

(1) Limited data available

We found no data for rate of medication errors in transition across care settings in primary care and care homes. Therefore, we were unable to estimate the prevalence of errors in transitions across care settings in primary care and care homes. We did not identify any studies that measure the number of dispensing errors in secondary care, only near misses and errors reported by patients. These are likely to over and underestimate the incidence of errors, respectively. We thus assumed that the primary care dispensing error rate was generalisable to secondary care. Similarly, we did not identify any studies that report the prevalence of monitoring errors in secondary care, and hence we assumed that the prevalence of errors in primary care was generalisable to secondary care.

(2) Generalisability from primary studies to the NHS.

We assumed that the estimates obtained from studies in a small number of centres were generalisable to the NHS in England. To minimise issues around generalisability, we included studies judged to be the highest quality in Review 1 for each sector and type of error.

(3) Assumptions

We made a number of assumptions to extrapolate the error rates obtained from these studies to the NHS in England (summarised in Table 30)

(4) Lack of data on the number of errors that actually reach patients.

Most of the studies on the prevalence of medication error investigate the number of errors at a particular setting and stage of the medication pathway, rather than the number of errors that were missed in each of subsequent stages of the pathway and actually reached patients.

Burden of errors in costs and health

There are four key limitations on the estimates of burden of errors: (1) the assumption that avoidable ADR/ADEs correspond to medication errors, (2) generalisability of the source studies to the NHS, (3) lack of primary data to inform estimates, and (4) assumptions about the valuation of healthcare resource use associated with errors.

(1) Assumption that avoidable ADR/ADEs are caused by medication errors

Throughout this report, we have used the term "medication error" which oversimplifies the act of prescribing a hazardous combination of medicines, for example, as being "bad", and thus to be prevented or avoided. In reality, the decision to use a medicine in a clinical situation where there may be increased risk of a side effect, happens every day in routine practice. Virtually all acts of prescribing involve some risk, but usually the intended benefits are judged to outweigh the risks of harm. When using the term 'hazardous prescribing' we mean prescribing where the evidence suggests that the risks are likely to outweigh the potential benefits. For example, if a GP has a patient over the age of 65, with arthritic pain, prescribing an NSAID can reduce pain, but increase risk of a gastrointestinal bleed. The patient should be prescribed gastroprotection, such as a proton pump inhibitor (PPI) to reduce the probability, or risk, of a bleed. In this situation, the PPI may be omitted by the prescriber unintentionally, which would be classed as an error. However, here may be conscious weighing up of relative risk and benefits of prescribing, by the prescriber and patient, as PPIs have side effects of their own. This action is better termed hazardous prescribing, but is not necessarily an error. The use of the term "error" also suggests that in the absence of the "error", there will be no harm, and in the presence of the error, there will be harm. In reality, the probability of harm is usually increased, rather than introduced in the event of hazardous prescribing. In the example given here, the risk of a gastrointestinal event is increased, not introduced, by the prescribing of the NSAID, and reduced, not removed, by the addition of the PPI.

Given the paucity of data directly linking errors to outcomes and costs, we cannot make conclusions about the harm associated with errors directly. Therefore, we based our estimates on UK observational data of healthcare resources used to treat ADRs/ADEs, as reported in the source studies. The source studies used published criteria to identify what proportion of all ADR/ADEs observed were avoidable. Notwithstanding the limitations of this approach, as described above, we have assumed that the occurrence of avoidable ADRs/ADEs and their associated burden and cost, can be used to approximate the burden and cost of harm from medication errors.

(2) Generalisability to the NHS

Most of the studies are at least 10 years old, and therefore, may not reflect current patient populations or practice pattern. The studies relate only to ADRs in primary care leading to hospital admissions, and ADRs in secondary care leading to longer hospital stays. There are no national datasets of these parameters to allow assessment of burden. For this reason, we have extrapolated from these observational studies of one or two hospital trusts, and therefore assume that these data are representative of the national picture. Additionally, we found no UK studies on the cost of medication errors, ADEs or ADRs leading to A&E or ICU admissions. Therefore, we have used primary data from single centre studies in Germany and France, respectively.

