Evaluating and Optimising the Retrieval of Research Evidence for Systematic Reviews of Adverse Drug Effects and Adverse Drug Reactions

A Thesis Submitted for the Degree of Doctor of Philosophy

By

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Abstract

Systematic reviews can provide timely, reliable evidence on which to make informed decisions. In order to make balanced decisions, information is not only needed on the benefits of an intervention, but also on its adverse effects. Yet few systematic reviews incorporate adverse effects data in their analysis. There is currently a lack of guidance on how to identify adverse effects data, this may impede systematic reviewers. This thesis helps address this situation by evaluating and optimising the methods for retrieval of research evidence for systematic reviews of adverse effects.

The first stage of this programme of research critically reviews the methodological literature relating to the retrieval and inclusion of adverse effects data, including aspects such as the impact of study design (for example RCTs and cohort studies), database search strategies (for example in MEDLINE and EMBASE), sources of data (including database and non-database sources), publication status and funding status.

Second, the results of a survey of the literature searching methods used in 849 systematic reviews of adverse effects are presented. Data were collated on aspects such as sources searched, search strategy design and the standard of reporting of the methods used. The reviews are published over a 17 year time period (1994-2011) thus enabling time trends analysis. The methods used in these systematic reviews of adverse effects are also compared with those reported in surveys of other types of reviews.

Further potentially relevant evidence is incorporated to address gaps identified in the literature. A detailed analysis is provided of the contribution of different sources of data for adverse drug reactions using 58 included studies from a case study systematic review. The same case study systematic review is then used to measure the performance of adverse effects search filters in MEDLINE and EMBASE.

Finally 242 included papers from a series of 26 systematic reviews are evaluated to strengthen the evidence base regarding adverse effects search filters and to assess individual adverse effects search terms in MEDLINE, EMBASE, and Science Citation Index (SCI).

The strengths and weaknesses of the analyses are discussed and implications for practice and guidance presented along with recommendations for future research.

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Dedication

I would like to dedicate this PhD to Mrs Norah Lawrence who bravely fought a terminal diagnosis of Motor Neurone Disease (MND) during my studies.

Publications

Related to Chapters 3 and 4

Golder SP, Loke YK, Bland M. Comparison of pooled risk estimates for adverse effects from different observational study designs: methodological overview. *PLoS One.* 2013 Aug 20;8(8):e71813.

Golder SP, Loke YK, Bland M. Meta-analyses of adverse effects data derived from randomised controlled trials as compared to observational studies: methodological overview. *PLOS Med* 2011;8(5) e1001026.

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Golder S, Loke YK. Sources of information on adverse effects: a systematic review. *Health Info Libr J* 2010;27(3):176-90.

Related to Chapters 3 and 6

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Related to Chapters 3 and 7

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Related to Chapter 12

Golder S, Loke YK. Sensitivity and precision of adverse effects search filters in MEDLINE and EMBASE: a case study of fractures with thiazolidinediones. *Health Info Libr J* 2012;29(1):28-38.

Related to Chapter 13

Golder S, Loke YK. Failure or success of electronic search strategies to identify adverse effects data. *J Med Libr Assoc* 2012;100(2):130-4.

Golder S, Loke YK. The performance of adverse effects search filters in MEDLINE and EMBASE. *Health Info Libr J* 2012;29(2):141-51.

Related to all Chapters

Golder S, Loke YK, Zorzela L. Optimising the retrieval of information on adverse drug effects. *Health Info Libr J [in press]*

Conference presentations

Related to Chapters 3 and 4

Golder S, Loke Y, Bland M. Methodological Overview: Meta-analyses of Adverse Effects Data from Case-Control Studies as Compared to Other Observational Studies. 21st Cochrane Colloquium, Quebec, Canada, 19-23 September 2013.

Golder, S. Loke, Y, Bland M. Comparison of adverse effects data derived from different study designs. 19th Cochrane Colloquium. Madrid, Spain, 19-22 October 2011.

Related to Chapters 3 and 8

Golder, S. Loke, YK, Burch J. Impact of funding source on reporting of adverse effects: methodological overview. 16th Cochrane Colloquium. Freiburg, Germany, 3-7 October 2008.

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Golder, S. Loke, Y. The usefulness of different information sources for retrieving adverse effects data for a systematic review. 19th Cochrane Colloquium. Madrid, Spain, 19-22 October 2011.

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Other presentations

Golder S. Finding and Incorporating Information on Adverse Effects. Systematic Reviews Issues and Updates Symposium (Syrius II). ScHARR, University of Sheffield, Sheffield. 21 March 2011.

Golder S. Finding adverse effects studies…the search is on! Cochrane Canada Live (webinar). 16 September 2010.

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Loke Y, Golder S. Retrieving data for systematic reviews incorporating adverse effects. 13th Annual Meeting of UK and Irish Contributors to The Cochrane Collaboration. York, UK, 11-12 March 2008.

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Author's declaration

The views expressed in this thesis are those of the author and not necessarily those of the funders. The author declares that the research in this thesis is the result of her own investigation, other than those acknowledged previously, and that none of the material contained in this thesis has previously been submitted for a degree in this, or any other, awarding institution.

This PhD was carried out over nearly six years on a part-time basis with two periods of maternity leave. The lack of continuous study may contribute to the differing currency of some of the chapters.

Chapter 1 Introduction

1.1 Background

Pharmaceutical interventions have bought about many benefits to health, improving the population's wellbeing and life expectancy. However, these interventions are not without potential harmful consequences. For over two thousand years, adverse effects of drugs have been known to cause significant morbidity and mortality.[1] While all healthcare interventions have the potential for harm, it is the adverse effects of pharmaceutical interventions that have received the most media attention.[2] Although the adverse effects of thalidomide in the 1950s and 1960s are perhaps most well-known, other cases still appear frequently in the media. Recent cases include the postulated association of seroxat (paroxetine) with suicide, vioxx (rofecoxib) with heart attack or stroke, statins (HMG-CoA reductase inhibitors) with diabetes risk, avandia (rosiglitazone) with fluid retention, and herceptin (trastuzumab) with cardiovascular events. These all highlight the need for accurate and complete information on adverse drug reactions.[3]

An explicit objective of the UK National Health Service (NHS) is to improve health and well-being.[4] This involves maximising beneficial effects and minimizing harm in order to do 'more good than harm'.[5, 6] Decision bodies, such as the National Institute for Health and Care Excellence (NICE) in the UK, provide guidance on the 'use of new and existing medicines, treatments and procedures within the NHS'.[7] The decisions made by NICE aim to maximise health on a population basis. Other initiatives in the UK aim to move towards a healthcare system with more individual choice[8] and more patient centred decision making.[9] In order for patients, clinicians and other decision makers (such as NICE) to make informed, balanced decisions, appropriate information is needed on both the intended benefits and unwanted harms of an intervention.[10, 11]

Currently, however, there is an absence of sufficient evidence-based information on the frequency and magnitude of adverse effects. Although there are long lists of potential adverse effects, there is little or no information available as to their severity, or of the probability of their occurrence.[12-14] One potential solution to this problem would be to incorporate data on adverse effects into systematic reviews.[15]

1.2 Systematic reviews and adverse effects

The main aim of implementing evidence-based healthcare is to objectively evaluate healthcare interventions in order to inform practice and thus enhance patient care. Great emphasis is placed on using the best available evidence. One of the most reliable forms of evidence is a well-conducted systematic review.[2, 16-21]

A systematic review attempts to identify, evaluate and summarise all the empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit transparent methods which aim to minimize bias, and provide more reliable findings from which conclusions can be drawn and decisions made.[22, 23]

Synthesis is an important stage of a systematic review. Many systematic reviews contain a quantitative synthesis using meta-analysis.

> *'Meta-analysis is the use of statistical methods to summarize the results of independent studies. By combining information from all relevant studies, meta-analyses can provide more precise estimates of the effects of health care than those derived from the individual studies included within a review. They also facilitate investigations of the consistency of evidence across studies, and the exploration of differences across studies.'*[22]

To be more useful to decision makers, however, such reviews should assess the balance of benefits and adverse effects of an intervention.[21, 24-26] A systematic review that assesses only benefits is likely to lead to unfair comparisons and one-sided conclusions.[27] However, the vast majority of systematic reviews focus on clinical effectiveness without addressing adverse effects.[19, 20, 28-31]

The current emphasis on evidence of beneficial effects, and the relative lack of rigorous evaluations of adverse effects creates a challenging conundrum.[13] Decision makers, prescribers and patients are obliged to struggle with a situation where they must evaluate quantitative effectiveness data from well-conducted systematic reviews against incomplete or inadequate adverse effects information of uncertain quality.[13, 25] This imbalance in information may lead to interventions being prescribed inappropriately, or in patients being harmed by potentially avoidable adverse effects.

In order to redress the over-emphasis on benefits, the development and improvement of methods to quantify adverse effects should be made a key research priority. This will ensure that information on harms can be considered at the same time, and on an equal standing, with information concerning benefits.

Although the methodology of conducting a systematic review of intended beneficial effects is well established and empirical research is available to support current recommendations, this is not the case for systematic reviews of adverse effects and many methodological issues remain unaddressed.

The first step towards quantifying adverse effects is to retrieve good quality data on their association and frequency with particular interventions. This requires the development of optimal search techniques to retrieve information on adverse effects. Where and how such information is identified markedly affects the range and frequency of adverse effects found.[14] A better understanding of the implications of using different sources and approaches to identifying data on adverse effects is urgently required.[21] Development of these search techniques is the primary aim of the programme of research described in this thesis.

1.3 Aims and objectives of the thesis

1.3.1 Aim

The aim of this research is to evaluate the most effective study designs, sources of information, and search strategies to retrieve information on adverse effects of pharmaceutical interventions. This will help to minimise any potential bias in the retrieval of information on adverse drug reactions and optimise the efficiency and utility of systematic reviews that incorporate adverse effects.

1.3.2 Objectives

1) To conduct a literature review of existing methodological studies that evaluate the impact of study design, sources searched, and search techniques used when adverse effects data are incorporated into systematic reviews.
2) To describe and critique the retrieval methods used in systematic reviews of adverse effects.

3) To undertake a case study systematic review of adverse drug reactions in order to evaluate:
    a. the contribution of information on adverse drug reactions from different sources;
    b. the effectiveness of different searching methods for identifying information on adverse drug reactions.
4) To evaluate the effectiveness of different searching methods using a series of systematic reviews of adverse drug reactions.
5) To develop guidance and recommendations for retrieving information on adverse drug reactions to incorporate into a systematic review.

1.4 Research questions

This programme of research addresses the following important questions pertinent to systematic reviews of adverse effects data for healthcare decision making:

A. Which study designs provide the best evidence on adverse effects in terms of availability, appropriate format, and being least prone to bias?
B. Which sources of information provide the most efficient yield of relevant data on adverse drug reactions?
C. Which search strategies are most effective in retrieving relevant data on adverse drug reactions from these sources in terms of sensitivity and precision?

1.5 Thesis structure

Chapter 2 discusses and clarifies the terminology surrounding adverse effects. It highlights the importance of adverse effects in healthcare. The value of systematic reviews of adverse effects is also discussed, as well as the challenges in identifying studies for inclusion in such reviews.

Chapter 3 describes the methodology of a systematic review of the current *methodological* literature related to the retrieval of information on adverse effects. The results of this review are then divided into six sections and form Chapters 4 to 9.

Chapter 4 presents the results of first section of the methodological review relating to the contribution of different study designs in providing adverse effects data.

Chapter 5 presents on the second section of the methodological review relating to sources of information on adverse effects.

Chapter 6 presents on the third section of the methodological review relating to database search strategies for information on adverse effects.

Chapter 7 presents on the fourth section of the methodological review relating to the impact of publication status on the reporting of adverse effects.

Chapter 8 presents on the fifth section of the methodological review relating to the impact of funding source on the reporting of adverse effects.

Chapter 9 presents on the last section of the methodological review relating to other issues linked to the retrieval of information on adverse effects, such as background of the author of a study or country setting.

Chapter 10 presents the results of a review of the retrieval methods used in published systematic reviews of adverse effects, highlighting areas where there are deficiencies in the methods used. In addition, this chapter presents comparisons with other types of reviews and an analysis of trends over time.

Chapter 11 reports on the results of an information audit carried out on a case study of a systematic review with an adverse drug reaction as its primary outcome, namely fractures associated with thiazolidinediones. This section presents a comparative analysis of the sources of information for data on adverse effects for this case study.

Chapter 12 evaluates the performance of using different search filters in MEDLINE and EMBASE for retrieving information for the case study systematic review of adverse drug reactions in Chapter 11.

Chapter 13 reports on the presence or absence of adverse effects terms in the title, abstract or indexing of database records relating to articles which contain adverse effects data in the full-text. The articles are identified from a series of 26 published systematic reviews of adverse drug reactions. This chapter includes an evaluation of published search filters for information on adverse drug reactions and individual search terms.

Chapter 14 brings together the results of all sections of the current research including the methodological literature review, the review of systematic reviews of adverse effects, the case study systematic review, and search term exploration of 26 reviews. A summary is included of the key findings, together with the implications of this research.

In relation to the findings of the research, specific recommendations for the retrieval of information on adverse effects are given. A summary of areas for further research is then followed by conclusions to the research.

Although public or patients were not directly involved in the planning, design, and execution of this project, (because of the methodological nature of the investigation), the output of this PhD will be of particular relevance to patients. Adverse effects and adverse reactions are important for health service users, their families, and their carers; unbiased, objectively derived, information on the harms as well as the benefits of an intervention is needed. Patients want to be sure that the treatments they receive are as safe and effective as possible.

1.6 Summary

There is an urgent need for accurate and complete information on adverse drug reactions.
Systematic reviews could provide this information in an unbiased way.
This programme of research evaluates the most appropriate study designs, data sources, and database search strategies for systematic reviews incorporating adverse drug reactions.

Chapter 2 Incorporating adverse effects into systematic reviews

Before describing the challenges of incorporating adverse effects into systematic reviews, it is important to clarify what constitutes an adverse effect and why systematic reviews of adverse effects are required.

2.1 What are adverse effects?

There is considerable confusion in the nomenclature used for adverse effects. This confusion stems from a lack of consistent terminology[32] and the plethora of terms available such as; 'side effect', 'harm', 'adverse effect', 'adverse event', 'complications', 'tolerability', 'toxicity', 'toxic effect', 'unintended effect', 'adverse drug reaction', 'adverse reaction' and 'adverse drug effect'.[33] The use of a wide range of terms for adverse drug reactions has been reported as far back as 1881 by Louis Lewin;

> *'There is a large variety of names in medical publications for the untoward symptoms that follow the use of drugs… in England they are sometimes called 'unpleasant symptoms''*[34]

Trends in terminology have emerged over the years. 'Side effect' is a relatively old term and can be defined as any unintended effect that occurs during treatment which is related to or likely to be related to the treatment.[35] Because, technically a 'side effect' can be a positive or negative effect, whereas 'adverse event', 'adverse effect' and 'adverse reaction' are all negative,[35] these latter terms are preferred in the medical literature and 'side effect' is generally restricted to patient information.

An 'adverse event', 'adverse effect' or 'adverse reaction' are all unfavourable outcomes that occur after a patient has taken a medicinal product or undergone some procedure.[34-36] However, an 'adverse event' differs from an 'adverse effect' or an 'adverse reaction' in that an 'adverse event' may or may not be attributed to the treatment.[34] For instance, a patient may be involved in a road traffic accident whilst on drug X and whilst this is an 'adverse event' it may not be attributable to drug X and therefore not an 'adverse effect' or 'adverse reaction'.[34] 'Adverse effects' or 'adverse reactions', on the other hand, are commonly used interchangeably, have similar meanings, and are 'adverse events' for which a causal relationship between the intervention and event is at least a reasonable possibility.[34, 37] The subtle

difference between ‘adverse effect’ and ‘adverse reaction’ is that adverse effects are usually detected by laboratory tests or clinical investigations whereas ‘adverse reactions’ are detected by their clinical manifestations (signs and symptoms).[38, 39]

A term that is used frequently in the current literature is ‘adverse drug reaction (ADR)’. The most widely accepted definition of this term is that of the World Health Organisation (WHO) and has been in existence for over 30 years. It states that an adverse drug reaction is:

> *‘a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function’*.[35]

An adverse drug reaction is, therefore, an adverse effect or adverse reaction which results from and is related to a medication.[10, 40]

Other terms sometimes used include ‘adverse drug event’ or ‘drug-related adverse event’. These terms have also caused further confusion as they have a wide spectrum of definitions.[41] Whilst some have defined ‘adverse drug events’ as ‘any injury resulting from administration of a drug’,[2] others disagree and state that the adverse event may or may not be related to the drug[36, 40] in which case such terms should generally be discouraged as they imply a causal relationship.[40]

Other related terms to ‘adverse effects’ include ‘harm’ (for damage or injury), ‘complication’ (for adverse effects of surgical or other invasive treatments),[37] ‘tolerability’ (for medically less important adverse effects, i.e. without serious or permanent sequelae),[37] and ‘toxicity’ (degree to which a substance is poisonous).

The study of adverse drug reactions comes under the umbrella of patient safety. Whereas adverse drug reactions are primarily concerned with the properties of the drug under normal use, the patient safety community is interested in harm resulting from a broader range of events, such as intentional and accidental poisoning (i.e. overdose), drug abuse, medication errors, or non-compliance.[35] Systematic reviews strive to assess injuries incurred by drugs that were properly prescribed and administered. As the focus of this programme of research is adverse effects related to drugs and broader patient safety issues are excluded, the terms adverse drug reaction and adverse drug effects are adopted here, or where both drug and non-drug adverse effects are discussed the term adverse effects will be used.

2.2 Why are adverse drug reactions important?

2.2.1 Incidence and cost

There are a number of factors which demonstrate the importance of adverse drug reactions, not least their incidence, severity and cost. Several studies have shown that adverse drug reactions are a major cause of ill health and death and result in substantial costs to healthcare systems.[42] Estimates on the incidence and cost of adverse drug reactions, however, have varied widely, dependent, in the main, on the methodologies used to detect suspected reactions, the differences in the definitions of an adverse drug reaction,[43] the nature of the patient group,[44] and the range of costs included. For instance, some studies restrict their data collection to serious adverse drug reactions, others to hospital stay.

2.2.2 Hospital admissions

The majority of studies that have measured the incidence and/or cost of adverse drug reactions have tended to focus on the proportion of hospital visits, hospital admissions, or the incidence in hospitalised patients, and have been based in the US.[45-59] However, a systematic review of the worldwide literature identified the rate of admissions to hospitals related to adverse drug reactions as 5.4%. This is lower than estimates from the UK.[44]

A systematic review in 2002, of nine studies from the UK, estimated that the rate of hospital admissions directly attributable to adverse drug reactions (excluding errors, non-compliance and overdose) as 7.5%[50] and that the burden of adverse drug reactions in hospital patients on the UK NHS is equivalent to 15 to 20 medium sized hospitals. This approximates to 4% of available bed days and a cost of £380 million per annum.[50] Similar results were reported in a more recent observational study from the UK,[60] which indicated that 6.5% of hospital admissions were due to adverse drug reactions. The median bed stay in patients with an adverse drug reaction is eight days, accounting for 4% of hospital bed capacity and at a cost to the UK NHS of around £466 million every year.[60]

2.2.3 In-patient incidence

As well as adverse drug reactions leading to admissions to hospitals, they can also occur during hospital stays.[48] A UK based study in 2009 estimated that 14.7% of

patients experienced an adverse drug reaction in hospital.[61] This study also estimated that an additional 1.9% of bed days were due to an adverse drug reaction, with an estimated cost to the NHS in England likely to exceed £171 million annually.[61]

2.2.4 Overall cost

The estimated cost of hospital admissions and adverse drug reactions in hospital to the NHS in England are in excess of £637 million per year.[61] This is likely to be an underestimate of the total cost of adverse drug reactions, as it is restricted to hospital costs, does not take into account the large proportion of under-reporting of adverse effects, and does not incorporate indirect costs such as loss of productivity, outpatient treatment, disability and the social cost of adverse drug reactions. A report by Compass suggests that the true costs of adverse drug reactions to the NHS are as high as £2 billion per annum.[62]

2.2.5 Incidence in the community

Although the incidence of adverse drug reactions in the hospital setting may be difficult to calculate, measuring the incidence of adverse drug reactions in the community is even more problematic, as drug exposure in the population is unknown and under-reporting of adverse drug reactions is likely to be higher. Some studies in the 1970s attempted to estimate adverse drug reactions in the community, however, and figures ranged from 2.6% to 41%.[36] The incidence of adverse effects is also likely to increase as the number of older people in the population, and hence the number of prescriptions for long-term diseases, increases.[63]

2.2.6 Mortality

While adverse drug reactions that result in hospitalisation or a prolonged stay in hospital are of serious concern, even more seriously, some adverse drug reactions result in death. Over 10,000 deaths per year in England and 106,000 deaths per year in the US have been estimated to be attributed to adverse drug reactions.[48, 60] This would suggest that, in the US adverse drug reactions rank from the fourth to sixth leading cause of death (after heart disease, cancer, stroke, pulmonary disease and accidents), even when used in proper doses for approved indications.[48] Another

study based in Sweden implicated adverse drug reactions as the seventh most common cause of death.[64]

2.2.7 Quality of life

Although studies on the incidence and cost of adverse drug reactions have tended to focus on the very serious adverse effects which can lead to hospitalisation, long-term disability, and even death, other adverse effects are also important. Less dangerous and less troublesome adverse effects are becoming of greater importance to patients, as interventions are increasingly being used for primary prevention (such as vaccines) in healthy patients or to treat self-limiting or relatively benign conditions.[17, 31, 37, 65] Common adverse effects such as coughing, depression, incontinence, swollen ankles, drowsiness and headache may significantly impair the quality of life of drug recipients and their willingness to continue the treatment.[37, 65, 66] For example, patients with hypertension may be unwilling to endure symptoms such as cold limbs, tiredness, and sleepiness in return for the potential benefits,[67] as patients may feel subjectively worse than before beginning their treatment.[66] Similarly healthy women taking oral contraceptives may be particularly concerned about relatively minor adverse effects, such as acne, weight gain, and disrupted menstrual pattern.[68] Consequently, from a public health perspective common but seemingly minor adverse effects may be more important than the stories of more severe adverse effects that reach the media headlines.[65]

2.2.8 Balancing efficacy with harms

As treatments are used for less serious conditions, they may have less pronounced benefits, and as more treatment options become available, rare events may assume more importance. A rare event may be sufficient to inhibit use of the drug for a self-limiting condition.[17] For example, an increased risk of dying, even if small, may be unacceptable to relieve the pain of a simple headache.[69] Where a treatment has small beneficial effects with a number needed to treat to achieve one beneficial outcome in the hundreds,[31] or where there are a number of competing alternatives with similar beneficial outcomes, the adverse effects of an intervention may assume more importance to patients and decision makers.[70] In addition, adverse drug reactions may lead to further treatments (and further costs) and cause patients to lose confidence in their doctors, and generate mistrust.[25]

In summary, all types of adverse effects are important, and although actual estimates may vary they all concur that the incidence and cost of adverse drug reactions is high.

2.3 What is known about adverse drug reactions pre-licensing?

When a new drug is licensed, not all its adverse effects are known because at this time only a limited number of healthy volunteers and highly selected patients are likely to have undergone exposure.[3, 19, 25, 69, 71-79] It has been estimated that on average only about 1500 patients (ranging between 340 and 5000) have been exposed to a new drug when a product license is granted.[11, 36, 80] In addition, pre-licensing clinical trials often lack the follow-up necessary to detect delayed consequences or long term adverse effects.[11, 71, 73, 74, 81, 82] The importance of quantifying adverse drug reactions post licensing is also particularly apparent in the case of drug treatment for patients with multiple disease states, and for children, women of childbearing age, and the elderly, because these population groups are rarely exposed to medication during its development.[11, 19, 71, 73] Approval of a new drug through licensing, therefore, does not exclude the possibility of adverse effects, particularly effects that are rare or delayed,[73] or which are differentially associated with particular sub-groups.[71]

Many adverse effects are recognised, therefore, during the post-marketing phase of the life of a drug, once it is in widespread clinical use.[75, 76, 83-87] Well known examples include fenfluramine and the risk of pulmonary hypertension, vigabatrine and visual field defects, and tolcapone and the risk of liver toxicity.[87] It is estimated that 51% of approved drugs have serious adverse drug reactions that are not detected until after marketing,[11] and in the UK, 4% of all licensed products are later withdrawn because of safety problems.[88] Surveillance and pharmacoepidemiological studies form an important part of the post-marketing phase.

2.4 Why are systematic reviews incorporating adverse effects needed?

Many of the benefits of conducting a systematic review of effectiveness also apply to systematic reviews of adverse effects.[18, 19, 65] For instance, systematic reviews of adverse effects have the potential to provide the most reliable evidence for decision-making, can demonstrate the need for further research, provide more timely results,

help decision-makers cope with large amounts of evidence, increase the generalisability of the results of research, enable explanatory analysis regarding, for example, subgroups of patients, and, if appropriate, can use meta-analyses to increase the precision of estimates and so reduce the relative width of the confidence intervals of summary effect measures.[71, 89]

2.4.1 More reliable evidence

The most important aspect of a systematic review is its transparent and objective approach. By systematically identifying, appraising and summarising the evidence, systematic reviews, whether of effectiveness studies or adverse effects studies, allow a more objective appraisal of the evidence. This makes systematic reviews less prone to bias and error than traditional narrative reviews and a more reliable form of evidence for decision-making.[90]

2.4.2 Cumulative approach

The cumulative nature of systematic reviews, in which pre-existing available evidence is synthesised, not only enables the identification of gaps in the research but also enables health professionals to base decisions on all the appropriate evidence already available.[6] In fact, ignoring previous research on adverse effects can lead to fatal results. For example, in 2001 a 24 year old healthy volunteer died from lung failure after researchers failed to uncover published research indicating the potentially lethal side effects associated with the inhalation of the drug hexamtheonium.[91, 92] If systematic searches on the adverse effects of hexamethonium had been carried out before the trial, the pulmonary complications of the drug would easily have been identified.[93]

2.4.3 More timely results

A cumulative approach to research not only encourages researchers to learn from past experience but can also result in more timely results. It has been reported that there can be long delays in getting adverse effects information from research into practice.[77] Systematic reviews of adverse effects may be a way to reduce such delays.[94-96] For example, a systematic review would have revealed the cardiovascular risks associated with hormone replacement therapy (HRT) much earlier than 1997,[97, 98] and a meta-analysis of rofecoxib (vioxx) would have revealed

a statistically significant excess risk of cardiovascular effects four years before the drug was withdrawn.[95, 99]

2.4.4 Information overload

The large volume of information on adverse effects in a range of formats from a diverse range of sources[2, 100] also increases the need for systematic reviews of adverse effects. Each year about 9000 articles on adverse drug reactions are published in the scientific literature.[101] In 2002, Meyler's Side Effects of Drugs (an international encyclopaedia of adverse drug reactions and interactions) alone contained approximately 17,000 references and 6,000 cross-references to the Side Effects of Drugs Annual (a world-wide yearly survey of adverse drug reactions).[31] By 2006, the latest edition of Meyler's Side Effects of Drugs contained over 40,000 references.[102] Systematic reviews of adverse effects are an invaluable tool for coping with this large amount of information and a possible solution to the problem of 'information overload'.[31]

2.4.5 Generalisability

Another advantage of systematic reviews is their potential to allow greater generalisability of results and to enable subgroup analysis. The adverse effects found in one particular study with one set of patients might not be valid for other patients with different characteristics. If the same adverse effects are seen in many studies, however, and in different types of patients, then it may be concluded that the adverse effects have some generality.[90]

Subgroup analysis is particularly useful for adverse effects data, as rates of adverse effects are highly environment dependent.[103] By combining data across studies, systematic reviews can be used to view and investigate variations and to assess whether the differences are likely to be plausible or chance findings.[103] For example, comparisons may be made of adverse drug reactions between different classes of drugs, different doses, and different subgroups of patients, such as older or younger patients, different ethnic groups, and men or women.[21, 65, 71, 73] Systematic reviews may also be able to make sense of conflicting results by investigating differences between studies.[71]

2.4.6 Sample size

Lastly, systematic reviews increase the sample size investigated. Although a single trial can be sufficiently well powered to detect differences in effectiveness, these usually tend to be seriously under-powered in order to detect differences in adverse effect rates.[18, 96, 104-106] A large number of patients need to be treated before a rare adverse effect is identified. With serious adverse effects even a low level risk of harm may produce a major public health problem if the medication is widely used. For example, although the increase in absolute risk of a cardiovascular event may be small with rofecoxib (Vioxx), when a medication is used by 80 million patients, the numbers of affected patients can be substantial.[80] While single trials may not have sufficient power to distinguish between adverse effects rates between drugs, a systematic review may be able to show small but significant differences.[13, 70, 73, 105]

2.5 Do systematic reviews incorporate adverse effects?

Although including adverse effects in systematic reviews may be as important as including intended beneficial effects,[19] the vast majority of systematic reviews focus on clinical effectiveness without addressing adverse effects.[19, 20, 28-31]

Ernst and Pittler 2001 categorised systematic reviews published on MEDLINE and the Cochrane Library as either reviews of effectiveness, reviews that included safety as a secondary outcome, or reviews with a primary focus on safety. They found that only 27% reviewed any harms data, with 4% assessing safety as their primary outcome.[29, 30]

More recent research indicates that the proportion of reviews that include any harms data may have increased since Ernst and Pittler's 2001 study. Moseley et al 2009[107] found that 22% of non-Cochrane physiotherapy reviews reported adverse effects whereas Hopewell et al 2007[108] found that 48% of reviews from the Database of Abstracts of Reviews of Effects (DARE) provided some mention of adverse effects as an outcome measure, and Moher et al 2007 found that 57% of non-Cochrane reviews from MEDLINE reported on some aspect of harm.[109] However, the proportion of reviews from DARE or non-Cochrane reviews (reviews not produced by the Cochrane Collaboration and not published in the Cochrane Database of Systematic Reviews) which have adverse effects as their primary outcome or

contained a meta-analysis of safety data has remained low since Ernst and Pittler's 2001 study ranging from 2% to 9%.[108, 110, 111]

Other studies have focused on the reporting of adverse effects in subsets of Cochrane Reviews and have found that between 18% and 86% of such reviews included specific adverse effects data,[20, 107-109, 111, 112] and that 10% of Cochrane Reviews had adverse effects as their primary outcome.[108]

Aronson et al 2002 examined the number of systematic reviews of adverse effects from a different perspective, by categorising all publications cited in the Side Effects Drug Annual (SEDA) 2000. The proportion of all publications of adverse effects that were systematic reviews was very low, at 1.25% (45/3604).[31]

Although it is difficult to compare these studies, as they used different sampling techniques to identify cohorts of systematic reviews, and different definitions of adverse effects, the literature indicates that the proportion of systematic reviews incorporating adverse effects is low but may be increasing, particularly in Cochrane reviews.

2.6 What are the challenges of retrieving information on adverse effects?

One of the main reasons for the relative lack of systematic reviews of adverse effects may be the difficulty in conducting these reviews and the lack of evidence-based guidance available.[113, 114] Although the same basic principles may be applied to systematic reviews of adverse effects as for reviews of effectiveness, there are also many specific procedures that need to be adapted to respond to the methodological challenges of identifying and incorporating adverse effects.[113, 115] The retrieval of information on adverse effects poses particular challenges,[14, 15, 19, 37, 116] and there are a number of factors contributing to this.

2.6.1 Searching beyond randomised controlled trials

Firstly, identifying information on adverse effects is particularly challenging because there is a diversity of study designs that might contain information of interest.[2, 21] For instance, although RCTs may be the most appropriate source for information on effectiveness, other study designs, such as cohort studies, case-control studies and case reports, may also be appropriate for adverse effects data.[2] Searching for non-

RCTs can be problematic, owing to inconsistent terminology, variable indexing and a lack of research into appropriate search filters (pre-set combinations of search terms to retrieve articles of a particular study design or topic area).

2.6.2 Sources of data

Secondly, the resources that contain data on clinical effectiveness may not be the most appropriate resources for retrieving information on adverse effects.[2] The identification of information on adverse effects often requires a much broader range of data sources.[21, 27, 100, 117] There are many specialist databases for adverse effects, toxicity and drug information, as well as post-marketing surveillance data and tertiary sources (such as Meyler's Side Effects of Drugs[102] or Reactions bulletin) which may provide adverse effect information.

2.6.3 Search strategies

Lastly, compared with reviews of effectiveness, developing efficient search strategies (combinations of search terms) for use in databases (such as MEDLINE and EMBASE) which capture all the relevant literature on adverse effects, is much more difficult.[2, 118] Specific difficulties arise when adverse effects terms are added to the search strategy. This is because adverse effects are poorly reported, inadequately indexed, inconsistently described, may not be limited to a particular condition, and specific named adverse effects may not be known at the time of searching.

The most prominent difficulty in developing efficient search strategies for adverse effects is that of poor reporting of adverse effects. Reviews that assess the beneficial effects of an intervention usually have the relatively straightforward task of searching for outcomes that were also primary outcomes in the included studies and therefore appear prominently in the title, abstract, or indexing terms of a database record.[119, 120] In contrast, systematic reviews which seek to examine adverse outcomes are likely to include studies where harms were only of secondary interest,[118, 121] and few authors of trials devote substantial amounts of space to safety data.[122] Adverse effects are, therefore, often not reported in the title, abstract or indexing of a database record, making the creation of search strategies to capture adverse effects difficult.[19, 70, 118, 121, 123]

Another issue in developing search strategies for retrieving adverse effects is the range of adverse effects searched for and the inconsistent terminology used. In contrast to the evaluation of effectiveness (where an intervention is likely to have only one or two beneficial outcomes), there is often a diverse range of potential adverse outcomes and for each outcome there can be a wide range of terms (such as lethargy, tiredness, malaise).[70]

It is not always appropriate to limit search strategies for adverse effects to a particular disease or condition, for instance, when the adverse effects are suspected to occur in any population taking the drug irrespective of the disease or condition it is intended to treat, or where there is limited data for the drug with a particular disease or condition. This means that very broad searches may be conducted which may retrieve an unmanageable number of records.

In many instances, the adverse effects of an intervention may be unknown or not predictable at the beginning of the systematic review process when the searches are conducted. Reliance on generic terms for adverse effect (such as side effects, adverse drug reactions, complications, toxicity) is unlikely to retrieve a large proportion of the available relevant studies,[118] and in many data sources the indexing of safety terms has been found to be inconsistent or non-existent.[19, 117]

In summary, although searching for information on adverse effects is problematic, it is also a fundamental part of the systematic review process. Difficult decisions need to be made on the study designs to search for (for example, RCTs, cohort studies or case series), the sources to search (for example, MEDLINE, EMBASE, TOXLINE), the concepts to include in any search strategies developed (for example, disease/condition, adverse outcomes, study design) and then the search terms to use to capture those concepts. It is these decisions which will be the focus of this programme of research.

2.7 Summary

The costs of adverse drug reactions to the NHS are estimated to be as high as £2 billion per annum.

Adverse drug reactions cause over 10,000 deaths in the UK per year and can lead to hospitalization and disability as well as affect patients' quality of life and compliance.

Systematic reviews can provide timely reliable evidence on adverse effects, yet the vast majority of systematic reviews focus on effectiveness without addressing adverse effects.

Research is urgently required into the most appropriate search techniques to identify information on adverse effects for systematic reviews.

Chapter 3 Methodological overview of the literature relating to the retrieval of information on adverse effects

3.1 Introduction

The preceding chapters demonstrated the need for systematic reviews incorporating adverse effects and presented many of the methodological challenges in the process of retrieving information on such effects. In particular, there is a lack of empirical evidence and guidance as to how and where to search for appropriate studies for inclusion in systematic reviews incorporating adverse effects, and a lack of clarity on how using different sources for retrieval may affect the clinical utility of the results of a review. It is, therefore, useful to conduct a review of the methodological research on the retrieval of information on adverse effects.

This will help to consolidate what is already known about the methodology of searching for studies for inclusion in systematic reviews that incorporate adverse effects, as well as highlighting gaps in the evidence.

3.1.1 Aim

The aim of this research was to review the methodological literature pertinent to the retrieval of information on adverse effects for inclusion in systematic reviews. Particular emphasis was placed on studies evaluating the impact of incorporating different study designs, searching different sources of information (including databases, industry submissions, and unpublished data sources) and using different electronic database search strategies (combinations of search terms).

3.1.2 Objectives

- To provide access to evidence on which to base decisions on the methods used in the retrieval of information on adverse effects for systematic reviews of healthcare interventions. This includes study design selection, sources of information searched and database search strategies used.
- To identity any gaps in this research area and to propose further research in order to fill these gaps.
- To identify potentially useful data sources and search strategies for testing in systematic review case studies.

3.2 Methods

3.2.1 Data sources

It was anticipated that much of the literature in this newly developing area would be identified by searching beyond MEDLINE and EMBASE, and that much of the relevant research would not be published as peer-reviewed journal articles. For example, a previous systematic review on a similar methodological topic only identified 13 out of 30 of the included papers through searching MEDLINE and EMBASE.[124] Therefore, a range of bibliographic databases were searched for this review. These databases were carefully chosen to allow the identification of reports, dissertations, and grey literature, in addition to journal articles. Handsearching of key journals in research methodology, drug safety, and librarianship was carried out to identify articles either not indexed, or not easily identifiable in electronic databases. Unpublished material was also sought by handsearching conference proceedings, scanning evidence-based websites, and from contacting experts in the field identified via the Cochrane Adverse Effects Methods Group and the East Anglia Research Synthesis Group. Conference proceedings and web sources were selected on the basis of their coverage of systematic review methodology. In addition, the bibliographies of any eligible articles identified were checked for additional references, and citation searches were carried out on all the included references using ISI Web of Knowledge. A list of the databases and other sources searched is given in Table 3.1.

3.2.2 Search strategies

Search strategies were devised to retrieve papers that evaluated any of the methodological aspects of searching for information on adverse effects for inclusion in a systematic review (Appendix A). Methodological aspects included study design selection, sources of evidence and literature searching.

Although searches of The Cochrane Methodology Register (CMR) and the Centre for Reviews and Dissemination (CRD) administration version of the Database of Abstracts of Reviews of Effects (DARE) can be easily limited to methodology papers, searching for methodology papers in other databases can prove very difficult. Most databases, such as MEDLINE and EMBASE, do not index methodology papers well nor use consistent terminology to describe them.

Table 3.1 Sources searched for included studies

Databases

Original searches were carried out on 26th or 27th September 2007 with the most recent update searches carried out between 22nd October and 6th November 2009.
Cochrane Database of Systematic Reviews (CDSR): methodology reviews only: 2009 Issue 4
Cochrane Methodology Register (CMR): 2009 Issue 4
Database of Abstracts of Reviews of Effects (DARE): November 2009
EMBASE: 1980 to 2009 Week 42
Health Technology Assessment (HTA) Database: November 2009
Health Management Information Consortium (HMIC): September 2009
Index to Theses: November 2009
Library, Information Science & Technology Abstracts (LISTA): Mid1960s-October 2009
MEDLINE: 1950 to October Week 3 2009
MEDLINE in process: 22 October 2009

Handsearching of Journals

BMC Clinical Pharmacology - 2001;1(1) to 2009;9(17)
BMC Medical Research Methodology - 2001;1 to 2009;9(69)
Drug Safety - 1998;18(1) to 2009;32(11)
Health Information and Libraries Journal (formally Health Libraries Review) - 1994;11(1) to 2009;26(3)
Journal of Clinical Epidemiology - 1998 to 2009;62(12)
Journal of Information Science - 1979;1(1) to 2009;35(5)
Journal of Librarianship and Information Science - 1969;1(1) to 2009;41(3)
Journal of the Medical Library Association (formally the Bulletin of the Medical Library Association) - 2000;88(2) to 2009;97(4)
Pharmacoepidemiology & Drug Safety - 1992;1(1) to 2009;18(11)

Handsearching of Conference Proceedings

Cochrane Colloquia 1994-2009
HTAi 2004-2009
Pharma-Bio-Med Conference and Exposition 2006-2008
Symposium on Systematic Reviews 1998-2002

Web Sources

Agency for Healthcare Research and Quality (AHRQ) via http://www.ahrq.gov/ Searched: 28/10/09
Health Technology Assessment Programme (HTA) via http://www.hta.ac.uk /index.shtml Searched: 28/10/09

A pragmatic approach was, therefore, required in the development of the search strategies in databases such as MEDLINE and EMBASE. This meant that search terms (such as, ‘search’, ‘safety’ or ‘trials’ terms) were often limited to the title field only and some potentially relevant text words and indexing terms (such as, ‘risk’) which retrieved thousands or tens of thousands of irrelevant records were omitted. All the search strategies were checked by a second experienced information scientist.

No date or language restrictions were applied to the searches. Although logistical constraints meant that non-English publications were not included in the review, an estimation of the size of the non-English literature was thought useful.

In addition to the search strategies for methodological papers (Appendix A), the full papers of systematic reviews with the primary outcome of an adverse effect indexed in either CDSR, (via The Cochrane Library, Issue 1:2010) and DARE (via the Centre for Reviews and Dissemination (CRD) website, March 2010) were checked to assess whether any methodological analysis of the retrieval of adverse effects data had been conducted within the review.

3.2.3 Inclusion/exclusion criteria

Any reports of empirical studies of the methods used in searching for information on adverse effects were eligible for inclusion. A research study was considered eligible for inclusion in this review if it used a standardised outcome measure to compare the identification and/or quantification of adverse effects from either different sources of information on adverse effects, different methods of identifying such information or the inclusion of different study designs.

Studies were excluded if they were:

A. examples of systematic reviews without a comparative evaluation of the different methodologies used to retrieve information on adverse effects
B. limited to drug-interactions, toxicology or poisoning
C. comparisons of animal or laboratory studies
D. studies of causation/etiology (for example, studies on environmental factors, such as pesticides and pollution or studies on risk factors, such as cigarette smoking and drug abuse)
E. studies that did not include a healthcare intervention

F. in a non-English language with no translation available at the British Library

Studies that did not meet the criteria were excluded and their bibliographic details listed with reasons for exclusion.

3.2.4 Identifying studies

Firstly, the author screened the titles and abstracts of all the retrieved records to identify obvious exclusions (i.e. articles that had been retrieved by the searches which were unrelated to adverse effects, for example, articles on self-harm, or safety in the workplace). The remaining articles were then assessed independently by both the author and a second reviewer for potential included studies. Full copies of the articles deemed potentially relevant by either the author or the second reviewer were obtained. These articles were then assessed by the author and at least one other reviewer to determine if they met the inclusion criteria.

3.2.5 Data extraction

Data extraction was performed by the author and then double checked by another reviewer. Data from studies with multiple publications were extracted and reported as a single study. Where there were discrepancies between conference abstracts and journal articles, data were extracted from the journal article.

3.2.6 Assessment of methodological quality

The methodological quality of the included articles was assessed by the author and then double checked by a second reviewer using pre-set criteria. The included studies were categorised according to their objectives. The quality criteria were then adapted for each category of article and presented in the proceeding chapters. Any disagreements were resolved through discussion.

3.3 Results

Searches were originally undertaken in September 2007 and 4609 records were retrieved. Update searches were subsequently performed in August 2008 and again in November 2009 retrieving an additional 704 records and 905 records respectively. A total of 347 full papers were ordered for more detailed examination from the results of the database searches and a further 92 from sifting reviews on

DARE, reference checking, handsearching, and contacting experts. A flow diagram detailing the decision process is presented in Figure 3.1.

There were 92 studies (from 95 publications) eligible for inclusion in the review. These studies were divided into six categories and form the next six chapters:

Chapter 4: Includes 51 studies which assessed the impact of study design selection (such as, RCTs, cohort studies and case reports) on the identification and/or quantification of adverse effects

Chapter 5: Includes 19 studies which compared the use of different sources of information on adverse effects (such as, MEDLINE, EMBASE and reference checking)

Chapter 6: Includes 3 studies which evaluated the search terms or search strategies used to retrieve information on adverse effects in electronic databases

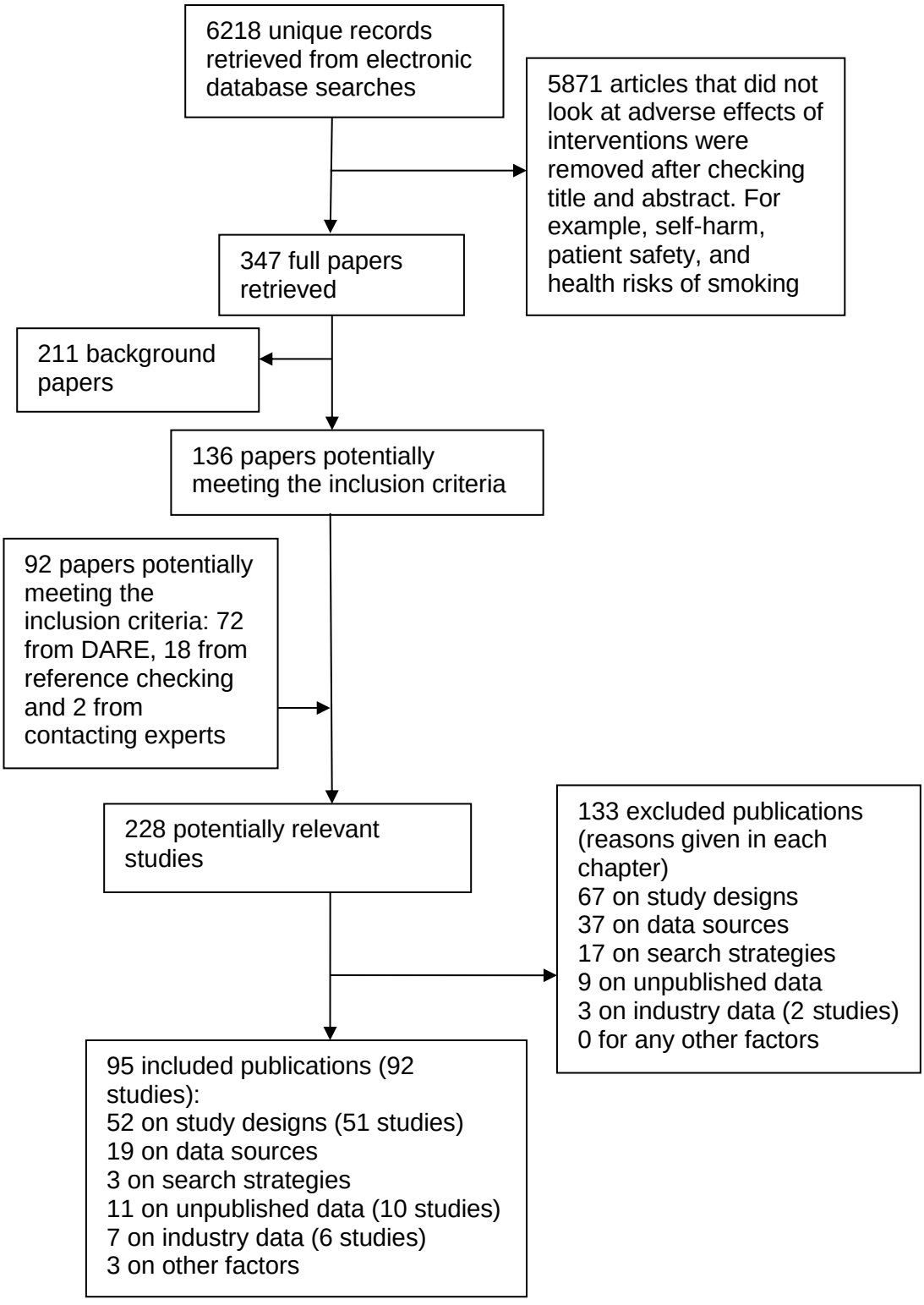
Chapter 7: Includes 10 studies which assessed the impact of publication status (such as published peer review journal articles versus unpublished studies) on the identification and/or quantification of adverse effects

Chapter 8: Includes 6 studies which assessed the impact of funding source (such as industry funded studies and government funded studies) on the identification and/or quantification of adverse effects

Chapter 9: Includes 3 studies which assessed the impact of other factors related to the retrieval of information on adverse effects.

In order to ascertain whether any substantive publications had been published since the last update searches in 2009, the methodological searches in Appendix A were repeated in February 2013. Additional papers on unpublished data and industry funded data were identified and incorporated in the main findings section 14.2 in Chapter 14. No potentially relevant articles were identified on study design, search strategies or data sources of adverse effects or adverse reactions.

Figure 3.1 Flow chart for included studies



3.4 Summary

A review of the methodological literature relating to the retrieval of information on adverse effects was carried out.

The included studies were categorized as related to the following;

a) study design
b) source of information
c) database search strategy
d) publication status
e) funding status
f) other

Chapter 4 Section A of the methodological overview: different study designs for information on adverse effects

4.1 Introduction

When devising a search strategy and selecting sources to search for a systematic review, it is important to know which study designs are specified in the inclusion criteria. Reviews may focus on particular types of study design, and the search strategies used and the sources searched should reflect this focus. Search terms or search filters (combination of search terms) may be used to restrict the search to specific study designs. For example, search filters are commonly used to restrict searches to randomised controlled trials (RCTs) in MEDLINE and EMBASE.[125, 126] The sources selected can also be dependent upon which study designs are sought. For example, the Cochrane CENTRAL database is an excellent source of RCTs, whereas Food and Drug Administration (FDA) surveillance data and specialist bulletins (such as the Adverse Drug Reaction Bulletin or Drug and Therapy Perspectives) provide access to case reports.

There is considerable debate regarding the relative utility of different study designs in generating reliable quantitative estimates of risk of adverse effects. A diverse range of study designs, encompassing RCTs and non-randomised studies (such as cohort or case-control studies) may potentially record adverse effects of interventions and provide useful data for systematic reviews and meta-analyses.[21, 127] However, there are strengths and weaknesses inherent to each study design, and different estimates and inferences about adverse effects may arise, depending on study type.[14]

4.1.1 Randomised controlled trials (RCTs)

In principle, RCTs are the most appropriate study design for evaluating adverse effects. This is because, when properly conducted, they limit the risk of bias, control for confounding factors, and form the most reliable source of evidence for treatment effects.[128] This makes RCTs the best study design for obtaining evidence on causation.[3] Furthermore, RCTs facilitate the calculation of Numbers Needed to Harm (NNH) (from the incidence with and without the exposure) and a benefit:harm ratio.[70] The process of randomisation within RCTs overcomes the potential problem

of confounding by indication, by controlling for unknown or not documented factors that could influence the risk of an adverse effect.[65, 73, 129-132] This may be particularly important for suspected adverse effects, where patients at perceived high risk may avoid potentially harmful interventions.

The presence of a control group is particularly important in studies of adverse effects as, it may be difficult to distinguish between an adverse effect and the symptoms of the disease being treated.[82, 132-134] For example, patients with severe chronic rheumatoid arthritis have an increased mortality risk from malignancy, infections and cardiovascular disease and these same patients are likely to receive new biological therapies.[133] Similarly, illnesses that require non-steroidal anti-inflammatory drugs (NSAIDs), rather than NSAIDs themselves, may be responsible for an increased risk in haemorrhage.[130] In the case of selective serotonin reuptake inhibitors (SSRIs) for depression, it may be difficult to decipher the number of suicides and suicide attempts that are due to the underlying illness rather than an adverse effect of the treatment. A control group, however, makes it possible to calculate the true or attributable rate in cases where the background incidence of such adverse events in untreated populations is reported.[14, 31, 132]

The lack of availability of RCT data on adverse effects is the most important disadvantage to this study design.[15, 114, 127, 131, 135, 136] It is often impractical, too expensive, or ethically difficult to investigate rare, long-term adverse effects with RCTs.[3, 15, 71, 73, 129, 131, 137-141] Empirical studies have shown that many RCTs fail to provide detailed adverse effects data, that the quality of those that do report adverse effects is poor,[20, 27, 81, 85, 122, 136, 142-156, 157 , 158-166] and that the reporting may be strongly influenced by expectations of investigators and patients.[167] One study found that if systematic reviews of the 11 products withdrawn because of safety reasons from the UK and US markets in 1999-2001 had been limited to RCTs of patient relevant outcomes, then evidence of harm would have been identified for only one of the products.[168]

In general, RCTs are designed and powered to explore efficacy.[14, 21, 32, 65, 85, 129] As the intended effects of treatment are more likely to occur than adverse effects and more likely to occur within the time frame, RCTs may not be large enough or have sufficient follow-up to identify rare, long-term adverse effects, or adverse effects that occur after the drug has been discontinued.[14, 19-21, 27, 42, 65, 76, 77, 85, 87, 89, 116, 127, 129, 132, 133, 139-141, 143, 144, 168-178] How far the size of RCTs limits their usefulness for information

on adverse effects is debatable. On the one hand, the number of trials with thousands of participants is increasing and with the use of meta-analysis the numbers of participants is increased further. However, on the other side, the extremely large numbers of participants that may be required (up to two million)[179] and the statistical power[106] required for rare events may mean that size of RCTs is still a major issue.[31, 69, 83, 115, 173, 179]

Another problem with RCTs is their generalisability. RCT data may be limited if, as is often the case, trials specifically exclude patients at high risk of adverse effects, such as children, the elderly, pregnant women, patients with multiple diseases, and those with potential drug interactions.[14, 21, 42, 76, 80, 114, 116, 127, 133, 140, 171, 180, 181]

Although RCTs may have limitations, particularly for rare, long-term or unexpected adverse effects, they are still cited as the best source of data for common or specific well recognised anticipated adverse effects which occur within a short-time frame of taking the intervention.[13, 14, 31, 182] For instance, the relationship between anti-arrhythmic drugs and an increased risk in sudden death was established through RCTs.[65, 130]

Given the limitations of RCTs, it may be important to evaluate the use of data from non-randomised studies in systematic reviews of adverse effects.

4.1.2 Observational studies

In observational studies, interventions tend to be allocated according to usual practice as opposed to being actively allocated as with an RCT. The term ‘observational study’ is used to describe any study in which individuals receive treatment based on usual practice or ‘real-world’ choices. The can be confusing, as it implies that the researcher observes an effect or behaviour (which is the case in all studies), without distinguishing design of the study, the level of investigator involvement in the design or the inherent rigour of the approach.

Whereas the term ‘observational study’ is generally used to describe epidemiological studies such as cohort studies or case-control studies, in other instances, a broader definition of observational study is accepted and case series and case reports are also included. This differing inclusion of studies may stem from the fact that case reports and case series can be generated from observational

studies or from investigator lead experiments, such as randomized comparisons with placebo or other interventions.

In either case there is a distinction between, for example, cohort studies and case-control studies on the one hand, and case series and case reports on the other. Cohort studies and case-control studies are analytical studies: they tend to be used to assess causal relationships and are thus 'hypothesis testing'. Case reports and case series, on the other hand, are descriptive studies and can be considered, in all but a few cases, 'hypothesis generating. In pharmacovigilance terms, the latter are useful in signal detection, the former in signal testing or verification.

For the purposes of this thesis the broader definition of observational studies is used.

Owing to the lack of randomisation, all types of observational studies are potentially afflicted by an increased risk of bias (particularly from confounding)[71, 183] and so may be a much weaker study design for establishing causation.[3] Nevertheless, observational study designs may sometimes be the only available source of data for a particular adverse effect and are commonly used in evaluating adverse effects.[21, 114, 129, 139, 178, 184, 185]

Observational studies can have an advantage over RCTs in terms of their feasibility and statistical power,[3, 65, 75, 132] and are assisted by the use of large databases within hospitals and primary care, such as the UK General Practice Research Database (GPRD) (now Clinical Practice Research Datalink (CPRD)), which allow researchers to conduct population based studies.[3, 132, 133, 186]

The biggest challenge in observational studies is to find an appropriate comparison group with similar baseline characteristics, so that expected event rates can be accurately determined.[129, 131, 133]

4.1.2.1 Cohort studies

In a cohort study, a defined group of individuals who receive a particular intervention are followed up over time and compared to another group of individuals who did not receive the intervention. Because of a lack of randomisation, and the way in which patients are selected in cohort studies, the groups being compared are likely to be

unequal with respect to known and unknown variables. However, the importance of controlling for confounding by indication for unanticipated adverse effects is debatable. Authors have argued that confounding is less likely to occur when an outcome is unintended or unanticipated than when the outcome is an intended effect of the exposure. This is because the potential for that adverse effect is not usually associated with the reasons for choosing a particular treatment, and does not influence the prescribing decision.[82, 178, 185, 187, 188] For instance, in considering the risk of venous thrombosis from different oral contraceptives in healthy young women, the choice of contraceptive may not be linked to risk factors for deep venous thrombosis (an adverse effect that is not anticipated). Thus, any difference in rates of venous thrombosis may be due to a difference in the risk of harm between contraceptives.[178, 188] However, care should be taken, as cohort studies may suffer from diagnostic suspicion bias whereby those taking the intervention are more likely to be monitored and more likely to receive a diagnosis.[3] In the case of deep venous thrombosis, for instance, this may be more frequently diagnosed in users of oral contraceptives, even if there was no causal link with the drugs.[3]

A particular disadvantage of cohort studies is that they, like RCTs, may take a long time to complete and may not be large enough to identify very rare adverse effects.[70, 73]

4.1.2.2 Case-control studies

Another, probably less reliable, study design for the identification of adverse effects is the case-control study. Case-control studies start with selecting people who have already developed the adverse effect of interest (cases). Controls are then identified who do not have the adverse effect, but who are similar to the cases with respect to important determinants (such as age, sex and concurrent medical conditions).[135] A particular problem with case-control studies is their susceptibility to recall bias.[189] The retrospective nature of this design means that sources such as medical records and interviews with patients about past behaviour are required. However, medical records are often incomplete and patients with an adverse effect may try harder to recall a potential culprit (recall bias) and interviewers may probe them more vigorously (interview bias).[96, 129, 135, 137, 190, 191]

Case-control studies, however, may be most useful for adverse effects that are either very rare, take a long time after exposure to develop, or are catastrophic.[3, 14,

[81, 129, 131, 132, 135, 139, 141, 175, 192] For example, case-control studies have identified the association between NSAIDs or SSRIs and upper gastrointestinal bleeding, the increased risk of venous thromboembolism with oral contraceptives,[135, 192-194] and the association between diethylstilboestrol (DES) ingestion by pregnant women and the development of vaginal adenocarcinoma in their daughters many years later.[21, 135, 194] If a prospective study had been undertaken to investigate the relationship between diethylstilboestrol and vaginal adenocarcinoma it would have taken at least 20 years and would have required hundreds of thousands of women.[135, 195]

4.1.2.3 Cross-sectional Studies

Another study design sometimes used to investigate the relationship between an intervention and potential adverse effects is the cross-sectional study. In cross-sectional studies the exposure and the potential adverse effect are measured at the same time, using for example a questionnaire or survey. Measuring the exposure and outcome simultaneously is a major problem with this study design, as it will not be known which came first,[114, 141] and it will be impossible to distinguish between cause and effect.

4.1.2.4 Ecological Studies

An ecological study in which at least one variable is measured at the group (not individual) level. The occurrence of disease is compared between groups that have different levels of exposure. An example would be fracture rates in people living in areas of water fluoridation compared to those living in areas without water fluoridation.

4.1.2.5 Case reports/case series

Many adverse drug reactions are first reported as case reports or small case series.[77, 87, 139, 196-200] Case reports are the mainstay of pharmacovigilance, whereby reports are submitted by health professionals and the public to national pharmacovigilance centres such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the Food and Drug Administration (FDA) in the US. Another system employed to monitor the safety of selected drugs is Prescription Event Monitoring (PEM). Doctors prescribing the selected drug are

provided with a special reporting form to record any adverse effects experienced by the patient.[175, 201]

In addition to pharmacovigilance reporting, case reports represent a substantial amount of the published literature on adverse effects[31] and are the main source of information used to withdraw a drug from the market for safety reasons.[86, 168, 186, 192] Indeed, many adverse effects have been successfully discovered through case reports, including the birth defects associated with thalidomide.[202]

Case reports may be especially useful for unusual serious adverse effects that occur early on in the treatment and are unrelated to the indication of the drug,[21, 73, 76, 129, 133, 139, 182, 192, 197] are extremely rare,[13, 77, 80, 82, 133, 137, 174, 203] or are typical of drug reactions (e.g. agranulocytosis, liver necrosis, Stevens-Johnson syndrome).[103] Some adverse drug reactions may be so convincing or dramatic that only one case report or at most a handful of reports are necessary to provide evidence of an association.[131, 141, 196, 204-206] However, adverse effects with a long latency period, that are unexpected, have a modest increase, or are common in non-exposed patients, are much harder to detect with case reports.[73, 80, 103]

There is always the danger of false positive signals when using case reports[73, 82, 200] and it should be noted that raising alarm about potential adverse effects can do more harm than good. For instance, the uptake of beneficial treatments were reduced or restricted in the case of the alleged associations between the measles, mumps and rubella (MMR) vaccine and autism,[207] between sertindole (an antipsychotic drug) and sudden death,[208] and between bendectin (used to treat nausea and vomiting) and birth defects.[129, 130, 200]

A particular problem with case reports is that they lack a numerator (as the total number of cases is unknown)[73, 209] and a denominator (as the number of exposed cases is unknown)[42, 133, 209-212] and with no comparator group, they cannot be used to determine the risks or incidence of adverse reactions, causal relationships,[14, 129, 131, 133, 212, 213] or even to compare different drugs.[175, 198, 212, 214]

Case reports are also likely to be more susceptible to publication bias than other study designs. Case reports that are new, interesting, unusual, unexpected, extreme, or associated with a useful teaching point, are more likely to be submitted by the author and accepted by the journal editor,[131, 198] and a published case report

may then stimulate further reports.[139, 209, 215] It is, therefore, not possible to know how representative the occasional case report is of overall medical experience.[212, 216]

Poor reporting is also a problem in published case reports, as they often do not contain sufficient information or detail,[204, 209-211, 217] and even when using case reports submitted to regulatory authorities, reporting of patient and drug information is often incomplete,[31, 139, 210, 212, 218] and many cases are not submitted, with estimates of under-reporting as high as 98%[213] and 99%.[219] Under-reporting is particularly apparent for older drugs, less serious adverse effects, predictable adverse drug reactions, or with less interesting adverse effects.[175] In addition, it has been found that few case reports are subsequently investigated or confirmed to be valid.[220]

Nevertheless case reports may alert health professionals to potential adverse effects and may be a useful tool for hypothesis generating.[31, 42, 114, 129, 141, 175, 177, 178, 188, 209] With the use of data mining techniques of case reports submitted as part of spontaneous reporting systems, this information also has a predictive value in identifying early signals of new adverse drug reactions.[221] These potential links between an adverse event and a particular drug can then, if necessary, be investigated further using other study designs.

With so many potentially useful study designs for identifying adverse effects, with varying advantages and disadvantages, a major question is whether findings from different types of study designs agree. The extent of any discrepancy between the pooled risk estimates from different study designs is a key concern for systematic reviewers. Previous research has tended to focus on differences in treatment effect between RCTs and observational studies.[222-228] However, estimates of beneficial effects may be prone to different biases to estimates of adverse effects amongst the different study designs. Bearing in mind the possibility of bias, increased workload, and difficulty in combining the data from diverse study designs, it is not clear whether the inclusion of all types of study designs results is most appropriate for systematic reviews incorporating adverse effects. This uncertainty has not been fully addressed in current methodological guidance on systematic reviews of harms,[116] probably because the existing research has so far been inconclusive, with examples of both agreement and disagreement in the reported risk of adverse effects between RCTs and observational studies.[17, 21, 77, 98, 134, 138, 140, 177, 229-234] It may be hypothesized that RCTs might provide more accurate results and that including observational

studies may simply increase bias in a systematic review. On the other hand observational studies may primarily be devoted to assessing specific adverse effects and provide more complete data.

This research aimed to systematically review meta-analyses or methodological studies comparing estimates of harm (for specific adverse effects) reported in one study design with those reported in another study design for the same adverse effect.

4.2 Methods

4.2.1 Inclusion criteria

A meta-analysis or methodological evaluation was considered eligible for inclusion in this review if it evaluated studies of more than one type of design (for example, RCTs versus cohort, or RCTs versus case-control studies) in the identification and/or quantification of adverse effects of healthcare interventions. The main outcome measure was an estimate of the impact of different study designs on the combined estimates of the risk of adverse effects in terms of risk ratio (RR), odds ratios (OR), or weighted means difference (WMD). Other outcome measures were incidence rate of adverse effects, or ranking of adverse effects from different study designs.

4.2.2 Data extraction

Information was collected on the primary objective of the meta-analysis or methodological evaluation, study designs, and the adverse effects and interventions evaluated. The number of primary studies included in the analysis and number of patients by study design; the number of adverse effects in the treatment and control arm or comparator group were also recorded as were the types of summary statistics used in assessing differences between studies, such as risk ratio, odds ratio, or weighted means difference. In each instance, the categorisation of study design as specified by the author of the meta-analysis or methodological evaluation was relied upon. For example, if the author stated that he/she compared RCTs with cohort studies, it was assumed that the studies were indeed RCTs and cohort studies.

4.2.3 Assessment of methodological quality

The following criteria were used to consider the validity of comparing risk estimates across different study designs:

1. Presence of confounding factors

   Discrepancies between the results from different study designs may arise because of factors other than study design (such as differences in population or age group, delivery of intervention, drug dosage or outcome measurement). A record was made of whether the authors of the meta-analysis or methodological evaluation reported checking whether the groups of different studies shared similar features in terms of population, interventions, comparators, and measurement of outcomes to improve the comparability of the risk estimates arising from different study designs.

2. Heterogeneity by study design

   A record was made of whether the authors of the meta-analysis or methodological evaluation explored heterogeneity by study design, using measures such as Chi^2 or I^2 statistic. An indication of heterogeneity of each set of pooled results by study design was assessed using a cut-off point of $P<0.10$ for Chi^2 test results and 50% for I^2 results. In the few instances where both statistics were presented, the results of the I^2 test were given precedence.[235]

3. Statistical analysis comparing study designs

   A record was made of whether the authors of the meta-analysis or methodological evaluation described the statistical methods by which the magnitude of the difference between study designs was assessed.

4.2.4 Analysis

Duplicate data were excluded from the analysis. Any relevant missing statistical data, such as confidence intervals, were calculated from the raw data presented wherever possible.

Potential discrepancies between the pooled odds (OR) from meta-analyses of different study designs were checked by (i) comparing the separate point estimates and overlap in confidence intervals, and (ii) making a quantitative and graphical comparison of the ratio of the pooled odds ratios from each study design.

A descriptive summary of the data in terms of confidence interval (CI) overlap between pooled sets of results by study design, and any differences in the direction of effect between study designs were presented. In order to be able to compare any disagreements in the results, each type of study design was compared to the others in turn. For instance, if a methodological evaluation included RCTs, cohort studies and case-control studies, RCTs were compared to cohort studies, then RCTs were compared to case-control studies, and lastly cohort studies were compared to case-control studies. The results were said to agree if both study designs identified a statistically significant increase, a statistically significant decrease, or no statistically significant difference in the adverse effects under investigation.

Potential quantitative differences or discrepancies between the pooled estimates from the respective studies designs for each adverse effect were illustrated by taking the ratio of odds ratios (ROR) from meta-analysis of one study design versus meta-analysis of another study design. The ROR was calculated using the pooled odds ratio for the adverse outcome from one study design divided by the pooled odds ratio for the adverse outcome from another study design. If the meta-analysis of one study design for a particular adverse effect yielded exactly the same OR as the meta-analysis of another study design (i.e. complete agreement, or no discrepancy between study designs), then the ROR would be 1.0 (and Ln ROR would be zero). Because adverse effects are rare, odds ratios and risk ratios were treated as equivalent.[236]

The estimated RORs from each study design comparison were then used in a meta-analysis (random effects inverse variance method - RevMan 5.1) to summarize the overall RORs between study designs across all the included reviews. The standard error (SE) of ROR was estimated using the standard errors for each type of study design respectively. For instance, in the case of comparing RCTs and observational study estimates, the SE was calculated as follows:

$$SE(ROR) = \text{square root of } [SE\ Ln\ OR(RCT)^2 + SE\ Ln\ OR(Observ)^2]$$

Standard errors pertaining to each pooled OR(RCT) and OR(Observ) were calculated from the published 95% confidence interval (CI). Statistical heterogeneity was assessed using I^2 statistic with I^2 values of 30-60% representing a moderate level of heterogeneity.[237]

Funnel plots were constructed to evaluate the distribution of the ROR against estimates of precision (1/SE). If there were no systematic differences or discrepancies between the pooled OR from the various study designs, then the ROR data points would be expected to be symmetrically distributed within the funnel shape. Conversely, if one set of study designs consistently generated either lower or higher estimates, then the RORs would be skewed to one side, with an asymmetrical funnel plot.

4.3 Results

4.3.1 Included studies

In total, 51 meta-analysis or methodological evaluations met the inclusion criteria (Appendix B: Table 15.1).[28, 136, 183, 238-286] Six were methodological evaluations with the main aim of assessing the influence of study characteristics (including study design) on the measurement of adverse effects,[136, 183, 242, 247, 248, 264, 269] whereas the remaining 45 were systematic reviews within which subgroup analysis by study design was embedded.[28, 238-241, 243-246, 249-263, 265-268, 270-286]

4.3.1.1 Adverse effects

Nearly two-thirds of the meta-analyses or methodological evaluations compared the results from different study designs using only one specific named adverse effect (31/51, 61%),[28, 238-241, 244-246, 249, 252-255, 257-262, 265, 266, 272, 274-281, 285] whilst six included one type of adverse effect (such as cancer, gastrointestinal complications, or cardiovascular events).[242, 243, 256, 268, 269, 271] Fourteen included a number of specified adverse effects (ranging from two to nine effects) or any adverse effects.[136, 183, 247, 248, 250, 251, 263, 264, 267, 270, 273, 282-284, 286]

The most commonly included adverse effect was cancer (nine methodological evaluations), followed by cardiovascular events (eight methodological evaluations), venous thromboembolism (six methodological evaluations) and then haemorrhage, falls, fractures, and gastrointestinal complications (each in three methodological evaluations).

The absolute numbers of adverse effects per type of study design were presented in only 18 methodological evaluations[28, 183 Vohra, 2007 #11306, 244, 245, 251, 256, 257, 263, 267, 269, 273,

[274, 277-279, 283, 285] and in eight of these the data were incomplete.[183, 244, 269, 274, 277, 279, 283, 285] The number of adverse effects reported in the pooled treatment arms ranged from 0 to 4615. However, most studies included rare adverse effects.

4.3.1.2 Interventions

The majority (44/51, 86%) of the meta-analysis or methodological evaluations included only one intervention (such as hormone replacement therapy (HRT) or nonsteroidal anti-inflammatory drugs (NSAIDs)),[28, 183, 238-251, 253, 254, 256-260, 263-280, 282-285] whilst seven methodological evaluations included more than one intervention, with a range of two to nine interventions.[136, 252, 255, 261, 262, 281, 286]

Most of the methodological evaluations (43/51, 84%) focused on adverse effects of pharmacological interventions.[28, 136, 183, 238, 239, 241-246, 249, 251-258, 260-266, 268, 269, 271-281, 283, 285, 286] Other topics assessed were surgical interventions (such as bone marrow transplantation and hernia operations),[136, 240, 247, 248, 250, 270] a public health intervention (water fluoridation),[259] blood transfusion,[267] diagnostic test (ultrasonography),[282]and a physical intervention (spinal manipulation).[284]

The most commonly studied intervention was hormone replacement therapy (HRT) (nine methodological evaluations),[238, 244, 249, 252, 253, 255, 266, 272, 280] followed by NSAIDs (eight methodological evaluations)[242, 245, 256, 263, 268, 269, 271, 277] and oral contraceptives (eight methodological evaluations).[183, 241, 246, 252, 254, 258, 260, 276]

4.3.1.3 Outcome measures

The majority of the methodological evaluations (39/51, 76%) compared pooled risk ratios and/or odds ratios from different types of study design.[136, 238, 240-246, 249-256, 258-263, 265-269, 271, 272, 274-277, 279-282, 286] Although risk ratio was sometimes used for case-control studies instead of odds ratios, most adverse effects are rare so this was assumed not to impede the results.

Seven methodological evaluations measured the incidence of adverse effects,[183, 247, 248, 257, 270, 273, 278, 283] three methodological evaluations reported the number of cases of an adverse effect (with no denominator),[28, 284, 285] one methodological evaluation measured weighted means difference (WMD) (in addition to risk ratios),[239] and another measured relative frequencies of adverse effects.[264]

4.3.1.4 Sample size

The number of included studies in each comparison set of pooled results ranged between two and 1885 primary studies. Those methodological evaluations with the highest number of primary studies tended to include case reports.

4.3.1.5 Study designs

Eleven methodological evaluations did not distinguish between cohort and case-control studies, and these study types were grouped by the authors under the umbrella term 'observational studies' and compared to RCTs.

4.3.2 Excluded studies

Sixty-seven studies were excluded from this section of the systematic review (Appendix B: Table 15.2). Nearly a third of these studies (20/67) did not compare a formally recognized study design (such as RCTs, cohort studies or case-control studies) but compared study designs using a categorisation such as, prospective versus retrospective studies, phase two versus phase three RCTs, nested versus non-nested case-control studies, case-controlled versus case-crossover studies, or studies divided by data collection methods.[287-306] Although these studies are methodologically interesting, it would not be possible to relate any differences identified to the retrieval of information on adverse effects. For example, it is very difficult to develop a search strategy to identify only nested case-control studies.

Twelve studies were excluded because their hypothesis stated that the intervention had a protective effect.[307-318] For example, in one study oral contraceptives were thought to provide a protective effect against ovarian cancer.[307] Fourteen studies discussed the differences between the results of study designs without all of the pooled results or estimates,[134, 319-331] and eight studies presented the results of each of the individual studies grouped by study design but did not present the pooled results.[171, 332-338] Five studies did not compare similar data, for example, similar adverse effects,[339, 340] similar comparators,[140] or similar outcome measures.[341, 342] For three studies only the abstract was available and not enough information could be ascertained.[230, 343, 344] Two studies contained duplicate data from studies already included,[345, 346] one study did not separate the pooled results of cohort studies and RCTs,[347] one study did not include a healthcare intervention,[348] and lastly, one study

did not measure the magnitude or direction of any adverse effects but looked at the decline in risk.[349]

4.3.3 Summary of methodological quality

1. Role of confounding factors

Although many of the methodological evaluations acknowledged the potential for confounding factors that might yield discrepant findings between study designs, no adjustment for confounding factors was reported in most instances.[28, 136, 183, 238-241, 243-246, 248-253, 256-262, 264-268, 270-286] However, a few authors did carry out subgroup analysis stratified for factors such as population characteristics, drug dose, or duration of drug exposure.

There were five instances where the authors of the methodological evaluations performed some adjustment for potential confounding factors.[242, 254, 255, 263, 269] Three carried out meta-regression,[242, 254, 263] one measured differences in heterogeneity when stratified by dose or duration,[255] and in the other methodological evaluation the adjustment method carried out was unclear.[269] In three of the methodological evaluations, other factors (such as drug dose and duration) were thought to be potentially responsible for any discrepancies between the results from different study designs.[254, 255, 269]

2. Heterogeneity by study design

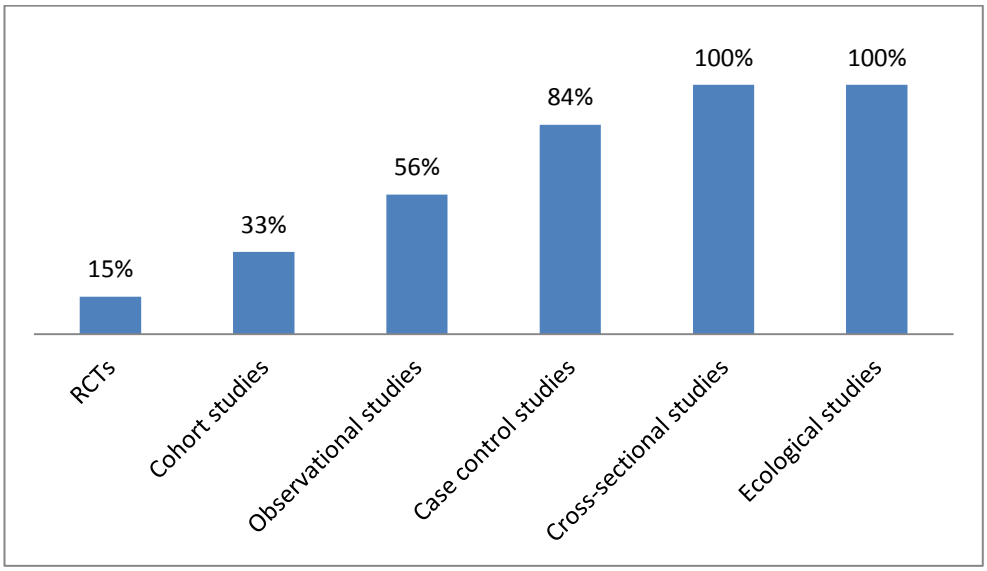
Twenty-two meta-analyses or methodological evaluations measured the heterogeneity of at least one set of the included studies grouped by study design using statistical analysis such as Chi^2 or I^2.[136, 239, 242-244, 246, 249, 251, 252, 256, 258, 259, 263, 265, 266, 269, 272, 277, 279-281]

The pooled sets of RCTs were least likely to exhibit any strong indication of heterogeneity; only five (15%)[136, 244, 279, 282] of the 33[136, 239, 243, 244, 249, 252, 263, 277, 279] sets of pooled RCTs were significantly heterogeneous (Figure 4.1) and in two of these sets of RCTs the heterogeneity was only moderate with I^2=58.9%[244] and I^2=58.8% (Appendix B: Table 15.1).[279]

In terms of least heterogeneity, RCTs were followed by cohort studies (7/21, 33%), 'observational' studies (as described by the authors) (14/25, 56%), then case-control studies (16/19, 84%), cross-sectional studies (1/1, 100%) and ecological

studies (1/1, 100%) (Figure 4.1). This reflects the traditional hierarchy of evidence for clinical effectiveness.

Figure 4.1 Significant heterogeneity between studies of the same design



3. Statistical analysis comparing study designs

Authors of eight methodological evaluations[136, 183, 240, 246, 248, 254, 258, 270] explicitly tested for a difference between the results by study design, seven reported p-values[136, 240, 246, 248, 254, 258, 270] and one presented risk ratio estimates.[183]

Six methodological evaluations[239, 246, 249, 258, 259, 280] reported on the heterogeneity of the pooled studies of one design, the pooled studies of another design, and the heterogeneity of all the studies combined. This can indicate statistical differences where the pooled study designs combined are significantly heterogeneous but no significant heterogeneity is seen when the study designs are pooled separately. One meta-analysis (breast cancer with hormone replacement therapy)[249] identified that although significant heterogeneity was observed with all studies, there was no significant heterogeneity when the studies were grouped by study design.

4.3.4 Preparation of data

4.3.4.1 Duplicate data

A major problem with the methodological evaluations was the issue of duplicate data. For instance, some methodological evaluations presented both fixed and

random effects models,[238, 246, 276, 281] some presented both grouped data (for example, all cancers, all NSAIDs, all diuretics or all doses of a drug) and discrete sets of data (for example, by type of cancer, by type of NSAID, by type of diuretic or by drug dose),[243, 262, 268, 276] one carried out analysis from adjusted and unadjusted data,[275] and lastly, one presented multiple data from systematic reviews of the same intervention and adverse effect. It is likely that the primary studies included in these systematic reviews overlapped considerably, again introducing duplicate data analysis.[269]

Some authors also carried out analysis on secondary outcomes which were related to or surrogates of the primary outcome. Examples include blood transfusion rates as well as total blood loss, bone mineral density as well as fractures, cancer recurrence as well as mortality, preterm birth as well as low birth weight, delayed speech as well as dyslexia, 30 day mortality, stroke and myocardial infarction as well as mortality, death as well as new infections, asystole as well as bradycardia, and ulcer bleeding/perforation and death attributable to ulcer bleeding/perforation as well as symptomatic ulcer.[183, 239, 265, 267, 270, 273, 283]

Using the same data set more than once or multiple related outcomes in any analysis may make the data appear inappropriately homogenous and may present relationships which do not exist. The following decisions were, therefore, implemented before data entry into the statistical software package STATA (version 12.0).

1) Where both random effects models and fixed effects models were presented,[238, 246, 276, 281] the random effects models were selected over the fixed effects models as they represented a more conservative approach, and studies were often heterogeneous (where measured).
2) The separate analysis for each named NSAID,[276] each named cancer,[243] each named diuretic,[262] and the two separate analysis by rofecoxib drug dose[268] were selected in preference to the grouped set of results of all NSAIDs, all cancers, all diuretics and all drug doses of rofecoxib.
3) Pooled adjusted data were selected in preference to unadjusted data where both were presented.[275]
4) The systematic reviews with the largest number of included studies were selected from McGettigan and Henry 2008.[269]
5) Primary outcomes of symptomatic ulcer,[183] fractures,[265] mortality,[267, 270] infections,[273] low birth weight,[247] dyslexia,[247] and bradycardia[283] were

selected in preference to the secondary outcomes of ulcer bleeding or perforation and death attributable to ulcer bleeding or perforation,[183] bone mineral density,[265] cancer recurrence,[267] 30 day mortality, stroke and myocardial infarction,[270] death,[273] preterm birth and other perinatal outcomes,[247] delayed speech,[247] and asystole.[283]

6) Where outcomes were reported as risk ratios and weighted means difference, risk ratios were selected in preference to weighted means difference. Re-exploration was therefore selected in preference to total blood loss or blood transfusions.[239]

4.3.4.2 Unreported data

Another problem in comparing the results of the methodological evaluations was that of unreported data. In two methodological evaluations, risk ratios were not presented for all the results by study design but were divided by specific study characteristics. In Bollini et al 1992[242] the case-control studies were pooled according to whether they were hospital-based or community-based case-control studies and in Douketis et al 1997[252] the cohort studies were pooled according to whether they were prospective or retrospective cohort studies. In order for all case-control studies in Bollini et al 1992[242] and all cohort studies in Douketis et al 1997[252] to be compared to the other study designs, these results were weighted appropriately and amalgamated to estimate risk ratios and confidence intervals of the studies combined.

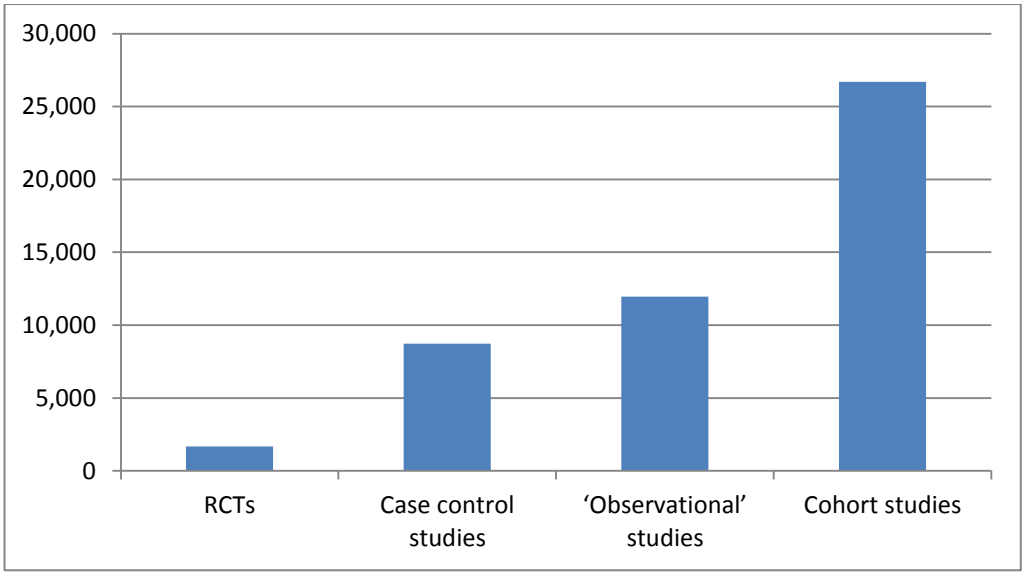
Confidence intervals were not presented for nine of the methodological evaluations.[28, 183, 257, 264, 273, 274, 283, 284,266] Confidence intervals could be estimated from the information given in five of these methodological evaluations, four of which presented the number of adverse effects[183, 257, 273, 283] and numbers of participants and one presented risk ratio estimates with p-values.[274] In the case of the methodological evaluations that presented incidence data,[183, 257, 273, 283] confidence intervals were estimated for the incidence of adverse effects only in the treatment arms, as in many cases no information on a control group was given or there was no control group - for example, with case series. Confidence intervals could not be calculated for four methodological evaluations: three presented only the number of adverse effects (with no denominator)[28, 284, 285] and the other presented relative frequencies of adverse effects.[264]

4.3.5 Size of studies

In 19 methodological evaluations the total number of participants was reported in each set of pooled studies by study design[238, 239, 241, 243, 245, 249-251, 256, 257, 263, 266, 267, 270, 273, 279, 282, 283] and in another 13 methodological evaluations the pooled number of participants was reported for at least one type of study design.[28, 136, 246, 254, 258, 264, 265, 269, 271, 274, 276, 277, 284]

Cohort studies contained the highest number of participants per study with a mean of 26,699 (4,966,061/186), followed by studies classified as observational with a mean of 11,953 (3,824,807/320) participants per study, and case control studies which had a mean of 8,717 (1,447,084/166) participants. RCTs had the lowest mean number of participants at 1,671 (840,354/503) (Figure 4.2).

Figure 4.2 Mean number of participants per study according to study design



4.3.6 Confidence interval overlap

4.3.6.1 Risk ratios or odds ratios

In almost all instances, the confidence intervals (CIs) for the risk ratios or odds ratios for the pooled results from the different study designs overlapped (94%, 151/160). However, there were nine pooled sets of results (in six methodological evaluations) where the confidence intervals did not overlap.[136, 249, 252, 255, 261, 280]

Six of the nine pooled sets of results where confidence intervals did not overlap investigated hormone replacement therapy (HRT) with a named adverse effect of either a named cancer, (such as breast cancer,[249] endometrial cancer[255] or cervical cancer[280]) or venous thromboembolism.[252] The other pooled sets of results were very specific, looking at psychotropic drugs and falls,[261] symptomatic intracranial bleed with anticoagulant versus antiplatelet,[136] and visceral or vascular injury with laparoscopy versus open surgery for inguinal hernia.[136]

The nine pooled sets of results without confidence overlap compared a range of different study designs with no consistent pattern. Four compared RCTs with observational studies, either 'observational' studies in general,[136, 249, 257] or case-control studies.[252] The five other pooled sets of results compared either cohort studies with case-control studies,[255, 280] or cohort studies and cross-sectional studies.[261]

4.3.6.2 Incidence rates of adverse effects

In just over three-quarters of instances (76%, 13/17) the confidence intervals for the incidence rates of adverse effects from the different studies overlapped (Table 4.1). There were only four instances where the confidence intervals did not overlap: general anesthesia and urinary retention;[257] regional anesthesia and urinary retention;[257] propofol and bradycardia;[283] and symptomatic ulcer and NSAIDSs.[183] Again, the pooled sets of results without overlapping confidence intervals compared a range of study designs with no consistent pattern. They compared RCTs with either 'observational' studies in general,[136, 249, 257] cohort studies,[183] or case series.[283]

Table 4.1 Confidence interval overlap between study designs in studies measuring incidence

Study design comparisons	Confidence interval overlap
RCTs versus 'observational' studies (N=4)	2 (50%)
RCTs versus cohort studies (N=7)	6 (86%)
RCTs versus case series (N=5)	4 (80%)
Cohort versus case series (N=1)	1 (100%)

Table 4.2 Confidence interval overlap and agreement between study designs in studies measuring risk ratios or odds ratios

Study design comparisons	Confidence interval overlap	Agreement in findings between the study designs			Discrepancy in findings between the study designs		
		Both showed a significant increase	Both did not identify any significant difference	Both showed a significant decrease	Significant risk increase in one versus significant risk decrease in the other	Significant increase in one versus no significant difference in the other	Significant decrease in one versus no difference in the other
RCTs versus all 'observational' studies (N=58)	54 (93%)	11 (19%)	23 (40%)	3 (5%)	1 (2%)	19 (33%)	1 (2%)
Subgroup analysis based on specific observational designs against RCTs							
RCTs versus 'observational' studies (N=32)	29 (91%)	6 (19%)	13 (41%)	3 (9%)	1 (3%)	8 (25%)	1 (3%)
RCTs versus cohort studies (N=16)	16 (100%)	3 (19%)	8 (50%)	0	0	5 (31%)	0
RCTs versus case-control studies (N=10)	9 (90%)	2 (20%)	2 (20%)	0	0	6 (60%)	0
Analysis of non-RCTs studies							
Cohort versus case-control studies (N=64)	60 (94%)	19 (27%)	23 (38%)	0	1 (2%)	20 (31%)	1 (2%)
Cohort versus cross-sectional studies (N=18)	17 (94%)	4 (22%)	11 (61%)	0	0	3 (2%)	0
Cohort versus ecological studies (N=1)	1 (100%)	0	1 (100%)	0	0	0	0
Case-control versus cross sectional studies (N=18)	18 (100%)	4 (22%)	11 (61%)	0	0	3 (2%)	0
Cross-sectional versus ecological studies (N=1)	1 (100%)	0	1 (100%)	0	0	0	0

4.3.1 Agreement and disagreement of results

4.3.1.1 Agreement

In the majority (111/160, 69%) of the methodological evaluations, the results of the treatment effect agreed between types of study design in terms of identifying a significant increase, significant decrease or no significant difference in the adverse effects under investigation.[136, 238, 241-243, 245, 250, 252, 254-256, 259-263, 265-269, 271, 272, 274-277, 279-282, 286] Most studies that demonstrated an agreement between study designs did not find a significant increase or significant decrease in adverse effects (70/111, 63%) (Table 4.2).

4.3.1.2 Disagreement

There were other instances[136, 238-240, 243, 246, 250-253, 258, 260-263, 265, 268, 269, 271, 276-278, 280-282] (29%, 47/160) where although the direction of the effects were not opposing, apparently different conclusions may have been reached had a review been restricted to just one type of study design and undue emphasis was placed on statistical significance tests. Table 4.2 shows that the most common discrepancy between study types occurred when one set of studies identified a significant increase whilst another study design found no statistically significant difference. For instance, a significant increase in an adverse effect could be identified in an analysis of RCT data, yet pooling the observational studies may have identified no significant difference in adverse effects between the treatment and control group.

Disagreements between RCTs and observational studies were fairly evenly balanced. There were eight instances where a significantly elevated risk with RCTs was demonstrated but no significant difference with observational studies and 11 instances where observational studies demonstrated a significantly elevated risk with no significant difference identified by RCTs.

There was a tendency for case-control studies to show a greater degree of harm than cohort studies. There were 14 adverse effects where meta-analyses of case-control studies found significant elevated risk, but meta-analyses of cohort studies did not confirm this risk. Conversely, there were six adverse effects where meta-analyses of cohort studies demonstrated significantly elevated risk, but the meta-analyses of case-control studies did not show significant risk.

Given the imprecision in deriving estimates of rare events, this may not reflect any real difference between the estimates from different study designs, and it would be more sensible to concentrate on the overlap of confidence intervals (CIs) rather than the variation in size of the p-values from significance testing.

Where possible, the sample sizes of the studies which disagreed were compared. It was hypothesized that those study designs which disagreed because one type of study design identified an increase or decrease in an adverse effect and another study design identified no significant difference, might be due to differences in sample size. Large sample sizes might be required to identify a significant difference in rare adverse effects. Nineteen of the 49 pooled sets of results which disagreed reported on the number of participants by study design. However, in only seven of the 19 sets of results, a smaller number of participants were reported for those studies which identified a non-significant difference when the larger set of pooled results identified a significant increase or decrease.

There were major discrepancies in only two pooled sets of results.[249, 255] In these instances, whilst one study design identified a protective effect another type of study design identified an increased risk of the outcome. Col et al 2005[249] found an increase in breast cancer with menopausal hormone therapy in RCTs (RR 3.41 (1.59-7.33)) but a decrease in observational studies (RR 0.64 (0.50-0.82)). Grady et al 1995[255] found that whilst cohort studies demonstrated a decrease in endometrial cancer with estrogen plus progestin (RR 0.4 (0.2-0.6)), case-control studies demonstrated an increase (RR 1.8 (1.1-3.1)).

4.3.2 Ratio of risk ratio or odd ratios estimates

Risk ratios or odd ratios from the different study designs were compared to other study designs by meta-analysis of the respective ratio of risk ratios or odds ratios (RORs) for each adverse effect. In instances where risk ratios or odds ratios were unavailable, the incidence or number of cases of adverse effects was compared from different study designs.

The RORs from the different study design comparisons are presented in Table 4.3 and the corresponding forest plots in Figure 4.3 and Appendix B: Figure 15.1 to Figure 15.6. The overall RORs from meta-analysis using the data from all studies that compared RCTs with cohort studies or case control studies or that grouped

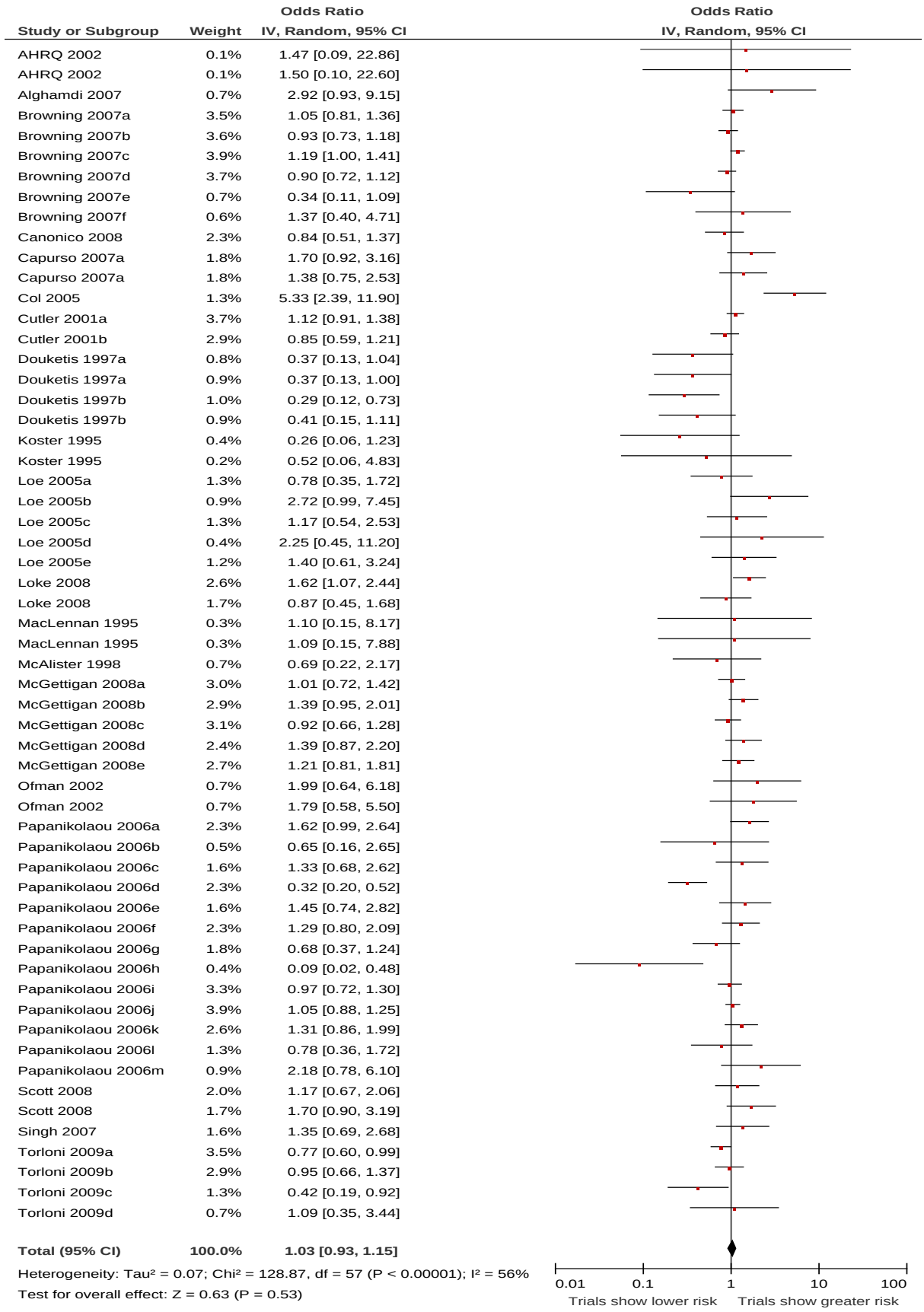
studies under the umbrella of 'observational' studies was estimated to be 1.03 (95% CI 0.93-1.15) with moderate heterogeneity (I^2=56%, 95% CI of I^2=38-67%) (Table 4.3 and Figure 4.3).

Generally, the pooled RORs from the study design comparisons show no significant difference between the results from different study designs with either low or moderate heterogeneity (Table 4.3 and Appendix B: Figure 15.1 to Figure 15.6). However, it was interesting to note that, on average, meta-analyses of cohort studies gave odds ratios that were a relative 6% lower than those of meta-analyses of case-control studies. Although this difference between cohort and case-control studies did not reach conventional threshold of statistical significance, the low to moderate heterogeneity seen overall is an indicator that there may be a consistent pattern of variation between these study designs.

Table 4.3 Ratio of odds ratios (RORs) of adverse effects in study design comparisons

Study design comparison	Pooled ratio of odds ratios (RORs) and 95% confidence intervals (CIs)	Heterogeneity (I^2)
RCTs versus all observational studies (N=58)	1.03 (0.93-1.15)	56%
RCTs versus cohort studies (N=16)	1.02 (0.82-1.28)	43%
RCTs versus case-control studies (N=10)	0.84 (0.57-1.23)	54%
RCTs versus 'observational' studies (N=32)	1.08 (0.94-1.22)	60%
Cohort versus case-control studies (N=64)	0.94 (0.87-1.01)	55%
Cohort versus cross-sectional studies (N=18)	0.97 (0.89-1.07)	10%
Case-control versus cross-sectional studies (N=18)	1.07 (0.95-1.21)	26%

Figure 4.3 Meta-analysis of RORs from RCTs versus all observational studies



NB: Studies are listed by first author's last name and year of publication. In some studies more than one outcome or intervention was assessed. In these instances, indicated by lowercase letters after the study year, the data were entered in the meta-analysis separately. Other studies compared RCTs to cohort studies and case-control studies separately and therefore are listed twice (with no lowercase letter after the study year).

4.3.3 Incidence of adverse effects

The pooled ratio of incidence from different study designs are presented in Table 4.4. These results suggest a higher risk of adverse effects in RCTs than cohort studies (1.75 (1.5-2.04)). However, there is a high level of heterogeneity in the pooled studies and these results are highly influenced by one study, Tramer et al 2000 (Appendix B: Figure 15.7 to Figure 15.9). The pooled ratio of incidence of adverse effects was greater in case series than cohort studies (0.24 (0.07-0.84)); these figures are based on only one study in which the number of cases of adverse effects was very small (seven and four).[278]

Table 4.4 Pooled ratio of incidence of adverse effects in study design comparisons

Study design comparison	Pooled ratio of incidence and 95% confidence intervals (CIs)	Heterogeneity (I^2)
RCTs versus cohort studies (N=7)	1.75 (1.50-2.04)	94%
RCTs versus studies described as 'observational' (N=4)	2.37 (0.70-8.05)	60%
RCTs versus case series (N=3)	1.98 (0.59-6.64)	85%
Cohort studies versus case series (N=1)	0.24 (0.07-0.84)	NA

4.3.4 Number of adverse effects

One methodological evaluation identified a higher number of adverse effects in RCTs (164 serious adverse effects, 4615 non-serious) than 'observational' studies (39 serious adverse effects, 3553 non-serious),[285] and another a higher number of adverse effects in the 'observational studies' (nine) than RCTs (zero).[28] However, the sample size of the studies was not reported.

Two methodological evaluations[28, 284] compared the number of adverse effects from RCTs and case series, or RCTs and case reports. One, however, did not separate the results from case reports and case series,[28] and the other reported small numbers of adverse effects (RCTs - four cases, case series - three cases and case reports - seven cases).[284]

4.3.5 Relative frequencies of adverse effects

One methodological evaluation compared the relative frequencies of adverse effects of amiodarone from trials and case reports.[264] The rank order of adverse effects from this methodological evaluation suggests that the frequencies of adverse effects may be different in clinical trials when compared to case reports.

4.3.6 Sensitivity analysis

There are no adverse effects where two or more separate meta-analyses have used exactly the same primary studies (i.e. had complete overlap of the included studies) to generate the pooled estimates. This reflects the different time periods, varying search strategies, and inclusion and exclusion criteria that have been used by authors of these meta-analyses, such that, even though they were looking at the same adverse effect, they used data from different studies in generating pooled overall estimates.

There were three adverse effects that were evaluated in more than one review; venous thromboembolism (VTE), gastrointestinal complications, and stroke. There was some, but not complete overlap of primary studies in: four separate reviews of venous thromboembolism (VTE) with hormone replacement therapy (involving three overlapping case-control studies from total of 31 observational studies analysed);[238, 244, 252, 272] three reviews of venous thromboembolism (VTE) with oral contraceptives (one overlapping RCT, six of 14 cohort studies, and two of 24 case-control studies);[241, 252, 260] three reviews of gastrointestinal complications with NSAIDs (involving six of 24 cohort studies and eight of 75 case-control studies);[242, 256, 271] and two reviews of stroke with oral contraceptives (involving one of seven cohort studies, and nine of 30 case-control studies).[246, 254]

For the sensitivity analysis, the older meta-analyses pertaining to venous thromboembolism (VTE), gastrointestinal complications and stroke were removed

so that the modest overlap could be further reduced, with only one review per specific adverse effect for the sensitivity analysis. The most recent meta-analyses for the RCTs comparisons with 'observational' studies (Canonico et al 2008 for venous thromboembolism (VTE) with hormone replacement therapy (HRT), Douketis et al 1997 for venous thromboembolism (VTE) with oral contraceptives) and for the comparisons of cohort and case-control studies (Agency for Healthcare Research and Quality 2002 for venous thromboembolism (VTE) with hormone replacement therapy (HRT), Bergendal et al 2009 for venous thromboembolism (VTE) with oral contraceptives, Henry et al 2003 for gastrointestinal complications with NSAIDs, and Chan et al 2004 for stroke with oral contraceptives) were used for analysis, yielding RORs that are very similar to the original estimates:

- 1.06 (95% CI 0.96-1.18) for the overall analysis of RCTs versus all observational studies
- 1.00 (95%CI 0.71-1.42) for RCTs versus case control studies
- 1.07 (95% CI 0.86-1.34) for RCTs versus cohort studies
- 0.94 (95% CI 0.87-1.02) for cohort versus case-control studies

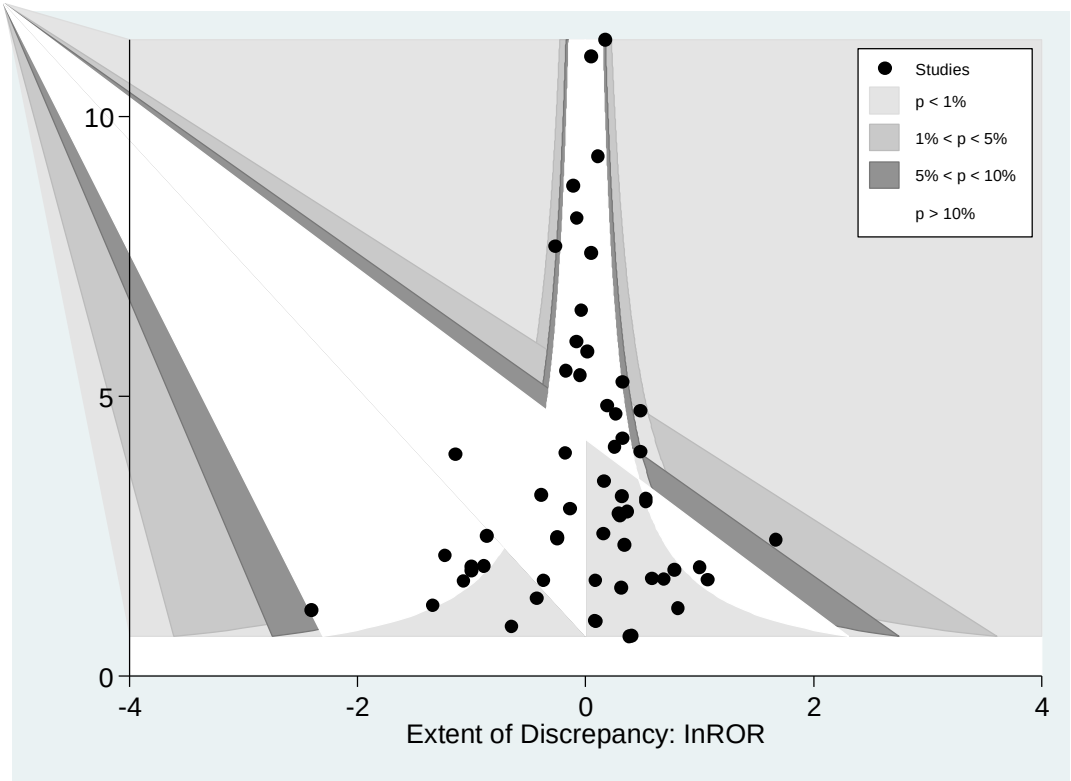
4.3.7 Funnel plots

4.3.7.1 RCTs versus all observational studies

In Figure 4.4 the magnitude of discrepancy in the RORs from each meta-analysis that compared RCTs with observational studies (cohort studies, case-control studies or studies grouped under the umbrella term 'observational studies) was plotted against the precision of its estimates (1/SE). Values on the x-axis show the magnitude of discrepancy, with the central Ln ROR of zero indicating no discrepancy or complete agreement between the pooled odds ratio estimated from RCTs and observational studies. The y-axis illustrates the precision of the estimates, with the data points at the top end having greater precision. This symmetrical distribution of the RORs of the various meta-analyses around the central Ln ROR value of zero illustrates that random variation may be an important factor accounting for discrepant findings between meta-analyses of RCTs as compared to observational studies. If there had been any systematic and consistent bias that drove the results in a particular direction for certain study designs, the plot of RORs would likely be asymmetrical. The vertically tapering shape of the funnel also suggests that the discrepancies between RCTs and observational studies are less apparent when the estimates have greater precision. This may support the

need for larger studies to assess adverse effects, be they RCTs or observational studies.

Figure 4.4 Funnel plot: Discrepancy between RCTs and observational studies in relation to precision of estimates



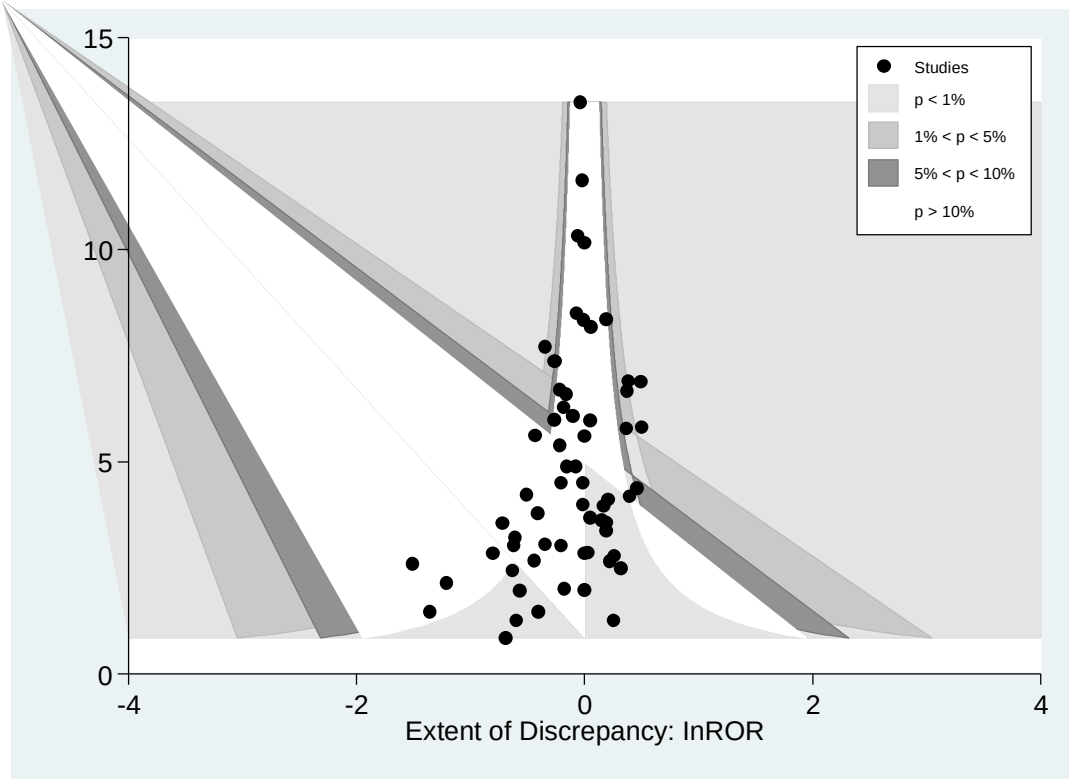
The forest plot in Figure 4.3 of RCTs and observational studies also demonstrates that there is no consistent systematic variation in pooled risk estimates of adverse effects from RCTs compared to observational studies.

4.3.7.2 Cohort studies versus case-control studies

Visual inspection of the Funnel Plot (Figure 4.5) and the results from the Egger test (p=0.02) suggests that there is an asymmetrical distribution of the discrepancy between cohort studies and case-control studies and that this asymmetry is statistically significant. There seem to be fewer instances where the meta-analyses of case-control studies gave lower estimates of harm and a relative predominance of studies on the left side of the plot showing that case-control studies frequently tended to give higher estimates of risk than those from cohort studies. The shape of this funnel plot would be consistent with the overall ROR estimate (0.94 (95% CI

0.87-1.01) described in Table 4.3 and Appendix B: Figure 15.4. In studies with greater precision at the top of the funnel plot, there did not appear to be as much discrepancy between study designs. Again, this may support the view that larger studies are needed to assess adverse effects.

Figure 4.5 Funnel plot: Discrepancy between cohort studies and case-control studies in relation to precision of estimates



4.4 Discussion

Most of the pooled results from the different study designs concurred in terms of identifying a significant increase or decrease, or no significant difference in risk of adverse effects. On the occasions where a discrepancy was found, the difference usually arose from a finding of no significant risk of adverse effects with one study design, in contrast to a significant risk of adverse effects from the other study design. This may reflect the limited size of the included studies to identify significant differences in rare adverse effects.

These analyses found little evidence of systematic differences in adverse effect estimates obtained from meta-analysis of RCTs and observational studies. The RORs did not suggest any consistent differences from meta-analysis of RCTs and observational studies. This interpretation is supported by the funnel plot, which shows that differences between the results of different study designs are equally distributed across the range. Some discrepancies may arise by chance, or through lack of precision from limited sample size for detecting rare adverse effects. The funnel plot shows that discrepancies may arise not just from differences in study design or systematic bias, but possibly because of the random variation, fluctuations or noise, and imprecision in attempting to derive estimates of rare events. There was less discrepancy between the study designs in meta-analyses that generated more precise estimates from larger studies, either because of better quality, or because the populations are more similar (perhaps because large RCTs capture a broad population similar to observational studies). Indeed, the adverse effects with discrepant results between different study designs were distributed symmetrically to the right and left of the line of no difference, meaning that RCTs and observational studies do not consistently over or under-estimate risk of harm as compared to another. It is likely that differences are attributable to other important factors, such as population and delivery of intervention. While there are a few instances of sizeable discrepancies, the pooled estimates indicate that overall (particularly where larger, more precise primary studies are available), meta-analysis of RCTs should yield adverse effects estimates that broadly match meta-analysis of observational studies.

Different types of observational studies may not obtain similar results. It was found that on average, meta-analysis of case-control studies tended to give slightly higher estimates of harm as compared to cohort studies. This finding was reflected in the asymmetrical shape of the funnel plot, showing that the direction of the discrepancies (as estimated by the RORs) was more frequently due to relatively higher estimates of harm from case-control studies than cohort studies. Alternatively, this could be interpreted as cohort studies being more susceptible to underestimating the extent of harm.

Although reasons for the few apparent discrepancies are unclear, specific factors that may have led to differences in adverse effects were discussed by the respective authors. The differences between observational studies and RCTs in McGettigan and Henry 2008's meta-analysis of cardiovascular risk were thought to

be attributable to different dosages of the anti-inflammatory drugs used.[269] Differences in Papanikolaou et al 2006[136] and Col et al 2005[249] were attributed to differences in exact definitions and study populations. The major discrepancy identified in Col et al 2005 on HRT and breast cancer is already well documented.[77, 98, 138, 177, 229-233] This discrepancy has also been explained by the timing of the start of treatment relative to menopause which was different between trials and observational studies. After adjustment, it has been found that the results from the different study designs no longer differ.[350, 351] Other methodological evaluations suggested that the nature of the study designs themselves were a factor that may have led to differences in estimates. For example, some stated that RCTs may record a higher incidence of adverse effects due to closer monitoring of patients, more sensitive and aggressive detection methods[270] and more thorough recording, resulting from regulatory requirements.[136, 271] Where RCTs had a lower incidence, it was suggested that this could be attributed to the exclusion of high-risk patients[249, 270] and possibly linked to support by manufacturers.[136]

Other well-known biases were discussed by the authors in relation to case-control studies. For instance it was suggested that case-control studies might overestimate risk because a more vigorous search for a drug history is likely in cases than controls (recall bias)[251] and doctors may be more likely to undertake diagnostic investigations in patients taking medications (diagnostic suspicion bias).[246] Lower estimates of risk in observational studies were often attributed to a healthy cohort bias,[183, 243, 249] the use of prescription drug databases with the limitation of leaving out over the counter drugs such as aspirin,[242, 277] and publication bias.[271, 346]

An explanation for the tendency towards slightly higher estimates of harm from case-control studies than cohort studies in this research is difficult to ascertain. However, there are a number of possible reasons. Firstly, this could be a spurious result as the values for the ROR do not reach statistical significance. Nevertheless, the asymmetrical funnel plot does demonstrate a fairly consistent discrepancy between cohort studies compared to case-control studies. One important factor here may be the greater statistical power of case-control studies to detect small, but significant risk of harm from rare adverse events. Another reason could be related to differences in susceptibility to bias amongst study designs, where bias in case-control studies may arise if cases and controls do not have equal opportunity for past exposure (or if there is bias in ascertaining exposure).[251] Nevertheless, case-control studies based on pharmacoepidemiological databases with pharmacy and

medical record linkage may not be susceptible to such recall bias. Conversely, bias in cohort studies can develop if the exposed and unexposed groups do not have equal opportunity for the adverse event happening (or being measured) and doctors may be more likely to undertake diagnostic investigations or recommend more frequent follow-up in patients taking certain types of medications.[246]

Equally, discrepancies between study designs could have stemmed from confounding, as a result of variation in characteristics of participants, timing and site of study, and definitions of exposure and outcomes. For instance, if one set of studies is carried out on a younger cohort of patients, with a lower drug dosage or with shorter duration of use, or is reliant on passively ascertaining adverse effects data,[136, 146, 178, 296] it might be expected that the magnitude of any adverse effects recorded would be lower. Nevertheless, the asymmetrical pattern of the funnel plot would tend to suggest a more systematic cause of discrepancy between study designs, rather than just chance variation in participants and definitions of exposure and outcome. The design of case-control studies may involve a greater extent of selection of risk factors for analysis and reporting, and significant findings may be more likely to be selectively published (and thus subsequently included in systematic reviews).

Finally, differences in observed and unobserved patient characteristics may have accounted for discrepancies between designs. The extent of statistical adjustment for potential confounders in observational studies is somewhat dependent on the variables measured in the primary dataset. Given the different starting points in data collection between case-control and cohort studies, the effect of unmeasured confounders may afflict either design to dissimilar extents.

4.5 Limitations

This systematic review of meta-analyses and methodological evaluations has a number of limitations. When comparing the pooled results from different study designs it is important to consider any confounding factors that may account for any differences identified. However, most of the methodological evaluations were not conducted with the primary aim of assessing differences in study design but were systematic reviews with some secondary comparative evaluation of study design embedded within them. It is not surprising, therefore, that many did not consider confounding factors. In many instances, it may also not have been possible to

control for numerous potential confounding factors as the primary studies may not have contained the required information. The small number of studies included (sometimes as low as one) may have not enabled statistical analysis such as meta-regression to be undertaken.

Another limitation of this overview is that it was constrained by information contained in the included evaluations, as it was not feasible to source and evaluate the thousands of primary studies contained in the meta-analyses. In each instance, the author's categorisation of the study design was used. However, the authors may not all have used the same definitions for each study design. This is a particular problem with the observational studies, where it is often difficult to decipher the methodology used in the primary study and categorise it appropriately. However, it was noted that most of the included reviews had passed DARE criteria or were from peer-reviewed sources i.e. both the primary study and systematic review had undergone peer review. Moreover, any misclassification is likely to be non-differential in impact, which should not lead to elevated risk estimates from any particular study designs. As an added precaution to help overcome this limitation, an analysis was carried out of RCTs compared to all 'observational' studies (either cohort studies, case-control studies or 'observational' studies), with a subgroup analysis based on different types of observational designs.

Another important limitation to this review is the potentially unrepresentative sample used. Systematic reviews with embedded data comparing different study designs may have been missed. The search strategy used was limited to a literature search to identify methodological papers whose primary aim was to assess the influence of study design on adverse effects and to a sift of systematic reviews of adverse effects (as a primary outcome) from the Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE). Nevertheless, it should be noted that the CDSR and DARE databases cover a large proportion of all systematic reviews and that systematic reviews in which adverse effects are included as a secondary aim are unlikely to present subgroup analysis by study design for the adverse effects data.

There was considerable heterogeneity between the comparisons of different studies, suggesting that any differences may be specific to particular types of interventions or adverse effects. It may be that particular types of adverse effects can be identified more easily via particular types of study designs.[2, 14, 73, 115]

However, it was difficult to assess the methodological evaluations by type of adverse effects. This would be of interest, given that the literature suggests that RCTs may be better at identifying some types of adverse effects (such as common, anticipated and short-term) more effectively than observational studies.

4.6 Conclusions

These findings have important implications for the conduct of systematic reviews of harm, particularly with regards to selection of a broad range of relevant studies. Although there are strengths and weaknesses to each study design, empirical evidence from this overview indicates that there is, on average, no difference between estimates on the risk of adverse effects from meta-analyses of RCTs and other study designs and slight differences (on average) between estimates on the risk of adverse effects obtained from meta-analyses of cohort and case-control studies. The differences between study designs are most apparent when the meta-analysis only has a few studies, suggesting that we should be particularly cautious in trusting single studies of rare harms. Instead of restricting the analysis to RCTs or certain study designs (which might lead to a potentially one-sided view), it might be preferable for systematic reviewers of adverse effects to evaluate a broad range of studies that could help build a complete picture of any potential harm and improve the generalisability of the review without loss of validity.

4.7 Summary

This review explores the concordance between estimates of the risk of adverse effects from different study designs.

51 meta-analyses or methodological evaluations were included.

Overall meta-analyses of RCTs tend to agree with meta-analyses of observational studies. However, there is a tendency for meta-analyses of case-control studies to give slightly higher estimates of harm compared to meta-analyses of cohort studies.

Chapter 5 Section B of the methodological overview: sources of information on adverse effects

5.1 Introduction

One aim of the systematic review process is to identify as many relevant studies addressing the question posed as possible. This process usually entails searching a range of different data sources, of which the selection is an important consideration for any systematic reviewer. The sources searched are likely to influence the amount and type of data retrieved.[14]

There are many potentially useful sources for information on adverse effects. In addition to those traditionally searched for effectiveness data, information on adverse effects can be identified from: specialist journals; bulletins and databases; drug monographs or summaries; trial registries; spontaneous reporting systems/post-marketing surveillance systems; or prescription-event monitoring (PEM) data. A summary of the types of sources for information on adverse effects with selected examples is contained in Appendix B: Table 15.3.

Despite the large number of potentially useful sources for information on adverse effects, a recent survey showed that most systematic reviews of adverse effects rely only on MEDLINE.[110, 352] This is probably due to familiarity, widespread availability, and a lack of knowledge of other sources. However, MEDLINE is unlikely to be the most definitive source of information on adverse effects.[31, 353]

Although MEDLINE may not be the most comprehensive source of information on adverse effects it is not known which data sources are most fruitful. A comparative evaluation of the different sources of information in identifying adverse effect data would, therefore, be useful for authors of systematic reviews. This chapter aims to systematically review existing methodological research studies that have investigated the impact of using different sources to identify information on adverse effects of healthcare interventions.

5.2 Methods

5.2.1 Inclusion criteria

A research study was considered eligible for inclusion if it compared the effectiveness of two or more data sources in identifying information on adverse effects of a healthcare intervention.

5.2.2 Data extraction

Information was collected on: the intervention and adverse effects search for; the data sources evaluated; the outcome measures used to compare data sources; and the results. The primary outcome was measures of the contribution from the sources tested, such as the number of relevant references retrieved and overlap with other sources. Secondary outcome measures included the cost of searching the data sources and the ease with which the records were retrieved.

5.2.3 Assessment of methodological quality

The included studies were assessed using the following questions:

1. Generalisability: Did the search queries cover a range of interventions and adverse effects? Was a large enough sample of relevant references used to compare the sources of information to make inferences about the results? (evaluated using 95% confidence intervals)
2. Database overlap: Were the number of unique relevant references and the total number of relevant references recorded for each data source?
3. Limitations of the search strategies: Were any of the limitations of the search strategies used to identify the relevant references taken into consideration? For example, relevant references may have been available on a particular database but limitations of the search strategy meant these references were not retrieved
4. Comparative outcomes: Were adequate comparisons made between the included sources of information?

5.2.4 Analysis

It was envisaged that the nature of the outcomes used here would not enable any formal statistical analysis to be carried out, although, the rank orders of the sources from the different studies were compared where possible.

5.3 Results

5.3.1 Included studies

Nineteen methodological evaluations met the inclusion criteria for this review (Appendix B: Table 15.4).[354-372] Seventeen of the methodological evaluations were published as full papers[354, 356-361, 363-372] and two were presentations.[355, 362]

5.3.1.1 Search strategies

The majority of the methodological evaluations (11/19) included more than one search for adverse effects data.[354, 356-358, 361, 364, 367, 369-372] Ninety-four separate searches were conducted for information on adverse effects, though four methodological evaluations (representing 36 searches) did not present the results of each search separately.[356-358, 372] In order to be able to compare the results of all 19 methodological evaluations, the combined results of the searches within each methodological evaluation were used wherever possible. In two instances, combining the results within a methodological evaluation was deemed inappropriate. One methodological evaluation contained searches for two different types of intervention - tooth extraction and a drug intervention - succinlycholine[371] and another included searches of different data sources.[369]

5.3.1.2 Types of interventions

Most of the methodological evaluations (16/19, 84%) included searches for named drug interventions.[354-362, 364-366, 368-371] Three methodological evaluations searched for natural products, such as herbal medicines[363, 372] or aromatherapy,[367] and one methodological evaluation included a search on tooth extraction (in addition to searches for a drug intervention).[371]

5.3.1.3 Types of adverse effects

Twelve methodological evaluations included searches for a wide range of adverse effects.[354, 355, 357, 360, 362, 364, 366-370, 372] Five methodological evaluations included searches for either named adverse effects,[359, 361, 365, 369, 371] such as pancreatitis,[365] hepatitis,[369] or hypoglycaemic coma,[361] or a group of adverse effects, such as gastrointestinal side effects,[359] or effects on the heart.[371] The other methodological evaluations did not specify the adverse effects included.[356, 358, 363]

5.3.1.4 Data sources included

The total number of data sources used to identify information on adverse effects was 61 (Table 5.1). The majority of the sources evaluated were bibliographic databases (25) or textbooks/drug monographs (17). The number of sources compared in each methodological evaluation varied widely between two and 24.

5.3.2 Excluded studies

Thirty-seven studies were excluded from this review (Appendix B: Table 15.5).[373-409] Eighteen compared data sources for drug information, such as drug interactions or chemical toxicology, but did not include adverse effects,[374, 377-381, 385, 386, 390, 393, 400, 401, 403, 405-409] eight included comparisons of sources of drug information, including adverse drug reactions, but did not present the results for identifying the information on adverse drug reactions separately.[373, 375, 376, 388, 389, 395, 399, 402] Eight were descriptive studies which contained no formal comparative evaluation of the source or sources discussed,[382, 383, 387, 392, 394, 397, 398, 404] two studies were conference abstracts with insufficient information to assess whether they met the inclusion criteria,[391, 396] and one study included only consumer health information sources.[384]

Table 5.1 Sources compared in the 19 included methodological evaluations

Source	Number of Methodological Evaluations
Internet Search Engines	
AltaVista	1
Full-text Databases	
Iowa Drug Information Service (IDIS)	5
Bibliographic Databases	
Adverse effects databases	
SEDBASE: Side Effects of Drugs*	1
TOXLINE (Toxicology Literature Online)	4
Pharmaceutical databases	
ADIS Inpharma	1
ADIS LMS Drug Alerts Online/ADIS	2
De Haen's Drugs in Research*	1
De Haen's Drugs in Use*	3
Derwent Drug File (previously RingDoc)	4
International Pharmaceutical Abstracts (IPA)	6
Pharma marketing	1
Pharmline	2
Generic databases	
BIOSIS Previews	3
CAB HEALTH	1
CINAHL	1
Core MEDLINE	1
EMBASE	9
ExtraMED	1
Health Reference Center (includes some full-text)	1
JICST-EPlus	1
MEDLINE	12
Mental Health Abstracts	1
National Technology Information Service (NTIS)	1
PASCAL	3
PsycINFO	1
Science Citation Index (SCI)	1
Uncover	1
Conference Databases	
British Library Inside Conferences	1
Conference Papers Index (CPI)	1
Referenced Summary Databases	
AltMedDex	1
Drug Information Fulltext	1
RUGDEX	1
Lexi-Comp Database	3
Micromedex	3
Micromedex Computerized Clinical Information Service (CCIS)	1
Natural Standard	1
Spontaneous Reporting Systems/Post-marketing Monitoring Data	
Internet	

Table 5.1 Sources compared in the 19 included methodological evaluations

Source	Number of Methodological Evaluations
Food and Drug Administration (FDA) website	1
Original Texts	
Bulletins/Newsletters	
Clin Alert	1
Reactions	1
Journals	
Handsearching	1
Textbooks/Monograph Collections	
Clinical Pharmacology	2
Epocrates Online Free	1
Epocrates Online Premium	1
Facts and Comparisons	2
Martindale The Extra Pharmacopoeia	1
Meyler's Side Effects of Drugs	1
Physician's Desk Reference (PDR)	1
Physician's GenRx	1
RxList.com	1
Side Effects of Drugs Annuals (SEDA)	1
Textbook of Adverse Reactions	1
Specialist Textbooks (electronic or paper)	
Natural Medicines Comprehensive Database	2
Physicians' Desk Reference for Herbal Medicines	1
The Complete German Commission E Monograph	1
The Lawrence Review of Natural Products	2
The Natural Pharmacist	1
Tyler's Honest Herbal	1
Other Sources of Published and Unpublished Information	
Authors/Experts	1
Industry	
Industry Submissions	3
In-house database	1
Reference Checking	1

Key * - database now closed

5.3.1 Summary of methodological quality

The methodological quality of the individual studies is summarized in Appendix B: Table 15.4.

1. Generalisability

The generalisability of many of the methodological evaluations was limited by the low number of relevant references studied and in some cases the limits on the type of interventions and adverse effects included.

2. Database overlap

Whilst most methodological evaluations compared data sources by the number of relevant references retrieved, only four fully described both the total number of relevant references and the unique relevant references,[359-361, 370] and five partially took account of total and unique relevant references.[357, 364, 366, 368, 371] This creates difficulty with the assessment of the overlap between sources and the value of their combinations.

3. Limitations of the search strategies

The majority of the studies did not take into account any limitations of the search strategies used to identify the relevant references. However, the precision of searches could be calculated for three methodological evaluations.[357, 370, 371] The precision in these studies was relatively high, suggesting that focused searches were undertaken. Three methodological evaluations[359, 360, 371] recorded the number of relevant references available in each database that were not retrieved by searching. The types of search strategies used varied considerably, as in some studies they were designed as part of a systematic review (using broad searches to maximise sensitivity) and in other methodological evaluations they were designed to answer specific questions and a more focused approach was adopted.

4. Comparative outcomes

Twelve methodological evaluations compared data sources by the number of relevant references. The other evaluations compared the number of case reports of adverse events,[365] the unique relevant publications,[366] or gave scores to the sources of information for ability to answer specific queries on adverse effects.[356, 358, 362, 363, 372]

The search functionality and cost of searching the databases was rarely considered. However, three methodological evaluations[356, 357, 369] mentioned cost implications, with one carrying out a cost analysis.[357] Three methodological evaluations recorded a score for the ease of use[356, 358, 362] and two recorded the time spent searching.[362,

[369] Results of these cost and ease of use elements will now be outdated as the cost and search interfaces for data sources change rapidly over time.

5.3.2 Database comparisons

5.3.2.1 MEDLINE

In four of the 12 methodological evaluations[355, 357, 359-361, 364-368, 370, 371] that included searches of MEDLINE, MEDLINE provided the highest number of relevant records. However, these evaluations either compared MEDLINE with International Pharmaceutical Abstracts (IPA) database only,[359] compared MEDLINE together with PASCAL against reference books,[361] or searched for non-pharmaceutical drugs.[367, 371]

The sources which retrieved more relevant references than MEDLINE were EMBASE (eight out of nine methodological evaluations),[355, 357, 360, 364, 366-368, 370, 371] Derwent Drug File (previously RingDoc) (three out of four methodological evaluations),[355, 366, 368, 370] TOXLINE (one out of four methodological evaluations),[355, 357, 360, 364] an internal database (one out of one methodological evaluation),[366] or industry submissions (one out of three methodological evaluations).[355, 360, 365]

5.3.2.2 EMBASE

Nine methodological evaluations (representing 10 case study searches) included EMBASE in their assessment,[355, 357, 360, 364, 366-368, 370, 371] and in eight of these searching EMBASE retrieved more relevant references than searching MEDLINE.[355, 357, 360, 364, 366, 368, 370, 371] In five methodological evaluations searching EMBASE retrieved the highest number of relevant references.[355, 357, 360, 364, 371]

The only databases which retrieved more relevant references than EMBASE in any search were Derwent Drug File (three out of four methodological evaluations),[366, 368, 370] MEDLINE (two out of nine methodological evaluations both of non-pharmaceutical drugs),[367, 371] and an in-house company database (one of one methodological evaluations).[366]

5.3.2.3 International Pharmaceutical Abstracts (IPA)

Six evaluations included International Pharmaceutical Abstracts (IPA),[354, 355, 357, 359, 367, 369] and in all but one[369] IPA retrieved either the lowest or joint lowest number of relevant records.

5.3.2.4 Iowa Drug Information Service (IDIS)

Five methodological evaluations included searches of Iowa Drug Information Service (IDIS).[354, 355, 357, 364, 369] In the three methodological evaluations that also included MEDLINE, EMBASE and TOXLINE – these databases retrieved more relevant references than IDIS. In three of the four methodological evaluations that compared IDIS with IPA, searching IDIS retrieved more relevant references than IPA.[354, 355, 357, 369]

5.3.2.5 Derwent Drug File

Three of the four methodological evaluations indicated Derwent Drug File's potential value over both EMBASE and MEDLINE.[366, 368, 370] The other methodological evaluation only carried out a search on Derwent Drug File for effectiveness studies and may have missed relevant references on adverse effects.[355]

In two of the four methodological evaluations that included searches of Derwent Drug File, Derwent Drug File retrieved the highest number of relevant references.[368, 370] In the other two methodological evaluations, one found that searching an in-house company database retrieved more references than Derwent Drug File,[366] and in another the searches on Derwent Drug File were for effectiveness studies only and not specifically for adverse effects data.[355]

5.3.2.6 TOXLINE

TOXLINE did not retrieve the highest number of relevant references in any of the methodological evaluations. However, in all searches TOXLINE provided at least one relevant reference and in at least two searches provided more relevant references than IDIS, PHARMLINE, PASCAL and IPA.

Although TOXLINE retrieved more relevant references than MEDLINE in one methodological evaluation,[357] this was not the case in the three other methodological evaluations, which included both MEDLINE and TOXLINE.[355, 360, 364]

5.3.2.7 BIOSIS Previews

In the three methodological evaluations that included BIOSIS Previews, it was found that MEDLINE and EMBASE retrieved more relevant records than BIOSIS Previews.[355, 357, 370] However, BIOSIS Previews retrieved more relevant records than IDIS, IPA, PASCAL and PHARMLINE in the two methodological evaluations that also searched these databases.[355, 357]

5.3.2.8 Other databases

Many of the databases were only searched in one or two methodological evaluations making any comparison between studies difficult. However, it is notable that these databases did not tend to retrieve a high number of relevant references, with the exception of an in-house industry database.[366]

5.3.2.9 Unique references

Seven methodological evaluations[357, 359-361, 366, 370, 371] recorded the number of unique relevant references from each data source for at least one search. However, all the databases within these evaluations produced unique records and there was little change in the comparative value of different databases when unique references were considered.

5.3.3

5.3.4 Comparisons of non-database sources

The majority of the methodological evaluations focused on bibliographic databases as sources of information. Other sources reviewed were: drug monographs from key textbooks (print and electronic); industry submissions; Internet sites (AltaVista, Health Reference Centre and Uncover); bulletins; reference checking; handsearching**;** personal communication; the Food and Drug Administration (FDA) website; and an in-house company database. All these sources retrieved relevant references, except for the website - Health Reference Centre,[367] and the tertiary

sources Physician's Desk Reference for Herbal Medicines and Tyler's Honest Herbal.[372]

5.3.4.1 Data from industry

The four methodological evaluations which included industry submissions or a company database also demonstrated the value of their inclusion. In two methodological evaluations, industry data retrieved the greatest number of adverse effects[365] or references on adverse effects.[366] In one methodological evaluation all of the data from industry were unique,[360] and in the other methodological evaluation industry submissions only retrieved less relevant records than MEDLINE and EMBASE out of the 23 sources evaluated.[355]

5.3.4.2 Micromedex versus Lexi-comp

Few of the non-database resources were included in more than one methodological evaluation and in some circumstances the numbers of relevant references or case reports retrieved were not recorded. This was particularly the case when drug monographs were evaluated. These sources tend to provide summary information and were more likely to be given a 'score' (such as on a scale of A to D or a points scale) or assessed in terms of answering specific questions regarding adverse drug reactions.[356, 358, 362, 363, 372] Although the overlap between sources included in the methodological evaluations was generally low, three methodological evaluations included both Micromedex and Lexi-comp and in each evaluation Micromedex scored higher than Lexi-comp.[356, 358, 362]

5.3.5 Comparisons of the data retrieved

As well as measuring the number of relevant references retrieved, other attributes of the references are important in terms of their impact on the identification and quantification of adverse effects. One methodological evaluation compared the number of different adverse effects identified from the included databases and the number of relevant references retrieved with an abstract.[368] However, this did not substantially alter the results.

One methodological evaluation[366] found that although a search of an in-house company database retrieved the most number of records, the majority of these were conference abstracts and that unique records identified in EMBASE tended to be

from non-English language sources. Conference abstracts often do not contain enough information to be included in a systematic review and non-English studies may be difficult or costly to translate.

5.4 Discussion

The lack of consistency of outcome measures and the use of different information sources in each methodological evaluation makes direct comparisons difficult. Some patterns in retrieval from the different sources did emerge, such as the relative value of EMBASE for adverse drug reactions and the potential value of Derwent Drug File over either MEDLINE or EMBASE.

It is not that surprising that searches in EMBASE tended to retrieve more relevant references for adverse drug reactions than MEDLINE, as EMBASE is a large pharmacological and biomedical bibliographic database renowned for its drug-related literature. However, it would be interesting to assess the value of this database and others in retrieving non-drug related adverse effects, especially as the only methodological evaluations to include non-pharmaceutical interventions found that MEDLINE retrieved more relevant references than EMBASE.[367, 371]

The relative value of Derwent Drug File over EMBASE and MEDLINE merits further analysis. Derwent Drug File covers aspects of drug development, synthesis, evaluation, manufacture, and use, including adverse effects. The one methodological evaluation that did not identify more records on Derwent Drug File than on MEDLINE and EMBASE only searched Derwent Drug File for effectiveness data, despite searching MEDLINE and EMBASE for both effectiveness data and adverse effects data.[355] Of the three methodological evaluations which indicated that searching Derwent Drug File retrieves more relevant records than other sources, one was produced by the providers of Derwent Drug File,[368] one only recorded unique records,[366] and two are over 15 years old.[366, 370]

5.5 Limitations

A major limitation of this review is the dearth of recent research identified in this area. This review did not incorporate a cut-off date, although it is realised that any papers regarding the value of different sources of information (such as databases) will quickly become out dated as electronic and paper sources are susceptible to

content change, closure/out-of-print, or the emergence of new information sources. For instance, the size of electronic databases (including the number and range of journals indexed) has increased dramatically since many of these methodological evaluations were published.

There are many other potentially useful sources of data not covered in these studies, particularly, Science Citation Index (SCI), database gateways (such as TOXICOLOGY http://library.dialog.com/bluesheets/html/bloT.html which searches 40 different databases), sources of conference proceedings, sources of post-marketing surveillance data (such as Vigibase),[410] industry clinical trial registries, specialist bulletins, textbooks and journals, discussion web sites,[397, 411, 412] contacting authors and citation searching. Nevertheless, review authors have highlighted concerns with the heterogeneous nature of information from Vigibase (the database of individual reports collected by the WHO Uppsala Monitoring Centre) as data are collected from many different National Centres with different criteria for reporting and acceptance. More recent studies have also identified problems with textbooks - for instance, only half of newly discovered adverse effects are documented in The Physicians' Desk Reference.[86] Variation in drug information from tertiary sources, such as reference books, has also been recorded[405] and many textbooks do not describe their methods for retrieving data on adverse effects or do not purport to be systematic or comprehensive and have been criticized for delays in incorporating adverse effects.[221]

Full-text searching was also rarely explored but may be useful for searching for adverse effects which are often addressed as secondary outcomes and not contained in the title, abstract or keywords of an article.

Although one methodological evaluation indicated the value of searching AltaVista,[367] other search engines such as Google or Google Scholar may be worth exploring. However, the majority of web pages (68%, 354/519) have been found to inadequately cover safety warnings,[404] and any evaluation of Internet search engines is problematic due to the inconsistency of repeating searches on the Internet and the fast pace of change in Internet search engines.

The majority of the methodological evaluations in this review used the number of relevant references from each database for comparison. However, this is not a sufficient criterion to evaluate the quality of a database. Other aspects such as

number of unique references, search interface, the size and accuracy of the database thesaurus, precision (or number needed to read (NNR)), overlap, updating time, cost of access, coverage (breadth of type of publications, years etc.), type of data retrieved, and the range and frequency of adverse effects information identified are also important. For instance, the completeness and currency of sources will affect their appropriateness for more recently developed healthcare interventions.

An analysis of precision may prove particularly useful as an indicator of the relative value of searching EMBASE. This database is notorious for over-indexing, which can lead to an unmanageable number of records retrieved.[413, 414] For instance, although searching EMBASE may retrieve the largest number of relevant records, it may also retrieve the most irrelevant records.