(3) Insufficient primary data

We have no primary data on burden in primary care. The cost of primary care errors treated in primary care is based on the proportion of errors that led to a GP visit based on the "PINCER errors". We assumed that the six "PINCER errors" are representative of the moderate and severe errors in primary care. The calculated cost is likely to be an underestimate of the primary care costs due to errors because it only considers prescribing and monitoring errors, and not errors in dispensing and administration.

We also have no data around longer term impact of medication error. Specifically, we found no data on the resource use subsequent to the initial hospitalisation or on patient outcome other than deaths during the index hospitalisation related to the avoidable ADR. Moreover, we found no data on medication errors which occur and are managed in the care home setting. Also, we did not include day case admissions in our extrapolation of inpatient ADRs since the ADR rate may not be generalisable from general ward to the day case setting. However, the purpose of some day case admissions is specifically to administer complex medications which may be at high risk of errors. For example in 2015/16 in the NHS there were 75,000 recorded day case admissions for 'Inflammatory, Spine, Joint or Connective Tissue Disorders', which would include intra-articular and intrathecal drug infusions. In summary, the base-case includes the cost of definitely avoidable ADRs in primary care leading to

hospitalisations and the cost of definitely avoidable ADRs occurring during overnight inpatient admissions.

(4) Assumptions about the valuation of healthcare resource use

The final assumption is the unit costs attached to the burden reported in the studies, primarily costs associated with unplanned hospitalisations and extended inpatient stays. We have used publicly available databases of prices which is necessarily an approximation of real costs incurred.

5.5.5. Reducing the burden of medication errors

Interventions to identify and reduce medication errors need to be designed and implemented thoughtfully given that the medicines use process is such a significant part of day-to-day work.

Clinical decision support (CDS) systems consist of point-of-care alerts to clinicians that relates to prescribing that may be hazardous or inappropriate.(153) The CDS system is 'interruptive' in that it requires the clinician to respond to the alert. It issues a safety alert on the computer screen immediately that an attempt is made to prescribe hazardous medication, after which the clinician can decide to accept the alert and cancel the prescription, or override the alert and pursue the prescription. CDS systems to flag potential hazardous prescribing events can be invasive, irrelevant and often occur at the point of generating the prescription, after the prescribing decision has been reached in the consultation process. For this reason, a large proportion of alerts tend to be ignored.(154) More complex interventions such as the PINCER intervention, an education and outreach intervention combined with practice-level error report generation, which consisted of pharmacists working with prescribers, have been shown to be effective and cost-effective,(155) but can be costly and time consuming so need to be applied thoughtfully.

For example, focusing on key prescribing areas, rather than attempting to address all areas at once was one of the reasons the PINCER intervention was effective and acceptable to general practices. A significant amount of work was done to identify clinically important and relatively commonly occurring errors to focus on. A systematic review identified 12 drug groups that account for 80% of hospital admissions that are medication-related and preventable.(16) This review identified particular problems with three groups of drugs that are responsible for over a third of these admissions; anticoagulants, antiplatelets and non-steroidal anti-inflammatory drugs (which all cause gastrointestinal bleeding). An important implication from this study is that reducing hazardous prescribing in general practice associated with specific groups of drug could prevent the majority of medication-related hospital admissions. Identifying errors and subsequent harm in routine practice is

not straightforward in all cases and a lot of work is also required to ensure that robust algorithms are developed, and validated (156-158), required for good levels of recording and reliable identification of patients who are genuinely at risk from hazardous prescribing.

The prescribing safety indicators recently developed by Avery and colleagues (153) were designed to address all these issues of clinical importance and identification and are currently being used to assess effectiveness of the wider implementation of the PINCER intervention in an NIHR funded study.

5.5.6. Conclusions to Section 5

Using published error rates, we estimated that there are 237 million medication errors in England in one year. Although this is a large number, 72.1% are minor with little or no potential for clinical harm. We estimated that 66 million potentially clinically significant errors occur in all health care settings, and 71.0% of these clinically significant errors occur in primary care. Prescribing in primary care accounts for 33.9% of all potentially clinically significant errors. It is likely that some of these errors are picked up later in the medication use process and never actually reach the patient, but we do not know how many.

Due to lack of direct data on the burden of medication error to the NHS, we assumed that definitely avoidable ADRs are a proxy for medication error. We estimated that definitely avoidable ADRs cost the NHS £98.5 million per annum, consume 181,626 bed-days, cause 712 deaths, and contribute to 1,708 deaths during the initial hospitalisation. Given the quality of the data available, there is a high level of uncertainty around this estimate of burden.