An assessment of the use of different data sources for information on adverse effects is complicated by database search functionality, updating time, and the reporting and indexing of adverse effects in database records. For example, it is difficult to standardise search strategies on all databases studied in a comparative analysis, as different keywords/indexing are used in each database. In addition, a database may cover a large proportion of the relevant literature on adverse effects, yet if this literature cannot be easily retrieved than the database may be of limited value. For example, Derry et al 2001 demonstrated that even searches of both MEDLINE and EMBASE could not feasibly retrieve all those RCTs on adverse effects contained in these databases due to a lack of appropriate terms in the title, abstract or indexing.[118] Only 66 of 107 RCTs which reported on adverse effects mentioned this in the title or abstract.[118] It has been suggested that the indexing problems found by Derry et al 2001 in RCTs in MEDLINE and EMBASE may also extend to non-randomised studies.[15]

Furthermore, when conducting literature searches the resource implications may need to be balanced against the potential yield of relevant information. This is particularly true when searching for adverse effects where data may be sparse and of limited quality and firm conclusions are difficult to reach. Comparing the cost of searching different data sources is difficult. One study compared the cost from different online databases of retrieving one relevant reference.[357] However, this study is relatively old and in recent years there has been a decline in users of online dial-up databases (such as those provided by DIALOG, Datastar or STN) and a sharp increase in users of databases through the Internet either freely or via

subscriptions. Other methodological evaluations simply listed subscription rates for the electronic information resources included.[356, 369] However, subscription rates vary depending on provider (e.g. OVID, EBSCO), licensing agreements (e.g. large site license), type of access (e.g. concurrent users), type of institution (e.g. private sector, charity), and format of access (e.g. CD-ROM, network) and are difficult to compare.

5.6 Conclusions

This review suggests that EMBASE, Derwent Drug File, MEDLINE and industry submissions may potentially provide the greatest number of relevant references for adverse effects information and that a range of sources may be useful in conducting a thorough search for information on adverse effects.

However, many of the methodological evaluations included in this review are over 10 years old and/or include a small set of relevant references for comparison with little consideration of the effectiveness of the search strategies used. A systematic evaluation of the value of an extensive range of different sources using a number of outcome measures with a large reference set of records is urgently required in order to provide guidance on the current sources available for information on adverse effects.

5.7 Summary

This review explores the relative contribution of different sources of information on adverse effects using 19 methodological evaluations.

Unfortunately many evaluations are outdated but evidence indicates that EMBASE, Derwent Drug File and industry data may be particularly valuable for adverse drug reactions. Although MEDLINE is also useful it rarely contributed the most number of relevant references.

Chapter 6 Section C of the methodological overview: database search strategies for information on adverse effects

6.1 Introduction

To identify as complete and unbiased a set of studies as possible and to strengthen the validity of the results of a systematic review, a methodical, reproducible, and thorough search for relevant research evidence is required.[22, 23, 415] Electronic bibliographic databases are the most commonly used source of information searched for systematic reviews of either effectiveness or adverse effects as they are a relatively efficient and accessible source of healthcare literature.[22, 23]

Searching bibliographic databases can be a difficult and time-consuming process and usually requires the skills of an information specialist or experienced searcher.[416-418] In order to search a database, a combination of text words (words in the title or abstract) and/or indexing terms (keywords assigned to bibliographic references) are usually selected. The choice of text words and indexing terms and how they are combined will affect the studies retrieved. The combined set of terms used in database searching is known as a search strategy. Search strategies need to be devised which balance *sensitivity* (the ability to identify as many relevant articles as possible) with *precision* (the ability to exclude as many irrelevant articles as possible). There is often a marked trade-off between sensitivity and precision, and a compromise between the two is needed. Although it is important not to miss relevant studies, retrieving a large number of irrelevant records is likely to increase the overall time and cost of doing a systematic review.[419, 420]

In recent years, research has been undertaken to improve search strategies to retrieve particular types of information, for example, to retrieve specified study designs (such as RCTs), or subject areas (such as public health), or specific populations (such as the elderly).[421] This research has led to the development of predefined search strategies, known as search filters or search hedges.[125, 421-423] A search filter is a predefined combination of search terms designed to retrieve information on a particular topic. The filter may be created and evaluated in various ways. For example, search terms in a filter may be subjectively derived by contacting experts in literature searching or the topic area. Alternatively, search terms may be objectively derived using word frequency analysis or statistical

analysis on a set of relevant records. The best combination of search terms can then be identified by running proposed search combinations and measuring how many relevant and irrelevant records are retrieved. Alternatively, word frequency or statistical analysis, such as logistic regression, can be used to suggest the best combination of search terms. Once a search filter has been developed, it may or may not then be tested against a different set of relevant records (a validation set).[421]

Methodological search filters have been developed for various study designs and have proved to be particularly useful for identifying effectiveness studies.[22, 23, 125, 126, 421, 424] Within The Cochrane Collaboration, for example, a highly sensitive search strategy is widely used for identifying reports of RCTs and has recently been updated.[22, 125] In PubMed the 'Clinical Queries' feature allows searchers to filter articles according to aetiology, diagnosis, prognosis, therapy or clinical prediction guides.[425] These filters have been developed using objective statistical analysis at McMaster University[423] and are revised periodically.

Although systematic reviews incorporating adverse effects have become increasingly important, there is little guidance on what constitutes the best search strategy.[116] The development of a search filter to identify information on adverse effects would be particularly useful given the problems of searching specifically for studies on adverse effects. This chapter aims to systematically review methodological studies that report on the development and evaluation of search filters to identify articles with information on adverse effects resulting from any healthcare intervention.

6.2 Methods

6.2.1 Inclusion criteria

Methodological evaluations were considered eligible for inclusion in this review if one of the main objectives was the evaluation of a search filter or search filters that could be used for retrieving articles with adverse effects data of a healthcare intervention from an electronic database. To be eligible, these methodological evaluations were also required to give at least one measure of the performance of the filters, such as, sensitivity/recall (proportion of relevant articles retrieved by the filter), precision (the number of relevant articles divided by the total number of

studies retrieved with that filter), accuracy (proportion of all articles that are correctly classified by the filter), numbers needed to screen/read (the inverse of precision), or specificity (proportion of irrelevant articles that were not identified by the filter).

6.2.2 Data extraction

Information was extracted on the databases and interface for which the search filter was devised, the type of intervention(s), the type of adverse effect(s) and the methods used to create/test the search filter, such as the source and size of the reference set of relevant records and validation set of relevant records. In addition, the outcome measures were recorded. Primary outcomes of interest were measures of sensitivity/recall, precision, accuracy, numbers needed to screen/read or specificity.

6.2.3 Assessment of methodological quality

The methodological quality of the included studies was assessed using published criteria adapted specifically for this review.[426] The included methodological evaluations were assessed using the following questions;

1. Were the tested and recommended search strategies/search filters described in sufficient detail to allow reproducibility? (i.e. were the exact search terms with relevant truncation, field limits and combinations presented and the search interface stated).
2. Were the tested search terms objectively derived? For example, by statistical analysis using word frequency counts comparing relevant and non-relevant records.
3. Was an adequate reference set of relevant records obtained? For example, did the set of relevant records used to develop the search filters cover a range of interventions and adverse effects, and was the set of records obtained from a range of resources (such as databases and handsearching) or a broad enough search strategy to capture a relatively comprehensive set of relevant records.
4. Did two or more researchers screen the retrieved records for relevant studies?
5. Were clear inclusion criteria for the reference set given? (i.e., in particular were details presented on the types of outcomes (adverse effects) included

and any exclusion criteria that may have implications for the search strategy, such as study design).

6. Were confidence intervals calculated for the performance estimates? Confidence intervals will enable the reader to assess the precise accuracy of the performance estimates, such as sensitivity and precision.
7. Were the results tested on a validation set of relevant records? (i.e. was the performance of the developed search strategy/filter tested on a different set of relevant records from those used to derive the search filter).

6.3 Results

6.3.1 Included studies

Three methodological evaluations met the inclusion criteria for this review (Appendix B: Table 15.6),[121, 360, 427-430] two were published as full papers and one was a conference presentation.[427, 428] Although this review was not limited by type of healthcare intervention all three methodological evaluations aimed to maximise the sensitivity of search strategies to identify papers on adverse effects of drug interventions.

The methodological evaluation by Wieland et al 2005 evaluated search strategies for a named specific adverse effect (breast cancer with oral contraceptives),[121, 429, 430] whereas the other two methodological evaluations by Badgett et al 1999 and Golder et al 2006 aimed to develop search strategies to capture all adverse effects or all serious adverse effects for a particular class of drugs.[360, 427, 428] All three methodological evaluations developed search strategies for use in MEDLINE and the methodological evaluation by Golder et al 2006 also included search strategies for use in EMBASE.[360]

6.3.2 Excluded studies

Seventeen studies were excluded from this review (Appendix B: Table 15.7). Eight contained no evaluation of the search strategies for adverse effects data that they proposed,[431-439] three were designed to identify sensitive search strategies for causation or aetiological studies, which although they might include adverse effects papers would also include papers on genes and environmental exposures,[440-442] two did not suggest any search filters but undertook co-word analysis (analysis of the

co-occurrence of words illustrated in a matrix),[443, 444] three were in a non-English language,[445-447] and one evaluated search strategies to retrieve systematic reviews of adverse effects, rather than primary data.[448]

6.3.3 Summary of methodological quality

The number of relevant records in the reference sets varied considerably (Appendix B: Table 15.8). The largest study was by Badgett et al 1999 and was based on several hundred records with a validation set of records. However, the precision of the searches could not be measured with this particular study design.[427, 428] The other two studies by Golder et al 2006 and Wieland et al 2005 tested their search strategies on only 84 and 58 records relevant records,[121, 360, 429, 430] and did not test the search strategies on a validation set of records (another set of relevant records) (Appendix B: Table 15.8**Error! Reference source not found.**).[121, 360, 429, 430]

Although each methodological evaluation used a number of sources to identify its reference set of records, it is possible that the original search strategies (despite searching a range of sources) failed to retrieve a substantial number of relevant records. The original search strategies might then have biased the results obtained. For instance, if the reference set is obtained using the term ‘adverse’ (among others) then this term is more likely to retrieve articles in the reference set and so more likely to have a higher sensitivity when tested on that reference set. In this way, evaluation of search filters is often in danger of becoming self-fulfilling. In order to overcome the potential bias of search strategies, handsearching can be used to identify a relevant reference set.[423]

Each methodological study was limited to a particular class of drugs, limiting the generalisability of their results. The derivation of search terms was not described in Badgett el al 1999,[427, 428] whilst Golder et al 2006 and Wieland et al 2005 used either terms derived from relevant records from a systematic review or terms used in previous studies.[121, 360, 429, 430]

Although none of the studies presented confidence intervals around their performance estimates, these could be calculated using the data reported (Appendix B: Table 15.6).

6.3.4 Comparison of recommended search strategies

All three methodological evaluations were able to create highly sensitive search strategies that had between 97% and 100% sensitivity. However, the results of the two methodological evaluations that also measured precision indicate that this can only be achieved with very poor precision (between 0.9% and 2.8%).[121, 360, 429, 430] This low precision indicates that in order to retrieve one additional article on adverse effects, between 36 and 125 records will need to be screened, which may be potentially unmanageable, given that full-text checking is often necessary.

The search strategy with the highest sensitivity in Wieland et al 2005[121, 429, 430] did not contain any text words for the intervention (oral contraceptives) and relied only on the adverse effect terms (breast cancer). Searching with terms for this intervention would have missed nine of the relevant references, as these records did not contain any terms for oral contraceptives in the title, abstract or indexing, despite being in the full paper. However, as the authors acknowledge, any search strategy that excludes terms for the intervention is likely to lead to unmanageable numbers of records for reviewers to sift.

The methodological evaluations by Badgett et al 1999[427, 428] and Golder et al 2006[360] both indicate the value of using floating subheadings (subject headings not attached to any indexing terms) for highly sensitive searches in MEDLINE. Badgett et al 1999[427, 428] suggests the use of the subheadings 'adverse effects', 'complications', 'poisoning' and 'drug effects', whereas Golder et al 2006[360] recommend the use of 'adverse effects', 'complications', and 'drug effects'.

Golder et al 2006[360] was the only methodological evaluation to attempt to develop a search filter for EMBASE. The suggested search strategy in Golder et al 2006[360] for EMBASE did not differ substantially from the suggested search strategy in MEDLINE, other than in the use of subheadings. While the MEDLINE search filter indicated the value of floating subheadings, the EMBASE search filter suggested that using subheadings attached to the named drug intervention (for example, vigabatrin/adverse drug reaction or vigabatrin/drug toxicity) performed better.

Badgett et al 1999[427, 428] and Wieland et al 2005[121, 429, 430] both included study designs in their filter, and Golder et al 2006[360] and Wieland et al 2005[121, 429, 430] both included specified known adverse effects. Text words (words in the title or abstract)

such as ‘adverse effects’, ‘side effect’ and ‘adverse reaction’ were only included in the filter by Golder et al 2006.[360]

6.4 Discussion

The complete search strategy for identifying papers in a systematic review on adverse effects is likely to depend on the inclusion criteria for the review. For example, if the inclusion criteria are limited to particular study designs then the search strategy may need to reflect this. Two of the included studies in this review recommend search strategies for adverse effects using not only adverse effects terms but also study design terms. Similarly, search strategies may need to be adapted in reviews designed to establish whether an association exists between an intervention and a suspected adverse effect, to assess the frequency of a known adverse effect, or to review the safety profile of an intervention. Depending on the question to be addressed, searches can be restricted to specific adverse effects as in the case of Wieland et al 2005[121, 429, 430] or searched using a generic search filter for all adverse effects, as in the case of Golder et al 2006[360] or Badgett et al 1999.[427, 428] The results here indicate that creating a highly sensitive search strategy with an acceptable level of precision is difficult, irrespective of whether the focus is on a specific named adverse effect, or a broad search for any (unspecified) potential adverse effects.

6.4.1 Use of adverse effects terms

The use of adverse effects terms alone may not be sufficient to identify papers with information on adverse effects, as adverse effects terms may not be in the title, abstract or indexing of some relevant papers. A study by Derry et al 2001[118] has also indicated that creating highly sensitive search strategies for information on adverse effects is problematic. They studied 107 trials that reported adverse effects data and assessed the number of papers that were indexed with relevant terms for adverse effects in MEDLINE and EMBASE, and how many titles or abstracts contained ‘adverse effects’ or related terms. They found that a combined search covering the two databases using both index and text word terms for adverse effects would have retrieved only 82 of 107 (77%) trials.[118] Other studies have also indicated the problems of searching on terms for adverse effects in the title and abstract.[119, 148, 449] One study found that of the adverse effects literature from one database, 64% (of 3,040 studies) contained adverse effects terms in the title,[119]

whilst two more recent studies found that adverse effects were mentioned in only 53% (130/243) and 63% (328/521) of abstracts of journal articles.[148, 449] A much smaller study on RCTs of drug therapy for dementia found that 94% (31/33) referred to harm in the title or abstract.[149] This may suggest that reporting varies depending on topic or study design.

6.4.2 Use of intervention terms

It is often assumed that search strategies should contain terms for the intervention under investigation. While this is probably true for clinical trials, the situation is different for observational studies that are focused on identifying the etiology or multiple risk factors behind a particular adverse outcome e.g. the risk factors for breast cancer. Wieland et al 2005[121, 429, 430] found that not all studies of adverse effects contained terms for one of the suspected drugs (oral contraceptives) in the bibliographic details. However, another study indicated that searching on drug terms in the title might be an effective method for searching for adverse effects, identifying 99% of papers.[119] It should be noted that this study was carried out in FDA Clinical Experience Abstracts and is now over 30 years old.

6.4.3 Use of subheadings

Some guidance on search strategies for adverse effects is currently available,[431-438] though the degree to which this is evidence-based is difficult to ascertain. Much of the guidance has tended to emphasize the usefulness of subheadings (such as 'adverse effects' or 'drug toxicity') in MEDLINE and EMBASE.[431, 432, 434-439] The results from Golder et al 2006[360] and Badgett et al 1999[427, 428] suggest that subheadings are useful.

6.5 Limitations

It is difficult to produce guidance on searching for information on adverse effects from the three studies meeting the inclusion criteria here. All three studies included a relatively limited set of studies on a specific class of drug and did not thoroughly test objectively derived search terms, although they do indicate the difficulties of searching for adverse effects and provide useful suggestions for structuring searches.

6.6 Conclusions

This review highlights the problems of achieving a balance between sensitivity and precision when searching for information on adverse drug reactions, and the lack of research in this area. Although high sensitivity can be achieved, this is likely to be associated with poor precision. Authors of systematic reviews may, therefore, need to take pragmatic decisions when creating search strategies for adverse effects and sacrifice sensitivity for precision. In order to compensate for this loss in sensitivity, searches of electronic databases could then be supplemented with other means of identifying papers, such as reference checking, contacting industry, and citation searches.

The limitations of the case studies identified by this review, and the large number of other search strategies that have been proposed but not yet empirically tested,[431-439] suggest that further research is needed to develop clear evidence-based guidance as to the most efficient means of creating search strategies for information on adverse effects.

6.7 Summary

This review presents on the results of three evaluations of published search filters for adverse drug reactions.

Current evidence suggests that search filters for specific named adverse drug reactions and unknown adverse drug reactions tend to record low precision and may miss relevant papers.

There is a dearth of research on search filters for adverse effects or adverse reactions: particularly useful areas for future research would include an analysis of subheadings (which is included in Chapter 13).

Chapter 7 Section D of the methodological overview: impact of publication status on the reporting of adverse effects

7.1 Introduction

A major issue in systematic reviews is the problem of publication bias.[22, 23] Potentially important data could be missing from a systematic review because of selective reporting and inadequate dissemination of results. If the missing data or unpublished results differ systematically from the published data, a systematic review may become biased, with an inaccurate assessment of the intervention's effects.[96] For instance, positive significant outcomes are more likely to be published than non-significant findings, and a systematic review based mainly on published literature might over-estimate the efficacy of the intervention.[450, 451] The impact of unreported or unpublished adverse effects data has not been fully clarified.[15, 89, 115]

Poor reporting of adverse effects is well-recognized. Published trials usually provide only brief descriptions of adverse effects, or report only statistically significant and life-threatening adverse effects.[452-457] Unpublished data might potentially have an important role in ascertaining information on adverse effects.[197] Company clinical trial reports and drug approval information (such as that prepared by the US Food and Drug Administration (FDA)) have been found to contain much more information on adverse effects than published papers.[21, 458-462] For example, although six pages were devoted to cardiovascular risk in an FDA statistical review on rofecoxib, only three lines were available in the New England Journal of Medicine article of the same trial,[21] and some adverse effects in an industry funded unpublished FDA data were not included in a peer-review journal publication of the same study.[459, 460, 463-465]

Given the considerable difficulties involved in retrieving unpublished data, and the uncertain yield, the impact of including unpublished safety data in safety reviews needs critical examination. This chapter aims to systematically review the methodological literature that has compared or analysed published versus unpublished adverse effects data.

7.2 Methods

7.2.1 Inclusion criteria

A methodological evaluation was considered eligible for inclusion in this review if it compared adverse effects of healthcare interventions according to publication status (i.e. published versus unpublished literature). Eligible articles were those that reviewed cohorts of published and unpublished studies and compared the quantitative reporting of adverse effects, in particular the frequency, rate, or risk of adverse effects. 'Published' articles were generally considered to be manuscripts that were found within peer-reviewed journals.

7.2.2 Data extraction

Information was collected on the interventions and adverse effects studied, the sources of published and unpublished data, and the outcome measures (such as effect size or number of cases) used to compare the information on adverse effects from studies with differing publication status.

7.2.3 Assessment of methodological quality

The following criteria were used to assess the validity of the included evaluations:

1) Confounding factors by study design: The results of published studies may differ from those of unpublished studies due to factors other than publication status, such as study design, type of participant, characteristics of the intervention, and methodological quality. Did the researchers select comparison groups that were equally matched – for instance, did the unpublished studies share similar aims, designs and sample sizes as the published ones? If not, were suitable adjustments made for potentially confounding factors?

2) Definition of publication status: Were explicit criteria used to categorise or define unpublished studies, and how did the investigators verify that a particular dataset was genuinely unpublished? For example, unpublished data may consist of information obtained from the manufacturers or regulatory agencies. Conversely, a broader definition of 'grey literature' may include information from websites, dissertations, policy documents, research reports, and conference abstracts.

3) External Validity and Representativeness: Did the researchers select a broad-ranging sample of studies (in terms of size, diversity of topics and spectrum of adverse effects) which were reasonably reflective of current literature?

7.2.4 Analysis

For methodological evaluations that measured incidence rates or number of cases of adverse effects only a descriptive comparison was presented. If the reviews presented risk ratios or odds ratio, a comparison of the magnitude of treatment effect was sought from unpublished studies versus that of published studies. The unpublished: published ratio was calculated simply by using:

> The pooled risk ratio for the adverse outcome from unpublished data, *divided by* the pooled risk ratio for the adverse outcome from published studies.

The estimated ratios of unpublished versus published treatment effects generated from each methodological evaluation were then used in a meta-analysis to summarize the overall difference in risk ratios between unpublished and published studies. The 95% confidence interval for the combined effect was estimated using a random effects model. The ratios for individual studies were weighted by the square of the standard error plus the variance between studies, using a least squares Normal approximation. Because adverse events are rare, odds ratios and relative risks could be treated as equivalent.[236]

In studies where the risk ratios for the unpublished data were not presented, these values were extrapolated from the risk ratio values of the published data and the combined (published and unpublished) risk ratio values using data analysis and statistical software (STATA). It was assumed that a fixed effects model had been used, as there was not enough information to do this assuming a random effects model so an estimate of the variance between studies could not be calculated. This was tested for the studies where the unpublished data were given.

If the methodological evaluation looked at more than one adverse outcome, ‘serious’ or ‘major’ adverse effects were selected. Alternatively, for studies looking at specific named adverse effects, the main analysis on the risk ratios was based on

the primary outcome of interest. A sensitivity analysis was conducted based on risk ratios of any secondary outcomes that were reported.

7.3 Results

7.3.1 Included studies

Ten methodological evaluations met the inclusion criteria (Appendix B: Table 15.9).[28, 264, 283, 458, 466-471] Published data tended to be retrieved from sources commonly used in systematic reviews, such as electronic databases and reference checking. However, one methodological evaluation used licensing applications to identify published trials.[458] Unpublished data was mostly obtained from regulatory authorities, although one methodological evaluation also solicited information from health professionals and the public as well as obtaining data from medical records[466] and one methodological evaluation contacted the manufacturer only.[469]

7.3.2 Excluded studies

Nine methodological evaluations were excluded from this review (Appendix B: Table 15.10).[197, 455, 472-478] Three compared published data and reported data for the same study, using either a primary reporting database,[455] Food and Drug Administration (FDA) submissions,[473] or data collected for Individual Participant Data (IPD) analysis,[478] three did not contain sufficient information,[472, 476, 477] one compared agreement of count rates of adverse effects from published studies and the FDA but did not present any numerical rates or frequencies,[474] one was a descriptive timeline review of published and unpublished studies,[197] and one reported preliminary findings of an included methodological evaluation.[475]

7.3.3 Summary of methodological quality

The methodological quality of the individual studies is summarized in Appendix B: Table 15.9.

1. Effect of Confounding factors

Only one methodological evaluation controlled for confounding factors.[468] Although this found differences between the results of published and unpublished trials, this was not the case after controlling for differences between the studies, such as quality and industry sponsorship (p=0.728). Here the differences in rates of adverse

effects were potentially due to variations in dose of the intervention, with high dose being associated with more than twice the rate of adverse effects as low or medium dose.[468]

2. Accuracy in classification of 'unpublished' data

Although all the methodological evaluations indicated where published and unpublished data were sought, only two studies provided clear details of the steps used in defining data as being 'unpublished'.[468, 469, 475] Researchers tended to classify unpublished data as that originating from regulatory agencies, but there is a risk of misclassification here if the data had been published in a journal that the researchers failed to identify. Overall, there was a potential risk of misclassification in most of the methodological evaluations.

3. External validity

All 10 methodological evaluations reviewed drug interventions but only two reviewed a broad range of drugs.[458, 466] Most of the methodological evaluations included a range of adverse effects. However, three were restricted to a specific adverse effect (dyspepsia,[468] thrombotic thrombocytopenic purpura (TTP),[28] or bradycardia,[283]) and one was restricted to a particular type of adverse effect (cardiovascular and thrombolytic events).[467] The number of included studies in each methodological evaluation varied between 11 and 1698. However, four methodological evaluations included less than 30 studies. Overall, the generalizability of the data would be rather limited due to the small range of interventions and adverse effects considered.

7.3.4 Completeness of reporting: published versus unpublished

Hemminki 1980[458] compared the percentage of trials that reported on adverse effects, and found that when compared to published trials, adverse effects data was found in a significantly greater proportion of unpublished trials submitted to the Finland regulatory authority.

7.3.5 Frequencies of case reports: published versus unpublished

Four methodological evaluations compared published case reports with unpublished reports.[28, 264, 283, 466] As part of a pharmacovigilance programme evaluating new safety alerts, Bennett et al 2005[466] looked at serious adverse reactions of 16 drug

interventions and found that the vast proportion of cases were from spontaneous unpublished reports in the FDA or the Centers for Disease Control and Prevention (CDC) database. Published case reports and cases from clinical trials made up only a small proportion of the total number of cases and in four instances there were no published cases of an adverse reaction despite unpublished data being available.

Similarly in Tramer et al 1997, which reported on case reports of bradycardia with propofol, more case reports were identified through national drug monitoring centres than from published case reports.[283] Cosmi et al 2000 was the only methodological evaluation that identified more cases from the published literature than the unpublished data, however, this study compared both published case reports and case series with unpublished case reports.[28]

Loke et al 2004[264] looked at the rank order for the relative frequencies of particular adverse reactions with amiodarone from published case reports as compared to the unpublished World Health Organisation (WHO) database. Published cases consisted most frequently of respiratory and nervous system adverse reactions, whereas thyroid and skin disorders were ranked as the more frequent adverse reactions in the unpublished data. According to Loke et al 2004[264] these differences may potentially arise from the publication process where authors and journal editors have a preference for manuscripts with interesting features.

7.3.6 Risk ratio estimates: published versus unpublished

Five methodological evaluations used meta-analytic techniques to combine the data from the published and unpublished studies.[467-471]

Three methodological evaluations presented risk ratios and confidence intervals for published studies and unpublished studies separately, as well as for the combined studies.[468, 469, 471] In each instance, to avoid the potential problem of duplicate data, only one set of results was included in the meta-analysis. In Hemminki 2000[467] the results for cardiovascular and thrombolytic combined were selected, as opposed to cardiovascular events alone. In Ross et al 1997[469] and Whittington et al 2004[471] the results for major/serious adverse effects were selected in preference to the more specific adverse effects of angina and suicide attempt or ideation.

Two methodological evaluations presented risk ratios and confidence intervals for published studies and for the combined studies, but not for unpublished studies.[467, 470] For these two methodological evaluations the risk ratio and confidence interval for unpublished studies which would be required to give the combined values was estimated (Table 7.1).

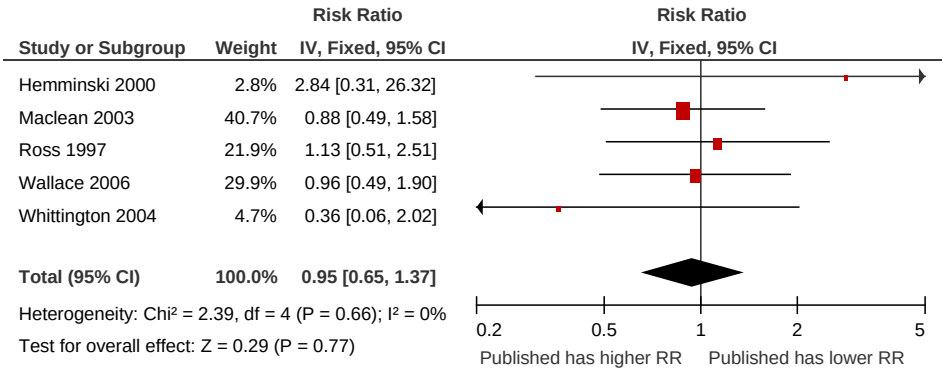
Table 7.1 Observed and estimated estimates of risk ratios with confidence intervals

Study	Observed risk ratio and 95% confidence intervals (CIs)	Estimated risk ratio and 95% confidence intervals (CIs)
MacLean et al 2003[468]	1.07 (0.70-1.63)	1.07 (0.69-1.64)
Ross et al 1997[469]	1.04 (0.64-1.71)	1.04 (0.63-1.70)
Whittington et al 2004[471]	1.87 (0.79-4.46)	2.00 (0.87-4.64)

When this method of extrapolation was checked for consistency against the three studies that had unpublished data available, the extrapolation yielded a good approximation to the actual figures. Two of these estimates were very close, with extrapolated values of 1.07 (95% CI 0.69-1.64) compared with actual values of 1.07 (95% CI 0.70-1.63)[468] and extrapolated values of 1.04 (95% CI 0.63-1.70) compared with actual values of 1.04 (95% CI 0.64-1.71).[469] However, there was a slight overestimate for the other study[471] where the extrapolated values were 2.00 (95% CI 0.87-4.64) compared with the actual values of 1.87 (95% CI 0.79-4.46). This may be due to the very large risk ratio and wide confidence interval for the published studies in this study (Figure 7.1). In these three instances where risk ratios were available, the actual reported data were used for the analysis rather than the extrapolated figures.

In Figure 7.1, the largest methodological evaluations gave a close approximation to a ratio of risk ratios of 1.0 whilst two smaller methodological evaluations gave estimates either side of the line of no effect (at 1.0) but with wide confidence intervals. There was no evidence of heterogeneity amongst the results of the methodological evaluations ($p=0.7$, $I^2=0$).

Figure 7.1 Meta-analysis of results from unpublished versus published studies



A ratio of risk ratios of 1.0 would imply that the estimates of effect from published and unpublished studies are the same. When pooled, the ratio of risk ratios, unpublished over published is estimated to be 0.95 (95% CI 0.65 to 1.37) (Figure 7.1). This suggests that there is no major systematic variation in risk estimates of adverse effects when studies were published or unpublished. A sensitivity analysis based on the use of risk ratios for secondary adverse effect outcomes from three studies yielded a pooled ratio of risk ratios of 0.94 (95% CI 0.64 – 1.40) similar to the main analysis.

Although the availability of unpublished adverse effects data did not change the direction or statistical significance of the risk, it is worth noting that owing to inclusion of a greater number of events the precision of the pooled estimate was increased, with narrower 95% confidence intervals (Table 7.2).

Table 7.2 Relative risks/odds ratios and confidence intervals for unpublished studies, published studies, and published and unpublished studies combined

Study	Unpublished studies relative risk/odds ratio and 95% confidence intervals (CIs)	Published studies, relative risk/odds ratio and 95% confidence intervals (CIs)	Published and unpublished studies combined relative risk/odds ratio and 95% confidence intervals (CIs)	Ratio of risk ratios/odds ratios, unpublished over published and 95% confidence intervals (CIs)
Hemminki and McPherson, 2000[467] Cardiovascular and Thrombotic	OR 4.65 (0.62– 35.15)*	OR 1.64 (0.65-4.21)	OR 1.97 (0.84-4.58)	OR 2.84 (0.31 – 26.32)
Hemminki and McPherson, 2000[467] Cardiovascular only	OR 4.35 (0.59 -32.21)*	OR 1.39 (0.48-3.95)	OR 1.78 (0.70-4.52).	OR 3.13 (0.33 – 30.06)
MacLean et al 2003[468]	RR 1.07 (0.70 – 1.63)	RR 1.21 (0.81-1.81)	RR 1.14 (0.85-1.53)	RR 0.88 (0.49 – 1.58)
Ross et al 1997[469] Major adverse effects	OR 1.04 (0.64-1.71)	OR 0.92 (0.49-1.72)	OR 0.99 (0.67-1.46)	OR 1.13 (0.51 – 2.51)
Ross et al 1997[469] Angina	OR 0.99 (0.50-1.97)	OR 0.92 (0.49-1.72)	OR 0.95 (0.60-1.51)	OR 1.08 (0.42 – 2.73)
Wallace 2006[470]	RR 1.92 (1.12 – 3.29)*	RR 2.0 (1.3-3.0)	RR 1.97 (1.42-2.75)	RR 0.96 (0.49 – 1.90)
Whittington 2004[471] Serious adverse effects	RR 1.87 (0.79 – 4.46)	RR 5.15 (1.17-22.56)	RR 2.55 (1.23-5.3)	RR 0.36 (0.06 – 2.02)
Whittington 2004[471] Suicide attempt or ideation	RR 1.23 (0.48 – 3.15)	RR 10.30 (0.58 -183.53)	RR 1.51 (0.62 – 3.69)	RR 0.12 (0.01 – 2.47)

* extrapolated values based on data given on published studies and combined studies

7.3.7 Quality of unpublished data compared to published studies

Although some methodological evaluations reported on the quality of the included studies, only three evaluations looked for differences in quality between the published and unpublished studies.[458, 466, 468] One methodological evaluation

compared the quality of the reporting of case reports and found that completeness of individual case reports of adverse effects varied depending on the source of data, with published case reports and reports from clinical trials being the most complete and MEDWATCH reports being the least complete.[466]

Three evaluations looked to see if methodological characteristics of study design were adequately reported.[458,468, 469] One found that the aspects of trial methodology were less well reported in FDA reviews as compared to published studies. Detailed descriptions of randomisation, allocation concealment and blinding were more frequent in the published studies.[468]

The methodological evaluation by Ross et al 1997 measured the mean quality score of studies on the Jadad scale.[469] Unfortunately the scores were not reported by publication status, however, the authors did note that the availability of far greater detail in the unpublished trials meant that these studies were rated as either of equal or higher quality than the published trials.[469]

The other methodological evaluation found no significant differences between published and unpublished trials of psychotropic drugs, in terms of numbers that are controlled, 'good' or the mean number of patients. However, in the same methodological evaluation some differences were reported among the small number of trials of non-psychotropic drugs. Published trials of non-psychotropic drugs were more likely to include a control group and more likely to include a larger mean number of patients.[458]

7.4 Discussion

This overview provides important information for systematic reviewers who are considering the inclusion of unpublished adverse effects data. The key finding is that unpublished studies do provide additional adverse effects data that is not otherwise covered in the published studies. However, there was insufficient data to conclude whether the inclusion of unpublished studies has a major impact on the results of meta-analyses. One methodological evaluation looked at proportion of trials with information on adverse effects, and found that a higher percentage of unpublished trials contained information on adverse effects compared to published trials.[458] This may reflect either that trials with information on adverse effects are less likely to be published, or selective reporting where information on adverse

effects is excluded from journal manuscripts. However, this may equally indicate that regulatory authorities require more detailed reports of adverse effects data than journal editors.

In this set of methodological evaluations, the addition of unpublished data did not lead to significant alterations in the risk ratio estimates for adverse effects. While the addition of unpublished data may not alter the effect estimates for adverse effects, the inclusion of unpublished data may enable reviewers to establish adverse effects estimates earlier,[470] and increase the precision of adverse effect estimates.[476] Improvements in precision may be particularly useful in situations where adverse effects are rare, such as the possible risk of suicide in patients taking antidepressants. Four methodological evaluations indicated that unpublished case reports can yield different information on the relative frequencies of potential adverse events.[28, 264, 283, 466] For those interested in case reports, limiting a review to published cases only could yield a very different picture of the safety profile.

However, concerns have been raised around the methodological and reporting quality of adverse effects data in unpublished studies, particularly as unpublished data are not peer-reviewed.[458, 467, 468, 479, 480] Although some evidence was identified that certain aspects of trial design or quality may be better reported in published studies[458, 468] evidence to the contrary was also identified.[469] The results of one methodological evaluation also suggest that published case reports have more complete reporting than unpublished studies, presumably because some peer reviewing and editing process has occurred during submission of the report[466] or that the authors took a different approach when preparing a regulatory notification to submitting a paper for publication. Other studies have also indicated problems in using unpublished data from regulatory agencies.[481] Problems include inconsistent terminology,[482] misspellings,[482] duplicate entries,[483] errors,[468] incomplete information,[482, 483] and discrepancies in the data.[473]

One potential problem related to publication bias but not covered in any of the methodological evaluations is that of multiple, or duplicate publications.[484] Repetitive publications could falsely elevate the number of case reports of a specific adverse effect.[485] There can be major difficulties in determining whether the ‘unpublished’ data had or had not already been reported in a journal article, and this issue was not fully addressed in most of the methodological evaluations.

The difficulties in identifying and accessing unpublished data should also be considered.[392, 454, 467, 468, 471, 480] Manufacturers have been unresponsive to requests for information on adverse effects,[471] or simply refused to give any data.[454] It took researchers 1.3 years and an appeal at the High Court in Finland to gain access to unpublished studies submitted with drug licensing documents,[467] and even when unpublished data is retrieved it can be difficult to decipher.[468] Information from authors may, however, be easier to obtain than from manufacturers.[486] Studies have indicated variable response rates of 24% (9/38),[392] 69% (356/519)[486] and 80% (12/15)[454] when authors are requested for unpublished safety data, although in the study by Chan et al 2005,[486] the contacted authors had recently published and the response rate could have been higher than in a systematic review.

The sources used in each methodological evaluation to retrieve published and unpublished data could possibly have influenced the results. In one methodological evaluation[466] unpublished case reports were sought from a wide range of sources including health professionals and the public. The sources used for unpublished data in all the other methodological evaluations were from drug regulatory authorities such as the Food and Drug Administration (FDA) and Committee on Safety of Medicines (CSM) or directly from industry. (In October 2005, the CSM was merged with the Medicines Commission, to form the Commission on Human Medicines (CHM). The Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) have an increasing profile within this organisation). Difficulties in differentiating between funding bias and publication bias are bought about as a result. Despite the potential for differences between studies (her than publication status) influencing the adverse effects estimates, only one of the methodological evaluations controlled for confounding factors, such as sponsorship.[468]

7.5 Limitations

There are a number of limitations to this review. Methodological evaluations are difficult to retrieve from electronic searches, and it is possible that review articles were missed where published and unpublished data were evaluated as secondary or tertiary outcomes. The diverse range of data sources in the methodological evaluations are a potential limiting factor when pooling the risk ratios of unpublished versus published, and this meta-analysis should be interpreted with caution, even though statistical heterogeneity was not detected.

From this review it is difficult to draw conclusions on the impact of other categories of literature that are distinct from peer-reviewed journals (for example, regulatory reports, websites, and conference proceedings). The methodological evaluations in this review did not focus on these sources, despite the increasing amount of evidence available in these forms. A comparative assessment of the association between such literature and the reporting of adverse effects would also be useful, particularly as this type of literature is difficult to search for in a systematic and reproducible way (for example, the Internet) and can be more difficult and expensive to retrieve (for example, reports and conference proceedings). Finally, there is a concern about the possibility of reporting or publication bias with respect to methodological evaluations, where investigators may have chosen not to write up their findings if they did not find any significant differences between published and unpublished studies.[487]

Given the above limitations, future methodological research should focus on checking the nature, quality and accessibility of adverse effects data from non-peer reviewed sources, such as regulatory authorities and pharmaceutical companies. This should clarify whether or not the yield is worth the additional efforts required to obtain such data. Finally, the impact of unpublished data on pooled risk ratio estimates could be more thoroughly assessed if the intention to compare data sources according to publication status was built in at the protocol stage of systematic reviews of adverse effects.

7.6 Conclusions

Although no clear evidence was found that data on adverse effects from published and unpublished data sources differ, there is some evidence that inclusion of unpublished data can provide more precise risk ratio estimates in a meta-analysis of adverse effects. Evaluation of unpublished case reports may also generate a different picture of the relative frequencies of specific adverse effects. However, the strength of these conclusions is limited by the lack of adjustment of confounding factors, particularly of study quality and industry funding.

Authors of systematic reviews who plan to include unpublished adverse effects data should take extra care in assessing the quality of the data, and in minimizing the possibility of data duplication.

7.7 Summary

This review includes 10 studies which compare published and unpublished data on adverse drug reactions.

Unpublished trial data may contain more complete adverse drug reaction data.

Frequencies of adverse drug reaction case reports may differ in published and unpublished sources.

Estimates of the risk of adverse drug reactions using ratio of risk ratios suggest that published and unpublished data do not differ.

It is unclear whether the quality of published adverse drug reaction information is better than unpublished data.

Chapter 8 Section E of the methodological overview: impact of funding source on the reporting of adverse effects

8.1 Introduction

In many countries manufacturers have a regulatory requirement to monitor the adverse effects of their drugs and may, therefore, be a useful source of additional information on adverse effects. A review of celecoxib concluded that clinical trial reports produced by or for manufacturers were an 'ideal source of information for systematic reviews and meta-analyses'.[462] Much of the data on adverse effects is contained in industry funded studies and this is likely to escalate as the percentage of studies funded by industry sources is increasing.[488]

Data from manufacturers is not always readily available[12] and may be classed as 'commercial in confidence' by the company owning the data. Furthermore, documents produced by manufacturers can be extremely long and difficult to navigate. In addition, studies produced by or for manufacturers may be subject to publication and selective reporting bias,[452, 489, 490] as adverse effects may be suppressed or omitted from published studies, particularly when they are not statistically significant,[452, 459, 460, 486] or results from only selected stages of the trial are presented.[490] Studies that find an increased risk of an adverse effect may never be published.[491]

There is a large body of literature that has identified an association between industry funding and better study outcomes.[489] These studies have tended to focus on effectiveness outcomes, with the primary aim of comparing the beneficial effects reported and the source of funding for a study. Better study outcomes, however, can be as a result of a more effective intervention or a lower adverse effects profile or a combination of the two. Research has indicated that industry sponsored meta-analyses yielded lower odds ratios for adverse effects than those reported by academic based meta-analyses.[21, 492, 493] However, this reporting of lower rates of adverse effects may not appear in primary studies. In palliative care and cancer care it has been suggested that pharmaceutical companies may report adverse effects more comprehensively than non-industry funded studies,[494] although the suppression of trial data on suicide with seroxat suggests that industry may withhold adverse effects data.[495] This research aims to systematically review the

methodological literature concerning the reporting of adverse effects and any potential association with source of funding (such as industry or non-profit organisations).

8.2 Methods

8.2.1 Inclusion criteria

A methodological evaluation was considered eligible for inclusion in this review if it compared the results or interpretation of reported adverse effects data according to funding source (for example**,** adverse effects data in pharmaceutical industry research versus data from non-profit organisations, or from one manufacturer versus another).

8.2.2 Data extraction

Information was collected on the selection criteria, interventions and adverse effects, the number, study design and funding sources of studies included in the methodological evaluation, and the outcomes used in assessing differences between studies.

8.2.3 Assessment of methodological quality

The following criteria were used to assess the quality of the existing methodological evaluations;

1. Confounding factors by study design: Did the researchers select comparison groups (i.e. data from different funding sources) that were equally matched? For instance, did the industry funded studies share similar aims, designs and sample sizes as those that were non-industry funded? If not, were there adjustments for potentially confounding factors that could affect the association between funding and the nature of the adverse effects data? The following confounding factors were looked for to see if they had been considered: study design; methodological quality; type of intervention and control intervention; sample size; disease area; type of adverse effects.
2. Missing data or misclassification: How often were the researchers able to reliably establish the source of funding for the reported data?

3. Blinding: Were the researchers aware of the funding source when they were judging the nature of the adverse effects data?
4. Validity and Representativeness: Did the researchers select an adequate sample of studies (in terms of size, diversity of topics and range of adverse effects) that were reasonably reflective of current literature?

8.3 Results

8.3.1 Included studies

Six methodological evaluations met the inclusion criteria (Appendix B: Table 15.11).[99, 496-501] All six were concerned with drug interventions, with five of the six evaluations limited to the adverse effects of a single agent or single class of drugs.[99, 498-501] Two methodological evaluations were limited to specific adverse effects,[99, 498] whereas the other methodological evaluations included any adverse effects. Only one methodological evaluation assessed funding source and reporting of safety data across a wide range of diseases and drugs.[496, 497] The number of studies included in the methodological evaluations ranged between 10 and 504 with only two methodological evaluations including more than 100 studies.[496, 497, 499]

Half of the methodological evaluations focused on adverse effects data within clinical trials[496, 497, 499, 500] and two included observational data.[99, 498] One had a mixture of reports of original research, reviews and letters.[501] Most methodological evaluations compared manufacturer funding with non-manufacturer funding, though one evaluation looked for differences in adverse effects data in research funded by competing manufacturers.[500]

8.3.2 Excluded studies

There were two methodological evaluations excluded from this review (Appendix B: Table 15.12).[247, 248, 502] One[502] contained duplicate data from an included methodological evaluation,[498] whereas another was excluded as the categories of funding source were unclear, but were unlikely to include industry funded studies.[247, 248]

8.3.3 Summary of methodological quality

Four of the methodological evaluations used some form of adjustment for potentially confounding factors, although the comprehensiveness of those factors varied (Appendix B: Table 15.11).[99, 496-499] A major constraint in assessing an association between source of funding and the reporting of adverse effects was the lack of information on funding source. Only two methodological evaluations described the number of studies not reporting any funding source, both these evaluations included only trial data and reported that 17.3% and 28.6% of studies did not disclose any funding source.[496, 497, 499] Blinding was reported in only two evaluations, one which tested the effect of blinding on a subsample of included studies and found that blinding did not impact on the results.[496, 497] Overall, the assessment of quality and validity showed that the Als-Nielsen et al 2003 evaluation, which included both studies not reporting funding source and considered blinding, was probably the most robust (Appendix B: Table 15.11).[496, 497]

Definitions of manufacturer associated funding varied, as did the methods and outcome measures used to assess the association between funding and adverse effects reporting, making it difficult to pool the results of the methodological evaluations identified.

8.3.4 Selective reporting

Als-Nielsen et al 2003 looked at a diverse range of RCTs and noted that trials funded by for-profit organizations were more likely to report adverse events (128/146, 88%) than trials funded by non-profit organisations (32/67, 48%).[496, 497]

8.3.5 Magnitude of risk of harm

It may be hypothesized that the risk of harm from the sponsor's product might be downplayed in industry funded studies. Three of the four methodological evaluations which measured the magnitude of the risk of adverse effects support this hypothesis.[99, 498, 499]

A subgroup evaluation from Kemmeren et al 2001's meta-analysis showed that the pooled data from industry funded studies yielded a weaker association between third generation oral contraceptives and venous thrombosis.[498] Similarly, Juni et al

2004's meta-analysis of cardiovascular events and rofecoxib showed that studies funded by Merck were associated with greater cardioprotective effects of naproxen (a comparator for rofecoxib), implying a lesser risk of harm from Merck's product (rofecoxib).[99] However, the weakness of this evidence is that they were post-hoc subgroup analyses, involving only a small number of studies (11 studies in Juni et al 2004[99] and 10 studies in Kemmeren et al 2001[498]) and subject to confounding, as no adjustments were made for any study design or patient characteristics.

Nieto et al 2007's evaluation of inhaled corticosteroids reported that statistically significant results for adverse effects were found less frequently in pharmaceutical industry funded studies, whereas non-industry funded studies were more likely to report significant harm.[499]

Conversely Als-Nielsen et al 2003 noted that a higher frequency of adverse effects tended to be found in the experimental arm of industry funded trials than trials funded by non-profit organisations.[496, 497]

8.3.6 Confounding factors

The differences between the results or conclusions of studies funded by industry and non-profit organisations could reflect other factors such as the chosen interventions and disease area, different study designs, methodological quality, and study size.

Nieto et al 2007 found that studies funded by industry differed from those not funded by industry and were more likely RCTs; multicentre; to use a parallel design in prospective comparative studies; to state that their primary objective was studying efficacy, to use lower dosages of the medication; and to have a larger sample size and shorter follow-up times. The studies also differed in the methods used to investigate adverse effects. Industry funded studies were more likely to limit the assessment to only non-specific clinical data (such as medical history) and/or laboratory data (such as blood count) or cortisol metabolism (such as plasma or urinary cortisol level), and less likely to assess other specific adverse effects such as growth (height) or bone metabolism (densitometry). An adjusted prevalence ratio as reported by Nieto et al 2007[499] 0.94 (95% CI 0.77 to 1.15) suggested that the difference associated with funding might be mediated by other variables in the analysis.

8.3.7 Interpretation of adverse effects data

The included studies revealed some interesting potential associations between funding source and the subjective interpretation or conclusions regarding adverse effects data. For example, Nieto et al 2007 found that authors of pharmaceutical company funded studies were more likely than authors of non-pharmaceutical studies to conclude that a drug was safe, even among studies that found a statistically significant increase in adverse effects.[499] Similarly, Rochon et al 1994 found that a manufacturer associated drug was often judged to be less toxic, even though this interpretation was not always supported by a test of statistical significance.[500] Finally, Als-Nielsen et al 2003 noted an association between favourable recommendations for a product and the manufacturer's sponsorship, irrespective of the actual magnitude of treatment benefit or safety results seen in the trial.[496, 497]

The study by Juni et al 2004[99] also indicated that conclusions might differ with studies funded by industry indicating larger protective effects of an adverse effect in the drug comparator. This enabled authors to conclude that the difference in adverse effects between the experimental group and the comparator was a result of a protective effect in the comparator group rather than an increased risk of adverse effects in the experimental group.

There is possible potential for error and bias when trying to judge whether the data interpretation and conclusions of a study are excessively favourable or not. Stelfox et al 1998[501] and Als-Nielsen et al 2003[496, 497] attempted some degree of blinding of the reviewers but none of the remaining four methodological evaluations used any blinding.

8.3.8 Competing manufacturers

Just as it may be hypothesized that studies by manufacturers with a financial interest in the intervention are more likely to have favourable conclusions, it may also be hypothesized that competing manufacturers are more likely to emphasize concern over safety of a rival intervention.[503] One methodological evaluation looked at this possible association,[501] finding that the reverse might be true and that authors who are neutral or supportive of the safety of an invention were more likely to have a financial interest with competing manufacturers. It would appear that

neutral or supportive authors are more likely to have a financial relationship with any manufacturer of the intervention or competing product. This study had some limitations, including a lack of a temporal analysis (it is not known whether support of the intervention preceded funding from the manufacturer), loose definitions of an association with industry funding, and failure in checking the appropriateness of the conclusions of the authors against the actual adverse effects data of the studies.

8.4 Discussion

This systematic review has identified somewhat mixed evidence surrounding the postulated link between industry funding and more favourable reporting of adverse effects data. Bearing in mind the limitations of this review (see below), it is only possible to draw tentative conclusions. Firstly, there is no strong evidence that funding source leads to selective reporting of adverse effects outcomes that favoured the sponsor's product. Indeed, Als-Nielsen et al 2003, probably the methodological evaluation with the strongest quality criterion, found that the opposite was true, with industry funded studies providing more complete reporting and higher rate of adverse effects for the experimental arm.[496, 497] Unlike non-profit organization funded studies, pharmaceutical companies hoping to submit a licensing application could be more focused on providing an accurate depiction of adverse events, as the data might be subjected to rigorous regulatory scrutiny. Indeed, it is possible that the information submitted to the regulatory authorities is less positive than that seen in the published articles.[504]

There is also no strong evidence that industry funded studies present a lower magnitude of risk of harm from the sponsor's product, although pharmaceutical trials have been accused of using design modifications to ascertain lower adverse effects. Such methods might potentially include: using lower doses of the intervention and higher doses for the controls; monitoring for adverse effects using open-ended or non-specific questions; the use of eligibility criteria and run-in periods to exclude patients prone to adverse effects; a focus on a single adverse effect or a narrow range of related adverse effects to obscure harms of the drug; repeated analysis of data until any extra risk of adverse effects disappears; and the choice of inappropriate comparators or interventions known to have few adverse effects.[27, 124, 146, 452, 490, 499, 500, 502, 505, 506]

This systematic review indicates that funding source may impact on the nature of the authors' interpretation and conclusions regarding the safety profile. However, the interpretation of adverse effects data relies not only on statistical significance, but also on subjective judgements on clinical relevance, preventability, and absolute risk.

8.5 Limitations

There were a number of methodological issues of concern with the evaluations included in this review. First of all, all the methodological evaluations were 'observational' in nature. While some of them had pre-defined objectives[496, 497, 501] others were post hoc or subgroup analyses. Confounding was a major problem in most of the methodological evaluations, where the baseline features (e.g. study design, patient population, primary objectives) of the industry funded studies might have differed from those of the non-industry funded studies. This is particularly apparent in Nieto et al 2007 where the observed differences became non-significant after adjustment for confounding factors.[499]

There is also the possibility of reporting or publication bias with respect to methodological evaluations.[487] Journal editors may look more favourably upon articles that show biased reporting of adverse effects in industry funded studies, or researchers who do not find any industry-related bias might choose not to submit their articles for publication. Equally, researchers finding evidence of industry funded bias may avoid publicizing the results so as not to jeopardize any industry funding ties that they might have.

The generalizability of the data is also contentious. It would be unfair to draw broad conclusions about bias in all industry funded studies when the data are limited to a few studies or to only a specific class of drugs. Moreover, reporting recommendations have changed over time, with tightening of regulatory requirements, and the publication of the Consolidated Standards of Reporting Trials (CONSORT) statement on harms.[32] Existing methodological evaluations have not taken into account temporal changes, or the availability of complete adverse effects data from unpublished company trial reports available from trials registries such as the GlaxoSmithKline Clinical Trials Registry (http://ctr.gsk.co.uk/welcome.asp) and ClinicalStudyResults.org (www.clinicalstudyresults.org).

Failure to accurately classify funding source is the most prominent weakness in the methodological evaluations. In Nieto et al 2007's evaluation, 87 studies (17.3%) were categorised as non-industry funded, despite there being no information on funding source.[499] Misclassification of such a large number of studies could have a major influence on the direction and magnitude of any link between funding and adverse effects data. The largest methodological problem though, lies with the difficulty in verifying authorship and the reliability of financial declarations in published papers. Two recent papers have highlighted problems with ghost authorship and inaccurate financial disclosures (e.g. not disclosing a financial interest in one article, but declaring industry funding in another publication).[507, 508] If studies categorized under non-industry funding were misclassified and were actually industry funded, this would dilute the strength of any argument that non-industry funded studies provided less-biased reports of adverse effects.

A considerable amount of subjectivity was involved in trying to determine whether the interpretation and conclusions of a study were biased towards the sponsor's product. Reviewers who were critical of the pharmaceutical industry might have taken a harsher view in finding fault with industry funded studies, while those supportive of the industry might have been less likely to judge the presence of bias. Unfortunately, blinding and inter-rater reliability were key parameters that were seldom specified by the methodological researchers.

8.6 Conclusions

Industry funding may not be a major threat to bias in the reporting of the raw adverse effects data, though bias might be introduced in the interpretation and conclusions of the industry funded studies.

The limitations of the included methodological evaluations in this review suggests that further research is required in this area in order to draw any firm conclusions on the impact of including or excluding industry sponsored studies in systematic reviews of adverse effects. In the meantime efforts should be made where possible to include all relevant studies and be explicit about the sources of funding of included studies.

8.7 Summary

This review of six methodological studies in the literature comparing reporting of adverse effects and funding source indicates that there is no strong evidence that funding source leads to selective reporting of adverse effects. However, funding source may impact on the author's interpretation and conclusions.
Additional information to that in the published literature can be obtained from industry funded data.

Chapter 9 Section F of the methodological overview: other issues related to the retrieval of information on adverse effects

9.1 Introduction

As well as the potential for publication bias and industry funding bias, there are other potential sources of bias that may impact on the reporting of adverse effects, including that from the author or journal editor, or by language, country setting or publication year. The potential bias from these sources may have an impact on the methods used to retrieve information on adverse effects. For example, limiting to core MEDLINE will help identify only those articles from high-impact factor journals, contacting clinicians in the field is more likely to retrieve articles by the clinicians themselves, and searches can be limited by country settings, language or date ranges.

This section of the review aims to systematically identify research studies that has investigated the impact of different sources of information on adverse effects and has not been covered elsewhere in this review (Chapters 4 to 8).

9.2 Methods

9.2.1 Inclusion criteria

A research study was considered eligible for inclusion in this review if it compared the impact of different sources of information on adverse effects and was not covered in the other sections of this review (Chapters 4 to 8).

9.2.2 Data extraction

Information was collected on the interventions and adverse effects studied, and the number and type of included studies. The main outcome measure was an estimate of the impact on the pooled estimates of adverse effects.

9.2.3 Assessment of methodological quality

The following criteria were used to assess the quality of the existing methodological evaluations;

1. Confounding factors by study design: Did the researchers select comparison groups (i.e. similar characteristics of the populations and interventions studied) that were equally matched? For instance, did the researchers select comparable studies in terms of study design, dose of drugs, and patient age structure? Did they use similar methods for ascertaining adverse effects data from participants? If not, were there adjustments for potentially confounding factors that could affect the association between the selected factors and the nature of the adverse effects data? The following confounding factors were looked for to see if they had been considered: type of study, characteristics of participants, methodological quality, type of intervention and control intervention, sample size, disease area, type of adverse effects and funding source.
2. Blinding: Were the researchers aware of the potential influencing factors when they were judging the nature of the adverse effects data?
3. Validity and Representativeness: Did the researchers select an adequate sample of studies (in terms of size, diversity of topics and range of adverse effects) which were reasonably reflective of current literature?

9.3 Results

9.3.1 Included studies

Only three methodological evaluations met the inclusion criteria,[247, 248, 301, 509, 510] two investigated the reporting of adverse effects of surgical interventions,[247, 248, 301] and one of these also carried out an analysis of a drug intervention (Appendix B: Table 15.13).[247, 248] The other methodological evaluation looked at diagnostic screening.[509, 510] All recorded the impact of author affiliation on the reporting of adverse effects, while two recorded the impact of year of publication[247, 248, 301] and one looked at country setting, and impact factor of journal publication.[247, 248]

9.3.2 Excluded studies

There were no excluded studies for this section of the review.

9.3.3 Summary of methodological quality

1. Confounding factors by study design: All the methodological evaluations reported on the influence of at least one other factor (such as study design) in addition to the factors (such as author affiliation) included in this review. Chou et al 2007 looked at a large number of factors including quality criteria, study design factors, severity of adverse effects and demographic or risk factor variables.[247, 248] Jorgensen et al 2007 only looked at one other factor, type of article (such as original research or editorial),[509, 510] and Rothwell et al 1996 looked at author affiliation, year of publication and whether studies were performed prospectively or retrospectively, and carried out a multiple regression analysis of these factors along with author affiliation.[301]
2. Blinding: Blinding was only reported by Jorgensen et al 2007. In this study, blinding would have been particularly important given the subjective nature of the outcomes measured.[509, 510]
3. Validity and Representativeness: The generalisability of all three methodological evaluations was poor. All were limited to a named intervention and two limited to named adverse effects.[247, 248, 301] In addition, the methodological evaluation which included a drug intervention was limited to only 16 RCTs.[247, 248]

9.3.4 Authorship

The two methodological evaluations which looked at the association between authorship and the reporting of adverse effects in surgical papers both identified significantly lower risks of complications in those studies with a single surgeon as the author,[247, 248, 301] against studies with neurologist or physician as an author[301] or at least one non surgeon as an author.[247, 248] In addition, Chou et al 2007 reported significantly lower risks in studies with multiple surgeon authors than those with at least one non surgeon.[247, 248] The methodological evaluation that looked at the reporting of adverse effects in diagnostic studies found similar results, with authors working in screening reporting less adverse effects and being less likely to acknowledge over-diagnosis.[509, 510]

9.3.5 Other factors

The study by Chou et al 2007 found that journals with a high impact factor reported higher rates of adverse effects for both surgical and drug interventions and that the rates of adverse effects were not significantly different by publication year or country setting.[247, 248] Rothwell et al 1996 also found no difference in the reporting of adverse effects by publication year once they had controlled for differences in study methodology and authorship.[301]

9.4 Discussion

The difference between reporting of adverse effects by surgeons and non-surgeons could be attributable to a number of factors, such as scientific fraud, differential diagnosis by surgeons and non-surgeons, a bias towards surgeons with a better success rate undertaking research, or publication bias by surgeon authors.[301] Similarly, the difference in the reporting of harm by authors working in screening could also be attributed to scientific fraud, better ascertainment of adverse effects by authors not working in screening, or publication bias.

If studies by surgeons and studies by authors working in screening were more likely to report lower risks of adverse effects this would lead to systematic reviewers relying heavily on contacting surgeons or clinicians in diagnosis for relevant studies to identify a lower risk of adverse effects.

The lack of difference in the reporting of adverse effects by publication year and country setting is reassuring to those reviewers who have restricted their searches with date limits or country of origin. Limits or emphasis on studies from particular countries can occur at the search stage of a systematic review, either directly by limiting search strategies, or indirectly by using language restrictions or databases with a particular country or regional bias. For example, MEDLINE originates in America and has a higher proportion of American studies than EMBASE, which originates in Europe. Even more obviously, LILACS is restricted to Latin American and Caribbean literature.

Higher reporting rates in journals with a high impact factor merits further investigation, as this may be indicative of a form of publication bias. Articles with more significant results might be more likely to be accepted in high impact journals,

or authors might perceive their results to be of greater interest and send them to high impact journals. These results suggest that systematic reviewers that rely heavily on handsearching high impact journals or limiting their searches to databases such as core MEDLINE might obtain higher rates of adverse effects than those systematic reviews with wider search criteria.

9.5 Limitations

The main limitations of this review are the lack of blinding and generalisability within the included studies. The low number of included studies in this chapter limits the generalisability of these findings even further.

9.6 Conclusions

Author affiliation and journal impact factor may be important predictors of the reporting of adverse effects. Authors of systematic reviews need to be cautious in over-reliance on contacting clinical experts in the area, such as surgeons or those involved in screening, or limiting their review to particular journal titles (through handsearching or databases such as core MEDLINE).

9.7 Summary

This review included three studies investigating the impact of author affiliation on the reporting of adverse effects, two studies recording the impact of year of publication, one recording the impact of country setting and one the impact of journal publication impact factor.

Surgeons and those working in screening reported fewer adverse effects than other authors, journals with a high impact factor reported higher rates of adverse effects, and there was no difference in the reporting rates of adverse effects by country setting or publication year.

Chapter 10 Methods used to search for adverse effects data in systematic reviews: 1994 to 2011

10.1 Introduction

Chapters 4 to 9 highlight the methodological challenges in conducting systematic reviews of adverse effects. For instance, the complexities of using search filters to retrieve adverse effects data are apparent in Chapter 6. The relative value of a range of different databases and other sources for information on adverse effects is shown in Chapter 5. The research from Chapters 4, 7, and 8 demonstrate the potential value of non-RCTs, industry data, and unpublished data. Given the empirical evidence from Chapters 4 to 9 on where and how to search, which study designs and types of data to include, and the value of searching for unpublished and industry funded data, it is interesting to assess how authors of systematic reviews of adverse effects currently undertake the search process. Any gaps between what methodological research indicates should be done and current practice in systematic reviews of adverse effects can then be identified.

Previous research has indicated deficiencies in the search quality and reporting of search strategies in systematic reviews,[511-537] including systematic reviews of adverse effects.[110, 352, 538, 539] It may be hypothesized that the research developments in search methodology identified in Chapter 5, on sources of information for adverse effects, and Chapter 6, on electronic search strategies, could have led to improvements in the search techniques used within systematic reviews. Research has indicated improvements over time in the overall quality of effectiveness reviews,[107, 540] and in the search methodology in dental systematic reviews,[541] but research on systematic reviews of adverse effects has not examined any time trends with respect to search quality and reporting.[110, 352, 538, 539] The research in this chapter aims to describe current practice in retrieving information on adverse effects for inclusion in systematic reviews and to summarize trends over the time period 1994 to 2011. This will give an indication as to whether methods used are becoming more in line with the research available in Chapters 4 to 9, give an indication of the breadth of methods used, and identify potentially useful techniques that can then be tested in future research on the retrieval of information on adverse effects.

10.2 Methods

10.2.1 Search strategy

Systematic reviews of adverse effects were identified by screening all records published since 1994 in the Cochrane Database of Systematic Reviews (CDSR) (via The Cochrane Library, Issue 6:2011) and the Database of Abstracts of Reviews of Effects (DARE) (via the Centre for Reviews and Dissemination (CRD) website, June 2011). No search strategy was implemented, as previous research has indicated that even very broad search strings would miss relevant records.[448] These databases were chosen because they are the most accessible major collections of systematic reviews of healthcare interventions. DARE is compiled through rigorous monthly searches of bibliographic databases, including MEDLINE and EMBASE, as well as handsearching of key journals, grey literature, and regular searches of the Internet.[542, 543] CDSR contains all Cochrane reviews, including new and updated reviews.

10.2.2 Inclusion/exclusion criteria

A review was included if the primary aim was to evaluate an adverse effect or effects, known to be, or suspected to be, associated with an intervention, regardless of whether the review author's hypothesis or conclusions stated that the intervention increased or reduced the outcome. Articles that investigated the complete safety profile of an intervention were included if this was their primary aim. The author and another researcher independently screened titles and abstracts and selected full articles for inclusion. Any discrepancies between the researchers were resolved by discussion and consensus.

10.2.3 Data extraction

Pre-defined descriptive data on review methodology were abstracted using a standardised form created in Microsoft Access 2007. For each review, baseline data were collected on: the year of publication; the types of intervention (for example, drug intervention, diagnostic procedure or surgical technique); the type of adverse effects evaluated (for example, pre-specified named adverse effects or generic adverse effects); and the types of study design included (for example, randomised controlled trials (RCTs) or cohort studies).

Details were extracted on how information on adverse effects was retrieved by the authors of the reviews, namely:

- which databases were searched, for example, MEDLINE or EMBASE
- which interfaces (software) were used, for example, PubMed, OVID, or SilverPlatter
- any other sources of information consulted or additional approaches to information gathering employed, for example, reference checking, handsearching, or contacting experts.

Details of search strategies were also extracted:

- on the category of search terms used from the standard categories of patient group, disease or condition, intervention, comparator and outcome (PICO) used for clinical effectiveness search strategies[22, 23]
- in which database fields such as title, abstract, or indexing the terms were searched
- whether any synonyms were used for text word searches and whether or not truncation was used
- whether a search filter was applied, for example, to identify a particular study design such as RCTs
- whether any language or date restrictions were applied
- whether the search strategy was reproducible.

Searches were judged to be reproducible if the review authors provided details of the combinations of search terms used, including Boolean logic, field restrictions, truncation, and search filters, as well as any date or language restrictions applied.

Finally, the qualifications of the searcher (for example, information scientist/librarian or other), the number of records identified by the searches, and the number of studies included in each review were recorded.

10.2.4 Analysis

Data were categorized and a descriptive summary presented. A record was made of changes in: the number and proportion of systematic reviews of adverse effects published; the study designs included in the reviews; the number and type of sources searched; the breadth or quality of the search strategies employed; date or

language restrictions applied to the searches, reproducibility of the search strategies employed; and any relationship between the quality of the searches and the qualifications of the searcher. Trends across time were investigated using a linear regression model, where applicable, and statistical significance was calculated.[544]

The results were then compared, where possible, with other surveys on the retrieval of information for systematic reviews. In order to facilitate meaningful comparisons with this survey, surveys were selected that evaluated similar parameters, such as similar databases and sources searched in the sample of reviews, details of reproducibility of search strategies, and presence or absence of language and date restrictions. Comparisons could not be made with surveys that simply reported on whether 'adequate searches' were undertaken with no further details.

10.3 Results

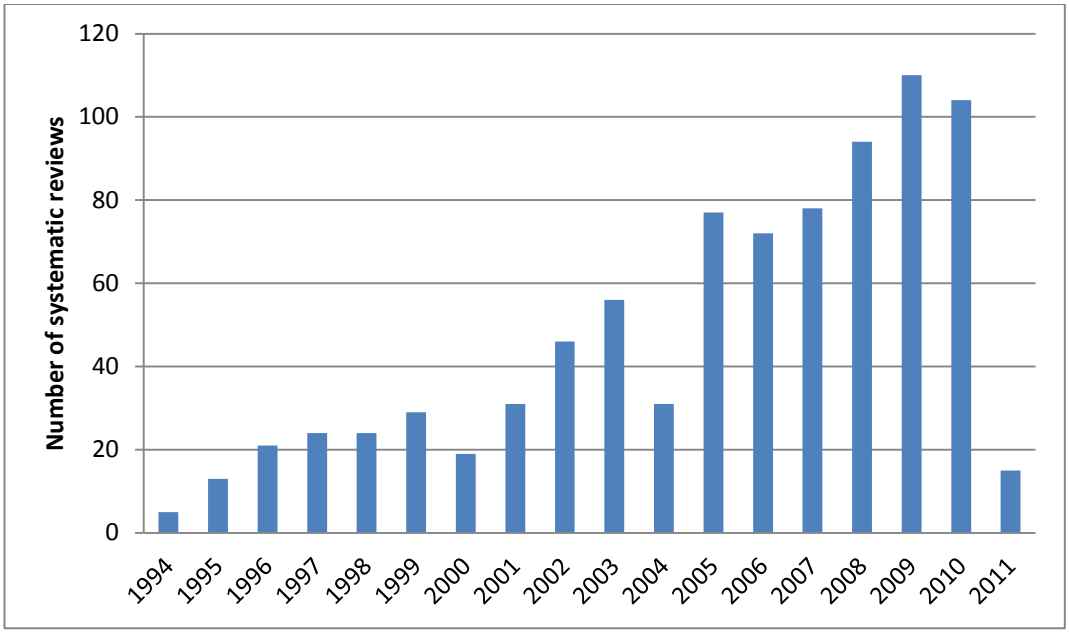
From 4656 Cochrane reviews and 11062 DARE abstracts screened, 918 full reports were retrieved and 849 reviews met the inclusion criteria (799 from DARE, 50 from CDSR). The reviews were dated from 1994 to 2011. Overall 5% (849/15812) of reviews in both databases focused on adverse effects, 1% (50/4656) of Cochrane reviews and 7% (799/11062) of DARE reviews. The number of reviews focusing on adverse effects has increased over time (trend P<0.001) (Figure 10.1 and Appendix C: Table 15.14) in line with the overall trend of increasing numbers of systematic reviews being published, such that the proportion of total reviews of adverse effects from CDSR or DARE has remained relatively stable.

10.3.1 Characteristics of the included studies

10.3.1.1 Types of interventions studied

Throughout the time period studied, the included reviews are dominated by those evaluating the adverse effects of drugs (73%). Only a few studies examined surgical or dental procedures (13%), physical interventions such as acupuncture (7%), or diagnostic or screening interventions (1%) (Appendix C: Table 15.14). The most common interventions studied were, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (59 reviews), Hormone Replacement Therapy (HRT) or contraceptives (mostly hormonal) (51 reviews each), corticosteroids (26 reviews), and antidepressants (25 reviews).

Figure 10.1 Number of systematic reviews of adverse effects 1994-2011



*2011 is incomplete as searches were carried out in July 2011 and it takes time for all reviews published in a year to appear in bibliographic databases and subsequently be identified and included in DARE. For the same reason data from the year 2010 may be incomplete.

10.3.1.2 Scope of adverse effects evaluation

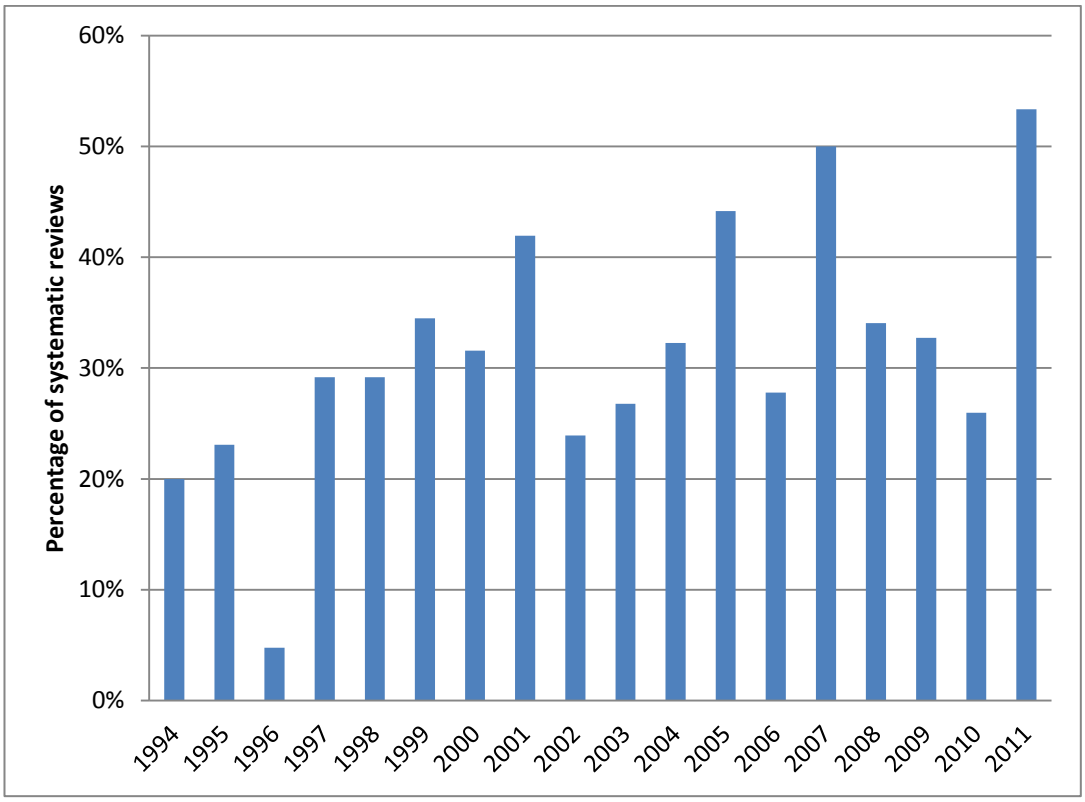
Some of the reviews (473/849, 56%) concentrated on pre-specified adverse effect outcomes (such as thrombosis or stroke) or a pre-specified class of effects (such as gastrointestinal or cardiovascular) (190/849, 22%), rather than analysing all potential adverse effects for a given intervention (186/849, 22%). This pattern remains consistent throughout the time period studied.

10.3.1.3 Study designs included

The reporting of study design appears to be improving as the proportion of reviews including unclear study designs (such as ‘epidemiological studies’, ‘prospective and retrospective studies’, or ‘empirical studies’) or with no study design reported has decreased (Appendix C: Table 15.15). Overall, about 3% (25/849) of reviews did not report on the types of studies included in their analysis and 19% (165/849) were unclear in their description of some of the included studies (Appendix C: Table 15.15).

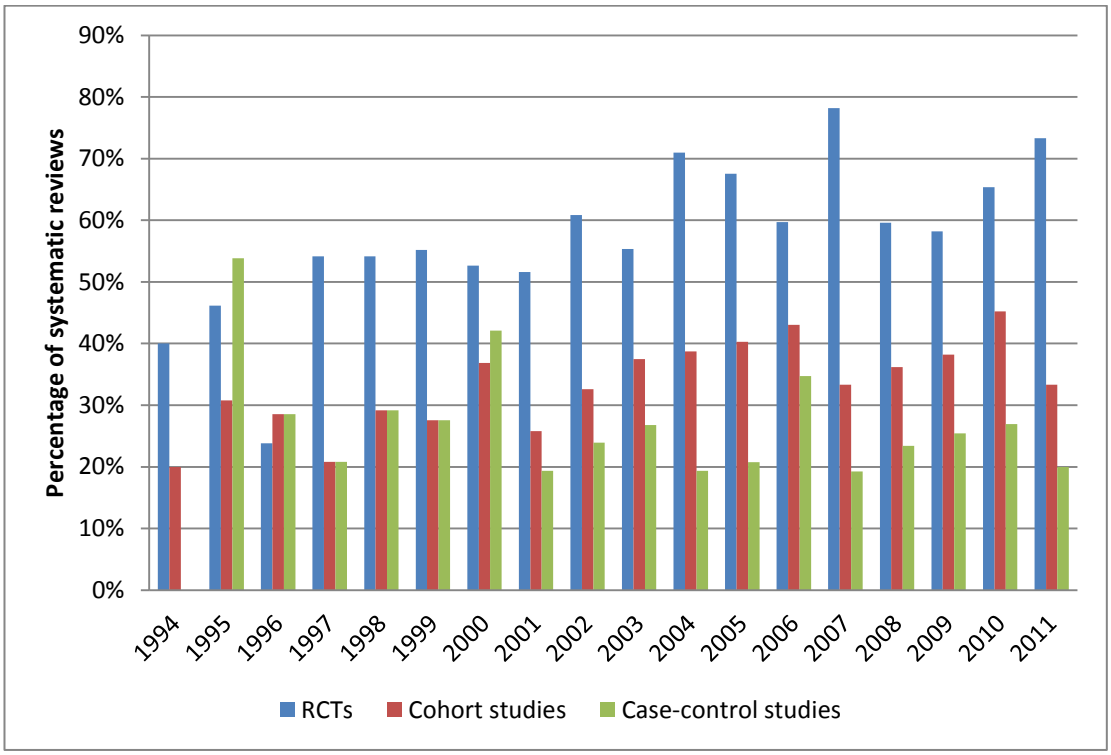
There has been a slight increase in reviews limited to data from RCTs since 1994 with an overall average of 33% (280/849) (Figure 10.2 and Appendix C: Table 15.15).

Figure 10.2 Percentage of systematic reviews of adverse effects with included studies limited to RCTs only 1994-2011



The proportion of reviews that include randomised controlled trials (RCTs) or cohort studies has seen a general increase since 1994, with an overall average of 61% (517/849), and 37% (310/849) respectively (Figure 10.3 and Appendix C: Table 15.15). However, the proportion of reviews including case-control studies has not increased, with an overall average of 25% (216/849). Case series and case reports were not included in many reviews, 8% (68/849) and 6% (55/849) respectively.

Figure 10.3 Percentage of systematic reviews of adverse effects including RCTs, cohort studies and case-control studies 1994-2011



10.3.2 Conduct of the review

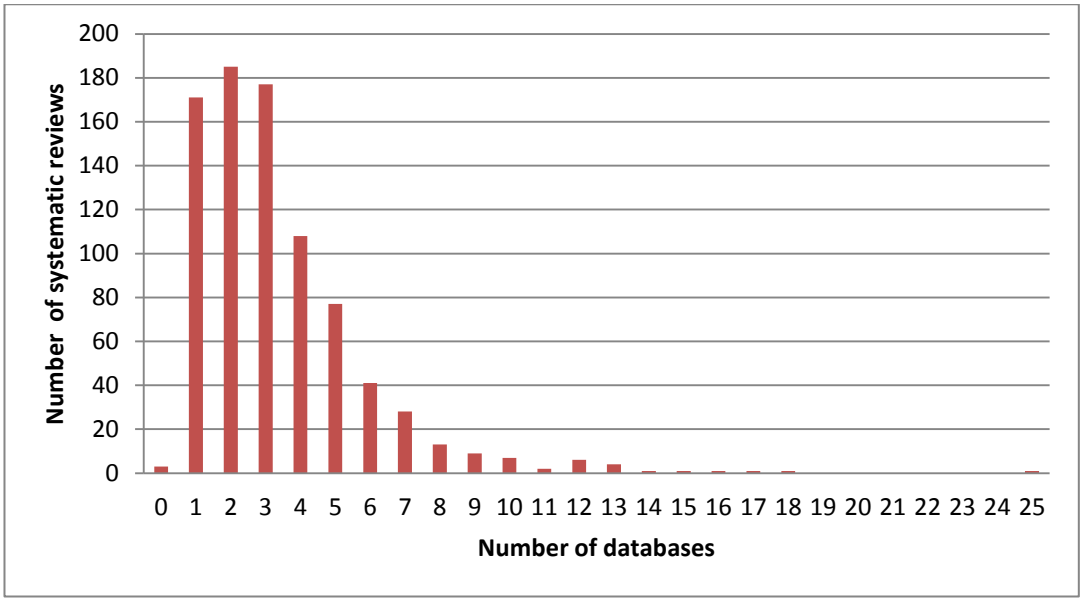
10.3.2.1 Resources searched

Nearly all of the reviews (837/849, 99%) listed the resources used to identify the primary studies for the review. Eight reviews did not report on the search methods used, and in four reviews it was not possible to accurately determine the data sources because of incomplete reporting or vague statements, such as ‘we used computer based searches and bibliographies of published articles’ or ‘studies were identified from review articles, computer aided literature searches and from discussion with colleagues’.

10.3.2.2 Databases and other sources searched

Twelve reviews did not specify the number of databases searched. Of those that did, the median number of databases searched was three (range 0 to 25). Four reviews stated that they did not search any bibliographic databases. One hundred and seventy one reviews (171/837, 20%) searched one database and in 164 cases this was MEDLINE. Less than half of the reviews searched two or fewer databases (359/837, 43%) and nearly a quarter (192/837, 23%) searched more than four databases (Figure 10.4).

Figure 10.4 Number of databases searched within each systematic review



The number of databases searched per systematic review appears to have increased since 1994, with a median of one or two databases in each year from 1994 to 2001 and three or four databases in each year from 2002 to 2011 (Appendix C: Table 15.16). The median number of non-database sources searched throughout the time period studied remained constant, at one or two each year (Appendix C: Table 15.16).

The most frequently searched database was MEDLINE (817/849, 96%), followed by EMBASE (462/849, 54%) (Table 10.1). Many reviews (88%, 743/849) reported searching at least one source other than databases. Reference lists were by far the most popular non-database resource (642/849, 76%) (Table 10.1). In addition, some more recent reviews are looking at manufacturers package inserts (13 reviews) and related articles feature in PubMed (10 reviews).

Table 10.1 Sources searched in order of frequency

Data Source	Reviews that searched each source, N=849
MEDLINE	817 (96%)
Reference lists of published studies	642 (76%)
EMBASE	462 (54%)
CENTRAL*	205 (24%)
Cochrane Library*	176 (21%)
Contacting experts	156 (18%)
Scanned conference reports	142 (17%)
Industry data	110 (13%)
CINAHL	107 (13%)
Cochrane Database of Systematic Reviews (CDSR)*	69 (8%)
Handsearching	65 (8%)
BIOSIS Previews/Biological Abstracts	64 (8%)
Current Contents**	56 (7%)
PsycINFO/PsycLit	52 (6%)
Web of Science***	52 (6%)
Database of Abstracts of Reviews of Effects (DARE)*	48 (6%)
FDA website	47 (6%)
Science Citation Index (SCI)**	45 (5%)
Cochrane Registers (e.g. Cochrane Schizophrenia Group')	38 (4%)
Textbooks	38 (4%)
Internet	34 (4%)
Personal files	31 (4%)
Citation searches	27 (3%)
HealthStar (no longer available)	29 (3%)
ClinicalTrials.gov	25 (3%)
International Pharmaceutical Abstracts (IPA)	25 (3%)
LILACS	25 (3%)
Surveillance data	22 (3%)
Scopus	21 (2%)
CancerLit (no longer available)	20 (2%)
Allied and Complementary Medicine Database (AMED)	19 (2%)
ACP Journal Club	17 (2%)
TOXLINE	17 (2%)
Dissertation Abstracts (now Dissertations and Theses: Abstract and Index (ProQuest))	16 (2%)
Google Scholar	15 (2%)
POPLINE	15 (2%)
Manufacturers Package Insert	13 (2%)
Current controlled trials.gov	12 (1%)
Centralised Information Service for Complementary Medicine (CISCOM)	11 (1%)
Health Technology Assessment (HTA) Database	11 (1%)
ISI Proceedings	10 (1%)
National Research Register (NRR)	10 (1%)
Related Articles in PubMed	10 (1%)
NHS Economic Evaluation Database (NHS EED)	9 (1%)
National Institutes of Health website	8 (1%)
OVID***	8 (1%)
Reprotox	9 (1%)
Web of Knowledge***	6 (1%)
Australian New Zealand Clinical Trials Registry (ANZCTR)	5 (1%)
Iowa Drug Information Service (IDIS)	5 (1%)
PASCAL	5 (1%)
SIGLE (now open sigle)	5 (1%)

Sources searched in four reviews or less are excluded.

*Searches of The Cochrane Library may have included CDSR, CENTRAL, DARE, NHS EED, and/or the HTA Database.
**Overlap exists between Current Contents and Science Citation Index (SCI).
*** Interface described as source in the review

10.3.2.3 Trends in databases searched

Almost all the reviews after 1998 searched MEDLINE and the proportion of reviews searching EMBASE, CENTRAL and 'The Cochrane Library' (which might also include CENTRAL) increased dramatically after the late 1990s (Figure 10.5 and Appendix C: Table 15.17).

Figure 10.5 Percentage of systematic reviews searching the top four databases 1994-2011

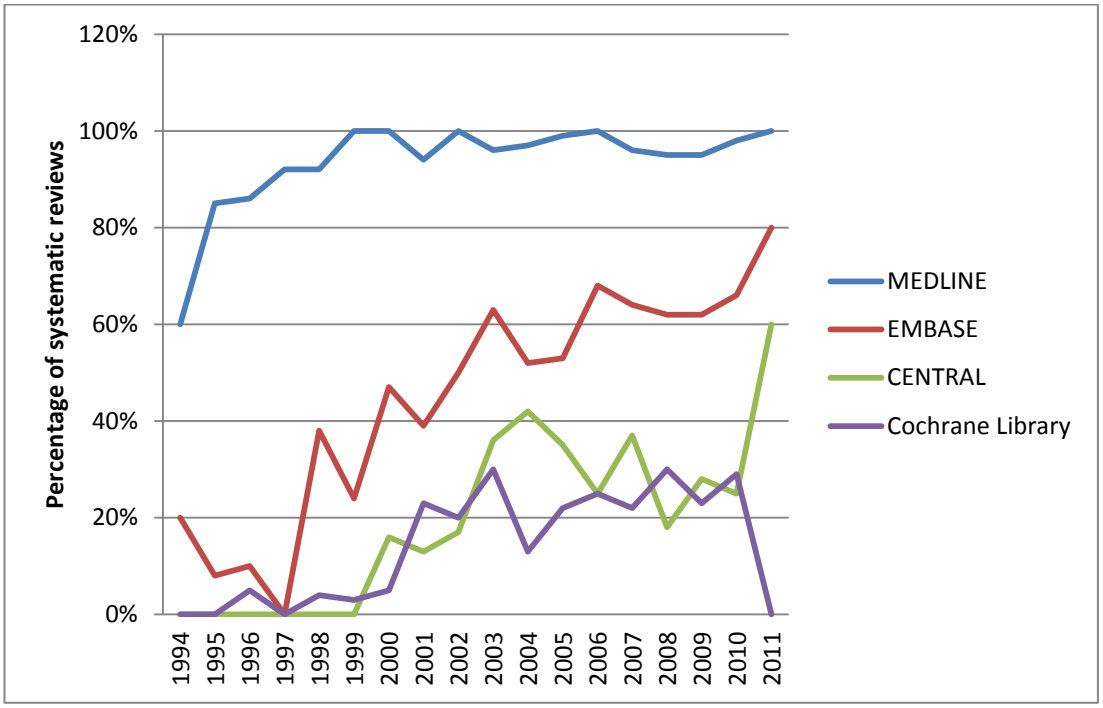
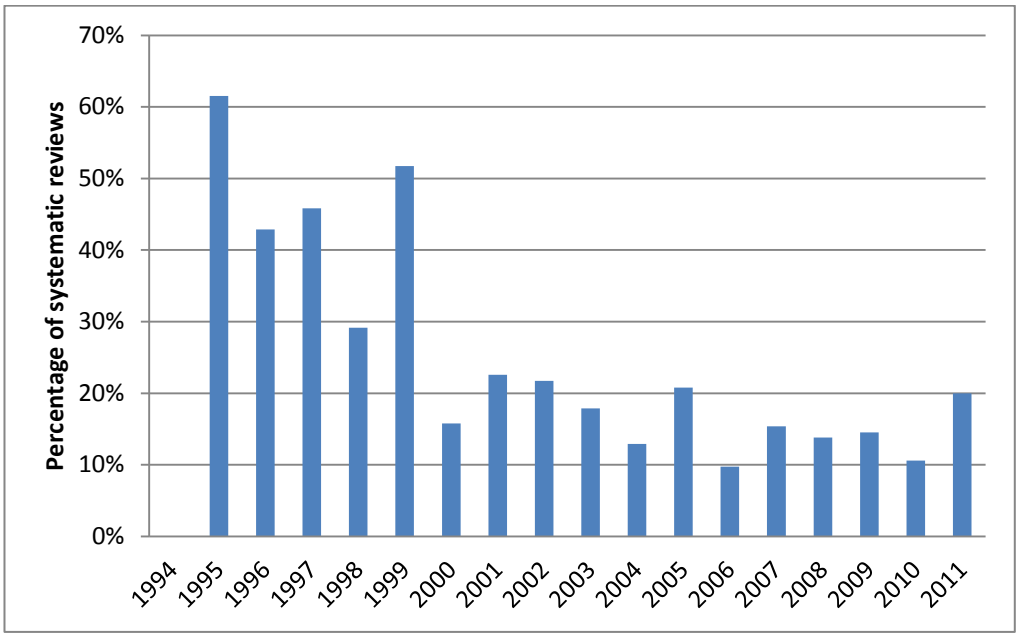


Figure 10.6 Percentage of systematic reviews searching only MEDLINE 1994-2011

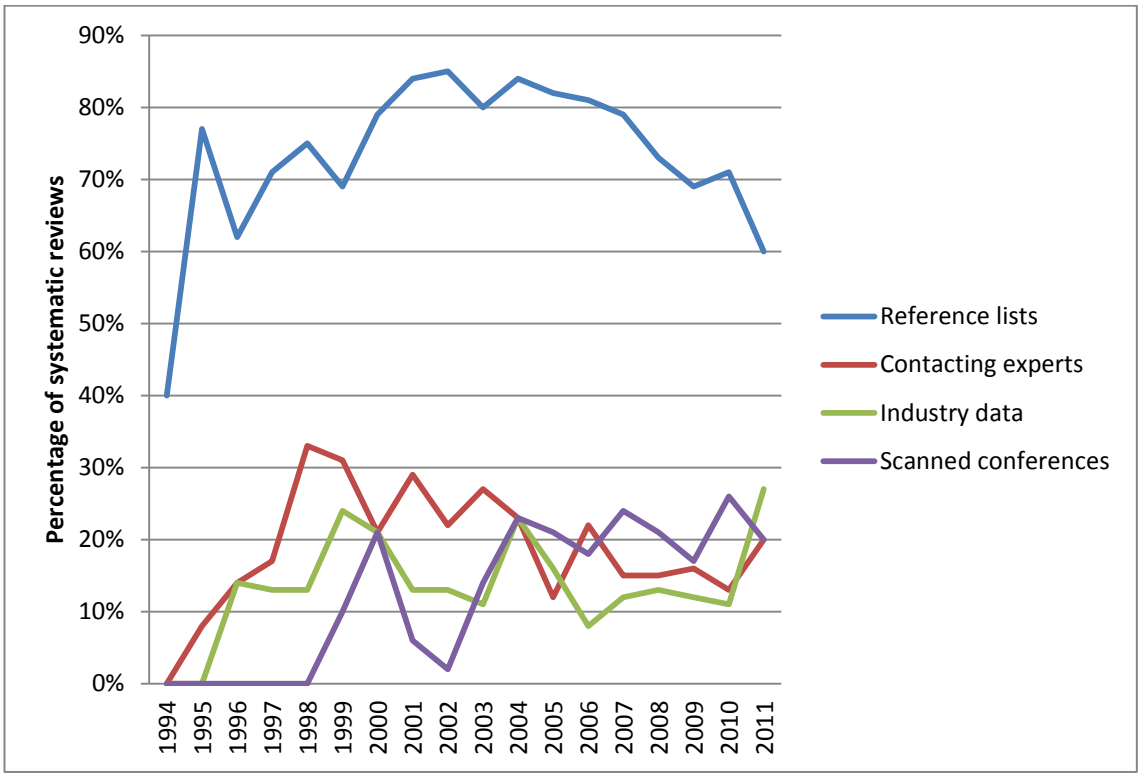


The percentage of reviews that included searches of MEDLINE with no other databases has decreased over the time period studied (Figure 10.6).

10.3.2.4 Trends in use of non-database sources

Reference lists remained the most popular non-database source throughout the time period studied (overall 76%), although scanning conference reports has seen an upsurge since 1999 (overall 17%) (Figure 10.7 and Appendix C: Table 15.18).

Figure 10.7 Percentage of systematic reviews searching the top four non-databases 1994-2011



10.3.2.5 Grey literature and unpublished data

Few attempts to retrieve grey literature or unpublished data via specialist database searches were reported. Sixteen reviews searched Dissertation Abstracts (now Dissertations and Theses: Abstract and Index (ProQuest)), 10 searched ISI Proceedings, five reviews reported searching SIGLE (now OpenSIGLE - System for Information on Grey Literature in Europe), and one review searched Conference Papers Index (CPI) (Table 10.1)

Non-database sources of unpublished data or grey literature included contacting experts (156/849, 18%), scanning conference reports (142/849, 17%), seeking pharmaceutical company data (110/849, 13%), searching the FDA website (47/849, 6%), and using surveillance data (22/849, 3%) (Table 10.1).

Fifty-five reviews (6%) sought ongoing studies by either searching ClinicalTrials.gov (25 reviews), Current controlled trials.gov (12 reviews), the National Research Register (NRR) (now discontinued) (10 reviews), the National Institutes of Health

website (eight reviews), Australian New Zealand Clinical Trials Registry (ANZCTR) (five reviews), the International Standard Randomised Controlled Trial Number (ISRCTN) Register (three reviews), the WHO International Clinical Trials Registry Platform (ICTPR) (three reviews), Ongoing Skins Trials Register (two reviews), Netherlands Trials Registry (NTR) (one review), University Hospital Medical Information Network (UMIN) Clinical Trial Registry (one review), or by searching a unspecified clinical trials register (10 reviews).

10.3.2.6 Dedicated adverse effects sources

Seventy-two reviews reported that they had searched at least one specialist resource for adverse effects. Many of these reviews had searched more than one source. Thirty-eight reviews consulted textbooks and although many did not specify the textbooks searched, of those that did the most popular were: Drugs in Pregnancy and Lactation and the Physicians' Desk Reference. Another 22 reviews attempted to retrieve surveillance data while others used specialist adverse effects databases, the most popular being TOXLINE (17 reviews). Other specialist sources consulted were Reprotox (nine reviews), DART (three reviews), Reactions (three reviews), Teris (three reviews), and Motherisk (one review).

Although few reviews searched specialist databases of adverse drug reactions, some reviews did search drug information databases such as International Pharmaceutical Abstracts (IPA) (25 reviews), Iowa Drug Information Service (IDIS) (five reviews), Derwent Drug File (three reviews) and Pharmline (two reviews). In addition, 47 consulted the U.S. Food and Drug Administration (FDA) website and eight consulted the European Medicines Agency (EMA) (previously EMEA) website.

10.3.2.7 Database interfaces/software

The use of different software for interrogating databases can impact on the results. For instance, MEDLINE via PubMed rather than OVID offers more records and automatic modification of search terms to enhance retrieval. The majority of the reviews did not give any indication of the database interfaces used (574/849, 68%). The most common interfaces stated were PubMed (184 reviews, 22%), OVID (67 reviews, 8%), and Web of Science (50 reviews, 6%).

10.3.2.8 Reporting of search strategies

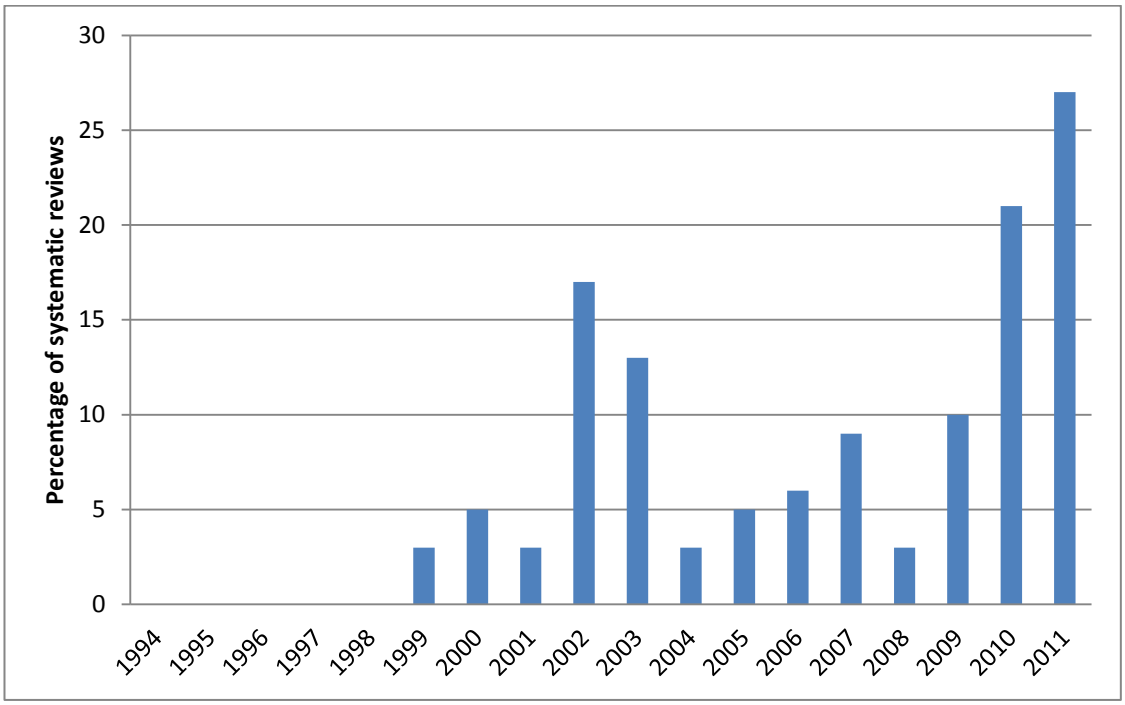
The proportion of reviews (725/849, 85%) providing some information on search strategies has increased over time, as has the proportion of reviews giving sufficient detail to allow the search to be reproduced according to the criteria stated earlier in this chapter. Overall, only 9% (74/849) of the reviews reported reproducible searches (even when web appendices and supplementary materials were considered) (Figure 10.8 and Appendix C: Table 15.19).

Those searches that were not reproducible typically used unclear terminology (such as 'the following **terms** were searched' or 'the **keywords** … were used' or simply 'we **searched** for XYZ') and gave no indication of the following:

- whether the terms were entered as text words, indexing terms, or subheadings
- if indexing terms had been exploded (for example, exploding the term 'neoplasms' will retrieve narrower terms such as breast neoplasm etc.)
- whether text words had been truncated (for example, smok* to retrieve smoking, smoke, smokers etc.)
- how the terms had been combined together (for example, using the Boolean operators, OR, AND or NOT)

Those reviews that contained reproducible search strategies tended to have either an appendix or table with the complete search strategy listed (65/74, 89%). Cochrane reviews were also more likely to contain reproducible search strategies (14 of the 74 reviews with reproducible search strategies were published in CDSR).

Figure 10.8 Percentage of systematic reviews with reproducible search strategies 1994-2011



10.3.2.9 Quality of search strategies

Research has indicated that the sensitive searches required for systematic reviews should generally incorporate a mixture of text words and indexing terms, a range of synonyms and truncation where appropriate.[22, 23] The search strategies reported in this survey were of variable quality. Of those reviews that provided information on their search strategies, few (152/725, 21%) reported the fields (such as title, abstract or indexing) to which the search terms were restricted. Over a third (60/152, 39%) used no text words for at least one category of terms (for example, intervention) relying solely on indexing terms. Nearly a fifth (28/152, 18%) used no indexing terms for at least one category of terms and relied solely on text words.

Of the 92 reviews that used text words, 26 did not use any synonyms for at least one of the facets and 12 of the 92 reviews that used text words did not use any truncation where it may have been appropriate.

10.3.2.10 Search terms used

Most reviews (725/849, 85%) indicated the actual terms used or the category of terms used, such as the population, disease, intervention, comparator, outcome (Table 10.2).

Table 10.2 Categories of search terms used in database search strategies

Category	Reviews using terms in category, N=849
Population (e.g. elderly)	97 (11%)
Disease	179 (21%)
Intervention	702 (83%)
Comparison	10 (1%)
Outcome: named adverse effect (e.g. headache)	393 (46%)
Outcome: generic adverse effect (e.g. adverse effects, side effects or complications)	39 (5%)
Outcome: named adverse effect and generic adverse effect	90 (11%)
Methodological filters (e.g. randomized controlled trials)	199 (23%)
Search strategy not stated	124 (15%)

Those search strategies that incorporated terms for the outcomes/adverse effects (in 522 reviews) tended to search on specific adverse effects (such as 'thrombosis' or 'headache') (393 reviews) rather than using a combination of specific adverse effects and generic adverse effects (such as adverse effects, side effects or complications) (90 reviews) or solely generic outcome terms (39 reviews). Five reviews relied on adverse effects terms alone, such as liver damage, root sensitivity, thrombocytopenia or ectopic pregnancy with no other category of terms used.

It was difficult to ascertain how many reviews used generic adverse effects indexing terms or subheadings, as only 32 reviews using generic outcome terms stated the fields searched. Fourteen reviews stated that they used generic adverse effects indexing terms (such as Medical Subject Headings (MeSH)) and 16 stated that they had used generic adverse effects subheadings/qualifiers such as 'adverse effects', 'complications', 'toxicity' or 'poisoning'. Only two reviews reported using 'floating' subheadings, that is, subheadings not attached to any indexing terms. One review

reported using the floating subheading ‘adverse events’ in MEDLINE (although the authors probably meant ‘adverse effects’, as this is the subheading available in MEDLINE) and the other review reported using the subheadings ‘adverse effects’ and ‘complications’.

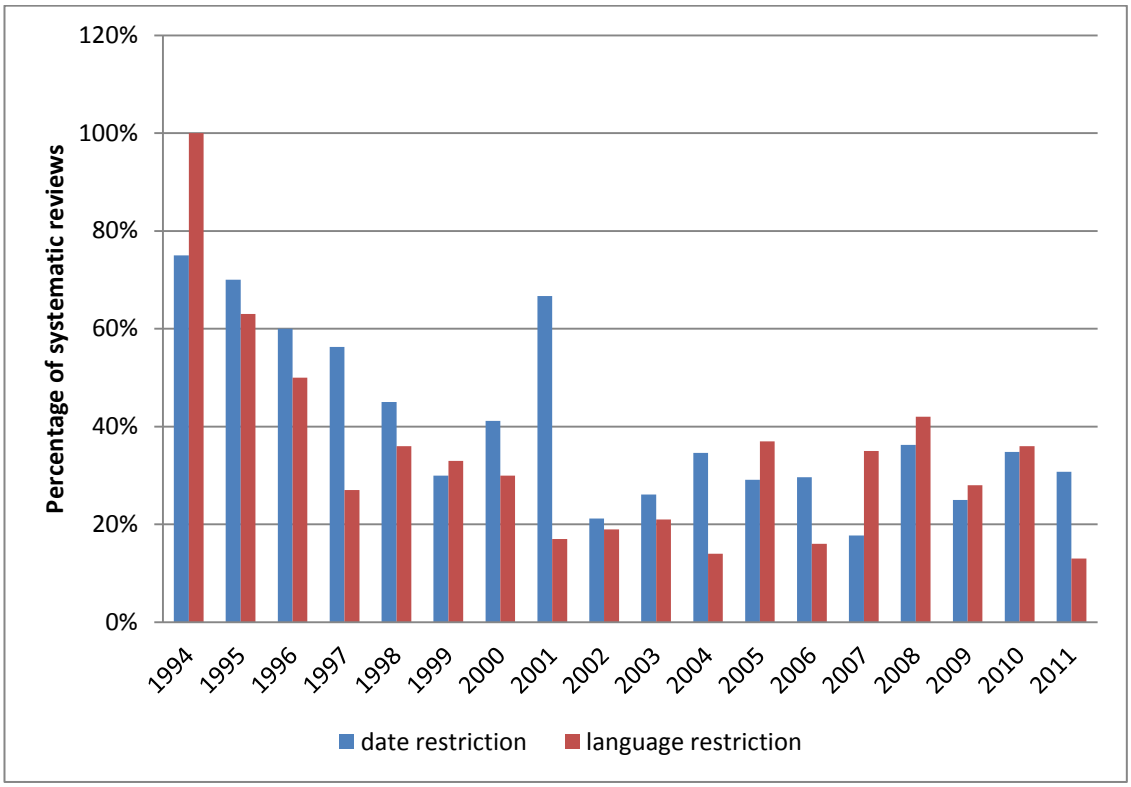
10.3.2.11 Search restrictions

Of the 661 reviews that gave a date range for the searches, 219 (219/661, 33%) applied date restrictions later than the year of inception of the databases searched. Only 61 (61/219, 29%) of the reviews that restricted by date gave a reason for this restriction. such as the review was an update of an existing review, the drug was only available since that date, or a change in medical practice meant that research before that date was not applicable.

In around half of the reviews (50%, 421/849) it was unclear whether the searches had been restricted by language; 17% (146/849) explicitly restricted by language and 33% (282/849) explicitly did not.

Using data from those reviews stating whether or not date restrictions or language restrictions were applied, there is some evidence that fewer reviews may be restricting their searches by date (other than the year of inception of the databases) or by language (Figure 10.9 and Appendix C: Table 15.20).

Figure 10.9 Percentage of systematic reviews with date or language restrictions 1994-2011



10.3.2.12 Conducting the searches

Only 109 (109/849, 13%) of the reviews gave any indication as to the qualifications of the person who conducted the searches. Of those that did, 73 were conducted by qualified librarians or information professionals and 36 by researchers. The literature searches performed by information professionals tended to be carried out in more databases (median 4) than those performed by non-information professionals (median 2) or where the searcher was not reported (median 3) (Table 10.3).

Table 10.3 Profession of searcher and number of sources searched

Searches conducted by	Median and range of databases searched	Median and range of other sources searched	Median and range of total sources searched
Information professional (N=73)	4 (1–25)	2 (0–48)	6 (1–58)
Non-information professional (N=36)	2 (0–10)	1 (0–6)	4 (1–10)
Unclear or not reported (N=740)	3 (0–17)	1 (0–37)	4 (1–50)

Reviews from this survey that list reproducible strategies were much more likely (25/73, 34%) to have been conducted by an information specialist than reviews which did not report reproducible searches – only 6% (48/775) of these were carried out by an information specialist. This was despite the fact that those searches produced by information specialists tended to include more search terms and were therefore more complex to report.

10.3.2.13 Precision of searches

Precision could be calculated in those reviews stating both the number of included studies and the total number of studies identified by the searches. Only 53% (449/849) of reviews stated the number of records retrieved by their literature searches. The median number of records retrieved was 631 (range 13 to 76,977) with 31 reviews reporting 5,000 records or more. The number of included studies was reported in all the reviews and ranged from one to 561 with a median of 18. The precision of the searches varied widely from 0.0026% (number needed to read, NNR, 380) to 63% (NNR, 2) with a median of 3% (NNR, 32).

Although some reviews included a flow diagram, the starting point was not always the number of records identified by the searches and the starting point was unclear. In some instances, it might have been the number of potentially relevant records (after a first sift) or the number of full-text papers examined. The arduous and impractical nature of repeating searches meant that this information was not gathered.

10.4 Discussion

In this survey, only 5% of systematic reviews on CDSR and DARE were systematic reviews of adverse effects. This finding is consistent with earlier surveys.[29, 108, 111] Although the number of reviews of adverse effects appears to have increased over time, this exponential increase is in line with an increase in all systematic reviews of healthcare interventions and has been identified in other surveys.[545] It would be interesting to assess the trend in the proportion of systematic reviews that primarily study effectiveness but also include adverse effects, as these might be increasing in line with Cochrane guidance, particularly in Cochrane reviews.

There are several findings from this survey regarding the nature and methodology of the retrieval of information on adverse effects in systematic reviews that merit further discussion and, where possible, comparison to other surveys of the conduct and reporting of retrieval in systematic reviews.

10.4.1 Characteristics of the included studies

10.4.1.1 Types of interventions studied

One area of concern is that systematic reviews identified in this survey have mainly been directed towards the adverse effects of pharmacological interventions throughout the time period studied. The disproportionate number of systematic reviews of pharmacological interventions is demonstrated when the results of this survey are compared to other surveys of systematic reviews.[109] This might occur as a result of licensing requirements, leading to more primary studies reporting adverse drug reactions, or a perception that medications can have more unwanted side effects than other types of healthcare intervention. This emphasis on drug therapy has already been identified as a key issue, given that surgical and other physical interventions are widely used in healthcare, and can have equally important or serious adverse effects.[110] In Chapters 4 to 9 the majority of the empirical evidence conducted in the retrieval of adverse effects data was also concerned with drug interventions. The lack of evidence for non-pharmaceutical research could also be a hindrance for authors of systematic reviews.

10.4.1.2 Scope of adverse effects evaluation

Throughout the time period studied, the proportion of systematic reviews that focused on pre-specified adverse outcomes of interest was high (78%). The possible indication is that many reviewers continued to have an ***a priori*** hypothesis when conducting a review and the detection of new, unrecognised adverse effects was of lesser interest. Indeed they might think that a systematic review is not a good way to identify new adverse effects. Similarly, a recent survey of drug safety reviews also found that 80% of reviews evaluated pre-specified adverse outcomes of interest.[546] It was interesting to note that the proportion of reviews attempting to conduct a complete safety profile had not declined over the years, given the relative ease of concentrating on a few major outcomes. Conversely, some researchers argue that the focused approach is more immediately able to yield clinically relevant results than broader reviews, which might not aim to prove or disprove specific hypotheses (but could help to identify important signals for further evaluation).[113]

10.4.1.3 Study designs included

Although reporting of study designs appears to be improving, many reviews still use unclear terminology to describe their included studies. However, it can often be difficult to decipher the type of observational study from the original full-text publication, as many primary studies either do not state the study type (e.g. cohort study or case-control study), do not report the methods used in enough detail or use methods that do not fit a predefined study design.

Compared to other non-Cochrane systematic reviews, fewer reviews in the current study were restricted to RCTs.[109, 140, 539] This probably stems from the widely held view that short-term trials in selected populations are not the best study design for the evaluation of rare or long-term adverse effects, and that reviewers might find it necessary to utilize other study designs.[14, 19-21, 27, 42, 65, 76, 77, 85, 89, 116, 127, 129, 132, 133, 139-141, 143, 144, 168-178] However, it was interesting to note that contrary to current evidence (Chapter 4),[22, 23, 547] the proportion of reviews limiting their included studies to RCTs does not appear to be decreasing, but may even be increasing in systematic reviews of adverse effects.

Cochrane reviews included in this survey were all limited to RCTs, in line with other studies that have found Cochrane reviews assessing adverse effects are generally restricted to RCTs meeting the effectiveness review eligibility criteria.[27, 29, 30, 539, 548]

10.4.2 Conduct of the review

10.4.2.1 Resources searched

In line with recommendations in the literature,[549-552] the majority of reviews in the current study explicitly reported on the databases and information sources searched. Possibly this reflects the source of the systematic reviews in this survey, as Cochrane reviews are expected to adhere to strict reporting guidelines[22] and have been found to be more rigorous than reviews published in peer reviewed journals[107, 109, 518, 540, 553, 554] and reviews included in DARE have met a basic quality threshold.[542, 543]

10.4.2.2 Databases and other sources searched

The number of sources searched (median 3, range 0 to 25) was similar to that reported in systematic reviews of cancer (median 3, range 1 to 25),[545] but lower than that reported in systematic reviews of qualitative data (median 5, range 1 to 23),[527] and higher than in systematic reviews of adverse drug reactions (median 2, range 1-13).[555] This might reflect the nature of searching for qualitative data and drug data. Specialist databases for qualitative data are sadly lacking, necessitating a wide selection of databases, and few affordable databases are restricted to drug information.

Many reviews in the current study (88%) reported searching at least one source other than databases. A survey of Cochrane and non-Cochrane reviews also identified a high proportion of reviews using non-database sources (91%).[533]

A number of other surveys of systematic reviews also indicated the sources searched in their individual reviews.[107, 516-518, 520, 521, 523, 531, 537, 546, 555] Table 10.4 gives a comparison of the database and non-database sources searched in this survey of systematic reviews of adverse effects with sources searched in other surveys of reviews. Comparisons could only be made with those surveys of other reviews publishing data on the number or percentage of individual sources searched.

Table 10.4 Sources searched in systematic reviews of adverse effects compared to other reviews

Data Source	Percentage of reviews, topic area and publication year
MEDLINE	100% Adverse drug effects 2009[555] 100% Medical education 2011[537] 99% Pediatric oncology 2009[545] 97% Dentistry 2003[523] **96% Adverse effects (current study)** 93% Complementary medicine and safety 2012[556] 93% Effectiveness 1998[516, 517] 91% Physiotherapy 2009[107] 89+% Drug safety 2012[546] 79% Emergency medicine 2001[520] 68% Qualitative data 2006[527] 68% Paediatric complementary and alternative medicine 2002[521] 66% Asthma interventions 2000[518]
Reference lists of published studies	87% Physiotherapy 2009[107] **76% Adverse effects (current study)** 72% Complementary medicine and safety 2012[556] 72% Pediatric oncology 2009[545] 72% Paediatric complementary and alternative medicine 2002[521] 70+% Drug safety 2012[546] 62% Emergency medicine 2001[520] 54% Asthma interventions 2000[518]
EMBASE	66% Complementary medicine and safety 2012[556] 65% Drug safety 2012[546] 59% Physiotherapy 2009[107] **54% Adverse effects (current study)** 49% Pediatric oncology 2009[545] 47% Adverse drug effects 2009[555] 28% Paediatric complementary and alternative medicine 2002[521] 26% Dentistry 2003[523] 24% Effectiveness 1998[516, 517] 3% Emergency medicine 2001[520]
CENTRAL	32% Pediatric oncology 2009[545] **24% Adverse effects (current study)** 15% Dentistry 2003[523]
Cochrane Library	82% Drug safety 2012[546] 68% Complementary medicine and safety 2012[556] 55% Physiotherapy 2009[107] 44% Adverse drug effects 2009[555] 36% Paediatric complementary and alternative medicine 2002[521] **21% Adverse effects (current study)** 12% Effectiveness 1998[516, 517]
Contacting experts	43% Physiotherapy 2009[107] 34% Paediatric complementary and alternative medicine 2002[521] 28% Asthma interventions 2000[518] 28% Pediatric oncology 2009[545] 24+% Drug safety 2012[546] **18% Adverse effects (current study)** 14% Emergency Medicine 2001[520]
Scanned conference reports	35% Drug safety 2012[546] 22% Pediatric oncology 2009[545] **17% Adverse effects (current study)** 17% Paediatric complementary and alternative medicine 2002[521]
Industry data	43% Drug safety 2012[546] **13% Adverse effects (current study)** 13% Paediatric complementary and alternative medicine 2002[521]
CINAHL	70% Qualitative data 2006[527]

Table 10.4 Sources searched in systematic reviews of adverse effects compared to other reviews

Data Source	Percentage of reviews, topic area and publication year
	52% Physiotherapy 2009[107] 42% Medical education 2011[537] 24% Complementary medicine and safety 2012[556] 21% Paediatric complementary and alternative medicine 2002[521] 15% Pediatric oncology 2009[545] **13% Adverse effects (current study)** 7% Effectiveness 1998[516, 517] 5% Drug safety 2012[546]
Handsearching	79% Medical education 2011[537] 26% Dentistry 2003[523] 24% Asthma interventions 2000[518] 23% Paediatric complementary and alternative medicine 2002[521] 10% Emergency medicine 2001[520] **8% Adverse effects (current study)** 6% Drug safety 2012[546]
BIOSIS Previews/Biological Abstracts	13% Paediatric complementary and alternative medicine 2002[521] **8% Adverse effects (current study)** 4% Physiotherapy 2009[107]
Current Contents	10% Effectiveness 1998[516, 517] **7% Adverse effects (current study)** 7% Physiotherapy 2009[107] 6% Paediatric complementary and alternative medicine 2002[521]
PsycINFO/ PsycLit	57% Qualitative data 2006[527] 34% Paediatric complementary and alternative medicine 2002[521] 18% Physiotherapy 2009[107] **6% Adverse effects (current study)** 4% Drug safety 2012[546]
Web of Science**	11% Drug safety 2012[546] **5% Adverse effects (current study)**
Science Citation Index (SCI)	14% Physiotherapy 2009[107] 11% Paediatric complementary and alternative medicine 2002[521] **5% Adverse effects (current study)**
Textbooks/ bulletins	12% Pediatric oncology 2009[545] **4% Adverse effects (current study)** 4% Drug safety 2012[546]
Personal files	6% Paediatric complementary and alternative medicine 2002[521] **4% Adverse effects (current study)**
HealthStar (no longer available)	8% Physiotherapy 2009[107] 4% Paediatric complementary and alternative medicine 2002[521] **3% Adverse effects (current study)** 2% Drug safety 2012[546]
International Pharmaceutical Abstracts (IPA)	**3% Adverse effects (current study)** 2% Drug safety 2012[546]
AMED	**2% Adverse effects (current study)** 49% Complementary medicine and safety 2012[556]
CancerLit	25% Pediatric oncology 2009[545] **2% Adverse effects (current study)**
Dissertations and Theses: Abstract and Index (ProQuest)	15% Paediatric complementary and alternative medicine 2002[521] 7% Physiotherapy 2009[107] **2% Adverse effects (current study)**
Google Scholar	**2% Adverse effects (current study)** 2% Drug safety 2012[546]
Manufacturers	**2% Adverse effects (current study)**

Table 10.4 Sources searched in systematic reviews of adverse effects compared to other reviews

Data Source	Percentage of reviews, topic area and publication year
Package Insert	2% Drug safety 2012[546]
CISCOM	**1% Adverse effects (current study)** 32% Complementary medicine and safety 2012[556]
OVID**	4% Drug safety 2012[546] **1% Adverse effects (current study)**
OPEN SIGLE	2% Drug safety 2012[546] **1% Adverse effects (current study)**

*In the current survey the terminology used by the authors of the systematic reviews was accepted. For example, where authors stated that they searched CDSR this was categorized as CDSR and where they stated that they had searched 'The Cochrane Library', this was categorized separately as 'The Cochrane Library'. Other surveys may have accepted statements such as 'we searched CDSR' to mean that 'The Cochrane Library' was searched.
**In some reviews the interface was described as if it was a database

The current survey demonstrates many similarities with other surveys of systematic reviews, in terms of the percentage of reviews that search particular sources. Table 10.4 illustrates the popularity of MEDLINE and reference checking among all types of reviews. Although the current survey is not limited to any particular type of intervention, the majority of the reviews evaluate adverse drug effects (621/849, 73%). In this survey, the percentage that search each resource is very similar to other studies of reviews of adverse drug reactions, with the exception of The Cochrane Library (Table 10.4).[546, 555] For example, MEDLINE is searched in 96% of the reviews in this survey, compared with 100% in the survey by Cornelius et al 2009[555] and over 89% in the survey by Alves et al 2012.[546] EMBASE is searched in 54% of reviews in the current survey, compared with 47% in the survey by Cornelius et al 2009.[555] The difference with respect to searching The Cochrane Library may arise from the different categorizations used, as searches of The Cochrane Library databases may be listed individually (such as CDSR, CENTRAL or DARE) or collectively as 'The Cochrane Library'. The present study distinguishes between reviews stating that they searched named databases in The Cochrane Library (such as CENTRAL) and reviews stating that they searched 'The Cochrane Library'.

Many of the differences between reviews as to the sources searched can largely be explained in terms of topic area or date. For example, CINAHL, which specializes in nursing and allied health, is searched more often in reviews of qualitative

research,[527] physiotherapy,[107] medical education,[537] and paediatric complementary and alternative medicine.[521] EMBASE, which is a well-known source for drug and general medical information, is searched more often in drug and physiotherapy reviews or more recent reviews. PsycINFO/PsycLit is searched more often in reviews of qualitative data[527] and reviews of paediatric complementary and alternative medicine.[521] In this survey, fewer reviews were restricted to MEDLINE (20%) than a previous survey of systematic reviews of orthodontics 2000-2004 (in which 56% searched only MEDLINE)[528] or in a survey of pediatric oncology reviews 1998-2007 (in which 31% searched only MEDLINE).[545] This may reflect the more diverse databases required for searching for adverse effects data, or the time period studied. There is also a general trend for more recent reviews to include more databases, particularly, with EMBASE and The Cochrane Library.

10.4.2.3 Trends in databases searched

The number of databases searched overall appears to be increasing over the time period 1994-2011, with a decline in the number of reviews of adverse effects searching only MEDLINE or only one database. This may be due to previous studies that demonstrated the usefulness of searching beyond MEDLINE or searching more than one source for clinical effectiveness information,[557-560] and other studies, such as those included in Chapter 5, which have indicated that MEDLINE is not the most useful source of information on adverse drug reactions.[355, 357, 360, 364-366, 368, 370, 561] Another factor could be the increasing number of databases available to researchers, either through institutional subscriptions, or free of charge via the Internet. Another survey also identified an increase in the searching of MEDLINE, EMBASE, CINAHL, The Cochrane Library, and reference checking. [562]

10.4.2.4 Trends in use of non-database sources

The number of other sources searched remains low, with a median of one or two sources searched per review for each publication year. The popularity of reference checking throughout the period studied is unsurprising given its low cost and relative ease.

10.4.2.5 Grey literature and unpublished data

The research in Chapters 7 and 8 demonstrate that data on adverse effects from industry and unpublished sources can make a major contribution to reviews of adverse effects. In this survey, relatively few reviews (110/849, 13%) reported an attempt to source information from pharmaceutical companies and attempts to source unpublished data and grey literature were lacking.

10.4.2.6 Dedicated adverse effects sources

The evidence reported in Chapter 5 also demonstrates the value of searching Derwent Drug File, yet only three of the 849 reviews searched this database. Other dedicated sources of adverse effects might also be useful but have rarely been searched.

10.4.2.7 Database interfaces/software

The majority of the reviews in this survey give no indication of the database interface used (68%). This is consistent with a survey of Cochrane reviews[535] in which 83% did not mention the database platform and a survey of Cochrane and non-Cochrane reviews[533] in which 64% failed to mention the database platform.

10.4.2.8 Reporting of search strategies

Detailed reporting of the full literature search process for systematic reviews is recommended and can impact on reader confidence in the results and conclusions.[22, 23, 563, 564,550] For nearly 25 years, guidelines on the reporting of systematic reviews have included recommendations that reviews should give a clear description of the methods of the literature search, including specifying the sources searched, search terms used and any language or date restrictions, in order that the search might be repeated.[5, 549-552, 564-567] As with other surveys[109, 528, 531, 533, 535, 537] a high proportion of reviews in this study (725/849, 85%) provide some information on their search strategy, though, few have given sufficient detail to allow the search to be reproduced according to the criteria stated earlier (74/849, 9%). This lack of detail causes difficulty with determining search adequacy, making it impossible for other researchers to replicate searches. The absence of a detailed search strategy creates obvious difficulties for future researchers who may need to

update a particular systematic review as well as for readers trying to assess its quality. Other studies have highlighted the failure of systematic reviews to report whether a comprehensive search strategy was undertaken,[511-532] with reproducibility of search strategies between 0% and 8.2%.[516, 517, 534, 537, 556]

It was reassuring to note an increase in the number of reproducible search strategies. The advent of electronic publishing and the potential for detailed search strategies to be published online as supplementary material might have been a contributing factor, as many of the reviews that reported reproducible search strategies published the full search strategy in an appendix or table.

Although other studies have highlighted the failure of systematic reviews to report on the undertaking of a comprehensive search strategy,[511-532] few studies have detailed analyses on the aspects of search methods that are poorly reported. However, two recent surveys of systematic reviews, one of 129 Cochrane Reviews and 168 non-Cochrane Reviews,[533] and another of 65 Cochrane reviews,[535] assessed the reporting of a number of different attributes of the search process that were similar to attributes assessed in the current survey (Table 10.5). Comparison suggests that reporting of searches in systematic reviews of adverse effects is as complete or incomplete as that for other systematic reviews. Similar results have also been found in other types of systematic review for the reporting of language restrictions,[109, 531, 533, 535, 537, 545, 556, 568] dates covered by searches,[521, 533, 568] and search terms used.[109, 531]

10.4.2.1 Quality of search strategies

Many of the reported literature searches relied solely on indexing or text word searches, with little use of synonyms and truncation, which are often crucial aspects for the type of sensitive search strategy required by systematic reviews.[22, 23] This may be particularly true in identifying information on adverse effects, given the inconsistent terminology and poor indexing in this area.[19, 70, 118, 121, 123]

Table 10.5 Reporting of items in systematic reviews

Reported Item	Current survey of systematic reviews of adverse effects (N=849)	Survey of Cochrane reviews by Yoshii et al 2009[535] (N=65)	Survey of systematic reviews identified on MEDLINE by Sampson and McGowan 2008[533] (N=297)
Databases used	837 (99%)	100%	293 (99%)
Database Platform	275 (32%)	17%	107 (36%)
Dates covered by search	661 (78%)		207 (70%)
Search terms used stated	725 (85%)	88%	254 (86%)
Other sources used	743 (88%)		271 (91%)
Language restrictions	428 (50%)	69%	166 (56%)
Qualifications of searcher	109 (13%)		34 (11%)

10.4.2.2 Search terms used

Of the 725 reported search strategies, the majority (702/725, 97%) searched on terms for the intervention, such as aspirin or acupuncture. It would be also expected that the vast majority of reviews of effectiveness would include intervention terms.

However, unlike searches for systematic reviews of clinical effectiveness the searches for systematic reviews of adverse effects in this survey tended to search for 'outcome' terms (in this case adverse effects terms) (72%). Difficulties exist with searching either generic adverse effects terms or specified adverse effects, with research indicating that the use of both generic adverse effects terms and specific adverse effects terms retrieves only 77% of the available literature in MEDLINE and EMBASE and that handsearching of journals may be the only way to identify some articles.[118]

For reviews that use databases to search for all adverse effects for a given intervention, a search using floating subheadings (such as 'adverse effects', or 'complications') is recommended.[360, 427, 428, 439] In this survey, only two of the 849

reviews reported using floating subheadings for adverse effects, although this could, in part, reflect the poor reporting of the search strategies.

Even when a search is carried out for named adverse effects, searching can be problematic. Wieland et al 2005[121, 429] demonstrated the difficulty of searching for a specific adverse effect (breast cancer) associated with a particular intervention (oral contraceptives) and showed that to achieve 100% sensitivity, a search on only the adverse effect outcome (in this case breast cancer) might be required, without any terms for the intervention.[121, 429] The majority of reviews in this survey searched on intervention and only four reviews searched for adverse effects terms alone. This probably reflects the impractical nature of searching on only adverse effects terms (due to the high number of records retrieved) but may also indicate that relevant studies were missed in many reviews.

10.4.2.3 Search restrictions

In line with current guidance, it was reassuring to see a decline in the use of date and language restrictions in systematic review search strategies, particularly as the dramatic increase in the literature available could make such restrictions more tempting.

10.4.2.4 Conducting the searches

Although good practice guidelines on the reporting of meta-analysis such as the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement[550] require the authors to provide details on the qualifications of the searcher, the majority of the reviews in this survey did not comply with this requirement (87%). The finding is similar to a survey of Cochrane and non-Cochrane reviews in which only 11% gave some indication of the qualifications of the searcher.[533] Overall, 9% (73/849) of the searches were reported to have been conducted by a qualified librarian or information professional. Low numbers of medical education reviews also reported the involvement of an information professional (15%).[537]

In this survey, literature searches carried out by information professionals were more likely to be reproducible, to include more search terms, and to search more databases. Booth 2006 also found that more databases were searched in reviews involving an information professional,[527] and Sampson and McGowan 2008 found

the reporting of the role of the searcher to be associated with greater reproducibility of searches.[569]

10.4.2.5 Precision of searches

The precision of the searches in the current survey (median of 3%, range 0.0026% to 63%) was similar to a study by Sampson et al 2011 (median of 3%, range 0.7% to 36%),[570] demonstrating that although searching for adverse effects may be difficult, searches tend to retrieve a similar proportion of relevant studies to other types of review. Decisions by searchers of adverse effects to be pragmatic and risk missing relevant studies, by for example including adverse effects/outcome terms, might account for this.

The problems identified with flow charts in this survey have been identified in previous research,[536] and few reviews have been found to include a flow diagram.[104]

10.5 Limitations

This survey is based on what authors of the included systematic reviews reported. Reporting was often unclear. For example, study design descriptions such as 'prospective' or 'retrospective studies' were used, databases were described only by their provider, such as, OVID, EBSCO and Web of Science, and searching descriptions such as 'handsearching' were used without stating the sources handsearched.

In the absence of better reporting, it is impossible make a more detailed judgement of the quality of the search strategies in systematic reviews of adverse effects. For the majority of the data collected for this survey it is also difficult to identify any trends over the time period covered, as information on search methodology reported by the review authors is lacking. However, the present study does indicate an increase in the number of sources searched and a reduction in search date limits over time, in line with other surveys that have also indicated improvements in the search process adopted.[107, 540, 541]

The reported numbers of sources searched by the 50 Cochrane reviews in this case study are also likely to be an underestimate, as most Cochrane reviews use

specialist registers that typically include extensive searches of bibliographic databases, such as MEDLINE, and handsearches of journals.

The results from this survey may not be representative of all systematic reviews of adverse effects. The study examined systematic reviews of adverse effects identified from CDSR and DARE, both of which have detailed criteria for considering the conduct of searches in systematic reviews. For instance, DARE requires one database plus at least one other source to have been searched, for example, another database, a handsearch, reference lists, or contact with authors. (This can be reported in the published review or the information obtained from elsewhere, such as a website, another publication, or the authors). Equally, the Cochrane Handbook provides explicit recommendations on the nature of the databases (such as CENTRAL, MEDLINE, and EMBASE) that should be included in searches. Hence, these findings may not be generalizable to wider situations, where "systematic" reviews are more loosely defined, and the quality of the searches might be less apparent.

This review also gives no indication of the reporting or search techniques used in systematic reviews where adverse effects are a secondary objective. At present, it is unclear how systematic reviews directed at effectiveness build in a component of adverse effects analysis as a secondary endpoint and further research is required.

10.6 Conclusions

Positive trends were seen in the conduct of searches with regard to the number of databases searched, including increased use of EMBASE and The Cochrane Library. Other improvements have included the decreasing proportion of systematic reviews limiting their search strategies by date or language, as well as more comprehensive reporting, by which reproducibility of search strategies is enhanced. However, these changes are not dramatic and few other improvements in search techniques were apparent throughout the time period studied.

Despite efforts to improve the reporting of search methodology in systematic reviews, comprehensive and transparent reporting of search strategies still poses a problem.

10.7 Summary

A survey was carried out of the search methodology in 849 systematic reviews of adverse effects published from 1994 to 2011.

Comparisons were made to other types of reviews and trends over the time reported.

Poor reporting of search strategies in systematic reviews of adverse effects made detailed analysis difficult. However, small improvements in search methodology were identified particularly in terms of the increasing number of databases searched and the decline in search restrictions applied.

Chapter 11 The contribution of different sources for information on adverse drug reactions: a case study of fractures with thiazolinediones

11.1 Introduction

The survey of reviews in Chapter 10 indicates that, as with reviews of effectiveness, authors of systematic reviews of adverse effects tend to focus on searching MEDLINE and reference checking to identify relevant studies. However, empirical evidence collected in Chapter 5 suggests that MEDLINE may not yield the most data on adverse effects, particularly when searches are made for drug-related adverse reactions. Derwent Drug File, EMBASE and industry submissions may provide the highest number of relevant references or unique relevant references with information on adverse effects. Findings in Chapter 5 are limited, particularly in light of the age of the methodological evaluations included in the review, the restricted range of sources compared in each single evaluation, and the failure to take into account the effect of search strategies employed in each source. There are major time and cost implications of searching beyond MEDLINE, so the yield and contribution of other sources merits careful consideration.

The results from the survey of reviews in Chapter 10 also indicate the varying methods used in systematic reviews of adverse effects. This variation may, in part, reflect the different questions posed in each review but also may reflect the lack of guidance on search methodology in this area. Further research should aim to clarify the value of specialist adverse effect databases, drug information databases, and other sources such as manufacturer's data, in order that the benefits of information available from such sources, and the most efficient combinations can be determined.

The objective of this stage of the research programme was to determine the contribution of searching a diverse range of sources to identify information on adverse drug reactions for a systematic review, taking into account any limitations of the search strategies.

11.2 Methods

11.2.1 Case study

A case study systematic review was carried out in order to be able to assess the contribution of different data sources. The following criteria were used to select the subject area for the case study systematic review:

a) the intervention was a named drug
b) the adverse drug reaction was a named discrete adverse effect, non-subjective in diagnosis and for which search terms were easily defined
c) there needed to be a large enough number of relevant studies with data on the adverse drug reaction to compare the retrieval rates from different sources
d) relevant RCTs and observational studies with data on the adverse drug reaction were available.

After discussion with clinicians and undertaking scoping searches on a number of potential topics, a case study systematic review of thiazolidinedione-related fractures in patients with type 2 diabetes mellitus was selected. This review was an update of a previous systematic review, with an increased number of sources searched.[265] The protocol for this review update is contained in Appendix D.

11.2.2 Search strategy

In order to be able to assess the efficiency of using different sources to identify information on adverse drug reactions, a wide range of sources was searched for relevant studies for this case study review. Bibliographic databases, such as MEDLINE and EMBASE, were included, as well as specialist drug databases, such as Derwent Drug file and Iowa Drug Information Service (IDIS), sources with grey literature, such as Google and Medscape DrugInfo, the Manufacturer's website, and databases of conference proceedings, such as Conference Papers Index (CPI) and Conference Proceedings Citation Index – Science. In addition to databases, other sources were searched, such as newsletters, bulletins, and referenced texts. A full list of sources searched is contained in the protocol in Appendix D.

The search strategy used in each database contained just two components, namely the interventions; thiazolidinediones (rosiglitazone and pioglitazone) and the outcomes; fractures or bone mineral density. Indexing terms and terms in the title

and abstract (including multiple synonyms) were used for each component, where available. The strategy was translated for each database and kept as consistent as possible across databases in order that a fair comparison between database results could be made. In order to be able to assess the effectiveness of searching Internet search engines such as AltaVista, Google and Google Scholar only the first three pages of results of Internet searches were screened for relevant articles. The first three pages were selected, in order to reflect common practice in searching the Internet[571-573] and due to the impractical nature of reviewing all the results from Internet searches, which can often be millions of pages. The full electronic search strategies used are contained in Appendix E.

11.2.3 Analysis

The included references from this case study systematic review formed the basis of the analysis. For the primary analysis, all publications with sufficient outcome data for meta-analysis (by either presenting enough data to calculate the odds ratio, relative risk, or weighted means difference, or by presenting the odds ratio, relative risk, or weighted means difference themselves) were included.

11.2.3.1 Individual assessment of sources

A record was made of the availability of each of the included references and where they were identified. For each reference available on a database but not identified by the search strategy, the bibliographic record was then examined to determine why it had not been identified. A record was also made of any relevant references identified or available from only one data source.

The sensitivity, precision, and numbers needed to read (NNR) for the searches in each of the databases was calculated using the following definitions;

$$\text{Sensitivity (\%)} = \frac{\text{number of included records retrieved}}{\text{total number of included records}} \times 100$$

$$\text{Precision (\%)} = \frac{\text{number of included records retrieved}}{\text{total number of records retrieved}} \times 100$$

Number Needed to Read (NNR) = total number of records retrieved OR 1/precision
number of included records retrieved

In addition, sensitivity*precision was calculated to allow equilibrium between sensitivity and precision to be assessed.[574]

11.2.3.2 Minimum combination of sources

The minimum combination of sources required to identify all included publications using the search strategies employed in this case study was recorded. In addition, a record was made of the minimum number of sources from which all the included publications were available, independent of the search strategy used.

11.2.3.3 Individual study identification

In order to allow for multiple publications for the same study, the analysis was repeated with all relevant individual studies, as opposed to all relevant publications.

11.2.3.4 Randomised controlled trials (RCTs) and observational studies

The analysis was then repeated with the included RCTs and observational studies separately, because certain databases may provide better access to specific study types, for example, CENTRAL focuses on clinical trials.

11.2.3.5 Marginal sensitivity and marginal precision

Although the sensitivity and precision of searching each individual source independently may be important to any potential searcher, the overlap in content between the sources in terms of relevant and non-relevant records is also important. Both the additional relevant records and non-relevant records retrieved from searching the sources in two particular orders were assessed. From the numbers of additional records retrieved, the marginal sensitivity, marginal precision, and additional numbers needed to read (NNR) for each additional resource could be calculated. Two different orders of sources chosen were selected on the basis that they reflected a theoretical order of sources and current practice:

a) Theoretical order: Beginning with the source from which the highest number of relevant records was retrieved, followed by the source from which the highest number of additional relevant records were retrieved and so forth, until all the relevant records were retrieved. In instances where the same number of additional relevant records would be retrieved from more than one source, then the source with the least number of irrelevant records was selected.
b) Order of Current Practice: An order of sources that reflects common practice in systematic reviews. The top ten most frequent sources were selected (in order of popularity) from the review of systematic reviews in Chapter 10.

11.3 Results

11.3.1 Records retrieved

From the database searches, 3591 unique records were retrieved (5663 before de-duplication). An additional 680 records (before de-duplication) were retrieved from searches for ongoing studies, 629 spontaneous case reports, 90 monographs or chapters from databases or texts, and 10 entries in databases or texts that listed adverse effects. Although the search strategies remained fairly consistent in all the databases, the searches in Scirus, EMBASE and BIOSIS retrieved particularly high numbers of records, 1928, 1017 and 880 respectively (Table 11.1)

11.3.2 Included studies

Fifty-eight references (representing 41 studies) were included in the case study systematic review; 29 references (representing 19 studies) were for RCTs and 29 references (representing 22 studies) were for observational studies. Most of the included references (31) were published as journal articles, 17 were conference abstracts and 10 were unpublished reports. A list of the included and excluded references is contained in Appendix F.

Two publications (DeFonzo 2008 and Seufert et al 2008) included in the previous systematic review by Loke et al 2008[265] were excluded from the analysis as they did not contain any fracture data. The data were identified by Loke et al 2008[265] from contacting the authors.

11.3.3 Where the **references** were identified

11.3.3.1 Bibliographic Databases

Using the search strategies with the drug and fracture terms retrieved at least one included reference in all the databases, except Inside Conferences (Table 11.1). The highest sensitivity was achieved from searching Science Citation Index (SCI) (60.34%), followed by BIOSIS Previews (46.55%), EMBASE (41.38%), and then MEDLINE (32.76%).

In the majority of the databases, precision was relatively high in the context of systematic review literature searches (Table 11.1). The highest precision was achieved in CENTRAL at 41.67%, followed by International Pharmaceutical Abstracts (IPA) and PASCAL at 25.00%. The lowest precision was achieved from searching Scirus at 0.88%, EMBASE at 2.36%, and BIOSIS Previews 3.01% (Table 11.1).

The database searches with the best combination of sensitivity and precision were PASCAL (sensitivity*precision 6.90%), Science Citation Index (SCI) (6.77%), and ADIS Clinical Trials (4.16%) (Table 11.1).

Other sources

Five references were not identified in any of the bibliographic databases. Two were identified through handsearching, one from reference checking, one from: Google Scholar, Litt's Drug Eruption Global Database, or AHFS Drug Information, and lastly one from either: Lexi-Comp, AHFS Drug Information, Clinical Pharmacology, Martindale: the complete drug reference, Merck, Side Effects of Drugs annual (SEDA), Medicine Safety Update, or Drugs and Therapy Perspectives (Table 11.2).