5.5.7. Recommendations

The studies used to support the estimates of burden are old studies of avoidable ADRs leading to hospitalisation, and updated versions of the studies are desirable, given the changes in disease epidemiology and management, medicines available and size and morbidity of target populations. However, even more recent versions of these studies will not solve the inherent subjectivity and hindsight bias problem associated with retrospective assessment of whether a hospitalisation is caused by a medication error. They also only look at one aspect of harm associated with one error type in one setting. The first key action arising from this work should be to facilitate routine data collection of clinically important errors and link them to outcome data to allow identification of priority areas for targeting interventions. The UK is a world leader in research in this area, and also has extensive high quality primary care and secondary care data sources, that if harnessed and integrated, could already

be used to record errors in some parts of the medication use process, particularly prescribing and monitoring, and link them to outcomes.

The second action should be to support implementation of evidence-based interventions to reduce incidence of clinically important errors, particularly in primary care prescribing. The first action would facilitate identification of priority areas for targeting interventions.

We know that current self-reporting systems (National Reporting and Learning System, NRLS) are thought to detect only 7-15% of all incidents including medication errors.(159) It is clear from the work carried out in this report that medication errors are a system failure, so the third action should focus on changing cultures to remove personal blame, which will improve self-reporting figures, and allow systems to be improved.

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APPENDICES

A.1 Review 1 literature search strategies

PubMed: NIH

6th September 2017

#	**Searches**
#1	Search ((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*))
#2	Search (incidence) OR prevalence
#3	Search ((great britain[MeSH Terms]) OR (national health service*[Title/Abstract] OR nhs*[Title/Abstract])) OR (gb[Title/Abstract] OR g.b.[Title/Abstract] OR britain*[Title/Abstract] OR british*[Title/Abstract] OR uk[Title/Abstract] OR u.k.[Title/Abstract] OR united kingdom*[Title/Abstract] OR england*[Title/Abstract] OR english*[Title/Abstract] OR northern ireland*[Title/Abstract] OR northern irish*[Title/Abstract] OR scotland*[Title/Abstract] OR scottish*[Title/Abstract] OR wales[Title/Abstract] OR welsh*[Title/Abstract])
#4	Search (((((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)))) AND ((incidence) OR prevalence)) AND (((great britain[MeSH Terms]) OR (national health service*[Title/Abstract] OR nhs*[Title/Abstract])) OR (gb[Title/Abstract] OR g.b.[Title/Abstract] OR britain*[Title/Abstract] OR british*[Title/Abstract] OR uk[Title/Abstract] OR u.k.[Title/Abstract] OR united kingdom*[Title/Abstract] OR england*[Title/Abstract] OR english*[Title/Abstract] OR northern ireland*[Title/Abstract] OR northern irish*[Title/Abstract] OR scotland*[Title/Abstract] OR scottish*[Title/Abstract] OR wales[Title/Abstract] OR welsh*[Title/Abstract]))
#5	Search (((((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)))) AND ((incidence) OR prevalence)) AND (((great britain[MeSH Terms]) OR (national health service*[Title/Abstract] OR nhs*[Title/Abstract])) OR (gb[Title/Abstract] OR g.b.[Title/Abstract] OR britain*[Title/Abstract] OR british*[Title/Abstract] OR uk[Title/Abstract] OR u.k.[Title/Abstract] OR united kingdom*[Title/Abstract] OR england*[Title/Abstract] OR english*[Title/Abstract] OR northern ireland*[Title/Abstract] OR northern irish*[Title/Abstract] OR scotland*[Title/Abstract] OR scottish*[Title/Abstract] OR wales[Title/Abstract] OR welsh*[Title/Abstract])) Filters: published in the last 10 years
#6	Search (((((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)))) AND ((incidence) OR prevalence)) AND (((great britain[MeSH Terms]) OR (national health service*[Title/Abstract] OR nhs*[Title/Abstract])) OR (gb[Title/Abstract] OR g.b.[Title/Abstract] OR britain*[Title/Abstract] OR british*[Title/Abstract] OR uk[Title/Abstract] OR u.k.[Title/Abstract] OR united kingdom*[Title/Abstract] OR england*[Title/Abstract] OR english*[Title/Abstract] OR northern

	ireland*[Title/Abstract] OR northern irish*[Title/Abstract] OR scotland*[Title/Abstract] OR scottish*[Title/Abstract] OR wales[Title/Abstract] OR welsh*[Title/Abstract])) Filters: published in the last 10 years; English