Table 11.1: References retrieved by databases, in order of sensitivity

Database	Records retrieved	Relevant records retrieved	Unique relevant records retrieved	Sensitivity (N=58)	Precision	NNR	Sensitivity* Precision	Relevant studies retrieved	Relevant records available	Missed references
Science Citation Index (SCI)	312	35	3	60.34%	11.22%	9	6.77%	24	42	7
BIOSIS Previews	880	27	1	46.55%	3.01%	34	1.40%	21	31	4
EMBASE	1017	24	2	41.38%	2.36%	42	0.98%	23	27	3
MEDLINE	251	19	0	32.76%	7.57%	13	2.48%	18	26	7
Scirus (journal sources)	1928	17	0	29.31%	0.88%	114	0.26%	17	23	6
Derwent Drug File	141	16	0	27.59%	11.35%	9	3.13%	15	21	5
PASCAL	64	16	0	27.59%	25.00%	4	6.90%	15	22	6
British Library Direct	117	15	1	25.86%	12.82%	8	3.31%	15	27	12
Thomson Reuters Integrity	96	15	0	25.86%	15.63%	6	4.04%	11	21	6
TOXLINE	141	14	0	24.14%	9.93%	10	2.40%	13	19	5
ADIS Clinical Trials Insight	70	13	0	22.41%	18.57%	5	4.16%	12	21	8
Iowa Drug Information Service (IDIS)	60	12	0	20.69%	20.00%	5	4.14%	11	16	4
GlaxoSmithKline Clinical Trials Registry	186	10	10	17.24%	5.38%	19	0.93%	10	10	0
International Pharmaceutical Abstracts (IPA)	28	7	0	12.07%	25.00%	4	3.02%	7	14	7
CINAHL	70	6	0	10.34%	8.57%	12	0.89%	6	10	4
Conference Proceedings Citation Index- Sci	45	6	0	10.34%	13.33%	8	1.38%	6	6	0
CENTRAL	12	5	0	8.62%	41.67%	2	3.59%	5	10	5
Medscape DrugInfo	115	4	1	6.90%	3.48%	29	0.24%	3	6	2
Conference Papers Index (CPI)	31	2	0	3.45%%	6.45%	10	0.50%	2	2	0
Inside Conferences	7	0	0	0%	NA	NA	NA	0	0	0

Table 11.2 References (RCTs and observational studies) retrieved by non-bibliographic databases

Source	Relevant references identified	Relevant RCTs identified	Relevant observational studies identified	Relevant references available	Unique relevant references	Relevant studies
Internet Search Engines						
Google Scholar*	3	2	1	33	0	3
Google*	2	1	1	45	0	2
AltaVista*	1	0	1	40	0	1
Intute	0	0	0	0	0	0
Internet Reference Collections						
The Drug Safety Research Unit (DSRU) Scientific Publications	0	0	0	0	0	0
MedWatch FDA website	0	0	0	0	0	0
Bulletins and Newsletters						
Reactions Weekly	5	2	3	5	0	5
Reactions PharmacoVigilance Insight (includes Reactions Weekly)	5	2	3	5	0	5
Drugs and Therapy Perspectives	4	2	2	4	0	4
Medicines Safety Update	2	2	0	2	0	2
Clin-Alert	1	0	1	1	0	1
Drug Safety Update	0	0	0	0	0	0
Adverse Drug Reactions Bulletin	0	0	0	0	0	0
Canadian Adverse Reaction Newsletter (CARN)	0	0	0	0	0	0
Referenced or Partially Referenced Sources						
Lexi-Comp database	7	3	4	7	0	7
AHFS Drug Information	5	3	2	5	0	5
Side Effects of Drugs annual (SEDA)	5	4	1	5	0	5
The Merck Manual	5	3	2	5	0	5
Martindale: the complete drug reference	4	3	1	4	0	4
Litt's Drug Eruption Global Database	2	1	1	2	0	2
Medical Evidence Matters	1	1	0	1	0	1

Table 11.2 References (RCTs and observational studies) retrieved by non-bibliographic databases

Source	Relevant references identified	Relevant RCTs identified	Relevant observational studies identified	Relevant references available	Unique relevant references	Relevant studies
Clinical Pharmacology	1	1	0	1	0	1
DRUGDEX	1	1	0	1	0	1
ADIS R&D Insight**	0	0	0	0	0	0
Drug Safety Portal**	0	0	0	0	0	0
eMedicine**	0	0	0	0	0	0
General Practice Notebook**	0	0	0	0	0	0
Adverse Drug Reactions (Lee)***	0	0	0	0	0	0
Davies Textbook of Adverse Drug Reactions***	0	0	0	0	0	0
Meylers's Side Effects Of Drugs***	0	0	0	0	0	0
ToxEd***	0	0	0	0	0	0
XPharm***	0	0	0	0	0	0

*search limited to the first three pages of results, as per current practice.[571-573]
**referenced monograph gave information on fractures with rosiglitazone or pioglitazone but did not reference any of the relevant references
***referenced monograph did not contain information on fractures with rosiglitazone or pioglitazone

11.3.3.2 Non-Referenced Sources

ABPI electronic Medicines Compendium (eMC), British National Formulary (BNF), Davis's Drug Guide, Drugs.com, Epocrates Online, Physicians' Desk Reference (PDR) and RxList listed or discussed fractures as an adverse effect but did not contain any citations.

Mosby's Medical Drug Reference and Rxmed Modell's Drugs in current use and new drugs did not include any information on fractures with glitazones.

11.3.3.3 Unique references identified by search strategies

The highest number of unique references (i.e. those that were found only in one particular source) were identified from the GlaxoSmithKline (GSK) Clinical Trials Registry (10 references), followed by Science Citation Index (SCI) (3 references),

EMBASE (2 references), and BIOSIS Previews, British Library Direct and Medscape DrugInfo (one reference each). In addition to unique references from databases, handsearching identified two unique references, and reference checking one unique reference.

11.3.4 Minimum combination of sources to identify all relevant references

The minimum combination of sources to retrieve all the relevant references with the search strategies used in this case study was: GlaxoSmithKline (GSK) Clinical Trials Registry; Science Citation Index (SCI); EMBASE; BIOSIS Previews; British Library Direct; Medscape DrugInfo; handsearching; reference checking; AHFS Drug Information; and Thomson Reuters Integrity or Conference Papers Index (CPI).

11.3.5 Where the **individual studies** were identified

11.3.5.1 Bibliographic Databases and other sources

A similar pattern emerged when limiting the evaluation of identified records to individual studies, as opposed to the individual publications. Science Citation Index (SCI) identified the greatest number of studies (24), followed by EMBASE (23 studies), BIOSIS (21 studies), and MEDLINE (18 studies) (Table 11.1).

11.3.5.2 Unique studies identified by search strategies

The highest number of unique studies were identified from the GlaxoSmithKline (GSK) Clinical Trials Registry (seven studies), followed by Science Citation Index (SCI) (two studies), EMBASE (two studies), BIOSIS Previews, British Library Direct, and Medscape DrugInfo (one study). In addition to unique studies from databases, handsearching identified one unique study.

11.3.5.3 Minimum combination of sources to identify all studies

The minimum combination of sources to retrieve all the studies with the search strategies used in this case study was GlaxoSmithKline (GSK) Clinical Trials Registry, Science Citation Index (SCI), EMBASE, BIOSIS Previews, British Library Direct, Medscape DrugInfo, and handsearching.

11.3.6 Where the **references** were available

11.3.6.1 Bibliographic Databases

The greatest number of relevant references available were on Science Citation Index (SCI) (42), followed by BIOSIS (31), British Library Direct (27) and EMBASE (27), and then MEDLINE (26).

The majority of the searches (using fracture and drug terms) did not retrieve all the relevant references available on each database (Table 11.1). The only databases in which all the relevant references available were identified were either conference proceedings databases or the drug company database. Due to the limitations of the interface for the drug company database, this database was searched with the drug terms only and all records sifted for the adverse effect. British Library Direct missed the highest number of relevant references (12 references), followed by ADIS Clinical Trials Insight at eight references, and then International Pharmaceutical Abstracts (IPA), MEDLINE and Science Citation Index (SCI), with seven missed references each.

Almost all the records missed did not contain any ‘bone’ or ‘fracture’ in the bibliographic details. However, in British Library Direct (which only allows searching of the title), two references were not retrieved as they contained no ‘drug’ terms and no ‘bone’ or ‘fracture’ terms in the title. One reference was not retrieved because it contained no ‘drug’ terms in the title, and another contained the phrase ‘rosiglitazone-associated fractures’ and was not identified owing to the use of the hyphen. In both PASCAL and Thomson Reuters Integrity one reference did not contain any relevant terms for the thiazolidinediones.

11.3.6.2 Other sources

The majority of the references were available on the Internet by a search on the specific reference using search terms from its citation (Table 11.2). Those articles that were not available on the Internet tended to be conference proceedings. The bulletins, newsletters, and referenced or partially referenced sources were all handsearched, and the number of relevant references identified from these sources matches the number of relevant references available (Table 11.2).

11.3.6.3 Unique references available

Seven references were unique in relation to their availability. Three references were only available from Science Citation Index (SCI), one from Medscape DrugInfo, one from BIOSIS Previews, one from British Library Direct and one from handsearching. The unique references identified from the GlaxoSmithKline (GSK) Clinical Trials Registry were also available from AltaVista, Google, or Google Scholar.

11.3.6.4 Minimum combination of sources with relevant references

The minimum number of sources that contained all the included references was Science Citation Index (SCI), Medscape DrugInfo, BIOSIS Previews, British Library Direct, and handsearching.

11.3.7 Where the randomised controlled trials (RCTs) were identified

When the analysis was restricted to RCTs only, the highest sensitivity was achieved from searching BIOSIS Previews (37.93%) followed by EMBASE (34.48%) and Science Citation Index (SCI) (34.48%) (Table 11.3). The databases which achieved a higher sensitivity when searching was limited to RCTs as opposed to all studies were CENTRAL, GlaxoSmithKline (GSK) Clinical Trials Registry, Thomson Reuters Integrity, and Medscape DrugInfo (Table 11.3).

The highest precision when searching for RCTs was achieved in CENTRAL at 41.67%, followed by PASCAL at 10.94%, and International Pharmaceutical Abstracts (IPA) at 10.71%. (Table 11.3).

The database searches with the best combination of sensitivity and precision were CENTRAL (sensitivity*precision 3.59%) followed by Thomson Reuters Integrity (2.91%), and PASCAL (2.64%) (Table 11.3).

Table 11.3 RCTs retrieved by databases, in order of sensitivity

Database	Relevant records retrieved	Unique relevant records retrieved	Sensitivity (N=28)	Precision	Number needed to read (NNR)	Sensitivity* Precision	Relevant studies retrieved (N=19)	Relevant records available	Missed relevant records
BIOSIS Previews	11	1	37.93%	1.25%	80	0.47%	8	14	3
Science Citation Index (SCI)	10	0	34.48%	3.21%	31	1.11%	6	16	6
EMBASE	10	1	34.48%	0.98%	102	0.34%	9	13	3
GlaxoSmithKline Clinical Trials Registry	9	9	31.03%	4.84%	21	1.50%	9	9	0
Thomson Reuters Integrity	9	0	31.03%	9.38%	11	2.91%	5	14	5
MEDLINE	7	0	24.14%	2.79%	36	0.67%	6	13	6
PASCAL	7	0	24.14%	10.94%	9	2.64%	6	11	4
Derwent Drug File	6	0	20.69%	4.26%	23	0.88%	6	11	5
Iowa Drug Information Service (IDIS)	6	0	20.69%	10.00%	10	2.07%	5	10	4
Scirus (journal sources)	6	0	20.69%	0.31%	323	0.06%	6	11	5
ADIS Clinical Trials Insight	5	0	17.24%	7.14%	14	1.23%	4	12	7
CENTRAL	5	0	17.24%	41.67%	2	3.59%	5	10	5
British Library Direct	4	1	13.79%	3.42%	29	0.47%	4	13	9
TOXLINE	4	0	13.79%	2.84%	35	0.39%	3	9	5
International Pharmaceutical Abstracts (IPA)	3	0	10.34%	10.71%	9	1.11%	3	9	6
Medscape DrugInfo	3	0	10.34%	2.61%	38	0.27%	2	4	1
CINAHL	2	0	6.90%	2.86%	35	0.20%	2	6	4
Conference Proceedings Citation Index- Sci	2	0	6.90%	4.44%	23	0.31%	2	2	0
Conference Papers Index (CPI)	1	0	3.45%	3.23%	31	0.11%	1	1	0
Inside Conferences	0	0	0	NA	NA	NA	0	0	0

11.3.8 Where the observational studies were identified

When the analysis was restricted to the observational studies, the highest sensitivity was achieved from searching Science Citation Index (SCI) at 86.21%, followed by BIOSIS Previews at 55.17%, and EMBASE at 44.83% (Table 11.4). The most notable difference in sensitivity for observational studies as opposed to all types of studies was for Science Citation Index (SCI) which increased from 60.34% to 86.21% (Table 11.4).

The highest precision, when the analysis was restricted to observational studies, was achieved in International Pharmaceutical Abstracts (IPA) (14.29%), followed by PASCAL (14.06%), and ADIS Clinical Trials Insight (11.43%) (Table 11.4).

The database searches with the best combination of sensitivity and precision were Science Citation Index (SCI) (sensitivity*precision 6.91%), followed by PASCAL (4.36%), and British Library Direct (3.56%) (Table 11.4).

The number of missed references in almost all the databases was notably higher when searching for RCTs than observational studies (Table 11.3 and Table 11.4).

Table 11.4 Observational studies retrieved by databases, in order of sensitivity

Database	Relevant records retrieved	Unique relevant records retrieved	Sensitivity (N=29)	Precision	NNR	Sensitivity* Precision	Relevant studies retrieved (N=22)	Relevant records available	Missed relevant references
Science Citation Index (SCI)	25	3	86.21%	8.01%	12	6.91%	18	26	1
BIOSIS Previews	16	0	55.17%	1.82%	55	1.00%	13	17	1
EMBASE	14	1	48.28%	1.38%	72	0.67%	14	14	0
MEDLINE	12	0	41.38%	4.78%	21	1.98%	12	13	1
British Library Direct	11	0	37.93%	9.40%	11	3.56%	11	14	3
Scirus (journal sources)	11	0	37.93%	0.57%	175	0.22%	11	12	1
Derwent Drug File	10	0	34.48%	7.09%	14	2.44%	9	10	0
TOXLINE	10	0	34.48%	7.09%	14	2.44%	10	10	0
PASCAL	9	0	31.03%	14.06%	7	4.36%	9	11	2
ADIS Clinical Trials Insight	8	0	27.59%	11.43%	9	3.15%	8	9	1
Iowa Drug Information Service (IDIS)	6	0	20.69%	10.00%	10	2.07%	6	6	0
Thomson Reuters Integrity	6	0	20.69%	6.25%	16	1.29%	6	7	1
CINAHL	4	0	13.79%	5.7%	18	0.79%	4	4	0
Conference Proceedings Citation Index- Sci	4	0	13.79%	8.89%	11	1.23%	4	4	0
International Pharmaceutical Abstracts (IPA)	4	0	13.79%	14.29%	7	1.97%	4	5	1
Conference Papers Index (CPI)	1	0	3.45%	3.23%	31	0.11%	1	1	0
GlaxoSmithKline Clinical Trials Registry	1	1	3.45%	0.54%	186	0.02%	1	1	0
Medscape DrugInfo	1	1	3.45%	0.87%	115	3.00%	1	2	1
CENTRAL	0	0	0	NA	NA	NA	0	0	0
Inside Conferences	0	0	0	NA	NA	NA	0	0	0

11.3.9 Marginal sensitivity and marginal precision

11.3.9.1 Order 1: Theoretical order

When the sources are searched in order of retrieval of the highest number of relevant records until all the relevant references are identified, the order for searching is as in Table 11.5.

The number needed to read is high in Medscape DrugInfo (110) and BIOSIS Previews (680). Although searching this combination of sources identifies all the relevant references (100% sensitivity), overall precision was low at 2.75%.

Table 11.5 Marginal sensitivity, marginal precision and additional number needed to read using the source with the highest number of relevant records first

Source	Additional records to sift	Additional relevant references	Marginal sensitivity (N=58)	Marginal precision	Additional number needed to read (NNR)
Science Citation Index (SCI)	312	35	60.34%	11.22%	9
GlaxoSmithKline Clinical Trials Registry	186	10	17.24%	5.38%	19
EMBASE	819	4	6.90%	2.81%	36
AHFS Drug Information*	2	2	3.45%	100%	1
Handsearching	N/A	2	3.45%	N/A	N/A
Conference Papers Index (CPI)	24	1	1.72%	4.17%	24
British Library Direct	46	1	1.72%	2.17%	46
Medscape DrugInfo	110	1	1.72%	0.91%	110
BIOSIS Previews	608	1	1.72%	0.16%	608
Reference checking	N/A	1	1.72%	N/A	N/A
TOTAL	**2107**	**58**	**100%**	**2.75%**	**36**

*AHFS Drug Information or a combination of Litt's Drug Eruption Global Database and either - Lexi-Comp Database, Clinical Pharmacology, Martindale: the complete drug reference, The Merck Manual or Side Effects of Drugs annual (SEDA), Medicines Safety Update or Drugs and Therapy Perspectives.

11.3.9.2 Order 2: Current practice in systematic reviews

Three references would not have been identified had the search been restricted to the top ten most popular sources of data used in systematic reviews of adverse effects (Table 11.6). These references could have been identified from Medscape DrugInfo (one reference), British Library Direct (one reference), and from Conference Papers Index (CPI) or Thomson Reuters Integrity (one reference). Only one review of the 849 systematic reviews of adverse effects from Chapter 10 included Conference Papers Index (CPI). Medscape DrugInfo, British Library Direct, and Thomson Reuters Integrity were not included in any of these reviews. If MEDLINE alone had been searched, along with reference checking, then only 34% (20/58) of the relevant references would have been identified. Even a search of MEDLINE, EMBASE, and CENTRAL along with reference checking, would have retrieved less than half (43%, 25/58) of the relevant references (Table 11.6).

Table 11.6 Marginal sensitivity, marginal precision and additional number needed to read using order of sources in current practice

Source	Additional records to sift	Additional relevant references	Marginal sensitivity (N=58)	Marginal precision	Additional number needed to read (NNR)
MEDLINE	251	19	32.76%	7.57%	13
Reference Checking	NA	1	1.72%	NA	NA
EMBASE	808	5	8.62%	0.62%	161
CENTRAL	0	0	0%	0%	0
GlaxoSmithKline Clinical Trials Registry	186	10	17.24%	5.38%	19
CINAHL	30	0	0%	0%	0
Handsearching	NA	2	3.45%	NA	NA
BIOSIS Previews	706	10	17.24%	1.67%	60
Science Citation Index (SCI)	58	6	10.34%	17.14%	6
Textbooks/ bulletins	NA	2*	3.45%	NA	NA
TOTAL	**2039**	**55**	**94.83%**	**2.85%**	**35**

11.4 Discussion

This case study demonstrates the value of searching multiple sources in order to identify data on adverse drug reactions for a systematic review. The minimum number of sources needing to be searched in order to identify all the relevant references with the proposed search strategy was ten. Even were it possible to devise a 'perfect' search strategy that could retrieve all the relevant references available on each source, a minimum of five sources would still need to be searched. The most common practice of searching just MEDLINE and reference checking would have failed to retrieve two-thirds of the relevant references (38/58, 66%). Even a search of MEDLINE, EMBASE, and CENTRAL along with checking of reference lists would have failed to retrieve over half the relevant references (33/58, 57%).

The results from searching each source varied enormously in terms of sensitivity and precision, with a general trade-off between the two. The high sensitivity achieved in Science Citation Index (SCI), BIOSIS Previews, and Scirus, in particular, warrant further investigation. As this is only one case study, it would be difficult to generalise the findings from this case study review to other systematic reviews without further research. Science Citation Index (SCI) has only been included in one previous evaluation and proved useful despite only being searched for effectiveness studies (Chapter 5). Scirus has not been included in other evaluations (Chapter 5) and although in previous case studies BIOSIS Previews provided a substantial number of relevant references and unique references, more relevant records tended to be identified from MEDLINE or EMBASE (Chapter 5). However, in the present case study, BIOSIS Previews identified more relevant records than either MEDLINE or EMBASE.

Other differences have been observed when the present case study was compared to previous case studies in Chapter 5. Whereas previous case studies indicated a higher yield from Derwent Drug File than MEDLINE or EMBASE, in this case study both MEDLINE and EMBASE retrieved a higher number of relevant references than Derwent Drug File. In addition, PASCAL also ranked better in this case study than in previous case studies identifying more relevant references than TOXLINE.

There are, however, many similarities between this case study and the previous case studies described in Chapter 5. For instance, all the case studies have indicated the value of BIOSIS Previews over Iowa Drug Information Service (IDIS), International Pharmaceutical Abstracts (IPA) and PASCAL. For drug interventions, EMBASE yielded more relevant references than MEDLINE. And MEDLINE, EMBASE and TOXLINE retrieved more relevant references than Iowa Drug Information Service (IDIS), and lastly Iowa Drug Information Service (IDIS) retrieved more relevant references than International Pharmaceutical Abstracts (IPA).

Although most case studies in Chapter 5 focused on comparative evaluations of databases, in some instances the value of non-database sources such as reference checking, handsearching, and textbooks was demonstrated. In this case study review, contacting manufacturers or searching manufacturer websites was particularly useful for identifying unique studies. However, the ease of retrieving industry funded studies will vary greatly depending on the drug company.

The low sensitivity achieved by some of the databases is not surprising. For instance, specialist conference databases such as Conference Papers Index (CPI) and Inside Conferences contain only conference abstracts, CINAHL specialises in nursing and allied health, the GlaxoSmithKline (GSK) Clinical Trials Registry contains only industry funded studies, and CENTRAL focuses on clinical trials.

Non-bibliographic databases do not tend to identify a high proportion of relevant references. Most of these sources are typically aimed at providing information for drug development, or for prescribers, or contain added value (such as synthesized data from studies in Medical Evidence Matters) and do not intend to be comprehensive. Such sources may be more useful at the developmental stage of a systematic review when the decision is made of which adverse effects to include in the search strategy.

In searching terms, this systematic review was relatively straightforward in that the adverse effect was known in advance and well defined. However, in most of the databases, relevant references were missed with the search strategy used, which included terms for both the drug (thiazolidinediones) and outcome (fracture)

only. Those sources in which references were not missed were either browsed (such as bulletins, newsletters and referenced texts or databases), searched with a simplified search strategy due to interface restrictions (such as the GlaxoSmithKline (GSK) Clinical Trials Registry), or were databases of conference proceedings (such as Conference Proceedings Citation Index- Science, Conference Papers Index (CPI), and Inside Conferences).

The large discrepancy between the number of references available on the Internet and the number retrieved can be partially explained by the fact that only the first three pages were viewed, that a more lateral or iterative searching approach was not applied (such as following links from search results or repetitive search attempts), and that the references of articles retrieved were not checked (many of the press articles identified on the Internet had references to the included studies). Of the bibliographic databases, British Library Direct missed the highest number of relevant references. This is likely to be a result of the search interface for this database, which does not allow searching of terms in the abstract. With the other databases, the variation in the references missed was mostly attributable to differences in indexing practices or the assignment of keywords for the adverse effect (fracture).

In all the databases, the number of missed references with the search strategies used was higher for RCTs than for observational studies. Adverse effects are more likely to be a secondary outcome in RCTs than in observational studies and, such that adverse effects terms are less likely to appear in the title, abstract or indexing/keywords of bibliographic records of RCTs than observational studies.

Interestingly, the minimum combination of sources required to identify all the relevant references did not include MEDLINE, and neither did the combination of sources identified through the selection of the sources with the highest sensitivity first. This is partially due to the fact that searching MEDLINE did not identify any unique references or have the highest sensitivity.

11.5 Limitations

The main limitation of this study is that it is based on only one case study, creating difficulty with the generalisability of the results to other systematic

reviews of other interventions or other adverse effects. Moreover, most of the trial reports with fractures came from the GlaxoSmithKline (GSK) Clinical Trials Registry, and other pharmaceutical company reports may not provide as much detail.

It was difficult to maintain consistency in the search strategy among the different interfaces for the different databases in order to make fair comparisons. In addition, it was not possible to conduct any type of cost analysis of searching each source, due to the complex pricing mechanisms employed by database providers, which can be dependent on the type of organisation, size of network, number of concurrent users, and the provider from which the database is purchased. Another limitation of this case study is that the searches using the Internet search engines do not necessarily reflect current practice as searches tend to be more idiosyncratic and opportunistic and may, therefore, have retrieved more relevant references.

11.6 Conclusions

This case study demonstrates the potential value of searching a number of sources to identify data on adverse drug reactions. In this instance, a combination of searching the GlaxoSmithKline (GSK) Clinical Trials Registry, Science Citation Index (SCI), EMBASE, BIOSIS Previews, British Library Direct, Medscape DrugInfo, handsearching, reference checking, AHFS Drug Information, and Thomson Reuters Integrity or Conference Papers Index (CPI) retrieved all the relevant references.

The case study here also demonstrates the failure of a broad search strategy with numerous synonyms, text words, and indexing terms to identify all the relevant references available on each database. Primarily, this was because of a lack of fracture terms in the title, abstract, or indexing/keywords of bibliographic records, again emphasising the need for authors of systematic reviews of adverse drug reactions to search a wide range of sources and authors of studies to ensure adverse effects terms appear in the title or abstracts.

11.7 Summary

A wide range of sources were searched in a case study systematic review of thiazolidinedione-related fractures.58 included references were analysed as to the sources from which they were identified, the availability of each reference, and whether each reference was unique to each source.

Using the search strategy employed in this case study, a minimum of 10 sources needed to be searched to identify all 58 included references.

Chapter 12 Search filters in MEDLINE and EMBASE: a case study of fractures with thiazolidinediones

12.1 Introduction

Developing efficient search strategies (combinations of search terms) for use in databases (such as MEDLINE and EMBASE) which capture all the relevant literature on adverse effects is challenging.[2, 118] Specific difficulties arise when adverse effects terms are added to the search strategy, because adverse effects are poorly reported, inadequately indexed, inconsistently described, and can be new or unexpected at the time of searching.[19, 117]

To avoid omitting any relevant studies, Derry et al 2001 proposed an arduous and highly resource intensive approach based on a broad search without adverse effects terms, where a large number of potentially irrelevant full-text articles would need to be manually screened. However, other methods of electronic searching have since been developed and tested to try and ease the process of identifying and retrieving studies of specific interest.

Attempts have been made to develop search filters for retrieving papers on adverse effects (Chapter 6). There are currently 12 published search filters for MEDLINE[121, 360, 427, 428, 430, 432, 434] and three for EMBASE (Appendix G).[360, 432] All these filters, with the exception of the filters by Buckingham et al 2005,[434] were developed to maximise sensitivity, that is, to retrieve a high proportion of all available relevant records. The search filters by Wieland et al 2005[121, 430] aimed to identify as many of the relevant records as possible for a named specific adverse effect (breast cancer with oral contraceptives), whereas the other filters aimed to capture all or all serious adverse effects for particular interventions. The search filters by Badgettt et al 1999, Golder et al 2006 and Wieland et al 2005 were developed using research techniques and tested.[121, 360, 427, 428, 430] However, the precision of the search filters is not recorded in Badgett et al 1999 and the search filters by Golder et al 2006 and Wieland et al 2005 are not validated with other case studies.[121, 360, 427, 428, 430] The other search filters available[432, 434] are based solely on expert opinion and have not yet been evaluated.

The aim of this case study was to explore the sensitivity (the ability to identify as many relevant articles as possible), precision (the ability to exclude as many irrelevant articles as possible), and number needed to read (NNR) (the number of records requiring sifting in order to identify one relevant article) with adverse effects search filters.

12.2 Methods

As with Chapter 11, the included references from an update of a previously published systematic review[265] on fracture related adverse effects associated with the use of thiazolidinediones (rosiglitazone and pioglitazone) formed the basis of analysis for this case study (Appendix D). The original search strategy used for this case study systematic review contained just two facets, the intervention; thiazolidinediones (rosiglitazone and pioglitazone) and the outcomes; fractures and bone mineral density. Indexing terms and terms in the title and abstract (including multiple synonyms) were used for each facet. No generic adverse effects terms (such as 'safety', 'side effect' or 'adverse event') were included in the search strategy, making it possible to assess the effect of the addition of adverse effects terms. The searches were carried out in MEDLINE and EMBASE, as well as numerous other sources (Appendix E).

The adverse effects search filters available for MEDLINE and EMBASE were then run to assess the number of relevant references that would have been retrieved had these filters been applied, and also the total number of records retrieved (Appendix G). Each search filter was run in turn, and a separate Endnote library created for the results from each strategy. This enabled calculation of the sensitivity, precision, and the number needed to read (NNR) of the searches to be carried out. These, and the sensitivity*precision[574] for the searches in each of the databases was calculated using the definitions described in Chapter 11.

As the adverse effect used in this investigation (fractures) was known before the searches were conducted, some adaptations were made to the generic adverse effects search strategies by Badgett et al 1999[427, 428] and Golder et al 2006[360] (Appendix H). Generic search filters are designed to identify any adverse effects of an intervention and contain only generic adverse effects related terms, such as 'side effects' and 'adverse events'. In this instance, the generic search

strategies proposed by Badgett et al 1999 and Golder et al 2006 were combined (ANDed) with the fracture terms.

The search strategies by Wieland et al 2005[121, 430] were translated from the PubMed interface to OVID MEDLINE. Two of the search strategies in Wieland et al 2005[121, 430] did not contain any intervention terms. These search strategies were not tested in this case study owing to the large volume of records (over 8,000 records with MeSH terms and over 40,000 records with text words) that running a search for 'fracture' and 'risk' terms alone generates, and thus the impractical nature of employing such a search strategy for this type of systematic review.

12.3 Results

Fifty-eight references (representing 41 studies) contained sufficient data to allow meta-analysis for the relevant outcomes of interest and were included in the systematic review. Of these 58 references, 19 were identified in MEDLINE (12 observational studies and seven RCTs) and 24 in EMBASE (14 observational studies and 10 RCTs).

12.3.1 MEDLINE

The original search strategy using only the drug terms for thiazolidinediones and the named adverse effect (fractures) retrieved 251 records of which 19 contained relevant adverse effects data (representing 18 studies) (Table 12.1). If the Golder et al 2006a/2006b search filter had been applied, in addition to the thiazolidinediones and fracture terms, then the same number of relevant references (19) would have been identified with 50 fewer records to sift (Table 12.1). The search filters by Badgett et al 1999,[427, 428] BMJ Clinical Evidence 2006,[432] and Wieland et al 2005f,[121, 430] each missed only one relevant reference (each filter missed a different reference). In the case of the Badgett et al 1999[427, 428] filter, the missed reference would have been identified had the text word 'safety' been included in the search strategy. The paper missed by the BMJ Clinical Evidence 2006[432] filter would have been retrieved had the subheading 'drug effect' been included (de.fs), and in the case of the Wieland et al 2005f[121, 430] filter the missed reference would have been identified had the MeSH term 'Fracture, bone/ci' been included (ci is the subheading 'chemically induced').

High precision was achieved by the Buckingham et al 2005b,[434] Wieland et al 2005a,[121, 430] Wieland et al 2005b,[121, 430] and Wieland et al 2005c[121, 430] filters (Table 12.1). These search strategies all rely only on MeSH terms. The Buckingham et al 2005b,[434] Wieland et al 2005a,[121, 430] and Wieland et al 2005c[121, 430] filters also achieved the best combination of sensitivity and precision (Table 12.1).

12.3.2 EMBASE

The original search strategy using only the drug terms for thiazolidinediones and the named adverse effect (fractures) retrieved 1017 records of which 24 contained relevant adverse effects data (representing 23 studies) (Table 12.1). Although fewer records required sifting with the addition of the search filters (328 less with the BMJ Clinical Evidence 2006[432] filter, 546 less with the Golder et al 2006b[360] filter, and 621 less with Golder et al 2006a[360] filter), if any of the filters had been applied then not all the relevant records would have been identified. Three of the four references missed by all the search filters included the text word 'risk' but did not include any other terms related to 'adverse effects' in the title, abstract or indexing. The other reference missed by all the search filters did not contain any generic adverse effects terms (but did include fracture terms).

The additional reference missed by the Golder et al 2006b[360] filter was identified by the BMJ Clinical Evidence 2006[432]search strategy by the text word 'complications'. The additional five references missed by the Golder et al 2006a[360] filter were identified by the BMJ Clinical Evidence 2006[432] filter with the subheading 'Adverse Drug Reaction' (/ae) (four references) or the text word 'complications' (one reference).

Although the addition of the search filters improved the precision of the searches, this still remained low at below 5% (Table 12.1). The best combination of sensitivity and precision was achieved by the Golder et al 2006b*[360] filter, although none of the filters achieved a good balance due to low precision.

Table 12.1 Sensitivity, precision, and number needed to read (NNR) using search filters in MEDLINE and EMBASE

	Number of records retrieved	Number of relevant records (sensitivity N=19)	Precision	Number needed to read (NNR)	Sensitivity* precision
MEDLINE					
Original search with no filter	251	19 (100%)	7.57%	13	7.57%
Badgett 1999*[427, 428]	148	18 (94.74%)	12.16%	8	11.52%
BMJ Clinical Evidence 2006[432]	118	18 (94.74%)	15.25%	7	14.45%
Buckingham 2005a[434]	49	10 (52.63%)	20.41%	5	10.74%
Buckingham 2005b[434]	11	6 (31.58%)	54.55%	2	17.23%
Golder 2006a/2006b*[360]	201	19 (100%)	9.45%	8	9.45%
Wieland 2005a[121, 430]	22	10 (52.63%)	45.45%	2	23.92%
Wieland 2005b[121, 430]	10	4 (21.05%)	40.00%	3	8.42%
Wieland 2005c[121, 430]	28	11 (57.89%)	39.29%	2	22.74%
Wieland 2005d[121, 430]	45	8 (42.11%)	17.78%	6	7.49%
Wieland 2005e[121, 430]	58	11 (57.89%)	18.97%	5	10.98%
Wieland 2005f[121, 430]	120	18 (94.74%)	15.00%	7	14.21%
EMBASE					
	Number of records retrieved	**Number of relevant records (sensitivity N=24)**	**Precision**	**Number needed to read (NNR)**	**Sensitivity* precision**
Original search with no filter	1017	24 (100%)	2.36%	42	2.36%
BMJ Clinical Evidence 2006[432]	689	20 (83.33%)	2.90%	34	2.42%
Golder 2006a*[360]	396	15 (62.50%)	3.79%	26	2.37%
Golder 2006b*[360]	471	19 (79.17%)	4.03%	25	3.19%

*adapted search strategy

12.4 Discussion

In MEDLINE, the search filters by Badgett et al 1999,[427, 428] BMJ Clinical Evidence.[432] Golder et al 2006a/2006b,[360] and Wieland et al 2005f[121, 430] achieved a high level of sensitivity (95% or 100%) with an improved level of precision from the original search strategies. This would indicate that these MEDLINE search filters could have been a useful addition to the search strategies.

The highest precision in MEDLINE was achieved from those search filters that relied on Medical Subject Headings (MeSH). The search strategies by Buckingham et al 2005[434] were designed to achieve high precision (whereas the other filters were designed with systematic reviews in mind) so it is not that surprising that the Buckingham et al 2005b filter achieved the highest precision. However, as with all searching there was a trade-off between sensitivity and precision.

In EMBASE, the BMJ Clinical Evidence 2006[432] and Golder et al 2006b[360] search filters achieved a level of sensitivity that might be considered acceptable by some authors of systematic reviews, with a reduction in the number of records to sift. None of the search filters achieved 100% sensitivity and precision was low using any of the filters. Although precision remained low with the addition of adverse effects filters in EMBASE, in practical terms, hundreds less records required sifting. Therefore, depending on the level of sensitivity judged to be acceptable, these filters could be of use in situations where unmanageable numbers of records would otherwise be retrieved.

In terms of precision, the results from searching MEDLINE and EMBASE differed remarkably. Searches in MEDLINE achieved a much higher precision (or lower number needed to read, NNR) than similar searches in EMBASE. This could be due to differences in the practice of indexing in the two databases. Other studies have indicated that searches of EMBASE result in lower precision than MEDLINE.[413, 414]

This research indicates the potential value of adverse effects search filters, although as 100% sensitivity was not achieved by the majority of the filters, they should be applied with caution. Authors of systematic reviews may, therefore,

need to take pragmatic decisions when creating search strategies for adverse effects and sacrifice sensitivity for precision. In order to compensate for this loss in sensitivity, searches of electronic databases could then be supplemented with other means of identifying papers, such as reference checking, contacting industry, and citation searches.

The complete search strategy for identifying papers in a systematic review on adverse effects is also likely to depend on the inclusion criteria for the review. For example, if the inclusion criteria are limited to particular study designs, then the search strategy may need to reflect this. These search filters could be adapted for the review in question, so need not be used prescriptively but more as a basis for ideas for terms.

12.5 Limitations

The main limitation to the present study is that only one case study systematic review was used, limiting the generalisability of the results. In addition this case study was of a named adverse effect, while a case study of a safety profile systematic review, in which all adverse effects are searched, might have given different results.

A further limitation is the adaptation of the search strategies by Badgett et al 1999[427, 428] and Golder et al 2006.[360] These filters were originally created and tested for use in searches where the adverse effects were not known in advance of searching. In the present study, these search filters were used in addition to fracture terms, though use of the filters without the fracture terms would be impractical, given the vast number of irrelevant records that would have been retrieved (over 4000 with the filter by Badgett et al 1999,[427, 428] and over 6000 with the Golder et al 2006[360] filters).

12.6 Conclusions

Adverse effects search filters in MEDLINE, when combined with specific adverse effects terms, can achieve a high level of sensitivity with an improved level of precision. In addition, a high level of precision can be achieved in MEDLINE with adverse effects indexing terms. It appears difficult to achieve similar high levels of sensitivity and precision with search filters in EMBASE.

Further research is required, with more case study systematic reviews, for a range of interventions (pharmacological and non-pharmacological) and a diverse variety of adverse effects to test the generalisability of these findings. A broad range of reviews where no adverse effects terms were used in the search process could be assessed to determine whether the addition of an adverse effect filter would have improved precision of the searches without loss of sensitivity. This should include not just systematic reviews for specific named adverse effects (such as fractures) but also reviews that aim to provide a broad evaluation of the safety profile of an intervention, thereby capturing all adverse effects.

Similarly, as adverse effects data are available from different study designs (often non-randomized designs), it would help to design and evaluate the value of specific filters for particular types of study, such as, case-control study designs.

12.7 Summary

The 58 included references from the case study systematic review of thiazolidinedione-related fractures in Chapter 11 were used to test the performance of published search filters in MEDLINE and EMBASE.
Sensitivity, precision, number needed to read (NNR) and sensitivityXprecision were all measured.
A high level of sensitivity with an improved level of precision could be achieved in MEDLINE.
Precision remained low in EMBASE, even with a decrease in sensitivity.

Chapter 13 Adverse effects terms in database records: an analysis of the included papers from 26 systematic reviews

13.1 Introduction

One of the key difficulties in conducting specific searches for adverse effects stems from the absence of adverse effects terms in the title, abstract or indexing of relevant articles. In 2001, Derry et al[118] evaluated trials that reported data on adverse effects and found that about 23% of such trials had no adverse effects terms (either generic, such as 'adverse effect' or 'side effect', or specific, such as 'headache' or 'rash') in the title, abstract or indexing of records in either MEDLINE or EMBASE. Hence, electronic searches based on specific adverse effect related terms could miss nearly a quarter of the relevant papers. The lack of adverse effects terms in the title, abstract or indexing of papers that contain adverse effects data is a major problem for the creation of adverse effects search filters (combinations of search terms to retrieve references on adverse effects). Any combination of search terms that needs to designate adverse effects (either as terms in the tile, abstract or indexing) has a high potential to miss relevant papers. The lack of confidence in adverse effects search filters has led current guidance to emphasize the use of non-specific searches (without relying on adverse effects search filters) as well as the need to check full-text versions of retrieved articles.[22] Unfortunately, implementation of such guidance in systematic reviews is onerous and time-consuming compared to running more specific adverse effects based searches.

Methodological developments in the past decade might have changed the situation since Derry et al 2001's study.[118] At the time of Derry et al 2001's[118] study there was no specific requirement for authors to mention adverse effects in the title and abstract, even where adverse effects data are described in detail in the full paper. In 2003, 10 new recommendations about the reporting of harms were added to the Consolidated Standards of Reporting Trials (CONSORT) including a recommendation that it should be stated in the title or abstract if the study collected data on harms.[32] Additionally, the Cochrane Adverse Effects Methods group (http://aemg.cochrane.org/), which was formed in 2007, as well as many other authors, have called for improved reporting of adverse effects.[85, 122, 144, 145, 147, 148, 153, 575-596] However, it is unclear if these developments have had

a meaningful impact on the prevalence of adverse effects terms in the title, abstract or indexing of relevant adverse effects papers.

The case study reported in Chapter 12 also suggests that some adverse effects search filters proposed for MEDLINE[121, 360, 427, 428, 430, 432, 434] and EMBASE[360, 432] may be useful in increasing the precision of searches for adverse effects without a dramatic decline in sensitivity. This may be due to improvements in the reporting of adverse effects terms since the Derry et al 2001 study,[118] although the findings from the case study in Chapter 12 may not be generalisable to other systematic reviews.

The research in this Chapter aims to ascertain whether the reporting of adverse effects terms in the title, abstract, or indexing of papers that contain adverse effects data has improved since the study by Derry et al in 2001.[118] This would enable searchers to make better use of terms for adverse effects in identifying papers with adverse effects data when searching electronic databases. In addition, this research aims to assess the ability of published search filters to identify papers with adverse effects data in MEDLINE and EMBASE, with a more detailed analysis of individual search terms within these filters.

This research expands the study conducted by Derry et al 2001[118] by including a larger sample of included papers from a wider range of systematic reviews (thus improving on the generalisability of the results), including Science Citation Index (SCI), taking account of non-RCTs, and evaluating published adverse effects search filters and individual adverse effects search terms.

13.2 Methods

13.2.1 Selection of systematic reviews with adverse effects data

A collection of papers that reported data on the frequency of adverse effects was sought from the included studies from systematic reviews of adverse effects. The use of included papers from systematic reviews has been shown to be effective in identifying a reference standard set of records for use in studies evaluating search strategies.[597]

The included reviews may have evaluated adverse effects in different ways, for instance, by singling out specific named adverse clinical outcomes of interest (such as fractures or myocardial infarction), or by taking a broader look at the general safety or tolerability profile without any limits to particular adverse outcomes.

The systematic reviews of adverse effects were identified through browsing the Database of Abstracts of Reviews of Effects (DARE). Systematic reviews published up to 2006 were thought unlikely to contain a large volume of studies published from 2002 onwards. A systematic review was, therefore, considered eligible for inclusion if it was published between 2007 and 2010 (when the search was conducted). This was deemed a long enough time period in which to generate a sufficient number of papers to compare with the Derry et al 2001 study. In addition, a systematic review was considered eligible for inclusion if:

a) An adverse drug reaction was the primary outcome.
b) Generic adverse effects search terms or specified named adverse effects search terms had not been used by the review authors. This enabled an unselected cohort to be built, where relevant articles had not already been chosen because of the presence of adverse effects terms. Typically, such reviews would have relied on search terms for population/condition and intervention only, such as type 2 diabetes and rosiglitazone.
c) The search included either handsearching or reference checking in addition to database searches.

13.2.2 Selection of primary studies with adverse effects data

The included references in each systematic review were checked for papers published in English after the year 2000, so that a contemporaneous study cohort could be obtained. Non-English language papers were excluded, as there was concern about obtaining valid matches for adverse effects terms in different languages. Full-text articles were checked to confirm the presence of adverse effects data that had been used in the systematic review. The papers were then de-duplicated, in order to remove copies of papers that had been included in more than one systematic review.

13.2.3 Data analysis

13.2.3.1 Availability in selected databases

The first stage of the analysis was to check whether each paper was contained in MEDLINE, EMBASE or Science Citation Index (SCI). MEDLINE and EMBASE were selected in order to compare the results with Derry et al 2001 and because they are the most frequently used databases in systematic reviews of adverse effects (Chapter 10). Science Citation Index (SCI) was selected, as this database contained the highest number of relevant references in a case study systematic review of fractures and rosiglitazone conducted by the authors (Chapter 11). In order to ascertain whether each paper was contained in the databases, several iterations using author names and words from the title were used.

13.2.3.2 Adverse effects terms in the database records

For each database the available papers were checked to ascertain if:

1. The authors mentioned terms synonymous with ‘adverse effects’ in the title or abstract, potentially enabling the paper to be found in an electronic search. Adverse effects terms, such as ‘adverse events’, ‘side effects’, ‘tolerated’, and ‘unwanted effects’ were accepted. This is in line with terms accepted by Derry et al 2001.[118]
2. The authors mentioned specific named adverse effects terms (such as ‘headache’ or ‘cancer’) in the title or abstract. The terms were accepted based on the adverse effects included in the systematic review. For example, for a systematic review on cancer as an adverse effect, only cancer-related terms were accepted. This part of the analysis was only conducted on included studies from reviews for a specific named adverse effect.
3. The papers had been indexed (using subject headings or subheadings) with relevant terms for adverse effects, potentially enabling the paper to be found in an electronic search. Adverse effects terms were accepted on the basis that they could be considered synonymous with ‘adverse effects’ and would have been accepted by Derry et al 2001.[118] Examples of included indexing terms are drug toxicity/ and side effects/. Examples of included subheadings are ‘adverse effects (ae)’, or ‘adverse drug reaction (ae)’.

4. The papers had been indexed with specific named adverse effects terms. The terms were accepted based on the adverse effects included in the systematic review. For example, for a systematic review on cancer as an adverse effect, only cancer-related terms were accepted. This part of the analysis was only conducted on included studies from reviews for a specific named adverse effect.

13.2.3.3 Published search filters

The papers available on MEDLINE and EMBASE were checked to ascertain if they would have been identified if a published search filter had been applied to the search strategy. Each filter was tested in turn and the sensitivity of using each filter recorded. Due to the logistical constraints of repeating search strategies it was not possible to measure the precision of the search filters. It is reasonable to assume that precision will be higher with a search filter as opposed to without a filter, as fewer records would be retrieved with a filter. The MEDLINE search filters tested were Badgett et al 1999,[427, 428] Golder et al 2006,[360] BMJ Clinical Evidence 2006,[432] and Buckingham et al 2005,[434] and the EMBASE filters were Golder et al 2006[360] and BMJ Clinical Evidence 2006[432] (Appendix G). The PubMed filters by Wieland et al 2005[121, 430] were not tested as these filters were designed specifically for a review on oral contraceptives and breast cancer (Appendix H).

The search filters by Badgett et al 1999[427, 428] and Golder et al 2006[360] did not contain any specific named adverse effects terms and could therefore be tested on all the included papers. The other filters[432,434] (including a second filter by Golder et al 2006)[360] used specific named adverse effects terms and were, therefore, only tested on those included papers identified from systematic reviews of a specific named adverse effect and not those reviews that aimed to carry out a generalised broad evaluation of safety.

In addition to the search combinations proposed in the published search filters, each term included in at least one search filter was tested individually and the sensitivity measured; this included terms from Wieland et al 2005.[121, 430] The test was carried out to ascertain whether specific terms included in the search filters were particularly useful in retrieving papers containing adverse effects data.

13.3 Results

13.3.1 Systematic reviews included

Twenty-six systematic reviews met the inclusion criteria.[239, 598-622] Half were concerned with the safety profile for an intervention,[598, 599, 603, 606-611, 614-616, 619] while the other half were limited to a named/specific adverse effect with an intervention.[239, 600-602, 604, 605, 612, 613, 617, 618, 620-622]

13.3.2 Primary studies included

A total of 474 papers were included in the systematic reviews; 232 papers were excluded from the analysis; 140 were published before 2001, 33 papers did not contain adverse effects data in the full-text relevant to the systematic review in which they were cited, 26 were not indexed on either MEDLINE, EMBASE or Science Citation Index (SCI), 25 were duplicate papers (contained in more than one systematic review) and eight were published in a non-English language. Those references not identified in any of the databases were 15 company reports, eight conference papers, two Food and Drug Administration (FDA) reports and one book.

The remaining 242 papers were eligible for use in the analysis. The majority of the references (89%, 216/242) were for randomized controlled trials (RCTs), although, there were 13 case series, five chart reviews, three case reports, three cohort studies, one non-RCT study, and one uncontrolled study.

13.3.3 Database records of primary studies

There were 231 references indexed on MEDLINE, 119 papers from reviews on a specified adverse effect and 117 from safety profile reviews (five references were included in both types of review).

On EMBASE there were 222 references indexed (two of which were not indexed on MEDLINE), 113 papers from reviews on a specified adverse effect and 114 from safety profile reviews (5 references were included in both types of review).

References indexed on Science Citation Index (SCI) numbered 238 (11 of which were not indexed on MEDLINE), 127 papers from reviews on a specified

adverse effect and 116 from safety profile reviews (five references were included in both types of review).

13.3.4 Comparison with previous research

In order to compare the results with Derry et al 2001,[118] the adverse effects terms in the title, abstract and indexing of records on MEDLINE and EMBASE were recorded. A list of accepted terms identified in at least one paper is given in Appendix I: Table 15.23.

The number of included studies with adverse effects terms in the title, abstract or indexing in each of the 26 systematic reviews is listed in Appendix I:Table 15.24 summarises these results and compares them to the Derry et al 2001 study.[118] The average percentage of papers per systematic review containing adverse effects terms in the title or abstract or indexing in MEDLINE or EMBASE is higher in the present study than in Derry et al 2001.[118] The variation between reviews is greater in the present study than in Derry et al 2001.[118]

Table 13.1 Average percentage of records with adverse effects terms in the title, abstract or indexing in the present study and in Derry et al 2001

	Adverse effects terms in title or abstract (range)	**Adverse effect indexing terms in MEDLINE or EMBASE (range)**	**Retrievable by a combined search (range)**
Present study	69% (21% to 100%)	90% (14% to 100%)	92% (43% to 100%)
Derry 2001[118]	59% (49% to 69%)	64% (54% to 76%)	77% (69% to 83%)

Overall, a combined search using terms in the title, abstract or indexing run in both MEDLINE and EMBASE would have failed to retrieve 19 papers (8%) of the 233 papers across all 26 systematic reviews. All of these were RCTs. This is much lower than the 23% of papers that would have been missed with a similar search approach in Derry et al 2001.[118]

13.3.5 Variation between types of review

Those papers included in reviews which aimed to identify a specific named adverse effect were more likely to contain an adverse effect term in the title or

abstract (74% versus 65%), or in the indexing (97% versus 84%) in MEDLINE or EMBASE than the papers from a review which provided a safety profile for an intervention (Appendix I: Table 15.24).

13.3.6 Performance of adverse effects terms

13.3.6.1 Generic adverse effects terms

Generic adverse effects terms (such as side effect or adverse event) may be used in either systematic reviews of a safety profile of an intervention or reviews of a specific named adverse effect. Although the use of generic adverse effects terms in the title and abstract is similar in MEDLINE, EMBASE and Science Citation Index (SCI) (at around two-thirds), the use of indexing terms and subheadings varies considerably (Table 13.2). EMBASE, in particular, assigns generic adverse effect indexing terms to records far more frequently (66%) than MEDLINE (0.4%) or the keywords in Science Citation Index (SCI) (7%). Adverse effects subheadings are also used more frequently in EMBASE (83%) than MEDLINE (53%) and are not available in Science Citation Index (SCI).

13.3.6.2 Specific named adverse effects terms

The use of specific named adverse effects search terms could only be assessed in systematic reviews of specific named adverse effects. Although the use of specific adverse effects terms in the title and abstract is similar in MEDLINE, EMBASE and Science Citation Index (SCI) at around 25%, again the use of indexing terms varies considerably (Table 13.2). EMBASE, in particular, assigns specific named adverse effect indexing terms to records far more frequently (56%) than MEDLINE (8%), or the keywords in Science Citation Index (SCI) (14%).

13.3.6.3 Generic and specific adverse effects terms together

Using any adverse effects terms in the title, abstract or indexing would have identified 89% of all relevant references in EMBASE, 80% in MEDLINE and 70% in Science Citation Index (SCI) (Table 13.2).

Table 13.2 Adverse effects terms in the title, abstract or indexing of records in MEDLINE, EMBASE or Science Citation Index (SCI)

Database (number of records)	**Generic adverse effects in title, abstract**	**Generic adverse effects in indexing or keywords**	**Generic adverse effects in subheadings**	**Any generic adverse effects**
MEDLINE (N=231)	147 (64%)	1 (0.4%)	122 (53%)	179 (77%)
EMBASE (N=222)	147 (66%)	147 (66%)	185 (83%)	197 (89%)
Science Citation Index (SCI) (N=238)	153 (64%)	16 (7%)	NA	155 (65%)
Database (number of records)	**Specific adverse effects in title, abstract**	**Specific adverse effects in indexing or keywords**		**Any specific adverse effects**
MEDLINE (N=119)	28 (24%)	10 (8%)		31 (26%)
EMBASE (N=114)	29 (26%)	63 (56%)		66 (58%)
Science Citation Index (SCI) (N=127)	28 (22%)	18 (14%)		36 (28%)
Database (number of records)	**Any adverse effects terms (generic or specific) in title or abstract**	**Any adverse effects terms (generic or specific) in indexing, subheadings or keywords**		**Any adverse effects terms (generic or specific)**
MEDLINE (N=231)	164 (71%)	122 (53%)		185 (80%)
EMBASE (N=222)	156 (70%)	192 (86%)		198 (89%)
Science Citation Index (SCI) (N=238)	162 (68%)	32 (13%)		167 (70%)

13.3.6.4 Search filters which exclude specific named adverse effects

Search filters based on generic adverse effects terms (such as ‘adverse effect’ or ‘side effect’ or ‘tolerability’ or ‘toxicity’) can potentially be used in any systematic review and were tested on all the included studies. In MEDLINE 28% (65/231) and 13% (29/231) of papers would have been missed respectively if the Badgett et al 1999[427, 428] and Golder et al 2006[360] search filters had been applied. In EMBASE 12% (26/222) of papers would have been missed if the Golder et al 2006[360] search filter had been applied (Table 13.3).

13.3.6.5 Search filters which include specific named adverse effects

Those filters dictating the use of specific named adverse effects terms were tested with the included papers from systematic reviews of specific named adverse effects. In MEDLINE 77% (92/119), 93% (111/119), 97% (116/119) and 7% (8/119) of papers would have been missed respectively if the BMJ Clinical Evidence 2006[432], the Buckingham et al 2005 variants,[434] and Golder et al 2006[360] search filters had been applied. In EMBASE 43% (49/113) and 4% (5/114) of papers would have been missed respectively if the BMJ Clinical Evidence 2006[432]and Golder et al 2006[360] search filters had been applied (Table 13.3).

The sensitivity of the BMJ Clinical Evidence filter[432] would have been improved if the specific named adverse effects terms had been ORed instead of ANDed with the generic adverse effects terms. In MEDLINE, 109 papers would have been retrieved with a sensitivity of 92% (109/119) and 109 in EMBASE with a sensitivity of 96% (109/113).

Table 13.3 Sensitivity of MEDLINE and EMBASE search strategies for adverse effects

	Number of Relevant Records	Sensitivity
Search strategies excluding specified named adverse effects terms		
MEDLINE (N=231)		
Badgett[427, 428]	166	72%
Golder[360]	202	87%
EMBASE (N=222)		
Golder[360]	195	88%
Search strategies including specified named adverse effects terms		
MEDLINE (N=119)		
BMJ Clinical Evidence[432]	27	23%
Buckingham[434] *Without the quick filter (hedge)*	8	7%
Buckingham[434] *With the quick filter (hedge)*	3	3%
Golder[360]	111	93%
EMBASE (N=114)		
BMJ Clinical Evidence[432]	65	57%
Golder[360]	109	96%

13.3.6.6 Retrieval of RCTs and observational studies

Of the 24 non-RCT studies in MEDLINE, all were retrieved by either the BMJ Clinical Evidence 2006[432] and the Golder et al 2006[360] search strategies. The search strategy by Badgett et al 1999[427, 428] retrieved all but three chart reviews and one non-RCT.

Twenty-three non-RCT studies were available in EMBASE and all 23 were retrieved by the BMJ Clinical Evidence 2006[432] and the Golder et al 2006[360] search strategies.

13.3.6.7 Individual search terms

Appendix I: Table 15.25 shows the number of relevant records retrieved using each individual generic search term contained in at least one published search filter.

In MEDLINE, terms which retrieved the highest number of relevant records were the subheadings ‘therapeutic use (tu)’ (77%, 177/231) and ‘adverse effects (ae)’ (51%, 117/231). This was followed by the terms ‘adverse adj3 event$’ (32%, 75/231), ‘safety’ (31%, 71/231), ‘adverse adj2 events’ (29%, 67/231) and ‘risk’ (28%, 64/231) in the title or abstract, and the subheadings ‘drug effects (de)’ (27%, 62/231), and ‘complications (co)’ (18%, 41/231). None of the indexing terms retrieved a large proportion of the relevant records and searching the title and abstract or all fields made little difference to the results.

In EMBASE, the highest number of relevant records were retrieved with the floating subheadings, ‘adverse drug reaction (ae)’ (83%, 185/222) and ‘side effect (si)’ (83%, 185/222). This was followed by the EMTREE indexing term exp drug safety/ (38%, 85/222), and then the terms ‘adverse adj3 event$’ (32%, 71/222), ‘safety’ (28%, 63/222), ‘adverse adj2 events’ (28%, 63/222) and ‘risk’ (27%, 61/222) in the title or abstract.

It should be noted that‘adj2’ and ‘adj3’ refer to the adjacency or proximity operator in OVID. A search for ‘adverse adj3 event$’ will retrieve records in which the word ‘adverse’ occurs within 3 words of the word ‘event$’. The $ symbol is the truncation symbol in OVID to search for multiple words with the same root. For example, ‘event’ and ‘events’ will be retrieved.

13.4 Discussion

It is reassuring to note that the use of adverse effects terms in the title, abstract or indexing, in MEDLINE and EMBASE for articles that are known to contain adverse effects data, has increased compared to previous findings.[118] In the past, specific searches for studies that contained adverse effects data have been hindered by the frequent absence of adverse effects terms. However, these findings now indicate that reviewers can, with caution, choose to use more focused search filters, or specific named adverse effects terms, rather than face the arduous task of broad non-specific searches followed by evaluation of full-text articles.

The variation in adverse effects terms in the title, abstract or indexing in the current study is much greater than in the study by Derry et al 2001.[118] This might reflect the greater number of systematic reviews included in the present study,

(26 as opposed to three in the study by Derry et al 2001),[118] and the greater variation in topic coverage in the present study. However, this variation raises concerns for searchers who may wish to use adverse effects terms in their search strategies, as although for some systematic reviews 100% sensitivity was achieved, this was much lower for other reviews.

The use of specific named adverse effects indexing terms and generic adverse effects indexing terms was much higher in EMBASE than MEDLINE or Science Citation Index (SCI), and reflects the general practice in EMBASE of assigning more indexing terms to records. The high sensitivity in EMBASE may be at the cost of low precision. Other studies have indicated that EMBASE gives more irrelevant material than MEDLINE.[413, 414]

There was a lack of relevant keywords for adverse effects in the records from Science Citation Index (SCI). This is not surprising, given that these terms are assigned either by the author when the paper is submitted for publication, or from words or phrases that frequently appear in the titles of the references cited by the paper. This means that the adverse effect would need to be a key aspect of the paper or in the title of references for that paper to appear as keywords. In addition, not all records in Science Citation Index (SCI) contain keywords. For example, meeting abstracts tend not to include any keywords as the authors of abstracts generally do not have to provide keywords and abstracts generally do not include references. MEDLINE and EMBASE, on the other hand, have controlled vocabularies and indexing is a manual process based on the full text of the article.

The search filters by Badgett et al 1999[427, 428] and Golder et al 2006[360] achieved fairly high sensitivity, and the filter by BMJ Clinical Evidence 2006[432] would also have achieved high sensitivity had the specific named adverse effects been ORed instead of ANDed with the generic adverse effects terms. Whether this level of sensitivity is acceptable for a systematic review search will depend on the topic under evaluation, resources available, and anticipated gain in precision. For example, if the search filters reduced the numbers of records needed to sift from an unmanageable set of tens of thousands of records, these search filters may be worth using. High precision is often at the loss of sensitivity. For instance, the Buckingham filters[434] aimed to achieve high precision and it is not surprising that these filters fared poorly with respect to

sensitivity. The inevitable trade-off between sensitivity and precision may or may not be problematic depending on the particular review. For example, in situations where the search filters reduced the numbers of records needed to sift by only a handful, then any loss in sensitivity might not be acceptable. Even in circumstances where search filters reduce the numbers needed to read by a significant amount, caution might be needed in the case of rare events, where any loss in sensitivity might impact on the results of a review.

To limit things further, the analysis of the utility of particular search terms can help in the design of new filters, or in guiding the modification of existing ones for improved performance. The most useful individual search terms in both MEDLINE and EMBASE were adverse effects subheadings. These tended to retrieve more relevant records than either text words or indexing terms. In the common scenario where a customized search strategy for a particular topic needs to be built from scratch, it would be sensible to design the search with a greater emphasis on inclusion of relevant subheadings, rather than rely on picking up specific terms in the title or abstract. Subheadings are likely to be more useful, as there is a dearth of appropriate indexing terms available. In addition, adverse effects terms are less likely to appear in the title and abstract and when they do there is a lack of consistency in the terms used.

Evaluation of adverse effects may involve the inclusion of a range of different study designs, such as non-randomized pharmacoepidemiological studies. The ability to accurately identify relevant observational studies would be a potentially useful feature of a search filter. It has been suggested that the problems identified by Derry et al 2001 may extend to non-RCTs.[15] Although based on a small sample, the results here indicate that the BMJ Clinical Evidence 2006[432] and the Golder et al 2006[360] search strategies might be particularly useful in retrieving non-randomized studies. Many observational studies are focused on adverse effects as primary, rather than secondary, outcomes and are therefore easier to retrieve.

It was interesting to note that not all the references to included studies from each systematic review contained adverse effects data relevant to the systematic review. Some contained information on other adverse effects, some were letters or reviews referring to primary studies, and some were studies which simply reported on efficacy. In practical terms, this brings about debate on

whether it is best to spend time perfecting the search strategy for adverse effects or to write to all authors of studies which may have collected adverse effects data.

13.5 Limitations

The main limitation of this research is that the precision of the search terms and search filters could not be measured. Although this study indicates which search terms are most effective in retrieving papers with adverse effects data, these terms may also retrieve a high proportion of irrelevant records (but less so than similar searches with no adverse effects terms at all). In developing any search strategy it is important to obtain a balance between sensitivity and precision.

Caution should be applied when using the results of this study, especially as some of the search terms appeared to have only a vague connection to adverse effects (such as ‘therapeutic use’, ‘pharmacology’ ‘follow-up’ or ‘risk’). Although systematic review searches aim to be as comprehensive as possible, such a search may yield several thousand articles and only a small fraction of them will be relevant. Search results should aim to be manageable in terms of the feasibility of screening all the potentially relevant studies, particularly as previous recommendations have suggested that checking full-text may be necessary.

13.6 Conclusions

There is increasing prevalence of adverse effects terms in the title, abstract and indexing terms on MEDLINE and EMBASE of articles that contain adverse effects data. However, there is considerable variation in the reporting between topic areas.

With respect to individual search terms, subheadings, either free floating or with subject headings, appear to be most useful in identifying papers with adverse effects data in both MEDLINE and EMBASE. Few indexing terms exist for adverse effects, and the sensitivity of those is low, particularly in MEDLINE. Although some free text terms for adverse effects in the title and abstract may be useful, they should be applied in addition to other terms.

The adverse effects search filters available varied considerably in terms of sensitivity, and although high sensitivity could be achieved in both MEDLINE and EMBASE, 100% sensitivity was not achieved. Search filters for adverse effects could, therefore, be useful for capturing relevant records for systematic reviews of adverse effects; nonetheless, they should be applied with caution.

Further research, which also measures precision of the search terms and filters is required to establish the full value of using adverse effects terms in search strategies. In the meantime, improvements in the allocation of subheadings to bibliographic records could ease the workload of the systematic reviewer.

13.7 Summary

Two hundred and forty-two articles with adverse effects data were selected from 26 systematic reviews for analysis. The sensitivity of adverse effects search filters and individual search terms were calculated.

The sensitivity of search filters for adverse effects varied but a high sensitivity could be achieved. Subheadings provided the highest sensitivity of the individual search terms assessed.

There is an increasing prevalence of adverse effects terms in the title, abstract, and indexing of records in MEDLINE and EMBASE. Overall a search on both MEDLINE and EMBASE would have failed to identify 8% of relevant articles. However variation exists between topic areas.

Chapter 14 Discussion

14.1 Overall summary

Healthcare professionals, patients and policy makers need to make informed decisions about the drugs they administer or recommend. To do this they require evidence about the effectiveness of drugs and their adverse effects. New drugs do not usually add many 'benefits' in comparison to current treatments so a full investigation of adverse effects can be a 'deciding factor'.

Systematic reviews are generally regarded as providing the best evidence to inform decision making and should provide a reliable and objective source of information on both the effectiveness and adverse effects of an intervention. Considerable research and effort has been undertaken in establishing optimal information retrieval methods for identifying studies of effectiveness. The overall aim of this thesis was to identify and evaluate optimal methods for retrieving information on adverse drug effects within systematic reviews.

The first stage was to identify and consolidate the existing research evidence in this area. A systematic review was undertaken, which summarised all aspects of the methodological literature to date on the retrieval of information on adverse effects and the impact of different sources of information (Chapters 3 to 9). Topic areas included: study design selection (such as RCTs versus cohort studies); the relative value of different sources of information (such as database and non-database sources) in identifying relevant information; the usefulness of adverse effects database search filters; the impact of the inclusion of unpublished material and industry funded studies; and potential bias by type of author (clinician or academic); journal impact factor; year of publication; and country setting.

The second stage of this programme of research aimed to summarise current practice in the retrieval of information in systematic reviews of adverse effects and identify any apparent time trends in the methodologies employed. An evaluation was undertaken of the search methods in 849 systematic reviews published between 1994 and 2011 (Chapter 10). The search methods used in

these systematic reviews of adverse effects were also compared with those methods used in other types of systematic reviews.

The final stage of this thesis was to carry out primary investigations into two major gaps in the research on the retrieval of information on adverse effects, namely the effectiveness of adverse effects database search filters and the relative value of searching different information sources for adverse effects data. These issues were addressed in a detailed analysis of a systematic review conducted by the author and an evaluation of a series of published systematic reviews.

The papers included in a systematic review of thiazolidinedione related-fractures were used to assess the relative contribution of different information sources (including databases and non-database sources) in identifying relevant references or studies (Chapter 11). This case study was then used to measure the sensitivity and precision of published adverse drug reaction search filters in MEDLINE and EMBASE (Chapter 12).

In addition, 242 included papers from 26 systematic reviews of adverse drug reactions were used to assess the sensitivity of individual adverse effects search terms in MEDLINE, EMBASE and Science Citation Index (SCI) and the sensitivity of adverse effects search filters in MEDLINE and EMBASE (Chapter 13).

As far as can be ascertained, this is the first attempt to amalgamate all the literature pertaining to the retrieval of information on adverse effects and the largest most comprehensive analysis of data sources and search strategies for adverse drug reactions.

14.2 Main Findings

There are a number of important findings from this research. On average, there is no difference in the risk estimates of adverse effects of an intervention derived from meta-analyses of RCTs and those from meta-analyses of observational studies. In almost all instances the confidence intervals from meta-analyses of RCTs and meta-analyses of observational studies overlap and there is agreement in terms of the conclusions reached.

The value of identifying unpublished data and industry funded studies is highlighted. This research found that unpublished studies and data from drug manufacturers can provide additional data that is not otherwise covered in published studies.There was mixed evidence surrounding the postulated link between industry funding and more favourable reporting of adverse drug reactions data. Industry funded studies contained more complete reporting of adverse drug reactions but tended to have more positive conclusions, irrespective of the raw adverse effects data. These findings are confirmed in more recent studies. For example, differences in the types of case reports in the published literature and unpublished pharmacovigilance systems have been identified,[623] a comparison of conference abstracts and journal articles to full reports in the GlaxoSmithKline (GSK) Clinical Trials Registry suggested that 87.9% of all adverse effects were not reported in publically available 'published' versions,[624] published studies on insomnia medication have also been found to report much less safety information than unpublished studies,[625] and industry sponsored trials have been found to be associated with better harm reporting.[626]

Based on the research evidence from this thesis, it is clear that no single information source contains all of the data on adverse effects for a particular systematic review and that MEDLINE may not yield the highest number of relevant articles. The most efficient combination of sources to identify information on adverse effects is still unknown. Neither is agreement on a hierarchy of information sources (based on their relative value) likely to be reached in the near future.

It was found that adverse effects search terms are increasingly prevalent in the title, abstract and indexing terms of records that contain adverse drug reactions data in MEDLINE and EMBASE. The value of using subheadings in MEDLINE and EMBASE (such as 'adverse effects' in MEDLINE and 'adverse drug reaction' in EMBASE) is also particularly apparent. It was interesting to note that 61% of systematic reviews of adverse effects analysed in this thesis include some outcome (adverse effects) terms in their search strategy.

Although there is a slight improvement in the reporting of search strategies in systematic reviews of adverse effects from 1994 to 2011, overall only 9% of such reviews report a reproducible search strategy. There is also some

improvement in the search methodology adopted in systematic reviews of adverse effects. The number of databases searched appears to be increasing, and the proportion of reviews limiting their searches to MEDLINE or using date or language restrictions to be decreasing. These changes are not dramatic, and few other improvements in search methods are apparent.

Particular areas of concern in the methodology of systematic reviews of adverse effects are the increase in the proportion of reviews limited to RCTs only between 1994 and 2011, the lack of any attempts to identify unpublished data or data from pharmaceutical companies, and the potentially inappropriate selection of information sources. There were large discrepancies between the individual information sources contributing the most information on adverse effects and those sources currently searched in systematic reviews of adverse effects (Appendix J). For instance, the highest sensitivity in the case study review was achieved by searching Science Citation Index (SCI) followed by BIOSIS Previews, yet only 5% and 8% of reviews respectively search these databases. No reviews searched Scirus, Derwent Drug File, British Library Direct, Thomson Reuters Integrity, and ADIS Clinical Trials Insight, yet these databases retrieved 29%, 28%, 26%, 22% and 21% of references respectively. Although MEDLINE is the most commonly used database and indeed is often the only database searched, only 33% of relevant references were retrieved with this database in the case study systematic review.

The results of this programme of research have important implications for practice, guidance and the direction of further research.

14.3 Implications for practice

The findings from this thesis have several implications for the conduct of systematic reviews. In particular the results suggest that rather than limiting systematic reviews to certain study designs it might be better to evaluate a broad range of studies. In this way a more complete, generalizable picture of harms of an intervention might be built, without any loss of validity. This is particularly relevant in reviews in which there are few RCTs identifying or reporting adverse effects, or where the reporting in RCTs is poor. When few RCTs are identified that report harms, this can lead to a misconception that a given intervention is safe, when its safety is actually unknown. Reviews which

assess long-term, rare or unexpected adverse effects may not identify adverse effects if their analysis is limited to RCTs. RCTs rarely assess harms as their primary outcome, so typically lack the power to detect differences in harms between groups. Usually designed to evaluate treatment efficacy/effectiveness, RCTs are often conducted over a shorter period of time, with relatively smaller number of participants than observational studies.

Evidence from this programme of research indicates that authors of systematic reviews incorporating adverse effects should consider including unpublished studies and industry funded data to enable adverse effects to be identified earlier and to obtain a more precise estimate of effect or incidence. However, including unpublished data and industry funded studies brings challenges. For example, particular care is required in assessing the quality of unpublished material that has not been through the rigorous peer review process many journal editors employ. Review authors also need to minimize the possibility of data duplication or double counting - as the same adverse effect may appear in the published and unpublished data. Authors may therefore need to reconcile the various adverse effects reports to establish which to use, especially if data differs between sources. In addition, extra vigilance could be required by systematic reviewers in assessing any author interpretation or conclusions in industry funded studies, as these might be unduly positive.

A further challenge is in identifying industry funded studies and the unpublished literature.[114] Searches might need to be extended beyond standard bibliographic databases to identify data from specialist websites, company and other study/trial registries, regulatory agencies (such as Health Canada and the FDA), conference abstracts, contacting experts, and reference lists. Contacting industry for information is notoriously slow and time consuming with low response rate. It would be helpful, therefore, if drug companies made all their data available publically, for example by making all study reports available on their websites or by depositing data in publicly accessible repositories such as clinicaltrials.gov. Improvements in the usability of websites, such as the FDA website and conference websites, and the accessibility (in terms of aspects such as cost and functionality) of databases of conference proceedings, could also help reviewers identify and/or obtain unpublished data.

The particular information sources that should be searched in any systematic review will vary depending on the topic area of the review and it is difficult to generalize the findings from this research to all reviews. However, it is clear from the research in this thesis, that authors of systematic reviews should not rely solely on MEDLINE for information on adverse effects but should attempt to identify data on adverse effects from multiple sources, and use additional techniques such as handsearching and reference checking. In light of these findings, searchers might need to rethink their current practice and choice of databases.

Previous research indicated that adverse effect search terms cannot be relied upon, and that any search strategy that includes adverse effects terms could miss a high volume of relevant references. Although caution still needs to be exercised, the situation has improved and search strategies in MEDLINE and EMBASE can now include adverse effects terms or adverse effects search filters with reasonable sensitivity. The improved reporting of adverse effects in bibliographic records may, in part, be a result of the implementation of guidelines for trial reporting such as CONSORT (Consolidated Standards of Reporting Trials)[626 , 627-631] and subsequent better indexing of adverse effects by database providers. If improvements continue, review authors will be able to use adverse effects search terms and search filters with more confidence.

Authors of systematic reviews still need to improve the reporting of search strategies for adverse effects and report more reproducible search strategies in order for readers to be convinced by the methodology and for update searches to be undertaken. A number of guidelines on reporting standards of systematic reviews are now available to help authors, such as AMSTAR[632] (Assessment of Multiple Systematic Reviews), RAMESES[633] (Realist And MEta-narrative Evidence Syntheses: Evolving Standards), MOOSE[550] (Meta-analysis of Observational Studies in Epidemiology), MECIR (Methodological standards for the conduct of Cochrane Intervention Reviews), PRISMA[546, 547,550] (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and PRISMA Harms Extension) and journal editors are encouraging adherence to these guidelines. These guidelines all include aspects on the reporting of search strategies (such as the search strategy itself) and on the information sources (database and non-database) searched. In addition to these guidelines more journals now allow the inclusion of web appendices and supplementary material,

enabling authors of systematic reviews to overcome restrictive word limits to journal articles and to report full search strategies for at least one of the databases searched.

In summary, carrying out a systematic review of adverse effects (as a standalone review or in addition to an effectiveness review) is an arduous task in which an attempt should be made to search multiple data sources (including unpublished data sources and industry data) for a range of study designs. The inclusion of all study designs, as well as published and unpublished studies and studies funded by industry and non-profit organisations, is likely to create a large workload for any systematic reviewer, especially where a safety profile review is undertaken, including all possible adverse effects. However, improvements in assigning adverse effects search terms to bibliographic records in databases may lead to opportunities to use adverse effects search filters with more confidence and help ease the workload of the reviewer. In addition, systematically reviewing all of the evidence for all possible adverse effects might be impractical, with decisions needing to be made to assess only those adverse effects that are important to decision makers and patients or to make transparent decisions to limit by other factors which can be justified based on the individual review.

14.4 Dissemination and implications for guidance

Guidance on searching for information on adverse effects needs to be updated in the light of the findings in this programme of research, and should be disseminated to a targeted audience. A wide variation in the search methodology employed in systematic reviews of adverse effects is identified in this thesis. The need for further development of guidance and a consensus in standards for retrieving adverse effects data is also highlighted. Current main sources of guidance for systematic reviewers are: The Cochrane Handbook;[22] and CRD's Guidance for undertaking reviews in healthcare.[23] Both of these texts have relevant sections on searching and incorporating adverse effects data, which can now be based on much stronger evidence.

Dissemination has been an integral part of this programme of research. Efforts have been made to present the research sections of this thesis as they are completed, to ensure the timeliness of the dissemination of the findings.

Dissemination has included publications in peer-review journals,[352, 547, 561, 634-640] presentations and workshops at international conferences, and seminars at national events.

Where papers were submitted was carefully considered in order to reach the most appropriate audience while satisfying academic requirements of achieving high impact publications. For example, papers on advanced searching techniques are mainly of interest to information specialists, therefore journal titles, such as Health Information Libraries Journal and the Journal of Medical Library Association, were selected. Academics/researchers were targeted through journals such as the Journal of Clinical Epidemiology, International Journal of Technology Assessment in Health Care, and BMC Medical Research Methodology. Clinicians and other health professionals through journals such as Therapeutic Advances in Drug Safety, PLOS Medicine, PLOS One and the British Journal of Clinical Pharmacology. These audiences overlap and in addition, these publications may be viewed by people from other fields. As of November 2013, 15 journal articles have been published with the findings from this research, and these have already been cited in over 250 publications (Google Scholar), including other journals, and textbooks on methodological standards in systematic reviews[641, 642] and clinical research.[643, 644] A complete summary of the thesis, which summarises all the pertinent findings, is also to be published in Health Information Libraries Journal

Presentations have also been targeted at a wide international and national audience with oral presentations at Cochrane Colloquia, Cochrane Entities meetings, a Cochrane Canada webinar, Pharma-Bio-Med conferences, National Institute for Health and Care Excellence (NICE) meetings, InterTASC Information Specialists' Sub-Group (ISSG) meetings and the School of Health and Related Research (ScHARR) symposium. Information on the dissemination products from this research are also listed on a CRD projects page[645] and some of the presentations are available on YouTube, the Cochrane Adverse Effects Methods Group website and the Cochrane Collaboration training website.

Positive critical summaries of this research are available in the safety section of the SuRe Info (Summarized Research in Information retrieval for HTA) resource on the HTAi (Health Technology Assessment international) Vortal[646] and the search strategy elements are appraised on the InterTASC Information

Specialists' Sub-Group (ISSG) Search Filter Resource.[426] A critical appraisal of this research has also been published in the Cochrane Newsletter.[647]

The search strategy elements from this thesis have already been incorporated into search guidance provided by Elsevier on searching EMBASE[648] and the author of this thesis has been approached to collaborate on an update of the adverse effects chapter in The Cochrane Handbook and to incorporate the findings from this thesis into the handbook.

The support and advice for authors of reviews of adverse effects (through groups such as the Cochrane Adverse Effects Methods group) has been enhanced by the research from this thesis. Regular workshops targeted at this challenging area of systematic reviewing are now far more evidence based. This support needs to continue to grow.

The provision of current evidence based guidance, support and training can lead to improvements in other people's work, improving the evidence that endorses policy and practice and ultimately enhancing patient care.

14.5 Implications for research

Although the research from this thesis addresses many questions, there are still questions that remain unanswered. The results from the comparisons of different types of study design could be explored further. For example, it would be useful (based on a case-control type of design) to carry out an in-depth examination of the meta-analyses (and their included primary studies) with substantial discrepancy amongst the RCTs and observational studies, as compared to other meta-analyses where RCTs and observational studies had close agreement. Any future research in this area should consider the role of confounding factors (such as different population selection, duration of drug exposure, drug dosage etc.) between studies, and the lack of precision in point estimates of risk for rare events that could have accounted for discrepant findings amongst RCTs and observational studies.

Different types of adverse effects may be identified by different study designs. This research compared study designs which reported on the same adverse effects for the same intervention and identified similar estimates. The types of

adverse effects reported in RCTs and non-RCTs can differ substantially, given differences in populations, length of follow-up, sample size and ascertainment. For example, observational studies tend to include larger sample sizes with a longer follow-up period than RCTs and could be more likely to identify long-term rare events.

The reason for the increase in the proportion of systematic reviews limiting their analysis to RCTs requires investigation. It might be due to the difficulties of including non-RCTs, in which case further support and guidance may be required for authors of reviews, or it may be inexperienced or under-resourced reviewers, or it may be a perception that RCTs are sufficient, or that observational studies are inferior or may introduce bias, or limiting to RCTs may be used to reduce large numbers of records.

The research in this thesis which assessed the contribution of different sources of information and the performance of different search strategies in terms of sensitivity and precision was based on only one case study systematic review. More case studies are needed if the generalisability of these results is to be improved.

Due to the retrospective nature of the analysis of the search strategies in the 26 published systematic reviews, the precision of the adverse effects search filters and adverse effects search terms could not be calculated. Further research evaluating the sensitivity ***and precision*** of adverse effect search filters and individual search terms in multiple reviews is required, including assessment of the inevitable trade-off between the two and impact on the results of reviews.

Research is needed into the development of adverse effects search filters in databases other than MEDLINE - in particular, filters with higher precision in EMBASE and filters in those databases providing a high yield of relevant records such as Science Citation Index (SCI), BIOSIS Previews, and Derwent Drug File. It was notable that search filters were predominately written for MEDLINE.

This thesis focused on the retrieval of adverse effects of pharmaceutical interventions. It is apparent that much of the research on adverse effects has focused on drug information and few systematic reviews of adverse effects

include a non-pharmaceutical intervention. Although some of the same principles may apply to other types of interventions, such as surgical procedures, medical devices, or diagnostic procedures, there are many differences that require exploration. Retrieval of information on the adverse effects of non-drug interventions may be even more problematic than for drug interventions, particularly given the scarcity of specialist information sources, inconsistent terminology, poor reporting in primary studies and a lack of acknowledgement that non-drug interventions have adverse effects.

Future research on information retrieval might benefit from sensitivity analysis of the results of systematic reviews, whereby meta-analyses are repeated with and without the inclusion of papers from different sources, as we need to answer the question of whether searching so widely actually makes a difference to the results and conclusions of systematic reviews and ultimately the decisions made by patients, health professionals and policy makers. However, with such research, caution needs to be applied as the generalisability of the results will always be questionable. In addition, if there is no bias or systematic difference in articles available from different sources (say MEDLINE versus EMBASE), any review that aims to be thorough and obtain a precise estimate of the results as possible may need to include as many studies as possible. This could be particularly the case with adverse effects, which, by their very nature, are rare.

Future research should help inform guidance even further and enable more definitive recommendations in the complexities of creating search strategies and the selection of sources, particularly in areas not covered in this thesis, such as non-drug interventions.

14.6 Conclusions

Although there have been improvements in the search methods used in systematic reviews of adverse effects, there are still some major discrepancies between the methods advocated in the literature and current practice. These are particularly apparent in the selection of databases searched, the lack of searches for unpublished data and industry funded studies, and the increasing restriction of included studies to RCTs only. In addition, poor reporting of search strategies in systematic reviews of adverse effects remains a major obstacle to

those wishing to replicate or update the searchers or assess the quality of the review.

The results of this programme of research support broad inclusion of sources in reviews of adverse drug reactions. Empirical studies suggest that including industry funded data, unpublished data and observational studies in a systematic review is unlikely to bias the results of a review but contribute extra data that might enable adverse effects to be identified earlier and more precise estimates of adverse effects to be obtained.

In relation to where and how to search, it is apparent that a combination of sources are required to identify adverse drug reactions data for systematic reviews and that MEDLINE is unlikely to contribute the highest yield of relevant papers. Evidence also suggests that using adverse effects search filters for databases such as MEDLINE and EMBASE can be useful and the success of adverse effects search terms and filters to capture relevant papers has improved.

The suggested recommendations for authors of systematic reviewers that have evolved from this research will hopefully lead to more systematic reviews incorporating adverse effects (either as a standalone review or in addition to an evaluation of effectiveness) and to improvements in the reporting and conduct of the literature searches in such reviews.

Chapter 15 Appendices

Appendix A: **Search strategies for methodological overviews in Chapters 3 to 9**

Cochrane Database of Systematic Reviews (CDSR): methodology reviews only
Interface: http://www.thecochrane library.com
Version: 2007 Issue 3 (original search), 2008 Issue 3 (first update search), 2009 Issue 4 (second update search)
Date Searched: 26/09/07 (original search), 17/08/09 (first update search), 22/10/09 (second update search)
In the original search 10 protocols and 12 systematic reviews were browsed for potentially relevant articles. None were deemed relevant. The first update search, only identified one new review and this was not deemed relevant. The second update search identified 3 new protocols and one new review and these were not deemed relevant.

Cochrane Methodology Register (CMR)
Interface: http://www.thecochrane library.com
Version: 2007 Issue 3 (original search), 2008 Issue 3 (first update search), 2009 Issue 4 (second update search)
Date Searched: 26/09/07 (original search), 17/08/09 (first update search), 22/10/09 (second update search)
The following search strategy, using terms in the title, abstract and keywords, retrieved 1517 records in the original search and an extra 249 records in the first update search and 344 in the second update search;

#1 adverse
#2 side next effect*
#3 unintended next effect*
#4 unintended next event*
#5 unintended next outcome*
#6 unintended next reaction*
#7 unintended next interaction*
#8 unintended next response*
#9 unintentional next effect*
#10 unintentional next event*
#11 unintentional next outcome*
#12 unintentional next reaction*
#13 unintentional next interaction*
#14 unintentional next response*
#15 unwanted next effect*
#16 unwanted next event*
#17 unwanted next outcome*
#18 unwanted next reaction*
#19 unwanted next interaction*
#20 unwanted next response*
#21 unexpected next effect*
#22 unexpected next event*
#23 unexpected next outcome*

#24 unexpected next reaction*
#25 unexpected next interaction*
#26 unexpected next response*
#27 undesirable next effect*
#28 undesirable next event*
#29 undesirable next outcome*
#30 undesirable next reaction*
#31 undesirable next interaction*
#32 undesirable next response*
#33 adrs or ades or adr
#34 drug next surveillance
#35 post next marketing next surveillance
#36 postmarketing next surveillance
#37 treatment next emergent
#38 complication*
#39 tolerability
#40 toxicity
#41 harm or harms or harmful
#42 safety
#43 safe
#44 tolerance
#45 tolerate
#46 toxic
#47 risk or risks
#48 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47)

Database of Abstracts of Reviews of Effects (DARE)
Interface: Administration CRD in-house database
Date Range: 1994 - Present
Date Searched: 26/09/07 (original search), 13/08/08 (first update search), 27/10/09 (second update search)
The search strategy was composed of two search facets, adverse effects and methodology papers. Searching for m in the st1 field enable the search to be limited to methodology papers and to exclude example systematic reviews. The following search strategy retrieved 341 records in the original search and 13 new records were identified in the first update search and 40 in the second update search;
The original and first update search were carried out in the old CAIRS interface as follows
S adverse or side(w)effect$ or unintended(w)effect$ or unintended(w)event$ or unintended(w)outcome$ or unintended(w)reaction$ or unintended(w)interaction$ or unintended(w)response$ or unintentional(w)effect$ or unintentional(w)event$ or unintentional(w)outcome$ or unintentional(w)reaction$ or unintentional(w)interaction$ or unintentional(w)response$ or unwanted(w)effect$ or unwanted(w)event$ or unwanted(w)outcome$ or unwanted(w)reaction$ or unwanted(w) interaction$ or unwanted(w)response$ or unexpected(w)effect$
S unexpected(w)event$ or unexpected(w)outcome$ or unexpected(w)reaction$ or unexpected(w)interaction$ or unexpected(w)response$ or undesirable(w)effect$ or undesirable(w)event$ or undesirable(w)outcome$ or undesirable(w)reaction$ or undesirable(w)interaction$ or undesirable(w)response$ or adrs or ades or adr or drug(w)surveillance or

post(w)marketing(w)surveillance or postmarketing(w)surveillance or treatment(w)emergent or complication$ or tolerability or toxicity or harm or harms or harmful or safety or safe or tolerance or tolerate or toxic or risk or risks
S s1 or s2
S m/st1
S s3 and s4

The second update search was carried out in the CMS interface as follows;
1) adverse
2) "side effect*"
3) "unintended effect*"
4) "unintended event*"
5) "unintended outcome*"
6) "unintended reaction*"
7) "unintended interaction*"
8) "unintended response*"
9) "unintentional effect*"
10) "unintentional event*"
11) "unintentional outcome*"
12) "unintentional reaction*"
13) "unintentional interaction*"
14) "unintentional response*"
15) "unwanted effect*"
16) "unwanted event*"
17) "unwanted outcome*"
18) "unwanted reaction*"
19) "unwanted interaction*"
20) "unwanted response*"
21) "unexpected effect*"
22) "unexpected event*"
23) "unexpected outcome*"
24) "unexpected reaction*"
25) "unexpected interaction*"
26) "unexpected response*"
27) "undesirable effect*"
28) "undesirable event*"
29) "undesirable outcome*"
30) "undesirable reaction*"
31) "undesirable interaction*"
32) "undesirable response*"
33) adrs
34) ades
35) adr
36) "drug surveillance"
37) "post marketing surveillance"
38) "postmarketing surveillance"
39) "treatment emergent"
40) complication*
41) tolerability
42) toxicity
43) harm
44) harms
45) harmful
46) safety
47) safe

48) tolerance
49) tolerate
50) toxic
51) risk
52) risks
53) #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52
54) RESTRICT RR 7 Methodology
55) #53 and #54

EMBASE

Interface: Ovid Biomed
Date Range: 1980 to 2007 Week 38 (original search), 1980 to 2008 Week 32 (first update search), 1980 to 2009 Week 42 (second update search)
Date Searched: 27/09/07 (original search), 14/08/08 (first update search), 23/10/09 (second update search)
The main search strategy contain three facets; adverse effects, systematic reviews and methodology. The strategy was very pragmatic in nature and some terms were limited to title or exclude if they created too much noise. In addition, because of the limitations of this pragmatic approach to searching the search was supplemented by searching for adverse effects terms along with known experts in the field of adverse effects. The original searches retrieved 1315 records and the first update search retrieved another 159 records and the second update search 203 records.

1 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
2 side effect$.ti,ab.
3 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
4 (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
5 (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
6 (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
7 (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
8 (adrs or ades).ti,ab.
9 drug safety.ti,ab.
10 (drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.
11 tolerability.ti,ab.
12 (harm or harms or harmful).ti,ab.
13 exp postmarketing surveillance/
14 exp iatrogenic disease/
15 drug safety/
16 exp drug toxicity/
17 treatment emergent.ti,ab.
18 drug toxicity.ti,ab.
19 (iatrogenic or iatrogenesis).ti,ab.
20 complication$.ti.

21 toxicity.ti.
22 safety.ti.
23 safe.ti.
24 meta-analysis/
25 meta-analysis.ti,ab.
26 meta-analyses.ti,ab.
27 metaanalysis.ti,ab.
28 metaanalyses.ti,ab.
29 metanalysis.ti,ab.
30 metanalyses.ti,ab.
31 metasynthesis.ti,ab.
32 metasyntheses.ti,ab.
33 meta-synthesis.ti,ab.
34 meta-syntheses.ti,ab.
35 narrative synthesis.ti,ab.
36 narrative syntheses.ti,ab.
37 bibliographic stud$.ti,ab.
38 data selection.ti,ab.
39 data pooling.ti,ab.
40 pooled analysis.ti,ab.
41 pooled analyses.ti,ab.
42 odds ratio.ti,ab.
43 odds ratios.ti,ab.
44 medical literature/
45 literature review$.ti,ab.
46 review of studies.ti,ab.
47 systematic review$.ti,ab.
48 Cochrane review$.ti,ab.
49 evidence synthesis.ti,ab.
50 research synthesis.ti,ab.
51 critical appraisal.ti,ab.
52 validity assessment$.ti,ab.
53 quality assessment$.ti,ab.
54 data extraction.ti,ab.
55 data synthesis.ti,ab.
56 study selection.ti,ab.
57 inclusion criteria.ti,ab.
58 literature searching.ti,ab.
59 (formulating adj3 question$).ti,ab.
60 locating.ti,ab.
61 (search or searches).ti.
62 searching.ti.
63 Publication/
64 information storage/ or information retrieval/
65 data base/ or exp bibliographic database/
66 databases.ti.
67 (medline or embase or derwent drug file or cinahl or psycinfo or idis or pharmline or toxline).ti.
68 information retrieval.ti,ab.
69 search strategies.ti,ab.
70 search filter$.ti,ab.
71 Different sources.ti,ab.
72 trials.ti.
73 ((random$ or clinical or multicent$ or case control or population based) and studies).ti.

74 RCTs.ti.
75 Study design$.ti.
76 (type adj2 study).ti. or types of study/
77 Case series.ti.
78 (Observational and studies).ti.
79 (cohort studies or case-control studies).ti.
80 Non-randomi?ed.ti.
81 nonrandomi?ed.ti.
82 Case reports.ti.
83 Anecdotes.ti.
84 Spontaneous report$.ti.
85 (conflict adj2 interest$).ti,ab.
86 (competing adj2 interest$).ti,ab.
87 (funding or funder or funded).ti,ab.
88 (financed or sponsored).ti,ab.
89 (grey literature or gray literature or unpublished).ti,ab.
90 publishing/
91 methodological issues.ti,ab.
92 methods.ti.
93 methodological.ti.
94 methodology.ti.
95 assessing.ti.
96 limitation$.ti.
97 bias.ti.
98 challenge$.ti.
99 how to.ti.
100 how do.ti.
101 suggestion$.ti.
102 instruction$.ti.
103 reporting$.ti.
104 quantify$.ti.
105 guidance.ti.
106 evaluation of methods.ti,ab.
107 or/1-23
108 or/24-90
109 or/91-106
110 107 and 108 and 109
111 derry s$.au. and 107
112 ioannidis j$.au. and 107
113 aronson j$.au. and 107
114 loke y$.au. and 107
115 chou r$.au. and 107
116 ashby d$.au. and 107
117 herxheimer a$.au. and 107
118 jefferson t$.au. and 107
119 etminan m$.au. and 107
120 or/110-119

Health Technology Assessment (HTA) Database
Interface: Administration CRD in-house database
Date Range: 1994 – Present
Date Searched: 26/09/07 (original search), 13/08/08 (first update search), 04/11/09 (second update search)

A search on all fields retrieved thousands of irrelevant records not relating to methodology as did the terms risk and safety, all search terms were therefore limited to the title field using the following search strategy and the risk and safety terms were removed. The original searches retrieved 43 records and the first update searches retrieved 6 records and the second update search 5 records. The original search and the first update search were carried out in the CAIRS interface with the following search strategy;

S (adverse or side(w)effect$ or unintended(w)effect$ or unintended(w)event$ or unintended(w)outcome$ or unintended(w)reaction$ or unintended(w)interaction$ or unintended(w)response$ or unintentional(w)effect$ or unintentional(w)event$ or unintentional(w)outcome$ or unintentional(w)reaction$ or unintentional(w)interaction$ or unintentional(w)response$ or unwanted(w)effect$ or unwanted(w)event$ or unwanted(w)outcome$ or unwanted(w)reaction$ or unwanted(w) interaction$ or unwanted(w)response$ or unexpected(w)effect$)/ttl
S (unexpected(w)event$ or unexpected(w)outcome$ or unexptected(w)reaction$ or unexpected(w)interaction$ or unexpected(w)response$ or undesirable(w)effect$ or undesirable(w)event$ or undesirable(w)outcome$ or undesirable(w)reaction$ or undesirable(w)interaction$ or undesirable(w)response$ or adrs or ades or adr or drug(w)surveillance or post(w)marketing(w)surveillance or postmarketing(w)surveillance or treatment(w)emergent or complication$ or tolerability or toxicity or harm or harms or harmful or tolerance or tolerate or toxic)/ttl
S s1 or s2

The second update search was carried out in the CMS interface with the following search strategy;

1) adverse:TI
2) "side effect*":TI
3) "unintended effect*":TI
4) "unintended event*":TI
5) "unintended outcome*":TI
6) "unintended reaction*":TI
7) "unintended interaction*":TI
8) "unintended response*":TI
9) "unintentional effect*":TI
10) "unintentional event*":TI
11) "unintentional outcome*":TI
12) "unintentional reaction*":TI
13) "unintentional interaction*":TI
14) "unintentional response*":TI
15) "unwanted effect*":TI
16) "unwanted event*":TI
17) "unwanted outcome*":TI
18) "unwanted reaction*":TI
19) "unwanted interaction*":TI
20) "unwanted response*":TI
21) "unexpected effect*":TI
22) "unexpected event*":TI
23) "unexpected outcome*":TI
24) "unexpected reaction*":TI
25) "unexpected interaction*":TI
26) "unexpected response*":TI
27) "undesirable effect*":TI
28) "undesirable event*":TI
29) "undesirable outcome*":TI

30) "undesirable reaction*":TI
31) "undesirable interaction*":TI
32) "undesirable response*":TI
33) adrs:TI
34) ades:TI
35) adr:TI
36) "drug surveillance":TI
37) "post marketing surveillance":TI
38) "postmarketing surveillance"::TI
39) "treatment emergent":TI
40) complication*:TI
41) tolerability:TI
42) toxicity:TI
43) harm:TI
44) harms:TI
45) harmful:TI
46) tolerance:TI
47) tolerate:TI
48) toxic:TI
49) #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48

Health Management Information Consortium (HMIC)
Interface: Ovid Biomed
Date Range: September 2007 (original search), July 2008 (first update search), September 2009 (second update search)
Date Searched: 27/09/07 (original search), 17/08/08 (first update search), 23/10/09 (second update search)
A similar approach was undertaken as with searching EMBASE. However, differences in the size, content and indexing meant that some changes needed to be made. The original search retrieved 92 records, and the first update search 17 records and the second update 7 records.
1 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
2 side effect$.ti,ab.
3 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
4 (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
5 (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
6 (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
7 (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
8 (adrs or ades).ti,ab.
9 drug safety.ti,ab.
10 (drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.
11 tolerability.ti,ab.
12 (harm or harms or harmful).ti,ab.

13 exp adverse drug reactions/
14 iatrogenic disease/
15 toxicity/
16 treatment emergent.ti,ab.
17 drug toxicity.ti,ab.
18 (iatrogenic or iatrogenesis).ti,ab.
19 complication$.ti.
20 toxicity.ti.
21 safety.ti.
22 safe.ti.
23 meta-analysis/
24 meta-analysis.ti,ab.
25 meta-analyses.ti,ab.
26 metaanalysis.ti,ab.
27 metaanalyses.ti,ab.
28 metanalysis.ti,ab.
29 metanalyses.ti,ab.
30 metasynthesis.ti,ab.
31 metasyntheses.ti,ab.
32 meta-synthesis.ti,ab.
33 meta-syntheses.ti,ab.
34 narrative synthesis.ti,ab.
35 narrative syntheses.ti,ab.
36 bibliographic stud$.ti,ab.
37 data selection.ti,ab.
38 data pooling.ti,ab.
39 pooled analysis.ti,ab.
40 pooled analyses.ti,ab.
41 odds ratio.ti,ab.
42 odds ratios.ti,ab.
43 literature review$.ti,ab.
44 review of studies.ti,ab.
45 systematic review$.ti,ab.
46 Cochrane review$.ti,ab.
47 evidence synthesis.ti,ab.
48 research synthesis.ti,ab.
49 critical appraisal.ti,ab.
50 validity assessment$.ti,ab.
51 quality assessment$.ti,ab.
52 data extraction.ti,ab.
53 data synthesis.ti,ab.
54 study selection.ti,ab.
55 inclusion criteria.ti,ab.
56 literature searching.ti,ab.
57 (formulating adj3 question$).ti,ab.
58 locating.ti,ab.
59 (search or searches).ti.
60 searching.ti.
61 exp information materials/
62 exp information sources/
63 databases/
64 databases.ti.
65 (medline or embase or derwent drug file or cinahl or idis or pharmline or toxline).ti.
66 information retrieval.ti,ab.

67 search strategies.ti,ab.
68 search filter$.ti,ab.
69 Different sources.ti,ab.
70 trials.ti.
71 ((random$ or clinical or multicent$ or case control or population based) and studies).ti.
72 RCTs.ti.
73 Study design$.ti.
74 (type adj2 study).ti.
75 Case series.ti.
76 (Observational and studies).ti.
77 (cohort studies or case-control studies).ti.
78 Non-randomi?ed.ti.
79 nonrandomi?ed.ti.
80 Case reports.ti.
81 Anecdotes.ti.
82 Spontaneous report$.ti.
83 (conflict adj2 interest$).ti,ab.
84 (competing adj2 interest$).ti,ab.
85 (funding or funder or funded).ti,ab.
86 (financed or sponsored).ti,ab.
87 (grey literature or gray literature or unpublished).ti,ab.
88 methodological issues.ti,ab.
89 methods.ti.
90 methodological.ti.
91 methodology.ti.
92 assessing.ti.
93 limitation$.ti.
94 bias.ti.
95 challenge$.ti.
96 how to.ti.
97 how do.ti.
98 suggestion$.ti.
99 instruction$.ti.
100 reporting$.ti.
101 quantify$.ti.
102 guidance.ti.
103 evaluation of methods.ti,ab.
104 methods/
105 exp research methodology/
106 research/
107 research design/
108 research methods/
109 or/1-22
110 or/23-87
111 or/88-108
112 109 and 110 and 111
113 derry s$.au. and 109
114 ioannidis j$.au. and 109
115 loke y$.au. and 109
116 chou r$.au. and 109
117 ashby d$.au. and 109
118 herxheimer a$.au. and 109
119 jefferson t$.au. and 109
120 etminan m$.au. and 109

121 or/112-120

Index to Theses
Interface: http://www.theses.com/
Date Range: 1716 - 8 August 2007 (volume 56 part 2) (original search), up to 17 July 2008 (volume 57 part 1) (update search), up to October 2009 (second update search)
Date Searched: 15/08/07 (original search), 13/08/08 (update search), 06/11/09 (second update search)
The content of this database is multi-disciplinary and thousands of irrelevant records would have been retrieved with searching all fields. The searches were therefore limited to terms in the title. In addition, terms such as toxicity (482), tolerance (529), tolerability (4), tolerate (1), safety (483), safe (55), toxic (217), risk (1374) and risks (123) were excluded as they retrieved many irrelevant studies relating to topics such as environmental risks, toxic waste, occupational safety, and the tolerance of populations.
Due to the constrictive interface a series of one word/phrase searches was carried out, and the results sifted on the web interface. The original searches retrieved 338 records before deduplication and 3 potentially relevant records were entered into the endnote library, an additional 12 records were retrieved by the first update searches and none were entered into the endnote library and 5 records were retrieved by the second update search and again none were entered into the endnote library. The search terms were;
Adverse, side effect, side effects, unintended effect, unintended effects, unintended event, unintended events, unintended outcome, unintended outcomes, unintended reaction, unintended reactions, unintended interaction, unintended interactions, unintended response, unintended responses, unintentional effect, unintentional effects, unintentional event, unintentional events, unintentional outcome, unintentional outcomes, unintentional reaction, unintentional reactions, unintentional interaction, unintentional interactions, unintentional response, unintentional responses, unwanted effect, unwanted effects, unwanted event, unwanted events, unwanted outcome, unwanted outcomes, unwanted reaction, unwanted reactions, unwanted interactions, unwanted interaction, unwanted response, unwanted responses, unexpected effect, unexpected effects, unexpected event, unexpected events, unexpected outcome, unexpected outcomes, unexpected reaction, unexpected reactions, unexpected interaction, unexpected interactions, unexpected response, unexpected responses, undesirable effect, undesirable effects, undesirable event, undesirable events, undesirable outcome, undesirable outcomes, undesirable reaction, undesirable reactions, undesirable interaction, undesirable interactions, undesirable response, undesirable responses, adrs, ades, adr, post marketing surveillance, postmarketing surveillance , drug surveillance, treatment emergent, complication, complications, harm, harms, harmful.

Library, Information Science & Technology Abstracts (LISTA)
Interface: http://www.libraryresearch.com
Date Range: mid-1960s - Present
Date Searched: 26/09/07 (original search), 13/08/08 (update search), 25/10/09 (second update search)
Due to the large number of irrelevant records relating to library management retrieved by the terms for complication, harm, tolerance, toxicity, safety and risk terms these terms were restricted to the title field only and safe and safety were replaced by drug safety and risk was removed. The original search retrieved 873 records and the first update search retrieved 226 records and the second update 306 records (restricted to academic journals and books).

(Adverse or side W1 effect* or unintended W1 effect* or unintended W1 event* or unintended W1 outcome* or unintended W1 reaction* or unintended W1 interaction* or unintended W1 response* or unintentional W1 effect* or unintentional W1 event* or unintentional W1 outcome* or unintentional W1 reaction* or unintentional W1 interaction* or unintentional W1 response* or unwanted W1 effect* or unwanted W1 event* or unwanted W1 outcome* or unwanted W1 reaction* or unwanted W1 interaction* or unwanted W1 response* or unexpected W1 effect* or unexpected W1 event* or unexpected W1 outcome* or unexpected W1 reaction* or unexpected W1 interaction* or unexpected W1 response* or undesirable W1 effect* or undesirable W1 event* or undesirable W1 outcome* or undesirable W1 reaction* or undesirable W1 interaction* or undesirable W1 response* or adrs or ades or adr or drug W1 surveillance or post W1 marketing W1 surveillance or postmarketing W1 surveillance or treatment W1 emergent) in any field
or (complication* or tolerability or toxicity or harm or harms or harmful or tolerance or tolerate or toxic or drug W1 safety or risks) in title

MEDLINE
Interface: Ovid Biomed
Date Range: 1950 to September Week 3 2007 (original search), 1950 to August Week 1 2008 (first update search), 1950 to October Week 3 (second update search)
Date Searched: 27/09/07 (original search), 17/08/08 (first update search), 23/10/09 (second update search)
A similar approach was undertaken as with searching EMBASE and HMIC. However, differences in the size, content and indexing meant that some changes needed to be made. The original search retrieved 900 records. Due to changes in indexing practice in MEDLINE, the MeSH term clinical trial/mt was no longer available in MEDLINE at the time of conducting the update search and was therefore excluded from the update search strategy. The update search retrieved 111 records and 152 records from the second update search.
1 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
2 side effect$.ti,ab.
3 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
4 (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
5 (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
6 (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
7 (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
8 (adrs or ades).ti,ab.
9 drug safety.ti,ab.
10 (drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.
11 tolerability.ti,ab.
12 (harm or harms or harmful).ti,ab.
13 product surveillance, postmarketing/
14 adverse drug reaction reporting systems/
15 exp Drug Hypersensitivity/
16 iatrogenic disease/
17 exp drug toxicity/

18 Abnormalities, Drug-Induced/
19 treatment emergent.ti,ab.
20 drug toxicity.ti,ab.
21 (iatrogenic or iatrogenesis).ti,ab.
22 complication$.ti.
23 toxicity.ti.
24 safety.ti.
25 safe.ti.
26 meta-analysis/
27 meta-analysis.ti,ab.
28 meta-analyses.ti,ab.
29 metaanalysis.ti,ab.
30 metaanalyses.ti,ab.
31 metanalysis.ti,ab.
32 metanalyses.ti,ab.
33 metasynthesis.ti,ab.
34 metasyntheses.ti,ab.
35 meta-synthesis.ti,ab.
36 meta-syntheses.ti,ab.
37 narrative synthesis.ti,ab.
38 narrative syntheses.ti,ab.
39 bibliographic stud$.ti,ab.
40 data selection.ti,ab.
41 data pooling.ti,ab.
42 pooled analysis.ti,ab.
43 pooled analyses.ti,ab.
44 odds ratio.ti,ab.
45 odds ratios.ti,ab.
46 odds ratio/
47 literature review$.ti,ab.
48 review of studies.ti,ab.
49 systematic review$.ti,ab.
50 Cochrane review$.ti,ab.
51 evidence synthesis.ti,ab.
52 research synthesis.ti,ab.
53 critical appraisal.ti,ab.
54 validity assessment$.ti,ab.
55 quality assessment$.ti,ab.
56 data extraction.ti,ab.
57 data synthesis.ti,ab.
58 study selection.ti,ab.
59 inclusion criteria.ti,ab.
60 literature searching.ti,ab.
61 (formulating adj3 question$).ti,ab.
62 locating.ti,ab.
63 (search or searches).ti.
64 searching.ti.
65 Periodicals as topic/
66 "information storage and retrieval"/
67 databases as topic/ or exp databases, bibliographic/
68 databases.ti.
69 (medline or embase or derwent drug file or cinahl or psycinfo or idis or pharmline or toxline).ti.
70 information retrieval.ti,ab.
71 search strategies.ti,ab.

72 search filter$.ti,ab.
73 Different sources.ti,ab.
74 trials.ti.
75 ((random$ or clinical or multicent$ or case control or population based) and studies).ti.
76 RCTs.ti.
77 Study design$.ti.
78 (type adj2 study).ti.
79 Case series.ti.
80 (Observational and studies).ti.
81 (cohort studies or case-control studies).ti.
82 Non-randomi?ed.ti.
83 nonrandomi?ed.ti.
84 Case reports.ti.
85 Anecdotes.ti.
86 Spontaneous report$.ti.
87 (conflict adj2 interest$).ti,ab.
88 (competing adj2 interest$).ti,ab.
89 (funding or funded or funder).ti,ab.
90 (financed or sponsored).ti,ab.
91 (grey literature or gray literature or unpublished).ti,ab.
92 exp publication bias/
93 methodological issues.ti,ab.
94 methods.ti.
95 methodological.ti.
96 methodology.ti.
97 assessing.ti.
98 limitation$.ti.
99 bias.ti.
100 challenge$.ti.
101 how to.ti.
102 how do.ti.
103 suggestion$.ti.
104 instruction$.ti.
105 reporting$.ti.
106 quantify$.ti.
107 guidance.ti.
108 evaluation of methods.ti,ab.
109 methods/
110 research/mt, st
111 exp research design/mt, st
112 clinical trial/mt [this term was excluded from the update searches]
113 or/1-25
114 or/26-92
115 or/93-112
116 113 and 114 and 115
117 derry s$.au. and 113
118 ioannidis j$.au. and 113
119 aronson j$.au. and 113
120 loke y$.au. and 113
121 chou r$.au. and 113
122 ashby d$.au. and 113
123 herxheimer a$.au. and 113
124 jefferson t$.au. and 113
125 etminan m$.au. and 113

126 or/116-125

MEDLINE(R) In-Process & Other Non-Indexed Citations
Interface: Ovid Biomed
Date Range: September 26, 2007 (original search), August 15, 2008 (first update search), October 22, 2009 (second update search)
Date Searched: 27/09/07 (original search), 16/08/08 (first update search), 23/10/09 (second update search)
The original search strategy retrieved 26 records and the first update search 73 records and the second update search 92 records.
1 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
2 side effect$.ti,ab.
3 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
4 (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
5 (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
6 (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
7 (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab.
8 (adrs or ades).ti,ab.
9 drug safety.ti,ab.
10 (drug surveillance or ((postmarketing or post marketing) adj2 surveillance)).ti,ab.
11 tolerability.ti,ab.
12 (harm or harms or harmful).ti,ab.
13 treatment emergent.ti,ab.
14 drug toxicity.ti,ab.
15 (iatrogenic or iatrogenesis).ti,ab.
16 complication$.ti.
17 toxicity.ti.
18 safety.ti.
19 safe.ti.
20 meta-analysis/
21 meta-analysis.ti,ab.
22 meta-analyses.ti,ab.
23 metaanalysis.ti,ab.
24 metaanalyses.ti,ab.
25 metanalysis.ti,ab.
26 metanalyses.ti,ab.
27 metasynthesis.ti,ab.
28 metasyntheses.ti,ab.
29 meta-synthesis.ti,ab.
30 meta-syntheses.ti,ab.
31 narrative synthesis.ti,ab.
32 narrative syntheses.ti,ab.
33 bibliographic stud$.ti,ab.
34 data selection.ti,ab.
35 data pooling.ti,ab.
36 pooled analysis.ti,ab.
37 pooled analyses.ti,ab.
38 odds ratio.ti,ab.

39 odds ratios.ti,ab.
40 odds ratio/
41 literature review$.ti,ab.
42 review of studies.ti,ab.
43 systematic review$.ti,ab.
44 Cochrane review$.ti,ab.
45 evidence synthesis.ti,ab.
46 research synthesis.ti,ab.
47 critical appraisal.ti,ab.
48 validity assessment$.ti,ab.
49 quality assessment$.ti,ab.
50 data extraction.ti,ab.
51 data synthesis.ti,ab.
52 study selection.ti,ab.
53 inclusion criteria.ti,ab.
54 literature searching.ti,ab.
55 (formulating adj3 question$).ti,ab.
56 locating.ti,ab.
57 (search or searches).ti.
58 searching.ti.
59 databases as topic/ or exp databases, bibliographic/
60 databases.ti.
61 (medline or embase or derwent drug file or cinahl or psycinfo or idis or pharmline or toxline).ti.
62 information retrieval.ti,ab.
63 search strategies.ti,ab.
64 search filter$.ti,ab.
65 Different sources.ti,ab.
66 trials.ti.
67 ((random$ or clinical or multicent$ or case control or population based) and studies).ti.
68 RCTs.ti.
69 Study design$.ti.
70 (type adj2 study).ti.
71 Case series.ti.
72 (Observational and studies).ti.
73 (cohort studies or case-control studies).ti.
74 Non-randomi?ed.ti.
75 nonrandomi?ed.ti.
76 Case reports.ti.
77 Anecdotes.ti.
78 Spontaneous report$.ti.
79 (conflict adj2 interest$).ti,ab.
80 (competing adj2 interest$).ti,ab.
81 (funding or funded or funder).ti,ab.
82 (financed or sponsored).ti,ab.
83 (grey literature or gray literature or unpublished).ti,ab.
84 methodological issues.ti,ab.
85 methods.ti.
86 methodological.ti.
87 methodology.ti.
88 assessing.ti.
89 limitation$.ti.
90 bias.ti.
91 challenge$.ti.

92 how to.ti.
93 how do.ti.
94 suggestion$.ti.
95 instruction$.ti.
96 reporting$.ti.
97 quantify$.ti.
98 guidance.ti.
99 evaluation of methods.ti,ab.
100 or/1-19
101 or/20-83
102 or/84-99
103 100 and 101 and 102
104 derry s$.au. and 100
105 ioannidis j$.au. and 100
106 aronson j$.au. and 100
107 loke y$.au. and 100
108 chou r$.au. and 100
109 ashby d$.au. and 100
110 herxheimer a$.au. and 100
111 jefferson t$.au. and 100
112 etminan m$.au. and 100
113 or/103-112

Appendix B: **Tables and figures for methodological overviews in Chapters 4 to 9**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
Agency for Healthcare Research and Quality 2002[238]	Systematic review of hormone replacement therapy and venous thromboembolism	***Venous thromboembolism*** **3 RCTs (N=3842)** RR 3.08 (0.21-45.14) **1 cohort study (N=112593)** RR 2.1 (1.2-3.8) **8 case-control studies (N=23544)** RR 2.05 (1.40-2.95)	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR (No significant heterogeneity among all 12 studies P>0.10) **Statistical analysis comparing study designs:** NR	**RCTs:** No significant difference **Cohort study:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes
Alghamdi et al 2007[239]	Systematic review of preoperative aspirin and bleeding	***Reexploration*** **4 RCTs (N=1002)** Aspirin 41/588 Control 7/420 RR 3.71 (1.74-7.91) Chi^2=1.00, df=3 P=0.80, I^2=0% **5 Cohort studies (N=716)** Aspirin 10/311 Control 11/405 RR 1.27 (0.54-2.98) Chi^2=1.95, df=3 P=0.58, I^2=0%	**Confounding factors by study design:** NR but carries out sensitivity analysis by era (before 1990 and after) which suggests effect size larger in early era studies. RCTs tended to be earlier era studies but no further analysis conducted. **Heterogeneity within study designs:** No significant heterogeneity: one set of RCTs, one set of cohort studies **Statistical analysis comparing study designs:** NR but no significant heterogeneity when all RCTs and cohort studies are pooled.	***Reexploration*** **RCTs**: Significant increase P<0.001 **Cohort studies:** No significant difference P=0.58 **CI overlap:** Yes
Bager et al	Systematic review of caesarean	***Asthma***	**Confounding factors by study**	**Cohort studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
2008[240]	delivery and atopy and allergic disease	**11 cohort studies (N=NR)** OR 1.22 (1.09-1.37) **2 case-control studies (N=NR)** OR 0.84 (0.64-1.10)	**design:** NR (Carries out stratified meta-analysis for adjustment of risk ratios, a priori aim, study design, year of birth, size of study population, country, exclusion, proportion of C-sections and age. For asthma significant variations were seen for age and study design. No further data shown) **Heterogeneity within study designs:** NR (significant heterogeneity among all 13 studies P<0.01) **Statistical analysis comparing study designs:** Higher ORs for cohort studies compared with case-control studies P<0.01. Summary OR variation with study characteristics, P-values two-tailed, based on likelihood ratio tests.	Significant increase **Case-control studies:** No significant difference **CI overlap:** Yes
Bergendal et al 2009[241]	Systematic review of progestogen-only contraception and venous thromboembolism	***Venous thromboembolism*** **1 cohort study (N=204)** OR 0.8 (0.2-3.9) **4 case-control studies (N=10004)** OR 1.45 (0.92-2.26)	**Confounding factors by study design:** NR but did not include the cohort study in the meta-analysis as deemed to deviate too much from other studies in terms of population and design. **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	**Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes
Bollini et al 1992[242]	Meta-analysis of NSAIDS and upper gastrointestinal tract	***Upper gastrointestinal tract disease***	**Confounding factors by study design:** Stated that type of study design	**Cohort studies:** Significant increase

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
	disease with primary aim to assess the impact of study design and research quality	**7 cohort studies (N=NR)** RR 2.0 (1.2 to 3.2) Chi^2 P<0.01 **27 case-control studies (N=NR)** RR 4.1 (3.2 to 5.3)**	was independently associated with risk estimates, even after adjustment. Used multivariate regression to adjust in the same model for drug investigated, type of study design, and methodological quality. **Heterogeneity within study designs:** No significant heterogeneity: Community-based case-control studies N=8 Chi^2 P>0.05. Significant heterogeneity: Hospital-based case-control studies N=19 and one set of cohort studies **Statistical analysis comparing study designs:** NR but states that cohort studies significantly lower risk ratio estimate than hospital based case-control studies.	**Case-control studies:** Significant increase **CI overlap:** Yes
Browning and Martin 2007[243]	Systematic review of statins and cancer	***Breast cancer*** **7 RCTs (N=60917)** RR 1.01 (0.79-1.30) I^2=43% **9 Observational studies (N=688052)** RR 0.96 (0.90-1.04) I^2=0% ***Prostate cancer*** **4 RCTs (N=21740)** RR 1.00 (0.85-1.17) I^2=0%	**Confounding factors by study design:** NR but acknowledges that confounding and other bias may have had an effect **Heterogeneity within study designs:** No significant heterogeneity: Five sets of RCTs and three sets of observational studies Significant heterogeneity: Two sets of observational studies **Statistical analysis comparing study**	***Breast cancer*** **RCTs:** No significant difference P=0.92 **Observational studies:** No significant difference P=0.31 **CI overlap:** Yes ***Prostate cancer*** **RCTs:** No significant difference P=0.99

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		5 Observational studies (N=375290) RR 1.08 (0.91-1.30) I^2=77% ***Colorectal cancer*** **9 RCTs (N=67656)** RR 1.02 (0.89-1.16) I^2=0% **5 Observational studies (N=508696)** RR 0.86 (0.77-0.96) I^2=89% ***Lung cancer*** **9 RCTs (N=69301)** RR 0.96 (0.84-1.09) I^2=0% **3 Observational studies (N=372592)** RR 1.07 (0.89-1.28) I^2=0% ***Melanoma*** **4 RCTs (N=24222)** RR 0.86 (0.62-1.20) I^2=17% **1 Observational study (N=18047)** RR 2.50 (0.83-7.55) I^2=NA ***Gastric cancer***	**designs:** NR	**Observational studies:** No significant difference P=0.38 **CI overlap:** Yes ***Colorectal cancer*** **RCTs:** No significant difference P=0.83 **Observational studies:** Significant decrease P=0.009 **CI overlap:** Yes ***Lung cancer*** **RCTs:** No significant difference P=0.49 **Observational studies:** No significant difference P=0.50 **CI overlap:** Yes ***Melanoma*** **RCTs:** No significant difference P=0.38 **Observational studies:** No significant difference P=0.10 **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		1 RCT (N=4444) RR 1.00 (0.35-2.85) I^2=NA **2 Observational studies (N=37838)** RR 0.73 (0.38-1.40) I^2=0%		***Gastric cancer*** **RCTs:** No significant difference P=0.99 **Observational studies:** No significant difference P=0.34 **CI overlap:** Yes
Canonico et al 2008[244]	Systematic review of HRT and venous thromboembolism	***Venous thromboembolism*** **9 RCTs (N=NR)** HRT 311/NR Placebo 146/NR OR 2.1 (1.4-3.1) Chi^2 P=0.03, I^2=58.9% **8 observational studies (N=NR)** OR 2.5 (1.9-3.4) Chi^2 P=0.03, I^2=53.3%	**Confounding factors by study design:** Acknowledges that 'This difference could be explained by inclusion of procedure related venous thromboembolism in the women's health initiative trials as well as the high degree of non-adherence to study drugs in the randomised controlled trials, resulting in an underestimation of hormone effects in the randomised controlled trials'. **Heterogeneity within study designs:** Significant heterogeneity: One set RCTs and one set of observational studies **Statistical analysis comparing study designs:** NR	**RCTs:** Significant increase **Observational Studies:** Significant increase **CI overlap:** Yes
Capurso et al 2007[245]	Systematic review of NSAIDS and pancreatic cancer	***Pancreatic cancer (low NSAID exposure)*** **1 RCT (N=39,876)** Aspirin/NSAIDS 30/19,934 Control 21/19,942 OR 1.43 (0.82-2.50) **3 Cohort studies**	**Confounding factors by study design:** NR but conducts subgroup analysis by factors such as gender, aspirin use only, and nurse occupation. **Heterogeneity within study designs:** NR (Significant heterogeneity among 7 studies with low exposure P=0.005, I^2	***Low exposure*** **RCT:** No significant difference **Cohort studies:** No significant difference **Case-control studies:** No significant difference

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=1,072,263) Aspirin/NSAIDS 883/244,404 Control 3668/827,859 OR 0.84 (0.64-1.09) **3 Case-control studies (N=7,254)** Aspirin/NSAIDS 347/3,302 Control 728/3,952 OR 1.04 (0.81-1.33) ***Pancreatic cancer (Intermediate NSAID exposure)*** **3 Cohort studies (N=906,924)** Aspirin/NSAIDS 363/79,065 Control 3,668/827,859 OR 0.94 (0.63-1.40) **3 Case-control studies (N=4,648)** Aspirin/NSAIDS 123/696 Control 728/3,952 OR 1.15 (0.69-1.91) ***Pancreatic cancer (High NSAID exposure)*** **3 Cohort studies**	=67.3%, 6 studies with intermediate exposure P=0.001, I^2=75.0% and 6 studies with high exposure P<0.0001, I^2=83.4%) **Statistical analysis comparing study designs:** NR but states no significant difference.	**CI overlap:** Yes ***Intermediate exposure*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes ***High exposure*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=851,932) Aspirin/NSAIDS 84/24,073 Control 3668/827,859 OR 0.94 (0.51-1.71) **3 Case-control studies (N=4,267)** Aspirin/NSAIDS 60/315 Control 728/3,952 OR 1.12 (0.52-2.41)		
Chan et al 2004[246]	Systematic review oral contraceptives and stroke	***Stroke*** **4 Cohort studies (N=>1,000,000)** OR 0.95 (0.51-1.78) Chi^2 P=0.01 **16 Case-control studies (N=15,106)** OR 2.13 (1.59-2.86) Chi^2 P<0.001	**Confounding factors by study design:** Authors comment on heterogeneity of studies, potential confounding and risk of bias e.g. cohort studies 'might be methodologically superior. present more valid assessment of stroke risk'. **Heterogeneity within study designs:** Significant heterogeneity: One set cohort studies and one set of case control studies (and when all studies pooled) **Statistical analysis comparing study designs:** Differences among subgroups were calculated using the standard Gaussian Z statistic. The pooled odds ratio of the cohort studies was significantly different from that of the case-control studies P=0.03	**Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** yes
Chou et al	Used studies from 4 systematic	***Stroke or death***	**Confounding factors by study**	**CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
2006[247] 2007[248]	reviews on carotid endarterectomy and stroke or death to assess the association between methodological shortcomings and estimates of serious complications	**9 RCTs (N=NR)** Rate 7.4% (4.5%-10.2%) **102 Observational studies (N=NR)** Rate 4.4% (3.8%-4.9%)	**design:** NR but carries out multivariate regression analyses carried out on quality criteria. Did not include type of study in this part of the analyses. **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** Univariate analysis identified significantly higher rates in RCTs (P=0.0444). RCTs 1.7 times more adverse effects than in case-control studies.	
Col et al 2005[249]	Systematic review of menopausal hormone therapy and breast cancer	***Breast cancer*** **2 RCTs (N=445)** RR 3.41 (1.59-7.33) Q=0.25 **8 Observational studies (N=3710)** RR 0.64 (0.50-0.82) Q=7.18	**Confounding factors by study design:** Acknowledges possible confounding factors such as younger population with more favourable prognostic profiles in observational studies. Also commented that observational studies lacked proper design and were more like reports of clinical experiences. **Heterogeneity within study designs:** No significant heterogeneity: one set of RCTs and one set of observational studies **Statistical analysis comparing study designs:** Significant heterogeneity exists if RCT and observational data are pooled.	**RCTs:** Significant increase P=0.0016 **Observational studies:** Significant decrease P=0.00041 **CI overlap:** No

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
Cosmi et al 2000[28]	Systematic review of ticlopidine plus aspirin and thrombotic thrombocytopenic purpura (TTP)	***Thrombotic thrombocytopenic purpura (TTP)*** **10 RCTs (N=NR)** Number of cases: 0 **7 Observational studies (N=>43322)** Number of cases : 9 **Case reports or series (N=72)** Number of cases : 72 **The WHO Monitoring Centre (N=0)** Number of cases: 0	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	**CI overlap:** NR
Cutler et al 2001[250]	Systematic review of allogeneic peripheral -blood stem-cell and bone marrow transplantation and acute and chronic graft-versus-host disease	***Transplantation (Acute graft)*** **5 RCTs (N=699)** RR 1.23 (1.05-1.45) **10 Cohort studies (N=1371)** RR 1.10 (0.96-1.26) ***Transplantation (Chronic graft)*** **5 RCTs (N=699)** RR 1.37 (1.08-1.74) **9 Cohort studies (N=1364)** RR 1.62 (1.24-2.12)	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	***Acute graft*** **RCTs:** Significant increase **Cohort studies:** No significant difference **CI overlap:** yes ***Chronic graft*** **RCTs:** Siignificant increase P=0.01 **Cohort studies:** Significant increase P<0.001 **CI overlap:** yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
Dolovich et al 1998[251]	Systematic review of benzodiazepine use in pregnancy and major malformations and oral cleft	***Major malformations*** **7 cohort studies (N=72,866)** Exposed 32/1090 Non-exposed 2783/71776 OR 0.90 (0.61-1.35) Chi^2 P=0.62 **4 case-control studies (N=6,136)** Exposed 84/166 Non-exposed 2141/5970 OR 3.01 (1.32-6.84) Chi^2 P=0.008 ***Oral cleft*** **3 cohort studies (N=138,286)** Exposed 1/2543 Non-exposed 93/135743 OR 1.19 (0.34-4.15) Chi^2 P=0.997 **6 case-control studies (N=14,971)** Exposed 105/285 Non-exposed 2742/14686 OR 1.79 (1.13-2.82) Chi^2 P=0.01	**Confounding factors by study design:** Acknowledges systematic differences between study design e.g. exposure to other medications, duration and indication for use of benzodiazepine and possible differences in populations. **Heterogeneity within study designs:** No significant heterogeneity: two sets of cohort studies. Significant heterogeneity: two sets of case-control studies **Statistical analysis comparing study designs:** NR	***Major malformations*** **Cohort studies:** No significant difference P=0.62 **Case-control studies:** Significant increase P=0.008 **CI overlap:** yes ***Oral cleft*** **Cohort studies:** No significant difference P=0.997 **Case-control studies:** Significant increase P=0.01 **CI overlap:** Yes
Douketis et al 1997[252]	Systematic review of oral contraceptives and hormone	***Venous thromboembolism (oral***	**Confounding factors by study design:** NR	***Oral contraceptives*** **RCT:** No significant

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
	replacement therapy and venous thromboembolism.	***contraceptives)*** **1 RCT (N=NR)** RR 1.1 (0.4-2.9) **7 cohort studies**** RR 3.0 (2.2-4.2) prospective studies Chi^2 P=0.8, retrospective studies Chi^2 P=0.3 **12 case-control studies (N=NR)** RR 3.0 (2.6-3.4) Chi^2 P=<0.001 ***Venous thromboembolism (Hormone replacement therapy)*** **2 RCTs (N=NR)** RR 0.7 (0.3-1.6) Chi^2 P=0.72 **1 cohort study (N=NR)** RR 1.7 (1.0-2.9) **5 case-control studies (N=NR)** RR 2.4 (1.7-3.5) Chi^2 P=0.24	**Heterogeneity within study designs:** No significant heterogeneity: one set of RCTs, one set of case-control studies, (one set of prospective cohort studies P=0.8 and one set of retrospective cohort studies P=0.3) Significant heterogeneity: One set of case-control studies **Statistical analysis comparing study designs:** NR	difference **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes ***Hormone replacement therapy*** **RCTs:** No significant difference **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** No, RCTs have a lower risk ratio than case-control studies.
Garg et al 1998[253]	Systematic review of hormone replacement therapy and ovarian cancer	***Ovarian cancer*** **1 Cohort study (N=NR)** RR 1.15 (0.94-1.42)	**Confounding factors by study design:** NR **Heterogeneity within study designs:**	**Cohort study:** No significant difference **Case-control studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		9 Case-control studies (N=NR) RR 1.16 (1.03-1.29)	NR (no significant heterogeneity for all 10 studies P=0.72) **Statistical analysis comparing study designs:** NR	Significant increase **CI overlap:** Yes
Gillum et al 2000[254]	Systematic review oral contraceptives and ischemic stroke	***Ischemic stroke*** **3 Cohort studies (1,069,840 person years)** RR 3.21 (1.96-5.27) **14 Case-control studies (N=9,920)** RR 2.77 (2.22-3.45)	**Confounding factors by study design:** Evaluated a number of potential confounders. Meta-regression analysis suggested estrogen dosage, control of smoking and firm diagnosis of ischemic stroke were the only study variables contributing to risk ratio estimates. Study design was not identified as contributing to risk ratio estimate. **Heterogeneity within study designs:** NR (Significant heterogeneity among all studies P=0.01) **Statistical analysis comparing study designs:** A 2 tailed z test was used to detect differences across subgroups but no p value was reported for study design. Authors state that similar positive associations found in case-control studies and cohort studies suggesting that this aspect of study design was unimportant.	**Cohort studies:** Significant increase **Case-control studies**: Significant increase C**I overlap:** Yes
Grady et al 1995[255]	Systematic review of postmenopausal estrogen therapy and estrogen plus progestin and endometrial cancer	***Endometrial cancer*** (***Postmenopausal estrogen therapy)*** **4 Cohort studies (N=NR)**	**Confounding factors by study design:** Heterogeneity substantially reduced or eliminated when the studies where stratified by dose or duration of	***Postmenopausal estrogen therapy*** **Cohort studies:** Significant increase

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		RR 1.7 (1.3-2.1) **25 Case-control studies (N=NR)** RR 2.4 (2.2-2.6) ***Endometrial cancer (Estrogen plus progestin)*** **2 Cohort studies (N=NR)** RR 0.4 (0.2-0.6) **3 Case-control studies (N=NR)** RR 1.8 (1.1-3.1)	estrogen use suggesting that these two variables account for most of the variation in risk estimates. **Heterogeneity within study designs:** NR (significant heterogeneity among all studies) **Statistical analysis comparing study designs:** NR	**Case-control studies:** Significant increase **CI overlap:** No ***Estrogen plus progestin*** **Cohort studies:** Significant decrease **Case-control studies:** Significant increase **CI overlap:** No
Henry and McGettigan 2003[256]	Systematic review of NSAIDS and gastrointestinal complications	***Gastrointestinal complications*** **8 Cohort studies (N=1,436610)** Treatment 2410/399,399 Control 2247/1037211 OR 2.29 (1.50-3.51) Chi^2 P<0.00001 **25 Case-control studies (N=74637)** Treatment 3800/13610 Control 5512/61027 OR 3.81 (3.17-4.58) Chi^2 P<0.00001	**Confounding factors by study design:** NR but carries out subgroup analysis by type of drug **Heterogeneity within study designs:**:Significant heterogeneity: one set of cohort studies and one set of case-control studies **Statistical analysis comparing study designs:** NR but authors state that there is a marked difference in pooled odds ratios.	**Cohort studies:** Significant increase P=0.0001 **Case-control studies:** Significant increase P<0.00001 **CI overlap:** Yes
Jensen et al 2002[257]	Systematic review of anesthesia and postherniorrhaphy urinary retention	***Postherniorrhaphy urinary retention (local anesthesia***	**Confounding factors by study design:** NR **Heterogeneity within study designs:**	***Local anesthesia*** **CI overlap:** Yes**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		2 RCTs (N=184) 0/81 (0%) (-2.18-2.18)** **70 nonrandomised studies (N=8991)** 33/8991 (0.37%) (0.24-0.49) **P*ostherniorrhaphy urinary retention (regional anesthesia)*** **1 RCT (N=25)** 5/25 (20%) (3.40-36.60)** **70 nonrandomised studies (N=6191)** 150/6191 (2.42%) (2.04-2.81) ***Postherniorrhaphy urinary retention (general anesthesia)*** **2 RCTs (N=78)** 0/78 (0%) (-2.26-2.26)** **70 nonrandomised studies (N=11471)** 344/11471 (3.00%) (2.69-3.31)	NR **Statistical analysis comparing study designs:** NR	***Regional anesthesia*** **CI overlap:** No** ***General anesthesia*** **CI overlap:** No**
Johnston et al 1998[258]	Systematic review of oral contraceptives and subarachnoid haemorrhage	***Subarachnoid haemorrhage*** **2 Cohort studies (person**	**Confounding factors by study design:** NR but presents risk ratio stratified by dose, smoking,	**Cohort studies:** No significant difference **Case-control studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		years=588,151) RR 1.92 (0.91-4.06) Chi^2 P=0.41 **10 Case-control studies (N=8,904)** RR 1.40 (1.10-1.78) Chi^2 P=0.30	hypertension, exposure classification and outcome measure. **Heterogeneity within study designs:** No significant heterogeneity: one set of cohort studies and one set of case-control studies (no significant heterogeneity when all studies are pooled) **Statistical analysis comparing study designs:** Summary estimates from subgroups of studies were compared using a z statistic. The difference between risk ratio from cohort studies and case-control studies was not significant (p>0.10).	Significant increase **CI overlap:** Yes
Jones et al 1999[259]	Systematic review of water fluoridation and fractures	***Fractures*** **2 Cohort studies (N=NR)** RR 1.20 (0.43-3.32) Chi^2 P=0.02 **6 Cross-sectional studies (N=NR)** RR 1.06 (0.92-1.22) Chi^2 P=0.009 **10 Ecological studies (N=NR)** RR 1.00 (0.93-1.08) Chi^2 P<0.000001	**Confounding factors by study design:** NR but created a model with statistically significant variables (p<0.10) and identified that the combination of gender, urban/rural index, and study quality explained 25% of the variation. Did not test study design in this model. **Heterogeneity within study designs:** Significant heterogeneity: one set of cohort studies, one set of cross-sectional studies and one set of ecological studies (significant heterogeneity when all studies are pooled)	**Cohort studies:** No significant difference **Cross-sectional studies:** No significant difference **Ecological studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
			Statistical analysis comparing study designs: NR but authors state that analysis stratified by study design did not show any difference between pooled estimates. No statistical data given.	
Koster et al 1995[260]	Systematic review of oral contraceptives and venous thromboembolism	***Venous thromboembolism*** **1 RCT (N=NR)** RR 1.1 (0.4-2.9) **6 Cohort studies (N=NR)** RR 2.1 (0.3-16) **8 Case-control studies (N=NR**) RR 4.2 (1.3-14)	**Confounding factors by study design:** NR but author states differences may be due to study bias **Heterogeneity within study designs:** NR (Significant heterogeneity among all studies P<0.001) **Statistical analysis comparing study designs:** NR	**RCT:** No significant difference **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** Yes
Leipzig et al 1999[261]	Systematic review of psychotropic medications and falls	***Falls (psychotropics)*** **11 Cohort studies (N=NR)** OR 1.66 (1.40-1.97) **6 Case-control studies (N=NR)** OR 2.57 (1.90-3.49) **2 Cross sectional studies ((N=NR)** OR 1.40 (1.08-1.81) ***Falls (antidepressants)*** **11 Cohort studies (N=NR)** OR 1.62 (1.23-2.14) **12 Case-control studies (N=NR)**	**Confounding factors by study design:** NR but stratification of studies by subject residence, community studies, age, ascertainment of medication and falls had no effect on the pooled odds ratios. **Heterogeneity within study designs:** NR (Significant heterogeneity among all studies of psychotropics, neuroleptics, and seductive hypnotics but not the other interventions) **Statistical analysis comparing study designs:** NR but authors state stratification by study design had no effect on the pooled odds ratios. No	***Psychotropics*** **Cohort studies:** Significant increase **Case-control studies:** Significant increase **Cross sectional studies:** Significant increase **CI overlap:** No, cohort studies have higher odds ratio than cross-sectional studies ***Antidepressants*** **Cohort studies:** Significant increase

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		OR 1.89 (1.41-2.52) **4 Cross sectional studies (N=NR)** OR 1.51 (1.16-1.98) ***Falls (neuroleptics)*** **10 Cohort studies (N=NR)** OR 1.90 (1.35-2.67)1 **10 Case-control studies (N=NR)** OR 1.20 (0.90-1.61) **2 Cross sectional studies (N=NR)** OR 1.59 (1.18-2.13) ***Falls (sedative/hypnotics)*** **9 Cohort studies (N=NR)** OR 1.25 (0.98-1.60) **9 Case-control studies (N=NR)** OR 1.63 (1.31-2.02) **4 Cross sectional studies (N=NR)** OR 1.60 (1.41-1.82) ***Falls (benzodiazepines)*** **8 Cohort studies (N=NR)** OR 1.40 (1.11-1.76) **3 Case-control studies**	statistical analysis presented.	**Case-control studies:** Significant increase **Cross sectional studies:** Significant increase **CI overlap:** Yes ***Neuroleptics*** **Cohort studies:** Significant increase **Case-control studies:** No significant difference **Cross sectional studies:** Significant increase **CI overlap:** Yes ***Sedative/Hypnotics*** **Cohort studies:** No significant difference **Case-control studies:** Siignificant increase **Cross sectional studies:** Siignificant increase **CI overlap:** Yes ***Benzodiazepines*** **Cohort studies:** Siignificant increase **Case-control studies:** significant increase