Embase 1974 to 2017 September 05

6th September 2017

#	**Searches**
1	incidence.mp.
2	prevalence.mp.
3	1 or 2
4	(medication and error).mp.
5	(inappropriate and prescribing).mp.
6	inappropriate medication.mp.
7	(preventable and adverse and drug and event*).mp.
8	(preventable and adverse and drug and reaction*).mp.
9	(prescribing and error*).mp.
10	(transcription and error*).mp.
11	(medication and discrep*).mp.
12	(medication and omission*).mp.
13	or/4-12
14	exp great britain/
15	(national health service* or nhs*).tw.
16	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).tw.
17	(gb or britain* or british* or uk or united kingdom* or england* or english* or northern ireland* or northern irish* or scotland* or scottish* or wales or welsh*).tw.
18	or/14-17
19	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)
20	18 not 19
21	3 and 13 and 20
22	limit 21 to (english language and yr="2007 -Current")

Cochrane Database of Systematic Reviews (CDR): Wiley Online. 1996-2017

Cochrane Central Register of Controlled Trials (CENTRAL): Wiley Online. 1898-2017

Health Technology Assessment Database (HTA): Wiley Online. 1995-2016

Database of Abstracts of Reviews of Effects (DARE)): Wiley Online. 1995-2015

NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015

6th October 2017

#	**Searches**
#1	cost
#2	econ*
#3	#1 or #2
#4	medication error
#5	#3 and #4 Publication Year from 2016 to 2017

CINAHL 1982 to 2017

6th September 2017

#	**Searches**
S1	(cost or econ*)
S2	(medication error or inappropriate prescribing or" inappropriate medication" or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)
S3	S1 AND S2 Limiters - Published Date: 20160101-20171231; English Language

A2. Review 2 Literature Search Strategies

PubMed: NIH

6th September 2017

#	**Searches**
#1	Search cost OR cost analysis OR econ*
#2	Search (medication error or inappropriate prescribing or "inappropriate medication" or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)

#3	Search ((cost OR cost analysis OR econ*)) AND ((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*))
#4	Search ((cost OR cost analysis OR econ*)) AND ((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)) Filters: Publication date from 2016/01/01 to 2017/12/31
#5	Search ((cost OR cost analysis OR econ*)) AND ((medication error or inappropriate prescribing or ”inappropriate medication” or preventable adverse drug event* or preventable adverse drug reaction* or prescribing error* or transcription error* or medication discrep* or medication omission*)) Filters: Publication date from 2016/01/01 to 2017/12/31; English

Embase 1974 to 2017 September 05

6th September 2017

#	**Searches**
1	cost.mp.
2	econ*.mp.
3	1 or 2
4	(medication and error).mp.
5	(inappropriate and prescribing).mp.
6	inappropriate medication.mp.
7	(preventable and adverse and drug and event*).mp.
8	(preventable and adverse and drug and reaction*).mp.
9	(prescribing and error*).mp.
10	(transcription and error*).mp.
11	(medication and discrep*).mp.
12	(medication and omission*).mp.
13	or/4-12
14	3 and 13
15	limit 14 to (human and english language and yr="2016 -Current")

A3. Table studies excluded at full-text

Study	Reason for Exclusion
Conroy 2007	Number of times pharmacists have to clarify of correct prescriptions (no denominator)
Dawson (32)	Intervention study
Franklin and O'Grady (42)	Intervention study
Hamad et al. (33)	Number and nature of errors reported on an electronic system only (no denominator)
Haw and Cahill (34)	Number and nature of errors reported on an electronic system only (no denominator)
Hitti et al. (35)	Intervention study
Jani et al. (36)	Intervention study
Jheeta and Franklin (37)	Intervention study
Michaelson 2017(38)	Not UK (Ireland)
Rashed and Tomlin (39)	Letter to the Editor
Ross 2013(40)	Number and nature of errors by junior doctors (no denominator)
Westbrook 2011(44)	Not UK (Australia)
Zaidi 2015(43)	Intervention study