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=NR) OR 2.57 (1.46-4.51) **2 Cross sectional studies (N=NR)** OR 1.34 (0.95-1.88)		**Cross sectional studies:** No significant difference **CI overlap:** Yes
Leipzig et al 1999[262]	Systematic review of cardiovascular medications and falls	***Falls (thiazides)*** **8 Cohort studies (N=NR)** OR 1.05 (0.96-1.21) **3 Case-control studies (N=NR)** OR 1.97 (0.89-4.36) **1 Cross sectional studies (N=NR)** OR 1.15 (0.70-1.90) ***Falls (loop diuretics)*** **7 Cohort studies (N=NR)** OR 0.90 (0.68-1.18) **3 Case-control studies (N=NR)** OR 0.76 (0.51-1.16) **1 Cross sectional study (N=NR)** OR 1.49 (0.77-2.89) ***Falls (digoxin)*** **9 Cohort studies (N=NR)** OR 1.29 (1.01-1.65) **5 Case-control studies**	**Confounding factors by study design:** NR but stratification of studies by subject residence, community studies, age, ascertainment of medication and falls had no effect on the pooled odds ratios. **Heterogeneity within study designs:** NR (no significant heterogeneity with all studies) **Statistical analysis comparing study designs:** NR but authors state stratification by study design had no effect on the pooled odds ratios. No statistical analysis presented.	***Thiazides*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Loop diuretics*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Digoxin*** **Cohort studies:** Significant increase **Case-control studies:** No significant difference **Cross sectional studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=NR) OR 1.31 (0.91-1.87) **3 Cross sectional studies (N=NR)** OR 1.13 (0.90-1.42) ***Falls (nitrates)*** **8 Cohort studies (N=NR)** OR 1.29 (0.99-1.68) **4 Case-control studies (N=NR)** OR 0.87 (0.59-1.28) **2 Cross sectional studies (N=NR)** 1.12 (0.82-1.54) ***Falls (beta-blockers)*** **9 Cohort studies (N=NR)** OR 1.00 (0.78-1.30) **7 Case-control studies (N=NR)** OR 0.83 (0.51-1.35) **2 Cross sectional studies (N=NR)** OR 0.87 (0.64-1.18) ***Falls (calcium channel blockers)*** **8 Cohort studies (N=NR)**		No significant difference **CI overlap:** Yes ***Nitrates*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Beta-blockers*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Calcium channel blockers*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		OR 1.05 (0.82-1.36) **4 Case-control studies (N=NR)** OR 0.88 (0.54-1.43) **1 Cross sectional study (N=NR)** OR 0.69 (0.44-1.09) ***Falls (ACE inhibitors)*** **7 Cohort studies (N=NR)** OR 1.09 (0.76-1.55) **2 Case-control studies (N=NR)** OR 1.69 (0.89-3.21) **1 Cross sectional study (N=NR)** OR 1.19 (0.68-2.07) ***Falls (Centrally acting antihypertensives)*** **4 Cohort studies (N=NR)** OR 0.80 (0.39-1.66) **5 Case-control studies (N=NR)** OR 1.41 (0.71-2.79) **2 Cross sectional studies (N=NR)** OR 1.21 (0.85-1.73)		**CI overlap:** Yes **ACE inhibitors** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Centrally acting antihypertensives*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross sectional studies:** No significant difference **CI overlap:** Yes ***Type 1A antiarrhythmics*** **Cohort studies:** No significant difference **Case-control studies:** Significant increase **Cross sectional studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Falls (type 1A antiarrhythmics) **5 Cohort studies (N=NR)** OR 0.95 (0.46-1.97) **4 Case-control studies (N=NR)** OR 3.68 (1.20-11.27) **1 Cross sectional study (N=NR)** OR 1.73 (0.87-3.41)		
Loe et al 2005[263]	Systematic review of neonatal safety and indomethacin tocolysis (an NSAID)	***Intraventricular hemorrhage*** **9 RCTs (N=533)** Study Group 22/263 Comparison group 23/270 OR 1.02 (0.55-1.89) Heterogeneity: P=0.93 **10 Observational studies (N=1241)** Study Group 134/572 Comparison group 126/669 OR 1.31 (0.79-2.15) Heterogeneity: P=0.01 ***Bronchopulmonary dysplasia*** **3 RCTs (N=156)** Study Group 15/76 Comparison group 6/80	**Confounding factors by study design:** Meta-regression analysis with study location, study year, and presence or absence of tocolytics as covariates did not alter the results for RCTs or observational studies. Acknowledges that discrepancies may be due to differences in interventions, population, clinical studies and follow-up, as well as confounding / selection bias in non-randomised study designs. **Heterogeneity within study designs:** No significant heterogeneity: Five sets of RCTs and two sets of observational studies Significant heterogeneity: Three sets of observational studies **Statistical analysis comparing study designs:** NR	***Intraventricular haemorrhage*** **RCTs:** No significant difference **Observational studies:** No significant difference **CI overlap:** Yes ***Bronchopulmonary dysplasia*** **RCTs:** Significant increase **Observational studies:** No significant difference **CI overlap:** Yes ***Patent ductus arteriosus*** **RCTs:** No significant difference **Observational studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		OR 2.80 (1.07-7.31) Heterogeneity: P=0.12 **9 Observational studies (N=998)** Study Group 118/451 Comparison group 136/547 OR 1.03 (0.76-1.40) Heterogeneity: P=0.49 ***Patent ductus arteriosus*** **6 RCTs (N=308)** Study Group 21/153 Comparison group 18/155 OR 1.25 (0.64-2.54) Heterogeneity: P=0.78 **11 Observational studies (N=1948)** Study Group 179/563 Comparison group 368/1385 OR 1.07 (0.76-1.52) Heterogeneity: P=0.05 ***Necrotizing enterocolitis*** **6 RCTs (N=329)** Study Group 7/162 Comparison group 2/167 OR 2.43 (0.73-8.03) Heterogeneity: P=0.95		No significant difference **CI overlap:** Yes ***Necrotizing enterocolitis*** **RCTs:** No significant difference **Observational studies:** No significant difference **CI overlap:** Yes ***Mortality*** **RCTs:** No significant difference **Observational studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		11 Observational studies (N=2725) Study Group 157/956 Comparison group 385/1769 OR 1.08 (0.37-3.13) Heterogeneity: P=0.00 ***Mortality*** **9 RCTs (N=572)** Study Group 15/283 Comparison group 11/289 OR 1.39 (0.65-2.97) Heterogeneity: P=0.99 **9 Observational studies (N=1234)** Study Group 69/547 Comparison group 84/687 OR 0.99 (0.70-1.40) Heterogeneity: P=0.21		
Loke YK et al. 2004[264]	Compares frequencies of adverse drug reactions of amiodarone from clinical trials identified from systematic reviews and MEDLINE, with case reports from MEDLINE and with spontaneous reports from the WHO International Drug Monitoring Programme	**Relative frequencies to respiratory adverse drug reactions** ***Heart*** Meta-analysis of 6 clinical trials 1.80 WHO cases (N=474), 0.44 Published case reports (N=13), 0.11	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR but different frequencies in the reporting of adverse effects were identified.	**CI overlap:** NA

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Thyroid WHO cases (N=1829), 1.70 Meta-analysis of 5 clinical trials 1.20 Published case reports (N=51), 0.44 ***Nervous system*** Meta-analysis of 5 clinical trials, 0.96 WHO cases (N=964), 0.89 Published case reports (N=54), 0.46 ***Liver*** WHO cases (N=832), 0.77 Meta-analysis of 5 clinical trials 0.49 Published case reports (N=31), 0.26 ***Gastrointestinal tract*** WHO cases (N=526), 0.49 Meta-analysis of 5 clinical trials, 0.47 Published case reports (N=2), 0.02 ***Eyes*** Meta-analysis of 4 clinical trials, 0.47 WHO cases (N=216), 0.20		

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Published case reports (N=12), 0.10 ***Skin*** WHO cases (N=1124), 1.04 Meta-analysis of 6 clinical trials, 0.35 Published case reports (N=31), 0.26		
Loke et al 2008[265]	Systematic review of thiazolidinediones and fractures	***Fractures among women*** **5 RCTs (N=4400)** Thiazolidinedione 111/1903 Control 76/2497 OR 2.23 (1.65-3.01) I^2=0% **1 Cohort study** OR 1.38 (1.03-1.82) **1 Case-control study** OR 2.56 (1.43-4.58)	**Confounding factors by study design:** NR but authors acknowledge that the trials contained relatively young participants and the case-control study involved an older population. **Heterogeneity within study designs:** No significant heterogeneity: one set of RCTs **Statistical analysis comparing study designs:** NR	***Fractures among women*** **RCTs:** Significant increase P<0.001 **Cohort study:** Significant increase **Case-control study:** Significant increase **CI overlap:** Yes
MacLennan et al 1995[266]	Systematic review of oestrogen replacement therapy and colorectal cancer	***Colorectal cancer*** **1 RCT (N=168)** RR 1.0 (0.14-7.1) **4 Cohort studies (N=169400)** RR 0.91 (0.60-1.38) Woolf's test, P=0.89 **9 Case-control studies (N=8631)** RR 0.92 (0.71-1.20)	**Confounding factors by study design:** Acknowledges insufficient information on dose duration to check variables. **Heterogeneity within study designs:** No significant heterogeneity: one set of cohort studies. Significant heterogeneity: one set of case-control studies. **Statistical analysis comparing study**	***Colorectal cancer*** **RCT:** No significant difference **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Woolf's test, P<0.01	**designs:** NR	
McAlister et al 1998[267]	Systematic review of perioperative allogeneic blood transfusion	***Mortality*** **5 RCTs (N=1923)** Treatment 164/978 Control 169/945 RR 0.94 (0.76-1.16) **1 Cohort Study (N=273)** Treatment 5/94 Control 7/179 RR 1.36 (0.44-4.17)	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR (No indication of heterogeneity for all 6 studies P>0.45) **Statistical analysis comparing study designs:** NR	***Mortality*** **RCTs:** No significant difference **Cohort Studies:** No significant difference **CI overlap:** Yes
McGettigan and Henry 2006[268]	Systematic review of NSAIDS and cardiovascular events	***Cardiovascular events (celecoxib)*** **3 Cohort studies (N=NR)** RR 1.22 (0.69-2.16) **8 Case-control studies (N=NR)** RR 1.01 (0.90-1.13) ***Cardiovascular events (rofecoxib < or = 25mg/d*)*** **2 Cohort studies (N=NR)** RR 1.51 (0.73-3.13) **3 Case-control studies (N=NR)** RR 1.21 (1.08-1.36) ***Cardiovascular events***	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR (Significant heterogeneity for all studies) **Statistical analysis comparing study designs:** NR	***Celecoxib*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes ***Rofecoxib < or = 25mg/d**** **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** Yes ***Rofecoxib > or = 25mg/d**** **2 Cohort studies** Significant increase **4 Case-control studies**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(rofecoxib > or = 25mg/d*) **2 Cohort studies (N=NR)** RR 2.46 (1.29-4.71) **4 Case-control studies (N=NR)** RR 1.89 (1.43-2.51) ***Cardiovascular events (naproxen)*** **3 Cohort studies (N=NR)** RR 0.94 (0.85-1.04) **12 Case-control studies (N=NR)** RR 0.96 (0.84-1.10) ***Cardiovascular events (diclofenac)*** **2 Cohort studies (N=NR)** RR 1.36 (0.51-3.65) **7 Case-control studies (N=NR)** RR 1.36 (1.21-1.54) ***Cardiovascular events (ibuprofen)*** **5 Cohort studies (N=NR)** RR 1.12 (0.90-1.38) **11 Case-control studies**		Significant increase **CI overlap:** Yes ***Naproxen*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes ***Diclofenac*** **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** Yes ***Ibuprofen*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes ***Any/Other NSAIDS*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=NR) RR 1.06 (0.95-1.18) ***Cardiovascular events (any/other NSAIDS)*** **5 Cohort studies (N=NR)** RR 1.10 (0.95-1.29) **14 Case-control studies (N=NR)** RR 1.10 (0.98-1.24)		**CI overlap:** Yes
McGettigan and Henry 2008[269]	Compares the risk ratios of cardiovascular events from systematic reviews of RCTs and systematic reviews of observational studies	***Cardiovascular events (rofecoxib)*** **Review 1: 37 RCTs (N=13053)** Treatment 98/6638 Control 72/6415 RR 1.38 (1.01-1.87) **Review 3: 13 observational studies (N=NR)** RR 1.36 (1.18-1.56) Chi^2 P<0.00001, I^2=84.3% ***Cardiovascular events (celecoxib)*** **Review 1: 41 RCTs (N=13929)** RR 1.51 (1.02- 2.04) Treatment 84/8976	**Confounding factors by study design:** Controlled for some study design factors including age, gender, dose, and type of drug. Found that discrepant estimates for celecoxib and ibuprofen were due to higher doses of drugs used in RCTs than in observational studies (where reported). **Heterogeneity within study designs:** Significant heterogeneity: 3 sets of observational studies **Statistical analysis comparing study designs:** NR	***Rofecoxib*** **RCTs:** Significant increase **Observational Studies:** Significant increase **CI overlap:** Yes *C**elecoxib*** **RCTs:** Significant increase **Observational Studies:** No significant difference **CI overlap:** Yes ***Naproxen*** **RCTs:** No significant difference **Observational Studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Control29/4953 **Review 3: 13 observational studies (N=NR)** RR 1.09 (0.95-1.25) Chi^2 P<0.00001 I^2=86.7% ***Cardiovascular events (naproxen)*** **Review 1: 42 RCTs (N=NR)** RR 0.92 (0.67-1.26) **Review 3: 15+ observational studies (N=NR)** RR 1.0 (0.91-1.09) ***Cardiovascular events (ibuprofen)*** **Review 1: 24 RCTs (N=NR)** RR 1.51 (0.96-2.37) **Review 3: 16+ observational studies (N=NR)** RR 1.09 (0.99-1.20) ***Cardiovascular events (diclofenac)***		***Ibuprofen*** **RCTs:** No significant difference **Observational Studies:** No significant difference **CI overlap:** Yes ***Diclofenac*** **RCTs:** Significant increase **Observational Studies:** Significant increase **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Review 1: 26 RCTs (N=NR) RR 1.63 (1.12-2.37) **Review 3: 12 observational studies (N=NR)** RR 1.35 (1.16-1.58) Chi^2 P<0.00001 I^2=87.0%		
Nalysnyk et al 2003[270]	Systematic review of in-hospital adverse effects Post-CABG	***Non-fatal Myocardial Infarction*** **34 RCTs (N=2604)** Mean 2.64% (1.82-3.46) **18 Cohort studies (N=9369)** Mean 2.21% (1.47-2.95) ***Non-fatal stroke*** **19 RCTs (N=3790)** Mean 1.00% (0.69-1.31) **33 Cohort studies (N=27342)** Mean 1.52% (1.17-1.87) ***Gastrointestinal bleeding*** **4 RCTs (N=730)** Mean 1.23% (0.43-2.03) **4 Cohort studies (N=12167)**	**Confounding factors by study design:** Acknowledges discrepancies and potential influences of variables, e.g. study (geographic location, number of study centres) and group variables (elective CABG only versus some patients with emergency CABG, some patients with a history of prior CABG versus primary CABG). **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** Reports significant difference between RCTs and cohort studies in non-fatal stroke p<0.01, renal failure p<0.05 and mortality p<0.05. No statistical analysis presented for non-fatal MI and too few studies to detect differences with GI bleeding.	***Non-fatal Myocardial Infarction*** **CI overlap:** Yes ***Non-fatal stroke*** **CI overlap:** Yes ***GI bleeding*** **CI overlap:** Yes ***Renal failure*** **CI overlap:** Yes ***Mortality*** **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Mean 1.53% (0.746-2.31) ***Renal failure*** **10 RCTs (N=2189)** Mean 0.39% (-0.06-0.84) **13 Cohort studies (N=20609)** Mean 0.98% (0.71-1.25) ***Mortality*** **48 RCTs (N=4949)** Mean 1.51% (1.10-1.93) **57 Cohort studies (N=70984)** Mean 1.80% (1.45-2.15)		
Ofman et al 2002[271]	Systematic review of NSAIDs and severe upper gastrointestinal complications perforations, ulcers and bleeds	***Gastrointestinal complications perforations, ulcers and bleeds*** **16 RCTs (N=4431)** OR 5.36 (1.76-16.1) **9 Cohort studies (N=758776 patient-years)** RR 2.7 (2.1-3.5) **23 Case-control studies (N=25732)** OR 3.0 (2.5-3.7)	**Confounding factors by study design:** NR but states that data were insufficient to justify subgroup analysis by age, comorbid conditions, drug or dose. **Heterogeneity within study designs:** NR (Only pooled homogeneous studies for each study design) **Statistical analysis comparing study designs:** NR	**RCTs:** Significant increase **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes
Oger and Scarabin	Systematic review of hormone replacement therapy and venous	***Venous thromboembolism***	**Confounding factors by study design:** NR	**Cohort study:** Significant increase

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
1999[272]	thromboembolism	**1 cohort study (N=NR)** RR 2.1 (1.2-3.8) **7 case-control studies (N=NR)** RR 2.1 (1.4-3.0) Chi^2, P=NS	**Heterogeneity within study designs:** No significant heterogeneity: one set of case-control studies **Statistical analysis comparing study designs:** NR	**Case-control studies:** Significant increase **CI overlap:** Yes
Papanikolaou et al 2006[136]	Compares evidence on 15 harms with drugs, vitamins, vaccines and surgical procedures in RCTs identified from Cochrane reviews and non-RCTs from MEDLINE	***Convulsions with pertussis vaccine*** **15 RCTs (N=124387)** RR 0.47 (0.31-0.73) **2 Non-RCTs (N=NR)** RR 0.29 (0.23-0.37) ***Hypotonic hyporesponsiveness with pertussis vaccine*** **11 RCTs (N=121573)** RR 0.26 (0.08-0.81) Q, P<0.10 **1 Non-RCT (N= NR)** RR 0.40 (0.18-0.89) ***Major extracranial bleed with oral anitcoagulant therapy*** **16 RCTs (N=22049)** RR 3.31 (2.35-4.67) **5 Non-RCTs (N=403397)**	**Confounding factors by study design:** Acknowledges differences in populations between randomised and non-randomised studies. **Heterogeneity within study designs:** No significant heterogeneity: 12 sets of RCTs and 4 sets of non-RCTs Significant heterogeneity: 2 sets of RCTs and 5 sets of non-RCTs. **Statistical analysis comparing study designs:** Differences in risk ratio beyond chance between randomised and nonrandomised studies occurred for 2 of the 13 topics. The estimated increase in risk ratio differed more than 2 fold in 7 of the 13 topics. The estimated increase in risk differed more than 2 fold in 5 of the 8 topics.	***Convulsions with pertussis vaccine*** **RCTs:** Significant decrease **Non-RCTs:** Significant decrease **CI overlap:** Yes ***Hypotonic hyporesponsiveness with pertussis vaccine*** **RCTs:** Significant decrease **Non-RCTs:** Significant decrease **CI overlap:** Yes ***Major extracranial bleed with oral anitcoagulant therapy*** **RCTs:** Significant increase **Non-RCTs:** Significant

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		RR 2.48 (1.39-4.44) Q, P<0.10 ***Symptomatic intracranial bleed with anticoagulant versus antiplatelet*** **15 RCTs (N=22794)** RR 2.64 (1.95-3.58) **2 Non-RCTs (N=273722)** RR 8.25 (5.58-12.18) ***Major extracranial bleed with anticoagulant versus antiplatelet*** **6 RCTs (N=11721)** RR 1.78 (0.93-3.40) **1 Non-RCT (N=4249)** RR 1.23 (1.05-1.44) ***Major extracranial bleed with antiplatelet therapy*** **9 RCTs (N=41399)** RR 1.68 (1.34-2.12) **2 Non-RCTs (N=24966)** RR 1.30 (0.85-1.97) Q, P<0.10 ***Symptomatic intracranial bleed with antiplatelet***		increase **CI overlap:** Yes ***Symptomatic intracranial bleed with anticoagulant versus antiplatelet*** **RCTs:** Significant increase **Non-RCTs:** Significant increase **CI overlap:** No ***Major extracranial bleed with anticoagulant versus antiplatelet*** **RCTs:** No significant difference **Non-RCTs:** Significant increase **CI overlap:** Yes ***Major extracranial bleed with antiplatelet therapy*** **RCTs:** Significant increase **Non-RCTs:** No significant difference **CI overlap:** Yes ***Symptomatic intracranial bleed with antiplatelet***

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		therapy **9 RCTs (N=41399)** RR 1.22 (1.00-1.50) **2 Non-RCTs (N=36190)** RR 1.80 (1.02-3.19) Q, P<0.10 ***Visceral or vascular injury with labaroscopy versus open surgery for inguinal hernia*** **22 RCTs (N=4914)** RR 1.56 (0.75-3.29) **1 Non-RCT (N=5506)** RR 17.30 (3.91-76.80) ***Wound infection with laparoscopy versus open surgery for appendicitis*** **34 RCTs (N=4324)** RR 0.56 (0.43-0.72) **2 Non-RCTs (N=150017)** RR 0.58 (0.50-0.68) ***Spontaneous miscarriage with folate supplementation*** **3 RCTs (N=7600)** RR 1.12 (0.98-1.29)		***therapy*** **RCTs:** No significant difference **Non-RCTs:** Significant increase **CI overlap:** Yes ***Visceral or vascular injury with labaroscopy versus open surgery for inguinal hernia*** **RCTs:** No significant difference **Non-RCTs:** Significant increase **CI overlap:** No ***Wound infection with laparoscopy versus open surgery for appendicitis*** **RCTs:** Significant decrease **Non-RCTs:** Significant decrease **CI overlap:** Yes ***Spontaneous miscarriage with folate supplementation***

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		2 Non-RCTs (N=20509) RR 1.07 (0.96-1.20) ***Multiple gestation with folate supplementation*** **3 RCTs (N=6241)** RR 1.40 (0.93-2.11) **3 Non-RCTs (N=690395)** RR 1.07 (0.98-1.17) Q, P<0.10 ***Major bleed with platelet glycoprotein IIB/IIIA blocker therapy in PCI*** **12 RCTs (N=17469)** RR 1.36 (1.04-1.77) Q, P<0.10 **1 Non-RCT (N=18821)** RR 1.74 (0.83-3.66) ***Acute myocardial infarction with rofecoxib versus naproxen therapy*** **1 RCTs (N=8076)** RR 2.86 (1.28-6.39) **1 Non-RCT (N=90629)** RR 1.31 (0.69-2.48) Q, P<0.10		**RCTs:** No significant difference **Non-RCTs:** No significant difference **CI overlap:** Yes ***Multiple gestation with folate supplementation*** **RCTs:** No significant difference **Non-RCTs:** No significant difference **CI overlap:** Yes ***Major bleed with platelet glycoprotein IIB/IIIA blocker therapy in PCI*** **RCTs:** Significant increase **Non-RCTs:** No significant difference **CI overlap:** Yes **Acute myocardial infarction with rofecoxib versus naproxen therapy** **RCTs:** Significant increase **Non-RCTs:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
Ross et al 1998[273]	Systematic review of granulocyte-macrophage colony-stimulating factor (GM-CSF) treated AIDS patients and new bacterial infections, opportunistic infections	***New bacterial infections, opportunistic infections*** **1 RCT (N=30)** Treatment 6/16 37.5% (14.28-61.72)** Control 3/14 **10 Case series (N=119)** Treatment 16/105 15% (8.13-21.87)** Control 3/14	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR (Assesses degree of heterogeneity to determine whether meta-analysis appropriate. Lack of quality and quantity of data meant could not pool data). **Statistical analysis comparing study designs:** NR	***New bacterial infections, opportunistic infections*** **CI overlap:** Yes **
Salhab et al 2005[274]	Systematic review of ovulation induction in IVF and breast cancer	***Breast cancer*** **11 Cohort studies (N=NR)** Treatment 601/60050 Control NR RR 1.06 (0.94-1.19)** (P=0.337) **4 Case-control studies (N=22233)** Cases 253/11303 Controls 273/10930 RR 0.88 (0.72-1.08)** (P=0.224)	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	**Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes
Schwarz et al 2008[275]	Systematic review of loratadine and hypospadias	***Hypospadias*** **2 Case-control studies** OR 0.95 (0.43-2.08)	**Confounding factors by study design:** NR **Heterogeneity within study designs:**	**Cohort studies:** No significant difference **Case-control studies:** No

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		2 Cohort studies OR 1.23 (0.32-4.69)	NR **Statistical analysis comparing study designs:** NR	significant difference **CI overlap:** Yes
Scott et al 2007[276]	Systematic review of NSAIDs and myocardial infarction	***Myocardial infarction (naproxen)*** **4 Cohort studies (N=571679 patient years)** RR 0.96 (0.90-1.03) **11 Case-control studies (N=384324)** OR 1.03 (0.83-1.29) ***Myocardial infarction (ibuprofen)*** **3 Cohort studies (N=552150 patient years)** RR 0.90 (0.82-0.97) **8 Case-control studies (N=286089)** OR 1.08 (0.80-1.46) ***Myocardial infarction (celecoxib)*** **3 Cohort studies (N=330651 patient years)** RR 1.06 (1.00-1.13) **7 Case-control studies (N=319841)**	**Confounding factors by study design:** Acknowledges that discrepancies may arise from selection of controls and populations studied. **Heterogeneity within study designs:** NR (Significant heterogeneity among all 6 cohort studies for a*ll NSAIDS* Chi^2 P<0.001, I^2=92.1% and for all 14 case-control studies Chi^2 P<0.001, I^2=97.9%) **Statistical analysis comparing study designs:** NR	***Naproxen*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes ***Ibuprofen*** **Cohort studies:** Significant decrease **Case-control studies:** No significant difference **CI overlap:** Yes **Celecoxib** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes **Rofecoxib** **Cohort studies:** Significant increase **Case-control studies:** No

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		OR 1.01 (0.73-1.39) ***Myocardial infarction (rofecoxib)*** **3 Cohort studies (N=322443 patient years)** RR 1.25 (1.17-1.34) **7 Case-control studies (N=203487)** OR 1.19 (0.70-2.01)		significant difference **CI overlap:** Yes
Scott et al 2008[277]	Systematic review of NSAIDS and cardiac failure	***Cardiac failure*** **6 RCTs (N=15750)** NSAIDS 40/8542 Placebo 13/7208 OR 2.31 (1.34-4.00) Chi^2 P=0.37, I^2=6.9% **2 Cohort studies (82785 patient years)** RR 1.97 (1.73-2.25) Chi^2 P=0.33, I^2= 0% **5 Case-control studies (N=50519)** OR 1.36 (0.99-1.85) Chi^2 P<0.001, I^2= 90.9%	**Confounding factors by study design:** NR but discusses the problems of over the counter NSAIDS in observational studies and that 2 RCTs and one case-control study excluded patients with previous cardiac failure. Also commented on short-term follow-up in RCTs. **Heterogeneity within study designs:** No significant heterogeneity: one set of RCTs and one set of cohort studies. Significant heterogeneity: one set of case-control studies. **Statistical analysis comparing study designs:** NR	**RCTs:** Significant increase **Cohort studies:** Significant increase **Case-control studies:** No significant difference **CI overlap:** Yes
Siegel et al 2009[278]	Systematic review of anti-tumour necrosis factor and immunomodulator therapy and lymphoma	***Lymphoma*** **9 RCTs (N=3399)** 2 cases, 5.2/10,000 patient years	**Confounding factors by study design:** NR but discusses the possible differences in patients by study design. **Heterogeneity within study designs:**	**CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		0.052% (0.013 – 0.207) **3 Cohort studies (N=4122)** 7 cases, 4.6/10,000 patient years 0.046% (0.022-0.097)** **14 Case series (N=1384)** 4 cases, 18.8 /10,000 patient years 0.188% (0.071-0.502)**	NR **Statistical analysis comparing study designs:** NR	
Singh et al 2007[279]	Systematic review of thiazolidinediones and heart failure	***Heart failure*** **3 RCTs (N=10731)** Treatment 314/5350 Control 210/5381 OR 2.10 (1.08-4.08) Chi^2 P=0.09, I^2=58.8% **4 Observational studies (N=67382)** OR 1.55 (1.33-1.80) Chi^2 P=0.13, I^2=46.9%	**Confounding factors by study design:** NR **Heterogeneity within study designs:** No significant heterogeneity: one set of observational studies Significant heterogeneity: one set of RCTs **Statistical analysis comparing study designs:** NR	**RCTs:** Significant increase P=0.03 **Observational studies:** Significant increase P<0.00001 **CI overlap:** Yes
Smith et al 2003[280]	Systematic review of hormonal contraceptives and cervical cancer	***Cervical cancer (short duration users of contraceptives)*** **4 Cohort studies (N=NR)** RR 1.8 (1.4-2.4) Chi^2 P>0.1 **16 Case-control studies (N=NR)** RR 1.1 (1.0-1.2)	**Confounding factors by study design:** NR but conducts subgroup analysis on other factors such as HPV status, sexual partners, cervical screening, smoking, barrier contraceptives, country, invasive cervical cancer, in situ cervical cancer, squamous cervical cancer, adenocarcinoma of the cervix but not by	***Short duration users*** **Cohort studies:** Significant increase **Case-control studies:** No significant difference **CI overlap:** No ***Medium duration users*** **Cohort studies:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Chi^2 P=0.004 ***Cervical cancer (medium duration users of contraceptives)*** **4 Cohort studies (N=NR)** RR 2.2 (1.7-2.9) Chi^2 P=0.007 **17 Case-control studies (N=NR)** RR 1.5 (1.4-1.7) Chi^2 P=0.03 ***Cervical cancer (long duration users of contraceptives)*** **3 Cohort studies (N=NR)** RR 3.3 (2.4-4.5) Chi^2 P=0.02 **10 Case-control studies (N=NR)** RR 2.0 (1.8-2.3) Chi^2 P=0.03	study design. **Heterogeneity within study designs:** No significant heterogeneity: one set of cohort studies Significant heterogeneity: 2 sets of cohort studies and 3 sets of case-control studies (significant heterogeneity when all studies are pooled) **Statistical analysis comparing study designs:** NR but authors state that RR consistently higher in the cohort studies than case-control studies even within stratified categories of duration. States that the reason for this is unclear.	Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes ***Long duration users*** **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** No
Takkouche et al 2007[281]	Systematic review of psychotropic medications and fracture	***Fracture (benzodiazepines)*** **7 Cohort studies (N=NR)** RR 1.31 (1.18-1.45) Q test P=0.36 **16 Case-control studies**	**Confounding factors by study design:** NR but conducts subgroup analysis by selected characteristics. ***Benzodiazepines:*** Did not find any evidence of a substantial difference in pooled RRs according to duration of	***Benzodiazepines*** **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(N=NR) RR 1.36 (1.23-1.51) Q test P=0.0001 ***Fracture (antidepressants)*** **3 Cohort studies (N=NR)** RR 1.28 (1.04-1.58) Q test P=0.79 **13 Case-control studies (N=NR)** RR 1.66 (1.41-1.96) Q test P=0.00001 ***Fracture (non-barbiturate antiepileptic drugs)*** **4 Cohort studies (N=NR)** RR 1.34 (0.96-1.88) Q test P=0.21 **9 Case-control studies** RR 1.64 (1.24-2.16) Q test P=0.00001 ***Fracture (antipsychotics)*** **2 Cohort studies** RR 1.11 (0.70-1.75) Q test P=0.42 **10 Case-control studies** RR 1.68 (1.32-2.14)	action, study quality score or by limiting to hip fractures alone. ***Antidepressants:*** Did not find any evidence of a substantial difference in pooled RRs according to study quality score. ***Antiepileptic drugs:*** Low quality studies had higher RR. ***Antipsychotics:*** Results similar according to anatomic site of fracture and quality scoring. ***Hypnotics:*** Results similar according to quality scoring. **Heterogeneity within study designs:** No significant heterogeneity: 6 sets of cohort studies. Significant heterogeneity: 6 sets of case-control studies. **Statistical analysis comparing study designs:** NR but authors state that they did not find any substantial difference in pooled risk ratio according to study design for studies of Benzodiazepines and that cohort studies showed a lower pooled risk ratio than case-control studies for studies of antidepressants.	***Antidepressants*** **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes ***Antiepileptic* drugs** **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** Yes ***Antipsychotics*** **Cohort studies:** No significant difference **Case-control studies:** Significant increase **CI overlap:** Yes ***Hypnotics*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **CI overlap:** Yes

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Q test P=0.00001 ***Fracture (hypnotics)*** **3 Cohort studies** RR 1.04 (0.86-1.25) Q test P=0.49 **10 Case-control studies** RR 1.22 (0.97-1.54) Q test P=0.008 ***Fracture (opioids)*** **3 Cohort studies** RR 1.32 (1.02-1.70) Q test P=0.18 **3 Case-control studies** RR 1.42 (1.04-1.93) Q test P=0.001		***Opioids*** **Cohort studies:** Significant increase **Case-control studies:** Significant increase **CI overlap:** Yes
Torloni et al 2009[282]	Systematic review of ultrasonography in pregnancy	***Low birth weight*** **10 RCTs (N=24271)** OR 1.06 (0.84-1.35) I^2=69.3% **6 Cohort studies (N=18622)** OR 1.11 (0.84-1.46) I^2=72.8% **1 Case control study(N=12,546)** 1.38 (1.25-1.51)	**Confounding factors by study design:** NR **Heterogeneity within study designs:** Significant heterogeneity: one set of RCTs and one set of cohort studies. **Statistical analysis comparing study designs:** NR	***Low birth weight*** **RCTs;** No significant difference **Cohort studies:** No significant difference **Case control study:** Significant increase **CI overlap:** Yes ***Dyslexia*** **RCT:** No significant difference

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		Dyslexia **1 RCT (N=603)** OR 0.75 (0.41-1.37) **1 Cohort study (N=806)** OR 1.78 (1.08-2.93) ***Impaired hearing*** **1 RCT (N=2008)** OR 0.97 (0.62-1.53) **1 Cohort study (N=723)** OR 0.89 (0.31-2.57)		**Cohort study:** Significant increase **CI overlap:** Yes ***Impaired hearing*** **RCT:** No significant difference **Cohort study:** No significant difference **CI overlap:** yes
Tramer et al 1997[283]	Systematic review of propofol and bradycardia	***Bradycardia*** **19 Trials (N=1208)** 23.3% (154/660) (20.07-26.53)** **2 Case series (N=24578)** 4.8% (1179/24578) (4.53-5.07)**	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR but authors state that compared with controlled studies bradycardia was 3-4 times less likely to be reported in the case series.	**CI overlap:** No**
Tramer et al 2000[183]	Presents a model to estimate the incidence of rare adverse events with NSAIDS using heterogeneous information	***Symptomatic ulcer*** **3 RCTs (N=NR)** Intervention 262/17 743 1.48% (1.30-1.66)** **1 Cohort study (N=NR)** Intervention 131/33 880 0.39% (0.32-0.46)**	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** Calculated difference in incidence by study design using risk ratio. Cohort study significantly lower incidence of symptomatic ulcer than	**CI overlap:** No

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
			RCTs RR 2.3 (1.7-3.1)	
Vohra et al 2007[284]	Systematic review of spinal manipulation	***All adverse events*** **2 RCTs (N=191)** Number of adverse events: 4 **1 cases series (N=NR)** Number of adverse events: 3 **6 case reports (N=NR)** Number of adverse events: 7	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	**CI overlap:** NR
Wang et al 2008[285]	Systematic review of medical cannabinoids	***Serious adverse events*** **23 RCTs (N=NR)** Number of serious adverse events: 164 **8 observational studies (N=NR)** Number of serious adverse events: 39 ***Nonserious adverse events*** **23 RCTs (N=NR)** Number of nonserious adverse events: 4615 **8 observational studies (N=NR)** Number of nonserious adverse events: 3553	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	**CI overlap:** NR

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
Woolcott et al 2009[286]	Systematic review of falls in the elderly	***Falls (antihypertensives)*** **3 cohort studies (N=NR)** OR 1.34 (0.93-1.91) **2 case-control studies (N=NR)** OR 1.09 (0.80-1.50) **1 cross-sectional study (N=NR)** OR 1.11 (0.78-1.58) ***Falls (diuretics)*** **1 cohort study (N=NR)** OR 1.05 (0.97-1.15) **5 case-control studies (N=NR)** OR 1.11 (0.94-1.32) **3 cross-sectional studies (N=NR)** OR 1.11 (1.00-1.24) ***Falls (b-blockers)*** **1 case-control study (N=NR)** OR 0.87 (0.55-1.37) **3 cross-sectional studies (N=NR)** OR 1.02 (0.79-1.24) ***Falls***	**Confounding factors by study design:** NR **Heterogeneity within study designs:** NR **Statistical analysis comparing study designs:** NR	***Antihypertensives*** **Cohort studies:** No significant difference **Case-control studies:** No significant difference **Cross-sectional study:** No significant difference **CI overlap:** Yes ***Diuretics*** **Cohort study:** No significant difference **Case-control studies:** No significant difference **Cross-sectional studies:** No significant difference **CI overlap:** Yes ***B-Blockers*** **Case-control study:** No significant difference **Cross-sectional studies:** No significant difference **CI overlap:** Yes ***Sedatives/hypnotics*** **Cohort studies:** Significant increase **Case-control study:**

Table 15.1 Characteristics of included studies in Chapter 4

Reference	Study Design	Included Studies	Methodological Assessment	Increase/decrease/no difference in adverse effects by study design
		(sedatives/hypnotics) **3 cohort studies (N=NR)** OR 1.24 (1.05-1.45) **1 case-control study (N=NR)** OR 1.62 (1.31-2.00) **3 cross-sectional studies (N=NR)** OR 1.56 (1.39-1.76)		Significant increase **Cross-sectional studies:** Significant increase **CI overlap:** Yes

Key
CI – Confidence Interval
N – Number of study participants
NR – Not reported
OR – Odds Ratio
RR – Risk ratio
WMD – Weighted Means Difference
**- data were calculated from information presented in paper

Table 15.2 Excluded studies in Chapter 4

Study	Reason for exclusion
Beral et al 2008[307]	Pools risk ratio for prospective studies and for case-control studies for ovarian cancer with oral contraceptive use. Hypothesis is that oral contraceptives have a protective effect.
Blankensteijn 2000[287]	Compares mortality and morbidity rates after conventional abdominal aortic aneurysm repair from prospective and retrospective studies. Does not categorise by study design (such as RCT, cohort study or case-control study).
Bonovas et al 2007 [308]	Compares risk ratio from RCTs, cohort studies and case-control studies for statins and the risk of colorectal cancer. Hypothesis suggests a protective effect of statins.
Boyd et al 1993[649] and update Boyd et al 2003[348]	Compares risk ratio of breast cancer from dietary fat from cohort studies and case-control studies. Does not include a health care intervention.
Brumback et al 1999[332]	Includes cohort studies and case-control studies for the adverse effects of chorionic villus sampling. Presents number of defects/1000 for each individual study. Does not pool or compare data.
Choi et al 2003[288]	Reports on the pooled risk of postdural puncture headache with neuraxial blockade in prospective and retrospective studies and RCTs. Does not compare RCTs to other formal study designs such as cohort studies or case-control studies.
Col et al 2003[319]	Discusses the differences in the results of observational and RCTs on the association of chronic heart disease and menopausal hormone therapy. Does not present pooled results from the different type of studies.
Curran et al 1999[290]	Summaries the complications of primary repair of colon injury using retrospective data, prospective studies and randomized studies. Does not categorise by study design (such as RCT, cohort study or case-control study).
Collaborative Group on Hormonal Factors in Breast Cancer, 1996 [289]	Presents the pooled risk ratio of breast cancer with oral contraceptives from prospective studies and case-control studies. Does not compare the results from case-control studies with other formal study designs such as cohort studies.
Costa and Doyle 2006[333]	Presents risk ratio data of trophoblastic neoplasm with oral contraceptives for individual RCTs and observational studies. Does not pool the results of the different study designs.
Demicheli et al 2003[339]	Pools adverse events following hepatitis B vaccination separately for RCTs and case-control studies. Does not compare similar adverse events. Any adverse events up to 5 days after vaccination are included in the RCTs, whereas the case-control studies include only MS and demyelinating disease up to a year after vaccination are included in the case-control studies.
Dezfulian et al 2003[291]	Includes RCTs, prospective and retrospective studies for infection rates with catheters. Compares odds ratios for all studies with odds ratios of RCTs and prospective studies combined. Does not compare RCTs with other formal study designs, such as cohort studies or case-control studies.

Table 15.2 Excluded studies in Chapter 4

Study	Reason for exclusion
Egger et al 1998[140]	States risk ratio from 6 observational studies comparing high and low B carotene intake or serum B carotene concentrations with risk ratio from 4 RCTs comparing B carotene supplementation to placebo. Does not compare risk ratio with similar comparators.
Eikelboom et al 2001[292]	Compares odds ratios of intracranial haemorrhage with bolus thrombolytic therapy in 9 phase 2 RCTs and 6 phase 3 RCTs. Does not compare RCTs to other study designs.
Ernst et al 1998[340]	Presents data from RCTs and case reports for adverse effects with St. John's wort. No data for the same adverse effects from the 2 study designs are presented.
Etminan et al 2003[309]	Includes case-control and cohort studies of NSAIDS and the risk of Alzheimer's disease. Hypothesis suggests NSAIDS may have protective effect.
Fernandez et al 2001[310]	Includes case-control and cohort studies of oral contraceptives and the risk of colorectal cancer. Hypothesis suggests oral contraceptives may have protective effect.
García Rodríguez et al 2001[293]	Pools risk ratio or upper gastrointestinal complications with aspirin for cohort and nested case-control studies together and non-nested case-control studies. Does not pool cohort studies separately from case-control studies.
Glanz et al 2006[305]	Uses a stimulation model to compare beta estimates for idiopathic thrombocytopenic pupura (ITP) with measles-mumps-rubella (MMR) vaccine in simulated cohort, risk-interval, self-controlled case series (SCCS), case-control designs. Does not compare different real life studies.
Gordon et al 2010[294]	Compares pneumothorax rates with and without ultrasonography guidance in 6 comparative studies and 2 RCTs. The 2 RCTs are included within the comparative study analysis.
Greiser et al 2005[347]	Pools the odds ratios and risk ratio of breast cancer with menopausal hormone therapy for cohort studies and RCTs combined and for case-control studies. Does not pool the results for cohort studies and RCTs separately.
Grullon and Grimes 1997[334]	Includes RCTs, cohort studies, case series, and a case-control study on the safety of early postpartum discharge. Presents the results for individual studies grouped by study design but does not pool the results by study design.
Hall and Lucke 2006[171]	Includes RCTs, observational studies and ecological studies on the risk of suicide with SRRIs. Presents the results of each of the individual studies grouped by study design but does not pool the results by study design
Hawkey CJ. *BMJ* 1990;300:278-84.[320]	Includes cohort studies and case-control studies on the risk of peptic ulcers with NSAIDs. Identifies higher risk estimates with NSAIDS in case-control studies than cohort (attributed to bias associated with this study design). Does not present pooled estimates by study design.
Henry et al 2001[230]	Compares agreement between RCTs and observational studies for the impact of laparoscopic cholecystectomy, compared with open or mini-laparotomy, on post-operative infections and bile duct injury; the impact of antioxidants on death from malignancy and cardiovascular disease; and the

Table 15.2 Excluded studies in Chapter 4

Study	Reason for exclusion
	effects of hormone replacement therapy (HRT) on cardiovascular and overall mortality (healthy cohort effect). Abstract only does not give enough information.
Herbert-Croteau 1998[311]	Pools risk ratio for cohort studies and for case-control studies for colon cancer with hormone replacement therapy (HRT). Hypothesis is that hormone replacement therapy (HRT) has a protective effect.
Herbert et al 2007[295]	Compares motor vehicle crashes with benzodiazepines using a case-controlled and case-crossover design with one dataset. Does not compare by study design such as RCT, cohort studies or case-control studies.
Janowsky et al 2000[335]	Includes cohort studies, case-control studies and cross-sectional studies on the risk of connective tissue diseases with silicone breast implants. Presents the results for individual studies grouped by study design but does not pool the data by study design.
Kashyap et al 2004[312]	Pools incidence data in cohort studies and case-control studies for ovarian cancer with assisted reproductive technology. Suggests that treated patients may have a lower incidence of ovarian cancer.
Katerndahl et al 1992[321]	Calculates the risk ratio of cardiovascular disease with oral contraceptives. Summarises study characteristics. Identifies that cohort studies has lower risk ratios than case-control studies but does not present any quantification of this difference.
Kuoppala et al 2008[322]	Presents risk ratio estimates for RCTs, cohort studies, and case-control studies in diagrammatic format but does not present pooled data. States that effect estimates do depend on study design.
Larsson et al 2006[313]	Pools case-control and cohort studies for the risk of pancreatic cancer with aspirin and NSAIDs. Hypothesis suggests aspirin may reduce the risk.
Lawlor et al 2003[323]	Includes RCT, cohort studies and case-control studies on the association between antidepressant medication and breast cancer. Presents a forest plot by study design but does not report the pooled risk ratios by study design.
Levine et al 1997[296]	Compares prospectively the impact of study design on safety data for ACE inhibitors. Study designs compared are one RCT, one phase IV postmarketing open clinical trial, one phase IV postmarketing open clinical trial and one postmarketing research survey. Does not compare multiple studies of the same design or compare traditional types of study design with the RCT.
Loke et al 2009[324]	Includes 4 RCTs and 2 case-control studies. Presents pooled ORs for serious atrial fibrillation and serious and non-serious atrial fibrillation and individual ORs of atrial fibrillation for the 2 case-control studies.
Magee et al 2001[325]	Descriptive comparison of characteristics of participants, interventions, and outcomes assessed between a meta-analysis of trials of beta-blocker therapy in pregnancy, and a prospective cohort of beta-blocker users. Does not include any quantification of the impact of different study

Table 15.2 Excluded studies in Chapter 4

Study	Reason for exclusion
	types on harm data.
Marang-van de Mheen et al 2007 [297]	Compares occurrence of adverse outcomes and mortality in in-hospital patients and after surgery with respect to data collection method, unit of analysis, number of reviewers and definition of adverse outcome. No comparison by type of study design (such as RCT or case-control study).
Marra et al 2006[298]	Compares the odds ratios of prospective and retrospective studies for asthma after antibiotic exposure during infancy. Does not compare study design, such as RCT, case-control or cohort studies.
Martel et al 2005[299]	Compares pooled odds ratio of thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis for RCTs and for RCTs and nonrandomized prospective studies combined. Does not compare the pooled results for RCTs with other discrete study designs.
Martin 2005[134]	Discusses the reasons for differences between observational and controlled trial data for the safety of albumin. No comparable data presented.
Miller et al 2002[345]	Contains duplicate data from Agency for Healthcare Research and Quality 2002[238]
Miwa et al 1997[326]	Discusses gastrointestinal, liver and skin events with NSAIDS in spontaneous reports and epidemiological studies. Does not include any quantification of the impact of different study types.
Meenan[346]	Contains duplicate data from Chou et al 2006,[247]and Chou et al 2007[248]
Molloy et al 2002[300]	Reports on the pooled odds ratios for bowel and major vascular injuries from laparoscopic entry in prospective and retrospective studies. Does not compare by study design (such as cohort and case-control studies).
Nakhai-Pour et al 2008[327]	Compares the pooled results of one RCT, 7 cohort studies and 22 case-control studies. Only presents the ORs for the pooled case-control studies.
O'Brien et al 2008[341]	Presents odds ratios for 3 pooled case-control studies for cardiac malformations and pooled differences in rates of cardiac malformations for 6 cohort studies. Does not present the same outcome measures for the different study designs.
Padwal and Laupacis 2004[336]	Includes case-control, cohort studies and RCTs on antihypertensive therapy and type 2 diabetes. Presents risk ratio by individual studies but does not pool by study design
Pladevall-Vila et al 1996[314]	Includes case-control and cohort studies of oral contraceptives and the risk of rheumatoid arthritis. Pooled risk ratio only given for cohort studies. Hypothesis suggests oral contraceptives may have protective effect.
Reynolds et al 2002[315]	Pools the results from RCTs and from RCTs and non-randomised trials for umbilical artery pH values and umbilical artery base excess after analgesia in labour. Suggests epidural analgesia is associated with improved neonatal acid-base status.
Rossi et al 1983[328]	Compares detection of new adverse drug reactions in

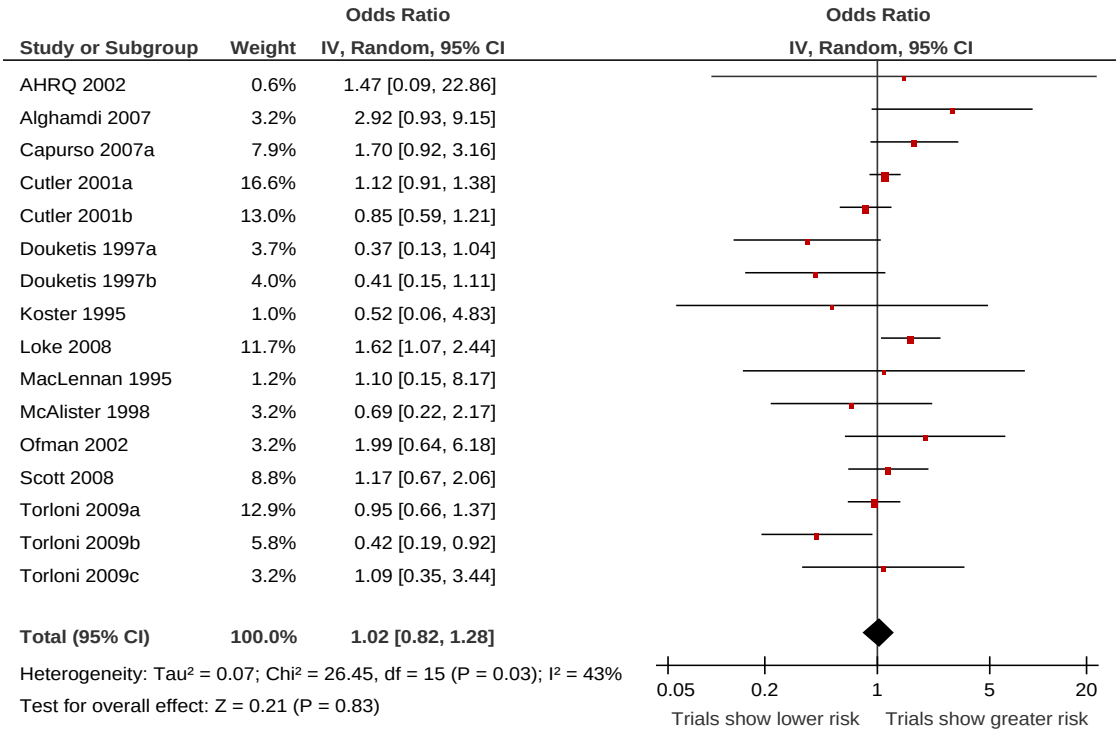
Table 15.2 Excluded studies in Chapter 4

Study	Reason for exclusion
	phase 4 studies with spontaneous reports. No quantification of the impact of different study types.
Rothwell et al 1996[301]	Pools the risk of mortality and stroke and/or death due to endarterectomy for prospective and retrospective studies. Does not group by formal study design (such as RCT, cohort.study or case-control study).
Safdar et al 2002[302]	Pools odds ratios of haemolytic uremic syndrome after antibiotic treatment for retrospective and prospective studies. Does not group by formal study design (such as RCT, cohort.study or case-control study).
Schaffer et al 2006[349]	Risk duration meta-analysis – looking at the decline in annualised risk of NSAID-related gastrointestinal events over time during long-term exposure in RCTs and cohort studies. Does not compare the magnitude of adverse effects by study design.
Shah et al 2005[337]	Compares odds ratios of observational studies (cohort and case-control studies combined) to hazard ratios from individual RCTs for the risk of breast cancer with postmenopausal hormone therapy. Does not pool RCT data and separates observational data by duration of use of therapy.
Singh and Loke 2006[342]	Presents odds ratio from observational studies and number of case reports/number of spontaneous reports for pancreatitis with statins. Difficult to compare odds ratios to numbers of cases.
Spector and Hochberg 1990[650]	Presents pooled odds ratios for case-control studies and cohort studies for the association of oral contraceptives and rheumatoid arthritis. Hypothesis suggests a protective effect of oral contraceptives.
Steffensmeier et al 2006[329]	Discussion comparing case reports and RCTs on the association between β-adrenergic blockers and depression. Does not present any quantification of the impact of the different study types.
Steinberg et al 1994[330]	Updated meta-analysis with primary aim to assess cancer risk by duration of estrogen use. Tests sources of heterogeneity such as source of controls, study design and types of estrogen. Does not report frequencies or risk ratio of adverse effects.
Thavagnanam et al 2007[331]	Systematic review of the association between children born by caesarean section and asthma. Analysis was conducted in subgroups of the studies defined by study design. However, the results are not reported.
Toh and Hernández-Díaz 2007. [316]	Pools odds ratios for fracture risk with statins for case-control and cohort studies. Hyposthesis suggests protective effect.
Uboweja et al 2006[338]	Includes case-control studies, cohort study and cross-sectional survey for the effect of inhaled corticosteroids on the risk of cataract. Presents the risk by individual study does not pool the results by study design.
Vamvakas 1995[303]	Presents pooled risk ratio for prospective and retrospective studies on perioperative blood transfusion and cancer recurrence. Does not group by formal study design (such as

Table 15.2 Excluded studies in Chapter 4

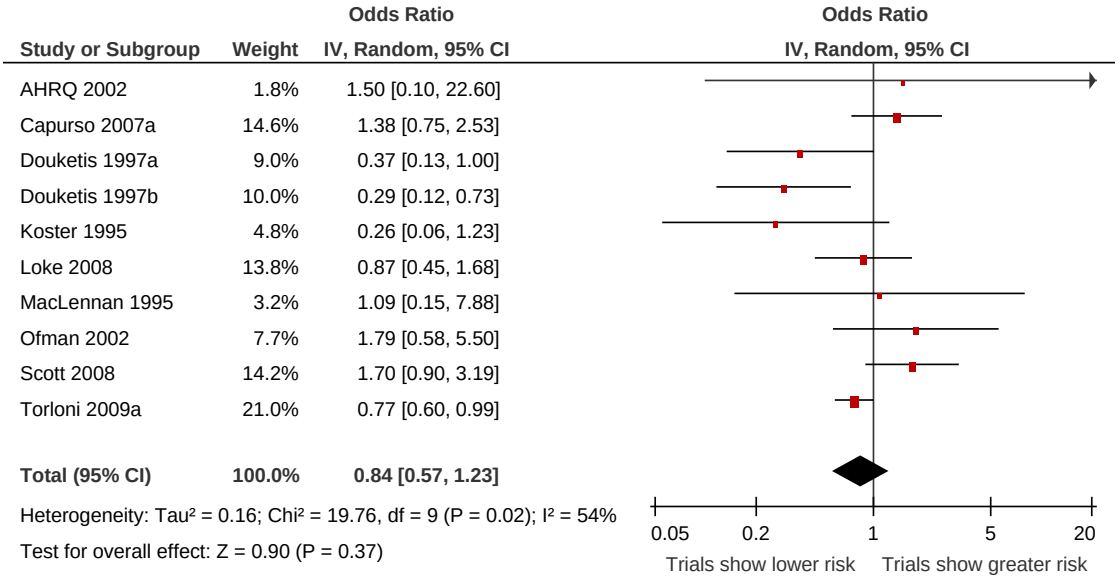
Study	Reason for exclusion
	RCT, cohort.study or case-control study).
Van staa et al 2008[306]	Uses a stimulation model to compare gastrointestinal events and myocardial infarction with Cox-2 inhibitors with data from General Practice Research Database (GPRD) (now Clinical Practice Research Datalink (CPRD)) and RCTs.
Vendermeer et al 2004[343]	Compares 2 systematic reviews one looked primarily at adverse events and included only observational studies and the other review looked solely at adverse events and included only RCTs. The results of the comparison are not presented as conference abstract only available.
Viboud et al 2001[304]	Compares statistical efficiency of case-crossover and case-control study designs using one dataset on severe cutaneous adverse reactions.
Wiens et al 2006[317]	Presents pooled risk ratio of fracture outcomes with antihypertensive drugs in case-control and cohort studies. Hypothesis suggests that antihypertensive drugs have protective effect on fracture outcomes.
Yaffe et al 1998[318]	Pools risk ratio for prospective cohort studies and for case-control studies for dementia with estrogen therapy. Hypothesis is that estrogen therapy has a protective effect.
Zhang et al 2001[344]	Uses a systematic review of analgesic nephopathy and chronic renal disease to compare case-control studies and cohort studies. Conference abstract only. Not enough information.

Figure 15.1 Meta-analysis of ratio of risk ratios from RCTs versus cohort studies



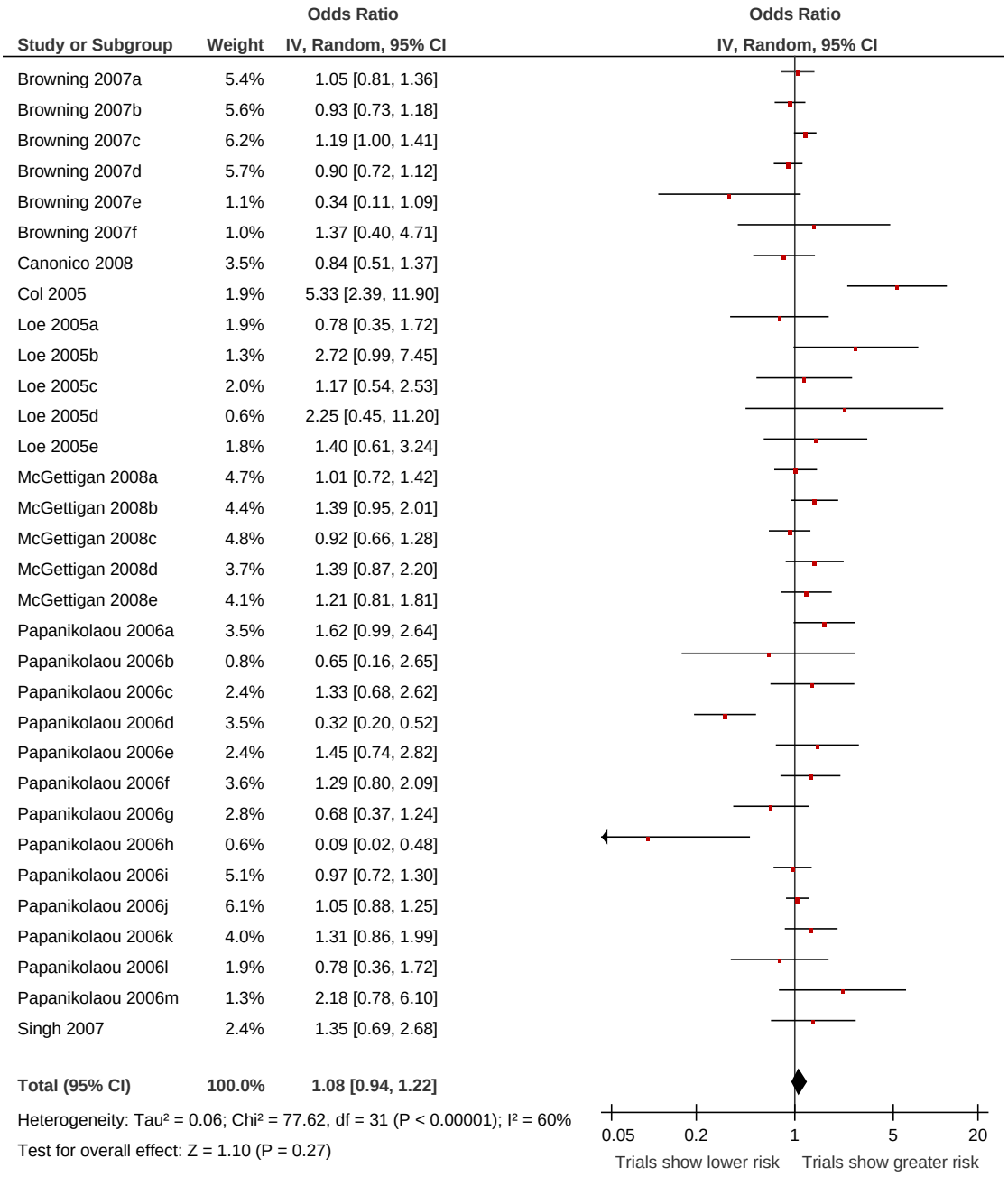
Only two methodological evaluations gave results that did not cross the line of no effect. Loke 2008 identified a greater incidence of fractures with thiazolidinediones in RCTs than cohort studies, although both study designs agreed that there was a significant increase in fractures. Torloni 2009b identified a greater estimate for dyslexia after ultrasonography in pregnancy in cohort studies than RCTs.

Figure 15.2 Meta-analysis of ratio of risk ratios from RCTs versus case-control studies



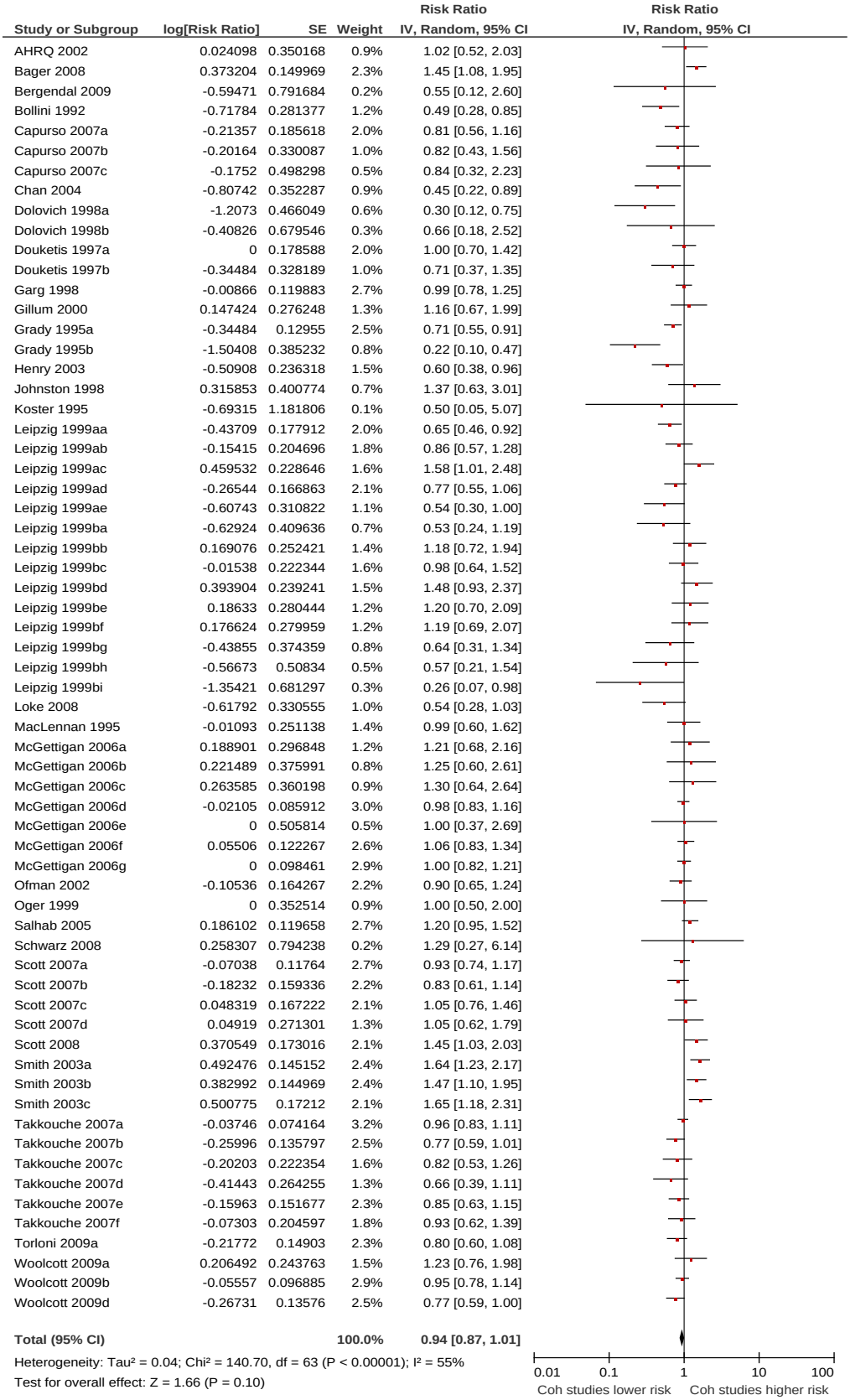
Only two methodological evaluations gave results that did not cross the line of no effect, Douketis 1997b (oral contraceptives and venous thromboembolism) and Torloni 2009a (low birth weight and ultasonography in pregnancy). Both identified higher estimates of an adverse effect with case-control studies than RCTs.

Figure 15.3 Meta-analysis of ratio of risk ratios from RCTs versus studies described as 'observational'



Col 2005 (HRT and breast cancer), Papanikolaou 2006d (anticoagulant and bleed) and Papanikolaou 2006h (labaroscopy and injury) were the only methodological evaluations which gave ratios of risk ratios that did not cross the line of no effect. Col 2005 identified a higher estimate in RCTs than 'observational studies', whereas Papanikolaou 2006d and 2006h identified a lower estimate of adverse effects in 'observational studies' than RCTs.

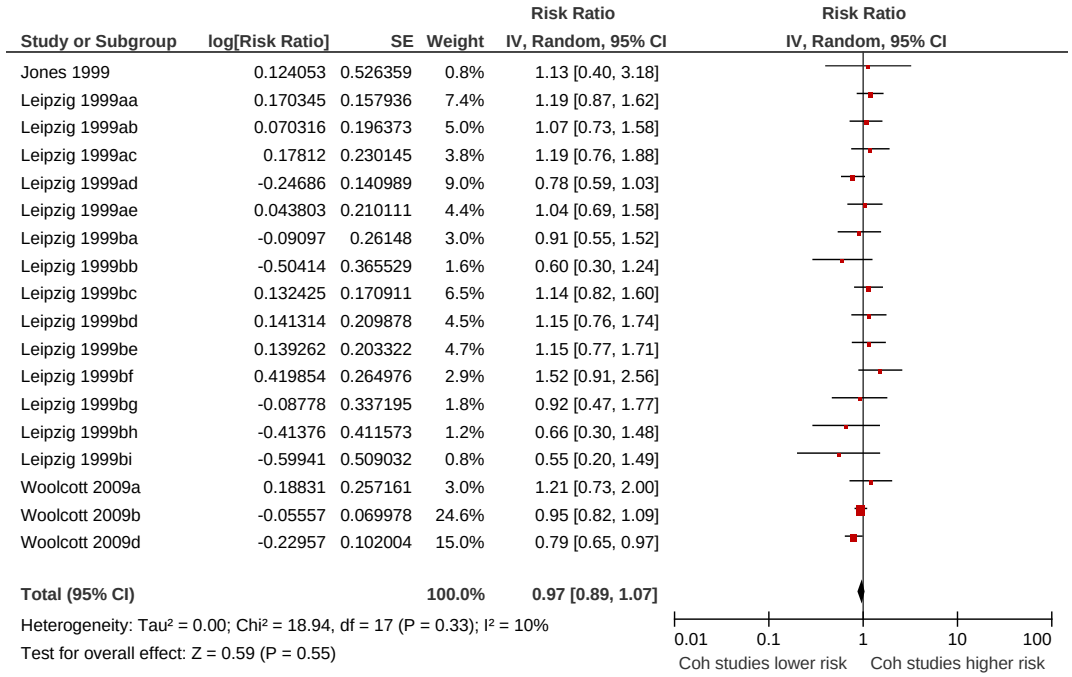
Figure 15.4 Meta-analysis of ratio of risk ratios from cohort versus case-control studies



14 sets of results gave ratios of risk ratios that did not cross the line of no effect. A higher estimate of adverse effects was identified in cohort studies than case-control studies in Bager 2008 (caesarean delivery and asthma), Leipzig 1999ac (neuroleptics and falls), Scott 2008 (NSAIDS and cardiac failure), Smith 2003a (short duration hormonal contraceptives and cervical cancer), Smith 2003b (medium duration hormonal contraceptives and cervical cancer) and Smith 2003c (long duration hormonal contraceptives and cervical cancer).

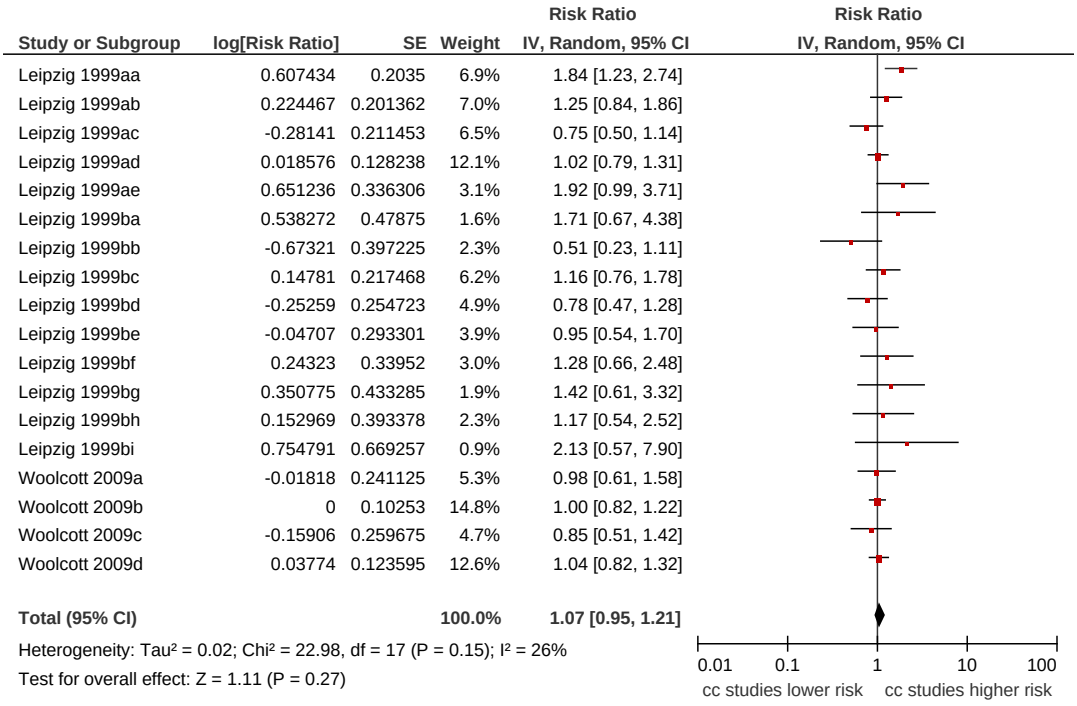
On the other hand, a lower estimate of adverse effects was identified in cohort studies than case-control studies in Bollini 1992 (NSAIDS and upper gastrointestinal tract disease), Chan 2004 (oral contraceptives and stroke), Dolovich 1998a (benzodiazepine in pregnancy and major malformations), Grady 1995a (HRT and endometrial cancer), Grady 1995b (estrogen plus progestin and endometrial cancer), Henry 2003 (NSAIDS and gastrointestinal complications), Leipzig 1999aa (psychotropics and falls), and Leipzig 1999bi (antiarrhythmics and falls).

Figure 15.5 Meta-analysis of ratio of risk ratios from cohort versus cross-sectional studies



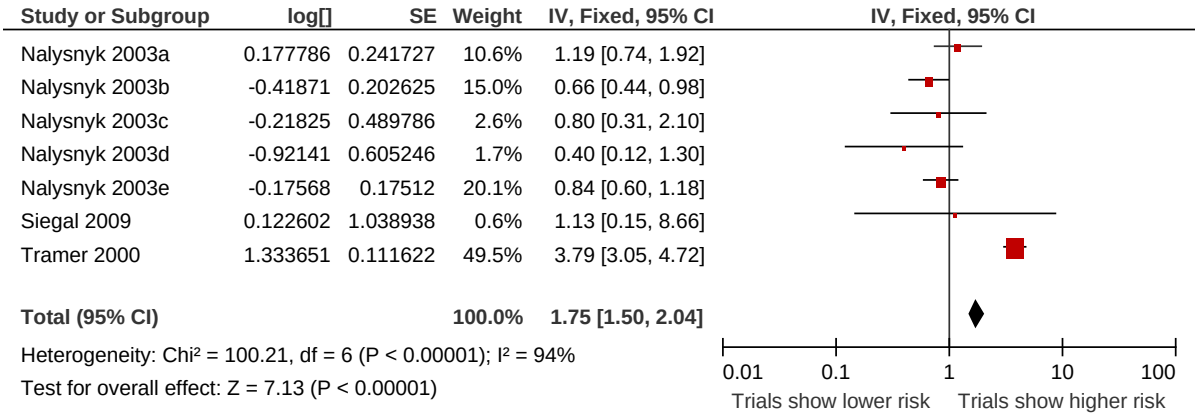
Although in Woolcott 2009d a significant increase in falls was identified from both the cohort studies and the cross-sectional studies, the ratio of odds ratios from these studies gave results that did not cross the line of no effect. A lower estimate of adverse effects was identified in Woolcott 2009d in cohort studies than in cross-sectional studies.

Figure 15.6 Meta-analysis of ratio of risk ratios from case-control studies versus cross-sectional studies



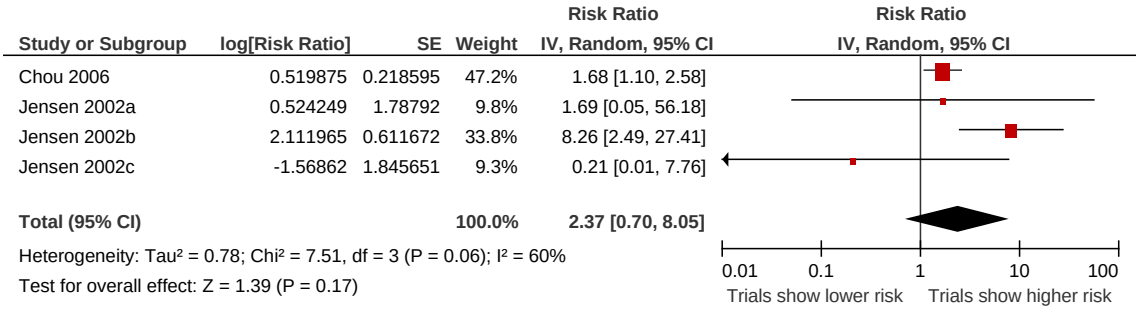
Although in Leipzig 1999aa (psychotropics and falls) there was an increase in falls identified from the case-control studies and the cross-sectional studies, the ratio of odds ratios for falls was higher in case-control studies than cross-sectional studies. In Leipzig 1999a case-control studies estimates of risk were higher than in cross-sectional studies.

Figure 15.7 Meta-analysis of ratio of incidence from RCTs versus cohort studies



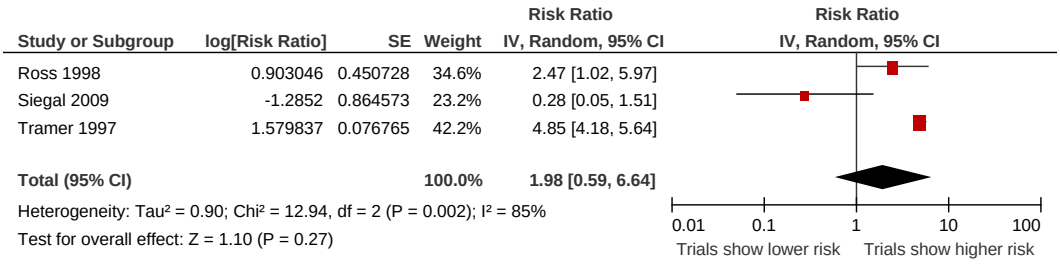
Two methodological evaluations gave results that did not cross the line of no effect, Nalysnyk 2003b and Tramer 2000. Nalysnyk 2003b identified a lower incidence of non-fatal stroke post-CABG in RCTs than cohort studies. Tramer 2000 identified a lower incidence of symptomatic ulcer with NSAIDS in cohort studies than RCTs.

Figure 15.8 Meta-analysis of ratio of incidence from RCTs versus studies described as 'observational'



The confidence intervals for the ratio of incidence from Chou 2006 (carotid endarterectomy and stroke/death) and Jensen 2002b (regional anesthesia and posthernioohaphy urinary retention) did not cross the line of no effect. In each case there was a higher incidence of adverse effects in RCTs than observational studies.

Figure 15.9 Meta-analysis of ratio of incidence from RCTs versus case series



Tramer 1997 (propofol and bradycardia) and Ross 1998 (granulocyte-macrophage colony-stimulating factor and infections) gave results that did not cross the line of no effect with both reporting a higher incidence of adverse effects in RCTs than case series. Siegel 2009 (anti-tumor necrosis factor and immunomodulator therapy and lymphoma) had very small numbers of adverse effects and therefore a very wide confidence interval.

Table 15.3 Data sources for information on adverse effects

Electronic Resources	Examples
Internet Search Engines These tools can provide information on adverse effects by searching the Internet. Internet searches may be a particularly good source for identifying grey literature, such as reports and conference proceedings.	**Google** (www.google.com/) **Yahoo** (www.yahoo.com/) **AltaVista** (www.altavista.com/)
Database Gateways These gateways enable searches of a selection of individual bibliographic databases at the same time.	**SAFETY** searches 41 different databases (http://library.dialog.com/bluesheets/html/bloS.html) **TOXCENTER (Toxicology Center)** searches 18 different databases (http://www.stn-international.de/stndatabases/databases/toxcenter.html) **TOXICOLOGY** searches 40 different databases. (http://library.dialog.com/bluesheets/html/bloT.html)
Full-text Databases These databases provide access to the full-text of articles and some enable searches of full-text articles.	**Iowa Drug Information Service (IDIS)** (www.uiowa.edu/~idis/idistday.htm) **PharmaNewsFeed** (includes full-text of the newsletters Inpharma, Pharmacoeconomics & Outcomes News and Reactions) (http://pharmanewsfeed.com/)
Bibliographic Databases These databases provide summary information of articles (typically the title, source, abstract and keywords). They can be divided into; those specifically related to adverse effects, those containing a large section of adverse effects information, such as pharmaceutical databases and generic databases that contain some information on adverse effects.	***Adverse effects databases*** **SEDBASE: Side Effects of Drugs** (closed in 1997 but its print counterparts, Meyler's Side Effects of Drugs, Side Effects of Drugs Annual (SEDA)[102], and Marler's Pharmacological & Chemical Synonyms continue to be up dated)[651] **TOXLINE (Toxicology Literature Online)** (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE) **ToxFile** (Dialog version of TOXLINE) (http://library.dialog.com/bluesheets/html/bl0156.html) ***Pharmaceutical databases*** **Derwent Drug File** (previously RingDoc) (http://scientific.thomsonreuters.com/products/drugfile/) **International Pharmaceutical Abstracts (IPA)** (http://scientific.thomsonreuters.com/products/ipa/) **Medicines Management** (www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Management/) **Pharmline** (www.pharm-line.nhs.uk/home/default.aspx) (closed 2010) **Generic databases** **BIOSIS** (www.biosis.org/) **EMBASE** (www.embase.com/) **MEDLINE** (www.nlm.nih.gov/) **PASCAL** (http://international.inist.fr/article21.html) **Science Citation Index (SCI)** (http://scientific.thomsonreuters.com/products/sci/)
Conference	**Conference Papers Index (CPI)**

Table 15.3 Data sources for information on adverse effects

Electronic Resources	Examples
Databases These databases contain abstracts from scientific conferences.	(www.csa.com/factsheets/cpi-set-c.php) **Inside Conferences** (www.bl.uk/services/bibliographic/datalicensing.html) **ISI Proceedings Science & Technology (STP)** (scientific.thomsonreuters.com/products/proceedings/) **ISI Proceedings Social Sciences & Humanities (SSHP)** (scientific.thomsonreuters.com/products/proceedings/)
Referenced Summary Databases These databases contain summary information on interventions (usually drugs) and are fully referenced.	**DRUGDEX** (www.micromedex.com/products/drugdex/) **Lexi-Comp Database** (www.crlonline.com/) **POISINDEX** (www.micromedex.com/products/reprorisk/) **REPRORISK** (www.micromedex.com/products/reprorisk/), **Thériaque Database** (www.theriaque.org) **XPharm** (www.xpharm.com/)
Internet Reference Collections Some Internet sites provide collections of bibliographies or reference lists related to adverse effects.	**The Drug Safety Research Unit (DSRU)** (www.dsru.org/) **Herbmed.org** (www.herbmed.org) **Motherisk** (www.motherisk.org/) **Organization of Teratology Information Specialists** (www.otispregnancy.org/)
Spontaneous Reporting Systems/Post-marketing Monitoring Data This includes mandatory reports from pharmaceutical companies on adverse events reported to them, and adverse event reports that physicians, pharmacists, nurses, dentists and the public submit directly to regulatory agencies. Some information is free from regulatory agencies on the Internet, [652] however, most data are available for a fee through databases or requests services.	***Internet*** **Adverse Drug Reactions Database** (www.adverse-drug-reaction.net) **FDA Drug Approval** (www.accessdata.fda.gov/scripts/cder/drugsatfda/) **Canada's Adverse Drug Reaction Database** (www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php) **MedWatch FDA** (www.fda.gov/medwatch/safety.htm) **Prescription-Event Monitoring (PEM)** (www.dsru.org/main.html) **UK Yellow Card scheme: Drug Analysis Prints (DAPs)** (www.mhra.gov.uk) **World Health Organisation's (WHO) International Drug Monitoring Programme in Uppsala** (which includes Britain and 76 other countries) (www.who-umc.org) ***Databases*** **DIOGENES**: Adverse Drug Events Database for data from the Food and Drug Administration (FDA) US MedWatch service (www.foiservices.com/brochure/diogenes.cfm). **PharmaPendium** (www.info.pharmapendium.com/) ***Request services*** **FDA's Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS)** (www.foiservices.com/brochure/ADR_search.cfm or www.ntis.gov/products/adverse.aspx or

Table 15.3 Data sources for information on adverse effects

Electronic Resources	Examples
	www.fda.gov/cder/aers/extract.htm). **Vigibase Services:** Uppsala Monitoring Centre (WHO) collects individual reports from 77 countries (www.umc-products.com/DynPage.aspx?id=10671).
Practice Based Databases These databases provide case reports of adverse effects. Analysis of information from these sources can be found in primary research, which may then be included in a systematic review.[397]	**Clinical Practice Research Datalink (CPRD)** http://www.cprd.com/intro.asp **(Previously General Practice Research Database (GPRD)** www.gprd.com/)
Original Texts	
Bulletins/Newsletters Some bulletins and newsletters specialise in summarising case reports of adverse effects.	**Adverse Drug Reaction Bulletin** (http://adr.org.uk/?page_id=97_) **Australian Adverse Drug Reactions Bulletin** (www.tga.gov.au/adr/aadrb.htm) Canadian Adverse ReactionNewsletter (CARN) (www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php) **Clin-Alert** (http://cla.sagepub.com/) **Current Problems in Pharmacovigilance** (www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/index.htm) **Drugs and Therapy Perspectives** (http://perspectives.adisonline.com/) **Reactions** (http://reactions.adisonline.com/or via http://pharmanewsfeed.com/)
Journals There are a number of specialist journals, however, most adverse effects appear in journals that do not specialise in adverse drug reactions.[31] Hand searching journals may be appropriate when the journals titles are not indexed or poorly indexed in databases.	***Specialist Journals*** **Drug Safety** (http://drugsafety.adisonline.com/) **Pharmacoepidemiology and Drug Safety** (www.pharmacoepi.org/publications/journal.cfm) **Toxicological Reviews** (toxicology.adisonline.com/) ***Generic Journals*** (with highest number of articles on adverse effects)[31] **Lancet** (www.thelancet.com/) **New England Journal of Medicine** (http://content.nejm.org/) **BMJ** (www.bmj.com/) **Annals of Pharmacotherapy** (www.theannals.com/) **Contact Dermatitis** (www.blackwellpublishing.com/submit.asp?ref=0105-1873)
Textbooks/Monograph Collections These can be in book and/or electronic format and may or may not contain references to	**Adverse Drug Reactions**[653] **AHFSFirst Professional Medicines Compendium** (www.medicinescomplete.com) **ABPI electronic Medicines Compendium (eMC)** (http://emc.medicines.org.uk/) **British National Formulary (BNF)** (www.bnf.org/)

Table 15.3 Data sources for information on adverse effects

Electronic Resources	Examples
the original research. Some simply provide lists of potential adverse effects for a drug whilst others provide detailed summary information. A few are organised by adverse effect rather than by the intervention.	**Clinical Pharmacology** (www.clinicalpharmacology.com) **Davies Textbook of Adverse Drug Reactions**[654] **Drugs.com** (www.drugs.com) **Drug Facts and Comparison** (www.factsandcomparisons.com/) **Emedicine** (www.emedicine.com/) **Epocrates Online** (www.epocrates.com/) **General Practice Notebook** (www.gpnotebook.co.uk) **Martindale: the complete drug reference** (www.medicinescomplete.com) **Medscape DrugInfo** (www.medscape.com/druginfo) **The Merck Manual** (www.merck.com) **Meylers's Side Effects Of Drugs**[102] **The Maudsley Prescribing Guidelines**[655] **Modell's Drugs in current use and new drugs**[656] **Mosby's Medical Drug Reference**[657] **Physicians Desk Reference (PDR)**[658] **PDR Guide to Drug Interactions, Side Effects and Indications**[659] **RxList** (www.rxlist.com) **Rxmed** (www.rxmed.com) **Side Effects of Drugs annual (SEDA)** [660] **The Merck Manual** (www.merck.com/mmpe/index.html) **USP DI® Volume I, Drug Information for the Health Care Professional** (http://library.dialog.com/bluesheets/html/bl0461.html)
Specialist Textbooks These specialise in particular populations (such as pregnant women), particular adverse effects (such as liver disease) or particular types of drug (such as psychotropic drugs).	**Catalog of Teratogenic Agents**[661] **Drugs in Pregnancy and Lactation**[662] **Drugs during Pregnancy and Lactation**[663] **Drug use in pregnancy**[664] **Drug Induced Liver Disease**[665] **Litt's Drug Eruption Reference Manual**[666] or **Litt's Drug Eruption Global Database** (www.drugeruptiondata.com/index.php?p=b_intro) Psychotropic Drug Directory[667]
Authors/Experts Authors or experts in the field may know of unpublished studies which include data on adverse effects.[392] Authors may have recorded data on adverse effects not reported in the published study.	**Clinical Pharmacologists** **Researchers** **Trialists**
Industry Drug companies or manufacturers of	***Individual Drug Companies*** **Eli Lilly** (www.lillytrials.com/) **GlaxoSmithKline** (www.gsk-clinicalstudyregister.com/),

Table 15.3 Data sources for information on adverse effects

Electronic Resources	Examples
medical devices may provide details of unpublished studies. However such data can be classed as commercially sensitive and therefore not be accessible. Drug company data can be identified through individual drug companies, drug company portals, regulatory agencies (see above) and conferences (see above)	**Roche** (www.roche-trials.com/results.html) ***Drug Company Portals*** **International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) clinical trials portal** (www.ifpma.org/clinicaltrials.html) **Lead Discovery** (www.leaddiscovery.co.uk) **Pharmaceutical Industry Clinical Trials database** (https://www.cmrinteract.com/clintrial/) **PhRMA Clinical Study Results Database** (www.clinicalstudyresults.org/)
Reference Checking Bibliographies and reference lists can be used to identify further studies.	For example, reference lists from included studies or from systematic reviews in the topic area.
Citation Searches/Cited Reference Searching Identifies studies which have cited a particular reference. This may be particularly useful for adverse effects data, as case reports/series of suspected new adverse effects may be followed up by more detailed studies.	**Google Scholar** (http://scholar.google.com/) **Scopus** (www.scopus.com/) **Web of Science** (scientific.thomsonreuters.com/products/wos/)
Discussion web sites/Emails Such sources can provide unique data on adverse effects.[397, 668]	For example, software 'robots' can be used to monitor the Internet for postings about specific products.[411]

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
Al Hefzi et al 1987[354]	51-250 relevant references on major side effects with 5 antineoplastic drugs **Case Study 1: Amsacrine** 29-57 relevant references **Case Study 2: Etoposide** 51-71 relevant references **Case Study 3: Ifosfamide** 17-29 relevant references **Case Study 4: Teniposide** 22-34 relevant references **Case Study 5: Vindesine** 35-59 relevant references	**Relevant references** **Case Study 1: Amsacrine** IDIS: 29 De Haen's Drugs in Use$: 25 IPA: 3 **Case Study 2: Etoposide** IDIS: 51 De Haen's Drugs in Use$: 20 IPA: 0 **Case Study 3: Ifosfamide** IDIS: 17 De Haen's Drugs in Use$: 10 IPA: 2 **Case Study 4: Teniposide** IDIS: 22 De Haen's Drugs in Use $: 11 IPA: 1 **Case Study 5: Vindesine** IDIS: 35 De Haen's Drugs in Use$: 23 IPA: 1 **All Case Studies: 5 antineoplastic drugs** IDIS: 159 De Haen's Drugs in Use$: 89 IPA: 7	**1. Generalisability:** The number of relevant references for each case study was low and each case study was limited to one drug. However, taking the results of the case studies collectively and the inclusion of multiple adverse effects improves the generalisabilty of the study. **2. Database overlap:** The authors recorded the number of records on adverse reactions for each of the five drugs retrieved from the three databases. No account of overlapping records or unique relevant references was made. **3. Limitations of the search strategies**: Although no consideration of any potential limitations of the search strategies were presented, the search strategies were very broad and only used variants of the drug names. **4. Comparative outcomes:** The total number of citations retrieved for each database is unclear so that precision or number needed to read could not be calculated. The cost and search functionality of each database were not reported.
Bagnall et al 2002[355]	52 relevant references from a systematic review[669] on 8 atypical antipsychotics for schizophrenia (amisulpride, clozapine, olanzapine, quetiapine, risperidone, setindole,	**Included papers (after duplication at retrieval stage)** EMBASE: 16 (95% CI 10 to 23) MEDLINE: 13 (95% CI 7 to 20)	**1. Generalisability:** The number of relevant references was relatively small at 52 and was limited to one class of drugs. However multiple adverse effects were included.

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	ziprasidone, zotepine) and death/suicide, tardive dyskinesia, neuroleptic malignant syndrome, agranulocytosis, seizures, weight gain, hepatic dysfunction, and cardiac dysfunction	Industry Submissions: 11 (95% CI 6 to 18) Reference Lists/Hand searching: 7 (95% CI 3 to 13) PsycINFO: 2 (95% CI 0 to 7) ADIS LMS Drug Alerts Online*: 1 (95% CI 0 to 5) BIOSIS*: 1 (95% CI 0 to 5) TOXLINE: 1 (95% CI 0 to 5) ADIS Inpharma*, British Library Inside Conferences*, CAB HEALTH*, CPI*, Derwent Drug File*, ExtraMED*, IDIS*, IPA*, JICST-EPlus*, Mental Health Abstracts$*, NTIS*, PASCAL*, Pharma marketing*, PHARMLINE$*, and SEDBASE$: 0 (95% CI 0 to 4) * searched with effectiveness search strategy only	**2. Database overlap:** The authors recorded the number of relevant references from each source after duplication (no record was made of the order in which the references were duplicated). No record was made of overlapping or unique relevant references. **3. Limitations of the search strategies**: The authors did not take into consideration any limitations of the search strategies, however, they used a broad search strategy for adverse effects and the results of an exhaustive search for effectiveness studies. They did not record whether the records were identified before duplication or whether the records were available from each data source but not identified. **4. Comparative outcomes:** The removal of duplicate relevant references before analysis is a major flaw in this study. Issues such as the precision or number needed to read as a result of searching each database, the cost, and search functionality were not reported.
Belgado 1997[356]	No details reported on the number of references or the adverse effects. 5 queries of drug interventions.	**Median score for overall ability to answer 5 questions** Drugdex: A Facts and Comparisons: A Lexi-Comp's Clinical Reference Library: B Clinical Pharmacology: C Drug Information Fulltext: C	**1. Generalisability:** It is difficult to asses generalisability as no details of the 5 queries tested or the relevant references retrieved were reported. **2. Database overlap:** Neither unique nor total relevant references were reported. **3. Limitations of the search strategies**: No consideration of the limitations of the search

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
		Physician's GenRx: C Physician's Desk Reference: D **<u>Median score for user-friendliness (0 is most user friendly, 100 least)</u>** Clinical Pharmacology: 14 Drugdex: 14 Physician's GenRx: 21.5 Lexi-Comp Clinical Reference Library: 28.5 Physician's Desk Reference: 35.5 Facts and Comparisons: 65.5 Drug Information Fulltext: 70	strategies were presented. **4. Comparative outcomes:** The comparisons were made using a scoring system the overall ability of each resource to answer 5 questions on adverse effects and a 0 to 100mm visual analogue scale for overall ease of use. The cost of each resource was discussed, however, sensitivity, precision or number needed to read were not reported.
Biarez et al 1991[357]	838-1826 relevant references on any adverse effects with 10 drugs (carboplatin, diclofenac sodium, dihydrotachysterol, dinitrochlorobenzene, fluconazole, hydrocortisone acetate, methergoline, methoxsalen, piromidic acid, tetrachlorodecaoxide).	**<u>Mean relevant references, precision (%) and cost per relevant item</u>** EMBASE: 84, 52%, $1.10 TOXLINE: 31, 31%, $0.66 MEDLINE: 22, 28%,$0.64 BIOSIS: 19, 31%, $1.96 IDIS: 16, 43%, $1.30 Core MEDLINE: 9, 32% PHARMLINE$: 6, 21%, $3.6 PASCAL: 3, 41%, $3.40 IPA:3, 30%, $1.52 **<u>Unique references (for one of the ten drugs only - Carboplatin)</u>** EMBASE: 62 BIOSIS: 26 TOXLINE: 10	**1. Generalisability:** The total number of records used to compare the databases is unclear. However, it can be assumed to be fairly large at between 838 and 826 records. A range of drugs and adverse effects were included. **2. Database overlap:** A more detailed analysis was carried out on one of the ten drugs which included unique and overlapping records. **3. Limitations of the search strategies**: The search strategies incorporated generic terms for the drugs and terms such as adverse effects, adverse reaction and side effect. The authors did not consider the limitations of the search strategies and did not record the availability of records on each

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
		IDIS: 8 PASCAL: 7 PHARMLINE$: 3 IPA: 2 MEDLINE: 2	data source. **4. Comparative outcomes:** The sensitivity of searching each database was recorded. Eight of the nine databases were searched via Datastar so search functionality would have been similar. A cost analysis was carried out for one of the ten drugs, however, the results of this will now be outdated.
Clauson et al 2007[358]	No details of the relevant references were reported on unspecified adverse effects of unspecified drugs in 13 queries.	**Mean scores for scope*, completeness** and ease of use***** Clinical Pharmacology: 13, 2.69, 3.62 Micromedex :13, 3.00, 2.69 Facts and Comparisons: 12, 2.92, 3.00 Lexi-Comp Online: 12, 2.92, 2.00 RxList.com: 10, 2.40, 3.00 Epocrates Online Premium: 9, 2.89, 1.78 Epocrates Online Free: 9, 2.89, 1.78 * correct answer present for any of 13 questions ** 1 is cursory answer, 3 is complete answer ***number of steps or clicks to reach answer	**1. Generalisability:** 13 queries on adverse drug reactions were assessed. However, it is difficult to assess the generalisability of the results as no details were given of either the drugs or adverse effects studied or the number of relevant references. **2. Database overlap:** Neither the number of total nor unique relevant references were reported. **3. Limitations of the search strategies**: No limitations of the search strategies were considered. **4. Comparative outcomes:** Comparisons were made using a scoring system. Scores were given for scope (if a correct answer was present in the database), completeness (how comprehensive an answer), and ease of use (how simple, direct and user friendly the database was). The differences between the results from subscription and free databases were presented. However, sensitivity, precision or number needed to read were not

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
			reported.
Fishman et al 1996[359]	7 relevant references on the gastrointestinal side effects of Cyclosporine.	**Relevant references** MEDLINE: 6 (5 unique) IPA: 3 (2 unique)	**1. Generalisability:** The generalisability of this study was limited by the small number of relevant references and a narrow inclusion criteria.. **2. Database overlap:** The total and unique number of relevant references was presented. **3. Limitations of the search strategies**: The authors recorded whether the records were identified using a specific search strategy of the drug and adverse effect terms. The availability of records on each data source was recorded as a total for all 10 queries (including the one query on adverse effects). In total one reference was identified in MEDLINE but not IPA because of variations in indexing vocabulary, and 4 references were identified in IPA but not in MEDLINE because of variations in indexing vocabulary and availability of an abstract. **4. Comparative outcomes:** The precision and cost of searching was not recorded, however, the authors did discuss searching functionality and content differences between the two databases.
Golder et al 2006[360]	84 relevant references from a systematic review[670] on any adverse effects of 7 antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and	**Included references** EMBASE: 73 (11 unique) MEDLINE: 67 (5 unique) Effectiveness search: 57 (1 unique from	**1. Generalisability:** The number of relevant references was fairly limited by size (84 records) and by inclusion criteria (one class of drugs), however, all types of serious

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	vigabatrin)	SCI) TOXLINE: 5 (1 unique) Industry Submission: 3 (3 unique) Personal Communication: 1 (1 unique)	adverse effects were included. **2. Database overlap:** The total and unique number of relevant references was presented. **3. Limitations of the search strategies**: In MEDLINE and EMBASE a record was kept of the number of records available from the set of included studies, not identified by the search strategies. **4. Comparative outcomes:** No analysis of the precision of the search strategies, cost of searching, or search functionality was carried out.
Haramburu et al 1991[361]	151 relevant references from 30 case studies **Case Study 1**: 5 relevant references (3 unique) on stomatitis with sotalol hydrochloride **Case Study 2:** 0 relevant references on hypoglycaemic coma with piridoxilate and erythrityl tetranitrate **Case Study 3:** 1 relevant reference (1 unique) on hypoglycaemic coma with triamterene and cyclothiazide **Case Study 4:** 3 relevant references (3 unique) on hypoglycaemic coma with cyamemazine **Case Study 5:** 1 relevant reference (1 unique) on hepatic cirrhosis with	**Relevant references** **Case Study 1:** MEDLINE and PASCAL: 4 Reference books: 3 **Case Study 2:** MEDLINE and PASCAL: 0 Reference books: 0 **Case Study 3:** MEDLINE and PASCAL: 1 Reference books: 0 **Case Study 4:** Reference books: 3 MEDLINE and PASCAL: 0 **Case Study 5:** Reference books: 1 MEDLINE and PASCAL: 0 **Case Study 6:**	**1. Generalisability:** The results are likely to be fairly generalisable as 151 relevant references were identified covering 30 drugs and 16 adverse effects. **2. Database overlap:** The total and unique number of relevant references was presented. **3. Limitations of the search strategies**: Only the number of identified records were recorded. However, with textbook searches this is likely to also represent the number of available records. **4. Comparative outcomes:** Precision and cost were not recorded although some indication as to search functionality was presented.

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	androgens **Case Study 6:** 1 relevant reference (1 unique) on erythematous eruption with chlorpropamide **Case Study 7:** 0 relevant references on hepatic cytolysis with fipexide **Case Study 8:** 3 relevant references (3 unique) on hepatic cytolysis with rifampicin **Case Study 9:** 0 relevant references on hepatic cytolysis with ifenprodil **Case Study 10:** 3 relevant references (3 unique) on hepatic cytolysis with hydroxysine **Case Study 11:** 0 relevant references on ulcerogenic colitis with fenofibrate **Case Study 12:** 8 relevant references (6 unique) on ulcerogenic colitis with altizide and spironolactone **Case Study 13:** 0 relevant references on ulcerogenic colitis with dihydralazine **Case Study 14:** 0 relevant references on pruritic eruption with betamethasone **Case Study 15:** 27 relevant references (25 unique) on galactorrhea with capipramine **Case Study 16:** 4 relevant references (3 unique) on galactorrhea with toloxatone **Case Study 17:** 0 relevant references on neutropenia with dihydroergotamine **Case Study 18:** 14 relevant references (10	Reference books: 1 MEDLINE and PASCAL: 0 **Case Study 7:** MEDLINE and PASCAL: 0 Reference books: 0 **Case Study 8:** Reference books: 2 MEDLINE and PASCAL: 1 **Case Study 9:** Reference books: 0 MEDLINE and PASCAL: 0 **Case Study 10:** MEDLINE and PASCAL: 3 Reference books: 0 **Case Study 11:** Reference books 0 MEDLINE and PASCAL 0 **Case Study 12:** MEDLINE and PASCAL 7 Reference books 3 **Case Study 13:** Reference books 0 MEDLINE and PASCAL 0 **Case Study 14:** Reference books 0 MEDLINE and PASCAL 0 **Case Study 15:** MEDLINE and PASCAL: 16 Reference books: 13 **Case Study 16:**	

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	unique) on hepatic cytolysis with acenocoumarol **Case Study 19:** 10 relevant references (9 unique) on hepatic cytolysis sotalol **Case Study 20:** 4 relevant references (4 unique) on subcutaneous necrosis with amikacin **Case Study 21:** 10 relevant references (7 unique) on hepatic cholestasis with pirprofen **Case Study 22:** 31 relevant references (20 unique) on hepatic cholestasis with penicillamine **Case Study 23:** 4 relevant references (3 unique) on thrombocytopenia with pefloxacin **Case Study 24:** 1 relevant reference (1 unique) on impotence with isosobide dinitrate **Case Study 25:** 11 relevant references (7 unique) on lupus with carbamazepine **Case Study 26:** 4 relevant references (4 unique) on hyperprolactinemia with ranitidine **Case Study 27:** 0 relevant reference on hyperprolactinemia with adrafinil **Case Study 28:** 6 relevant references (5 unique) on thrombocytopenia with clobazam **Case Study 29:** 0 relevant references on hepatic cholestasis with theophylline **Case Study 30:** 0 relevant references on	Reference books: 3 MEDLINE and PASCAL: 2 **Case Study 17:** Reference books: 0 MEDLINE and PASCAL: 0 **Case Study 18:** Reference books: 10 MEDLINE and PASCAL: 8 **Case Study 19:** MEDLINE and PASCAL: 8 Reference books: 3 **Case Study 20:** Reference books: 4 MEDLINE and PASCAL: 0 **Case Study 21:** Reference books: 7 MEDLINE and PASCAL: 6 **Case Study 22:** MEDLINE and PASCAL: 22 Reference books: 20 **Case Study 23:** MEDLINE and PASCAL: 3 Reference books: 2 **Case Study 24:** MEDLINE and PASCAL: 1 Reference books: 0 **Case Study 25:** MEDLINE and PASCAL: 8 Reference books: 7 **Case Study 26:**	

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	photosensitivity with domperidone	Reference books: 3 MEDLINE and PASCAL: 1 **Case Study 27:** Reference books: 0 MEDLINE and PASCAL: 0 **Case Study 28:** MEDLINE and PASCAL: 5 Reference books: 2 **Case Study 29:** Reference books: 0 MEDLINE and PASCAL: 0 **Case Study 30:** Reference books: 0 MEDLINE and PASCAL: 0 **All Case Studies: 30 drugs** MEDLINE and PASCAL: 100 (68 unique) Reference books (Martindale The Extra Pharmacopoeia, Meyler's Side Effects of Drugs, Side Effects of Drugs Annuals, Textbook of Adverse Reactions, Clin Alert, and Reactions): 83 (51 unique)	
Kahn and Joseph 2004[362]	No details of the relevant references were reported on various adverse effects of Carbamexepine.	**<u>Total points* and search time</u>** Micromedex: 11, 36 minutes Lexi-Comp: 11, 57 minutes *graded for completeness and accuracy out of 21	**1. Generalisability:** The generalisabilty of this study is likely to be low as the analysis was limited to one named drug. **2. Database overlap:** Neither the number of total nor unique relevant references were reported. **3. Limitations of the search strategies**: No

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
			limitations of the search strategies were considered. **4. Comparative outcomes:** The time spent answering the queries using each resource gives an indication of their comparative usefulness along with the graded score for the query. The authors also gave a narrative comparison of the databases.
Lapidus and Bond 2008[363]	Scores presented for adverse reactions to garlic.	**Score (0 = no information, 3=extensive information)** Micromedex 3 The Review of Natural Products 3 Natural Medicines 3 Natural Standard 3	**1. Generalisability:** The generalisabilty of this study is likely to be low as the analysis was limited to one named herbal intervention. **2. Database overlap:** Neither the number of total nor unique relevant references were reported. **3. Limitations of the search strategies**: No limitations of the search strategies were considered. **4. Comparative outcomes:** Scores were based on the completeness of answers to questions (no information, minimal, partial, extensive).
Madden et al 1977[364]	40-171 relevant references on any adverse effects of 3 drugs **Case Study 1:** 13-49 relevant references on Beclomethasone dipropionate **Case Study 2:** 39-72 relevant references on Bleomycin	**Relevant references** **Case Study 1: Beclomethasone dipropionate** Excerpta Medica Drugdoc (EMBASE) 14 Medlars (MEDLINE): 13 TOXLINE: 8 ADIS: 6	**1. Generalisability:** Between 57 and 171 relevant references were included for 3 drugs and unspecified adverse effects. **2. Database overlap:** The total number of relevant references primarily discussing adverse drug reactions was given. Unique references were only presented for selected databases in combination with only one other

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	Case Study 3: 40-50 relevant references on Tolbutamide	De Haen$: 4 IDIS: 4 **Case Study 2: Bleomycin** Excerpta Medica Drugdoc (EMBASE) : 28 Medlars (MEDLINE) : 16 TOXLINE: 12 ADIS: 6 De Haen$: 5 IDIS: 5 **Case Study 3: Tolbutamide** Excerpta Medica Drugdoc (EMBASE) : 15 ADIS: 14 Medlars (MEDLINE) : 9 TOXLINE: 8 De Haen$: 3 IDIS: 1 **All Case Studies: 3 drugs** Excerpta Medica Drugdoc (EMBASE) : 57 Medlars (MEDLINE) : 38 TOXLINE: 28 ADIS: 26 De Haen$: 12 IDIS: 10	database at a time. For example, common and unique records were presented for, Excerpta Medica Drugdoc and Medlars, Excerpta Medica Drugdoc and Toxline, Medlars and Toxline, DeHaen and IOWA, Medlars and ADIS, and lastly IOWA and ADIS. **3. Limitations of the search strategies**: No limitations of the search strategies were stated, however, the authors used a simple approach in which they searched for the drug terms only and then classified each reference (one classification being adverse drug reactions). **4. Comparative outcomes:** The precision and cost of searching was not recorded, however the authors did discuss searching functionality and content differences between the databases.
Roush et al 1991[365]	50-56 case reports were identified for Pancreatitis with Enalapril.	**Cases reported** Manufacturer: 50 MEDLINE: 3 (5 references) Food and Drug Administration (FDA) : 3	**1. Generalisability:** The searches were conducted for one named drug with a specific adverse effect and between 50 and 56 case reports were identified.

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
			2. Database overlap: It was unclear to the authors whether the reported cases were the same. **3. Limitations of the search strategies**: The search strategy was limited to MeSH terms only for the named drug and adverse effect. No consideration of the limitations of this approach were presented and case reports may have been missed on MEDLINE. **4. Comparative outcomes:** The precision and cost of the searches was not recorded. Comparisons are difficult to conduct with such a specific and small sample, however, the number of case reports identified from the manufacturer is striking and requires further investigation.
Sodha et al 1994[366]	111 unique publications (to one database) on any adverse effects of Carbamazepine. Total numbers of the relevant references are not presented.	**Unique publications** Ciba-Geigy internal database, CG-DOC: 82 RingDoc (now Derwent Drug File) : 19 EMBASE: 7 MEDLINE: 3	**1. Generalisability:** The total number of relevant references was not reported and references were limited to adverse reactions to a named drug. **2. Database overlap:** Only the numbers of unique references were presented. **3. Limitations of the search strategies**: The limitations of the search strategies were not presented. However the discussion suggests available records not retrieved by the searches were recorded. **4. Comparative outcomes:** The total number of relevant records, the precision, cost and search functionality would have

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
			been useful measures for comparison. Details of how the content of the CG-DOC database is compiled would also have been useful.
Stone et al 1998[367]	8-24 relevant references on any adverse effects of 2 natural products **Case Study 1:** 8-18 relevant references on aromatherapy **Case Study 2:** 2-6 relevant references on colloidal silver	**Relevant references** **Case Study 1: Aromatherapy** MEDLINE: 8 CINAHL: 4 Alta Vista: 3 EMBASE: 3 CCIS: 0 Health Reference Center: 0 IPA: 0 Uncover: 0 **Case Study 2: Colloidal silver** MEDLINE: 2 Alta Vista: 1 EMBASE: 1 IPA: 1 Uncover: 1 CINAHL: 0 CCIS: 0 Health Reference Center: 0 **Both Case Studies: 2 natural products** MEDLINE: 10 CINAHL: 4 Alta Vista: 4 EMBASE: 4 IPA: 1	**1. Generalisability:** The number of relevant references for each case study was small and each case study was limited to one named intervention. **2. Database overlap:** The total number of relevant records was recorded for each source for each case study. The percentage of unique references was given for each source for all 10 case studies (2 of which were on adverse effects). **3. Limitations of the search strategies**: Details of the search strategies used were not presented, however, the difficulties of searching for the topics were highlighted. **4. Comparative outcomes:** The sensitivity, precision, cost and search functionality would have been useful measures for comparison.

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
		Uncover: 1 CCIS: 0 Health Reference Center: 0	
Thompson Scientific 2004[368]	32 relevant references on any adverse effects (including possible fatal toxicity, nausea, abdominal pain, fever, hypertension) with Velcade (bortezomib)	**Relevant references, references with abstract** Derwent Drug File (previously RingDoc) 16 16 (44% unique) EMBASE: 14, 5 MEDLINE: 6, 2 **Number of adverse effects identified** Derwent Drug File: 39 MEDLINE and EMBASE: 10 (no unique)	**1. Generalisability:** The number of relevant references was relatively small (32 records) and was limited to one drug. However, a range of adverse effects were included **2. Database overlap:** The author states the unique records for one of the three databases only (Derwent Drug File). **3. Limitations of the search strategies**: No details of the search strategies or their limitations were presented. **4. Comparative outcomes:** No record of sensitivity, precision, or cost of the searches were presented. The study was carried out by the producers of Derwent Drug File, resulting in a conflict of interest from the authors.
Tourville and McLeod 1975[369]	**Case Study 1:** 11-32 relevant references on any adverse effects with amoxcillin and ampicillin **Case Study 2:** 62-200 relevant references on Hepatitis with Halothane **Case Study 3:** 22-80 relevant references on Aplastic anemia with Chloramphenicol **Case Study 4:** 14-47 relevant references on	**Relevant references and search time (minutes)** **Case Study 1: Amoxcillin and ampicillin** DeHaen Drugs in Research$: 11, 4mins DeHaen Drugs in Use: Card Search$: 7, 8mins IPA: 6, 15 mins IDIS: 5, 20 mins DeHaen Drugs in Use: Index Search$: 3, 7mins	**1. Generalisability:** The total number of relevant references was 129 - 418 and included 7 drugs and a mixture of adverse effects were included **2. Database overlap:** No account of unique references was made. **3. Limitations of the search strategies**: The search strategies were not presented or discussed. **4. Comparative outcomes:** No record of sensitivity, or precision were presented. The

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
	Blood dyscrasias with Phenytoin **Case Study 5:** 4-16 relevant references on Interstitial nephritis with Methicillin **Case Study 6:** 19-43 relevant references on Nephrotoxicity with Amphotericin **Case Studies 2-6:** 386 relevant references on 5 drugs	**Case Study 2: Halothane-induced hepatitis** DeHaen Drugs in Use: Card Search$ 62 31mins IPA: 48 11 mins DeHaen Drugs in Use: Index Search$: 46 11 mins IDIS: 44, 28 mins **Case Study 3: Chloramphenicol-induced aplastic anemia** IDIS: 22, 27 mins DeHaen Drugs in Use: Card Search$: 21, 26mins IPA: 21, 11mins DeHaen Drugs in Use: Index Search$: 16, 8 mins **Case Study 4: Phenytoin and blood dyscrasias** IPA: 14, 10mins IDIS: 13, 30mins DeHaen Drugs in Use: Card Search$: 12, 26mins DeHaen Drugs in Use: Index Search$: 8, 5 mins **Case Study 5: Methicillin and interstitial nephritis** DeHaen Drugs in Use: Card Search$ 4, 15mins IPA: 3, 8mins IDIS: 6, 8mins	study considered the time taken to search the different data sources and discussed the cost of each source.

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
		DeHaen Drugs in Use: Index Search$: 3, 12 mins **Case Study 6: Amphotericin-induced nephrotoxicity** DeHaen Drugs in Use: Card Search$: 19, 24 mins DeHaen Drugs in Use: Index Search$: 12, 5 mins IPA: 7, 9 mins IDIS: 5, 13 mins **Case Studies 2-6: 5 drugs** DeHaen Drugs in Use: Card Search$: 122, 122 mins IPA: 93, 99 mins IDIS: 90, 106 mins DeHaen Drugs in Use: Index Search$: 85, 41 mins	
Van Putte 1991[370]	97-283 relevant references on any adverse effects on 2 named drugs **Case Study 1:** 56-82 relevant references on Doxycycline **Case Study 2:** 97-201 relevant references on Corticosteroids	**Relevant References and Precision** **Case Study 1: Doxycycline** RingDoc (now Derwent Drug File) 56 (36 unique), 51% (56/109) EMBASE: 42 (15 unique), 41% (42/103) MEDLINE: 21 (2 unique), 55% (21/38) BIOSIS: 13 (0 unique), 62% (13/21) **Case Study 2: Corticosteriods** RingDoc (now Derwent Drug File) 97 (75 unique), 82% (97/119) MEDLINE: 64 (34 unique), 48% (64/134) EMBASE: 44 (26 unique), 51% (44/86)	**1. Generalisability:** The case studies included between 56 and 82 relevant references, and 97 and 201 relevant references. Each case study was either limited to a named drug or class of drugs, however, a range of adverse effects were included **2. Database overlap:** The total number of relevant references and unique relevant references were presented. **3. Limitations of the search strategies**: The number of records retrieved by the search strategies were reported but not

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
		BIOSIS: 44 (32 unique), 47% (44/93) **Both Case Studies : 2 types of drugs** RingDoc (now Derwent Drug File): 153 EMBASE: 86 MEDLINE: 85 BIOSIS: 57	those available in each database. Details of the searches were not presented. **4. Comparative outcomes:** The number of non-relevant references were presented, enabling the calculation of precision. No record of cost or search functionality were presented.
Verheijen-Voogd 1974[371]	**Case Study 1:** 18 relevant references on Endocarditis lenta with tooth extraction **Case Study 2:** 48-54 relevant references on the effects on the heart with Succinlycholine	**Relevant references and precision** **Case Study 1: Tooth extraction** MEDLINE: 16 (15 unique), 89% (16/18) EMBASE: 3 (2 unique), 100% (3/3) **Case Study 2: Succinylcholine** EMBASE: 36 (33-36 unique), 67% (36/54) MEDLINE: 18 (15-18 unique), 67% (18/27) **Relevant references not retrieved (because of errors in indexing or search formulation)** **Case Study 1: Tooth extraction** MEDLINE: 2 EMBASE: 8	**1. Generalisability:** The number of references was not reported. The sources were evaluated as to whether they answered queries on side effects **2. Database overlap:** Partially. the total number of relevant references was presented for both case studies, however, unique relevant references were only presented for one of the case studies. **3. Limitations of the search strategies**: Although some discussion of the difficulties of searching were presented, full details of the search strategies were not presented. The number of relevant references not retrieved as a result of errors in indexing or search formulation were calculated for one case study. **4. Comparative outcomes:** No record of cost was presented, but precision of the searches and some discussion of search functionality were presented.
Walker	Any adverse effects with unspecified Herbal	**Number of questions answered (out**	**1. Generalisability:** The number of

Table 15.4 Characteristics of included studies for Chapter 5

Reference	Sample size, type of adverse effect and intervention	Outome Measures and Results	Methodological Assessment
2002[372]	Products. No details of the relevant references were reported.	**<u>of 8)</u>** AltMedDex: 7 Natural Medicines Comprehensive Database: 6 The Natural Pharmacist: 5 Lawrence Review of Natural Products: 2 The Complete German Commission E Monograph: 2 Physicians Desk Reference for Herbal Medicines: 0 Tyler's Honest Herbal: 0	references was not reported. The sources were evaluated as to whether they answered 8 queries on side effects, details of the queries were not presented. **2. Database overlap:** The overlap between the sources was not reported **3. Limitations of the search strategies**: The search strategies were not presented or discussed. **4. Comparative outcomes:** No record of precision or cost were presented.

Key
* - searched together, $ - database now closed

Abbreviations
CCIS - Micromedex Computerized Clinical Information Service
CPI - Conference Papers Index
FDA - Food and Drug Administration
IPA - International Pharmaceutical Abstracts
IDIS - Iowa Drug Information Service (IDIS)
JICST-EPlus - Japan Science and Technology Corporation, Information Center for Science and Technology
NTIS - National Technical Information Service

Table 15.5 Excluded studies in Chapter 5

Study	Reason for exclusion
Abuelsoud and Alnaim 2005[373]	Compares DrugDex and Altavista for answering 100 drug information queries, including unknown number on adverse drug reactions. Does not separate the results for the questions on adverse drug reactions.
Akaho and Miyake 1983[374]	Compares Iowa Drug Information Service (IDIS) and EMBASE for answering one query on the efficacy of a drug and Chemical Abstracts (manual and online) for 2 queries on chemical substances. Does not include any questions on adverse effects.
Alnaim and Abuelsoud 2007[375]	Compares DrugDex, Lexi-Drugs and AltaVista for 100 drug information queries, including unknown number on adverse drug reactions. Does not separate the results for the queries on adverse drug reactions.
Alper et al 2001[376]	Compares STAT!Ref, MDConsult, DynaMed, MAXX, MDChoice.com, American Family Physician, SUMSearch, Medical Matrix, Primary Care Clinical Practice Guidelines, Medscape, Webdoctor, Virtual Hospital, CliniWeb, and Turning Research into Practice (TRIP) in answering 20 queries, including 2 on adverse drug reactions. Does not separate the results for the queries on adverse drug reactions.
Anderson et al 2000 [377]	Compares TRACE, BIOSIS, CAB, CAS, EMBASE, Life Sci, MEDLINE, and TOXLINE for answering 10 queries on toxicity/ecotoxicity of chemicals. Does not include any queries on adverse effects.
Barillot et al 1997[378]	Compares EMBASE, MEDLINE, TOXLINE, BIOSIS, Chemical Abstracts (CAS), PHARMLINE International Pharmaceutical Abstracts (IPA), PASCAL, and BIBLIOGRAPHIF for 20 specific drug interactions. Does not include any adverse effects.
Bawden et al 1982 [379]	Compares Chemical Abstracts (printed), Excerta Medica (printed), TOXLINE, Ringdoc, books and reference citations for answering 8 queries on chemical toxicology. Explicitly excludes adverse reactions and side-effects of drugs.
Bell et al 1976[380]	Compares seven reference publications (Evaluation of drug interactions, Drug interactions, Stockley's drug interactions, Cohen's drug interactions: Grant's drug interaction index: Hartshorn's handbook of drug interactions S. Garb's undesirable drug interactions) for answering information on 20 potential drug interactions. Does not include any adverse effects.
Bergk et al 2005[381]	Compares German summary of product characteristics (SPC) with DRUGDEX, Hansten/Horn's Drug Interactions Analysis and Management, and Stockley's Drug Interactions for information on drug interactions. Does not include any adverse effects.
Brown 1998[382]	Descriptive study of MEDLINE and EMBASE for pharmaceutical information. No formal evaluation.
Butros and McGuinness 2004[383]	Descriptive study of textbook drug information sources on adverse effects, toxicology, poisoning. No formal evaluation.
Choi et al 1999[384]	Compares The Corner Drug Store, Home Medical Advisor, Mayo Clinic Family Pharmacist, Medical Drug Reference, Mosby's Medical Encyclopedia, and PharmAssist for consumer drug prescription information for 20 drugs. Includes separate analysis for side effects but limited to consumer information sources only.

Table 15.5 Excluded studies in Chapter 5

Study	Reason for exclusion
Cluxton et al 1979[385]	Compares deHAEN Drugs in Use system, the Iowa Drug Information Service (IDIS), Index Medicus, MEDLINE and International Pharmaceutical Abstracts (IPA) for obtaining bioavailability data to on 5 drugs. Does not include any adverse effects.
Cohen 2001[671]	Compares doses in the Physicians' Desk Reference and articles from MEDLINE.
Cohen 2001[66]	Compares initial doses recommended by the Joint National Committee and the Physicians' Desk Reference.
Costigan and Wood 1986[386]	Compares a printed index, a text searching computer system, and a computerised chemical databank system for searching NIOSH Registry of Toxic Effects of Chemical Substances (RTECS) to answer 7 queries on the toxic effect of chemical substances. Does not include any adverse effects.
Day 1993[387]	Descriptive comparison of AHFS Drug Information, Drug Evaluations Annual, Drug Facts and Comparisons, Martindale, Physicians' Desk Reference and USP Drug Information. No formal evaluation.
Duffull and Begg 1992[388]	Compares Drugdex, Drugs and Pharmacology, MEDLINE and IDIS, Inpharma, Reactions and an in-house database to answer 60 drug-related queries, including 32 on adverse drug reactions. Does not separate the results for the questions on adverse drug reactions.
Galt et al 2005[389]	Compares Eprocrates Rx-Pro, Lexi-Drugs, and Micromedex using 47 drug information queries, including 10 queries on adverse drug reactions. Does not separate the results for the questions on adverse drug reactions.
Gehanno et al 1998[390]	Compares BIOSIS, EMBASE, MEDLINE, NIOSH-TIC, and TOXLINE for 2 toxicology queries. Does not include any adverse effects.
Frost Widnes and Schjott 2008[672]	Compares advice from the product monographs in the Felleskatalog (FK), published by the pharmaceutical companies, and the five regional Drug Information Centres (DICs) in Norway.
Haramburu et al 1989[391]	Conference abstract. Not enough detail.
Ioannidis et al 2002[392]	Examines the feasibility of obtaining information on adverse effects from the authors of RCTs. No comparative evaluation.
John 1985[393]	Compares MEDLARS, EMBASE, ISI BIOMED, BIOSIS, CancerLit, PsycINFO, Psyndex, ISI ISTPB (Index to Scientific and Technical Proceeding and books) for medical information by authors from Frankfurt University, categorised by medical faculty. No category for adverse effects was included.
Joy et al 1986[394]	Descriptive analysis of 1448 requests from health-care professionals and consumers in a university hospital drug information service. Presentation of the 10 most frequently used sources for drug information but no formal comparative evaluation.
Kupferberg et al 2004[395]	Compares AHFS Drug Information, Drugdex, eFacts (Drug Facts and Comparison), Lexi-Drugs Online (Lexi-Comp) and PDR Electronic Library) for 10 drug information queries, including 2 on adverse drug reactions. Does not separate the results for the queries on adverse drug reactions.

Table 15.5 Excluded studies in Chapter 5

Study	Reason for exclusion
Majekodunmi et al 2006 [396]	Conference abstract. Not enough detail.
Medawar et al 2002[397]	Discusses the potential value of web site discussion lists, but includes no formal comparative evaluation.
Medawar and Herxheimer 2003[398]	Compares yellow card reports with patient reports but includes no formal comparative evaluation.
Milne 1978[399]	Compares MEDLINE and IDIS for 60 queries, including unknown number of queries on adverse drug reactions. Does not separate the results for the queries on adverse drug reactions.
Robinson et al 2000[400]	Compares TOXLINE, BIOSIS, EMBASE, MEDLINE, CAS, LifeSci, and TRACE in answering 10 toxicology queries. Does not include any adverse effects.
Rosenberg et al 1983[401]	Comparative content evaluation of the De Haen and Drugdex information systems. No analysis of information on adverse effects but does include drug interaction content scores.
Rovers et al 1993[402]	Compares EMBASE, MEDLINE, TOXLINE and TOXLIT for 26 drug information queries, including unknown number on adverse drug reactions. Does not separate the results for the queries on adverse drug reactions.
Snow 1982[403]	Compares Information Retrieval Limited, BIOSIS, SciSearch, MEDLINE, Excerpta, CA Search, and IPA in answering 9 toxicology, drug-interaction and other general pharmacy queries. Does not include any queries specifically on adverse drug reactions.
Tatsioni et al 2003[404]	Uses 20 safety warnings from the US FDA web site and assesses whether they are available on the Internet by searching seven search engines (Google, Lycos, Excite, Yahoo, HotBot, Infoseek, and Copernic). No comparative evaluation of search engines.
Vidal et al 2005[405]	Compares the BNF, Martindale, AHFS and Drug Prescribing in renal failure for drug information, particularly dose adjustment. Does not include any queries on adverse drug reactions.
Wilkinson and Hollander 1973[406]	Compares Index Medicus and Drug Literature Index for toxicity studies for 8 drugs. Does not include adverse drug reactions.
Wright 2001[407]	Descriptive account of numerous factual and bibliographic databases supplied by 11 producers for toxicology information. Does not include adverse drug reactions.
Wukovitz 2001[408]	Descriptive account of Internet search engines and library catalogs for toxicology information. Does not include adverse drug reactions.
Yokel et al 1978[409]	Compares Poisindex, ToxiFile, Clinical Toxicology of Commercial Products, and the National Clearinghouse for Poison Control Centers' cards for toxicity and poisoning information. Does not include adverse drug reactions.

Table 15.6 Characteristics of included studies in Chapter 6

Reference	Study Design	Reference set of relevant records and validation set of relevant records	Search strategy	Sensitivity	Precision
Badgett et al 1999[427, 428]	Any serious adverse drug reactions of 9 antidepressant agents in MEDLINE (Interface unclear)	Reference set of 323 records (32 controlled studies, 19 publications of postmarketing databases and 272 case reports) from 3298 records identified from MEDLINE (254), EMBASE (99), and PsycLit. Search strategies then tested on 9076 records and identified 644 records (576 case reports/series, 15 uncontrolled cohorts, 45 controlled studies, 27 publications of postmarketing databases) from 9076 MEDLINE (545), EMBASE (493), and PsycLit (22). Validation set of 132 records on adverse effects of antihypertensive agents on foetuses from 1240 records from MEDLINE and toxicology textbooks.	**Reference Set** (ae or co or po).fs (ae or co or po).fs or CASE REPORT/ and HUMAN/ **Validation Set** (ae or co or po).fs or CASE REPORT/ and HUMAN/ (ae or co or po or de).fs or CASE REPORT/ and HUMAN/	95% (520/545) (95% CI 93% to 97%) 99% (539/545) (95% CI 98% to 100%) 86% (113/132) (95% CI 78% to 91%) 95% (125/132) (95% CI 89% to 98%)	Because of the study design precision could not be determined
Golder et al 2006[360]	Any adverse effects of 7 antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin) in EMBASE and MEDLINE using OVID Biomed	84 studies (uncontrolled trials, cohort studies, case-control studies) from 8095 records from systematic review which searched MEDLINE, EMBASE, TOXLINE, industry submissions, carried out reference checking, contacted experts, and results of effectiveness searches. No validation set of records.	**MEDLINE** (ae or co or de).fs or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab 'Named adverse effects'$ or (ae or co or de).fs or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab	96% (64/67) (95% CI 87% to 99%) 97% (65/67) (95% CI 90% to 100%) 97% (71/73) (95% CI 90% to	2.8% (64/2325) (95% CI 2.1% to 3.5%) 2.8% (65/2329) (95% CI 2.1% to 3.5%) 2.3% (71/3127)

Table 15.6 Characteristics of included studies in Chapter 6

Reference	Study Design	Reference set of relevant records and validation set of relevant records	Search strategy	Sensitivity	Precision
			EMBASE DRUG/ae,to or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab 'Named adverse effects'$ or (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab	100%) 99% (72/73) (95% CI 93% to 100%)	(95% CI 1.8% to 2.9%) 2.8% (72/2557) (95% CI 2.2 % to 3.5%)
Wieland et al 2005[121, 430]	Breast cancer as an adverse effect of Oral contraceptives in PubMed	58 reports (48 case-control studies, 7 cohort studies, 1 RCT) from unclear sample size obtained from a systematic review which searched databases, checked references and contacted experts. No validation set of records.	A1. Exploding MeSH term search 1966:1995 [dp] AND "human" [MESH] AND journal article [pt] AND breast neoplasms [mh] AND (contraceptives, oral [mh]) AND (risk [mh] OR follow-up studies [mh] OR case-control studies [mh]) A2. MeSH term search with major topics and subheadings 1966:1995 [dp] AND "human" [MESH] AND journal article [pt] AND "breast neoplasms" [majr:noexp] AND (contraceptives, oral [mh:noexp] OR contraceptives, oral/pharmacology [mh] OR contraceptives, oral/therapeutic use [mh] OR estrogens/therapeutic use [mh] OR contraceptives, oral/adverse effects [mh]) AND (risk [mh:noexp] OR risk factors [mh:noexp] OR follow-up studies [mh:noexp] OR odds ratio [mh:noexp])	83% (48/58) (95% CI 71% to 91%) 83% (48/58) (95% CI 71% to 91%) 83% (48/58) (95% CI 71% to 91%) 100% (58/58) (95% CI 94% to 100%)	6% (48/797) (95% CI 4.5% to 7.9%) 11% (48/424) (95% CI 8.5% to 14.7%) 2% (48/2525) (95% CI 1.4% to 2.5%) 0.9% (58/6120) (95% CI 0.7% to 1.2%) 2% (49/2754)

Table 15.6 Characteristics of included studies in Chapter 6

Reference	Study Design	Reference set of relevant records and validation set of relevant records	Search strategy	Sensitivity	Precision
			A3. MeSH term search without study methodology terms 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND breast neoplasms [majr:noexp] AND (contraceptives, oral [mh:noexp] OR contraceptives,oral/pharmacology [mh] OR contraceptives, oral/therapeutic use [mh] OR estrogens/therapeutic use [mh] OR contraceptives, oral/adverse effects [mh]) A4. MeSH term search without intervention terms 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND breast neoplasms [majr:noexp] AND (risk [mh:noexp] OR risk factors [mh:noexp] OR follow-up studies [mh:noexp] OR odds ratio [mh:noexp]) A5. Text word search with automatic term mapping 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND breast cancer AND (oral contraceptive OR oral contraceptives OR estrogen OR estrogens OR hormones OR hormonal) AND (risk OR follow-up OR epidemiologic) A6. Text word search with truncation and double quotes 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (oral contraceptiv* OR “estrogen” OR “hormones” OR “hormonal”) AND (“risk” OR epidemiologic) A7. Text word search without study methodology text	84% (49/58) (95% CI 73% to 93%) 84% (49/58) (95% CI 73% to 93%) 84% (49/58) (95% CI 73% to 93%) 100 % (58/58) (95% CI 94% to 100%)	(95% CI 1.3% to 2.3%) 3% (49/1456) (95% CI 2.5% to 4.4%) 0.7% (49/7268) (95% CI 0.5% to 0.9%) 0.8% (58/7240) (95% CI 0.6% to 1.0%)

Table 15.6 Characteristics of included studies in Chapter 6

Reference	Study Design	Reference set of relevant records and validation set of relevant records	Search strategy	Sensitivity	Precision
			words 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (oral contraceptiv* OR “estrogen” OR “hormones” OR “hormonal”) A8. Text word search without intervention text words 1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (“risk” OR epidemiolog*)		

KEY
MEDLINE abbreviations; ae = adverse effects, co = complications, po = poisoning, de = drug effects
EMBASE abbreviations; ae = adverse effects, de = drug effects, to = drug toxicity
OVID syntax; .fs refers to floating subheadings, / indicates subject heading, * indicates truncation, Adj2 indicates proximity searching within 2 words, .ti,ab limits to title or abstract, $ indexing terms for named adverse effects were used (e.g. LIVER DISEASES/ci). In small number of instances were no appropriate indexing term was available, textwords were searched in title and abstract.
Pubmed syntax; [dp] limits to date of publication field, “” overrides any automatic mapping and searches for term as textword, [pt] limits to publication type field, [mh] limits to MeSH, [MESH] limits to MeSH, [majr] indicates a major MeSH, assigned to records where the term relates to one of the main topics discussed in the article, [mh:moexp] limits to MeSH with no automatic explosion, so does not include more specific MeSH terms further down the hierarchy, [majr:noexp] limits to major MeSH with no automatic explosion.

Table 15.7 Excluded studies in Chapter 6

Study	Reason for exclusion
Adept 2004[431]	MEDLINE search for adverse effects. No evaluation.
BMJ Clinical Evidence 2006[432]	MEDLINE and EMBASE search filters for adverse effects. No evaluation.
Brass 1987[433]	No search terms reported. No evaluation.
Buckingham et al 2005[434]	Guidance on searching for adverse effects in PubMed. No evaluation.
Centre for Reviews and Dissemination 2001[435]	Guidance on searching for adverse effects in MEDLINE and EMBASE. No evaluation.
Cleyndert 2006[436]	Guidance on searching EMBASE for adverse effects. No evaluation.
Deng 2008[447]	Non-english. No translation available.
Haynes et al 2005[440]	This study aimed to develop search filters for detecting clinically sound and relevant causation studies in EMBASE. Causation studies were studies that looked at genes, treatments and environmental exposure.
Garcia and Guzman 2008[673]	Evaluates the contribution of the MeSH Term "Drug Toxicity" for searching for drug-related adverse events in PubMed/MEDLINE. Abstract only.
Golder et al 2006[448]	Evaluates search strategies for retrieving systematic reviews of adverse effects in CDSR and DARE. Does not include any searches for primary studies.
Institute of Medicine 1991[437]	Presents search strategies for adverse effects after pertussis and rubella vaccination. No evaluation.
Rikken and Vos 1994[443]	Co-word-analysis. No filter proposed.
Rikken and Vos 1995[444]	Co-word-analysis. No filter proposed.
Schellevis and Van Der Horst 2006[445]	Non-english. No translation available.
Thompson Dialog 2004[438]	Guidance on searching MEDLINE and EMBASE for adverse effects on DIALOG. No evaluation.
Van Den Bruel 2005[446]	Non-english. No translation available.
Walker-Diks et al 2008[441]	This study aimed to develop search filters for detecting clinically sound and relevant causation studies in CINAHL. Causation studies were studies that looked at genes, treatments and environmental exposure.
Wilczynski et al 2003[442]	This study aimed to develop search filters for detecting clinically sound and relevant causation studies in MEDLINE. Causation studies were studies that looked at genes, treatments and environmental exposure.

Table 15.8 Methodological quality of included studies in Chapter 6

	Badgett 1999	Golder 2006	Wieland 2005
Were the search strategies used adequately described to allow reproducibility?	The combinations of search terms tested is unclear but the recommended search strategy is stated. However, the interface used is not stated and can only be inferred from the syntax of the search strategies.	5 approaches to searching are stated. However, all the combinations tested are not presented. The recommended search strategies are stated for MEDLINE and EMBASE.	8 search approaches are clearly stated.
Were the search terms objectively derived?	It is unclear how the search terms for testing were derived.	No, 5 approaches to searching identified from previous guidance and systematic reviews were used.	No, search terms for testing were identified by visually examining the title, abstract and MeSH of each relevant record.
Was an adequate reference set obtained?	The references were obtained from MEDLINE, EMBASE, PsycLit. The search strategies for each database are not presented in detail. However, the authors searched for nine antidepressant agents (MeSH and text words) and terms for specific known adverse effects or the following textwords, malignan$, rare, surviv$, risk#, adverse, serious, severe, poison$, pathology$ or toxic$. The use of some adverse effects terms in the search strategy is a limitation of the	The reference set was obtained from a large number of sources with a fairly broad search strategy. The use of adverse effects terms in the search is a major limitation, however.	The reference set was taken from a systematic review which identified studies from review articles, computer searches and discussion with colleagues. Details of the search strategies and databases are not presented.

Table 15.8 Methodological quality of included studies in Chapter 6

	Badgett 1999	Golder 2006	Wieland 2005
	study.		
Did two or more researchers screen the records for relevant studies?	No, the studies were screened by a single physician.	Yes, 2 researchers independently screened the records.	Unclear
Were clear inclusion criteria for the reference set given?	No, the authors state that 'reports of serious adverse drug reactions' were included. Study designs identified for inclusion were controlled studies, publications of postmarketing databases, and case reports.	Yes, in the full HTA publication. All adverse effects were considered from RCTs and observational studies.	Yes. Epidemiological studies with over 100 women with breast cancer were included that contained data on the use of hormone contraceptives and reproductive history.
Were confidence intervals calculated for the performance estimates?	The reference sets were fairly large at 254 records and 545 records. The authors did not describe the confidence intervals around the point estimates of sensitivity.	The reference set contained 84 relevant records. The authors did not describe the confidence intervals around the point estimates of sensitivity.	The reference set contained 58 relevant records. The authors did not describe the confidence intervals around the point estimates of sensitivity.
Were the results tested on a validation set of records?	Yes, the search was tested for sensitivity on 132 records (precision could not be calculated). An additional term of 'drug effects' was added to the search strategy, it is unclear how this term was identified.	No.	No.

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
Bennett et al 2003 [480]	Compares number of case reports of 14 specific serious adverse reactions associated with 16 different drugs.	Published cases identified via MEDLINE. Unpublished cases mainly from FDA Adverse Events Reporting System, but included queries to physicians and pharmaceutical companies and patients. Identified 350 published case studies and 1353 unpublished case studies.	There were a far greater number of unpublished cases than published case reports for 15 adverse reactions, except for deep vein thrombosis/pulmonary embolism with thalidomide where published cases greatly outnumbered unpublished.	**Confounding**: Not assessed, as this study looked principally at case reports. **Misclassification**: Duplicate case reports were classified as published. **External validity**: Good, covered wide range of topics .in 2001.
Cosmi et al 2000 [28]	Compares cases of thrombotic thrombocytopenic purpura (TTP) with Ticlopidine plus aspirin in RCTs, observational studies and case reports/series	Published case reports from MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. Unpublished case reports from The WHO Monitoring Centre	72 published case reports/series 0 unpublished case reports	**Confounding**: Not assessed, as this study looked principally at case reports. **Misclassification**: Not clear how authors distinguished published from unpublished **External validity**: Limited to ticlopidine plus aspirin
Hemminki 1980 [458]	Comparison of proportion of trials that gave information on adverse effects.	Both published and unpublished data licensing applications of psychotropic drugs in Finland and	% of controlled trials giving information on adverse effects. **Psychotropic drugs Finland** 201 published trials: 56%* 116 unpublished trials: 77%*	**Confounding:** While there was some assessment of trial quality, there was no assessment or adjustment for potential differences in design or

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
		Sweden and applications in Finland of random sample of non psychotropic drugs. Covered 335 published trials and 301 unpublished trials.	**Sweden** 104 published trials: 73% 99 unpublished trials: 83% **Non-psychotropic drugs** **Finland** 30 published trials: 43%* 24 unpublished trials: 83%* * difference significant at 5% level	characteristics amongst published and unpublished studies. **Misclassification**: Not clear how the author searched for published data, presumably from reference lists of licensing applications. Authors state that "A report was defined as published if it had appeared in or been accepted for a journal or book, or was a report of a meeting." **External validity**: Wide range of drugs from 191 licensing applications, but these covered the 1960's and 70's and may not reflect current practice.
Hemminki and McPherson 2000 [467]	Comparison of cardiovascular and thrombolytic events with postmenopausal hormone therapy from meta-analysis of published trials[97], with analysis using unpublished	Published trials from MEDLINE and reference checking. Unpublished trials from access to confidential drug licensing documents from Finnish Drug Agency.	**Cardiovascular events** 22 published trials OR 1.39 (0.48-3.95) 28 unpublished and published trials OR 1.78 (0.70-4.52). **Cardiovascular and thrombolytic events** 22 published trials OR 1.64 (0.65-4.21)	**Confounding**: No mention of confounders. **Misclassification**: No definitions of published and unpublished studies were presented and the authors acknowledge that not all the data in the unpublished category may

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
	data.	There were 22 published and 6 unpublished trials.	28 unpublished and published trials OR 1.97 (0.84-4.58)	have been genuinely unpublished. **External validity**: Poor, only a few studies within a single class.
Loke et al 2004 [264]	Comparison of relative frequency of specific adverse events related to amiodarone therapy	Amiodarone case reports, obtained from MEDLINE search as compared to spontaneous report collected by WHO Uppsala Monitoring Centre.	Rank order of frequency of specific adverse effects was different between the published cases compared to unpublished.	**Confounding**: Not assessed as this study looked principally at case reports. **Misclassification**: As the unpublished data was aggregated (with no individual data available), there was no way of checking if any of the cases had been published. **External validity**: Limited to amiodarone only.
MacLean et al 2003 [468, 475]	Meta-analysis of dyspepsia with NSAIDs.	Published trials from MEDLINE, EMBASE, HEALTHSTAR, and BIOSIS. Unpublished trial from FDA New Drug Applications obtained through Freedom of Information request.	15 published trials (N=1455) RR 1.21 (0.81 – 1.81) 11 unpublished trials (N=2368) RR 1.07 (0.70 – 1.63) combined RR 1.14 (0.86 – 1.53)	**Confounding**: Compared by publication status; population (age and gender) and dosing characteristics (drug indication and dose level), methodological attributes (randomization, withdrawals, blinding) and sponsorship of included studies. Meta-regression used to assess

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
				differences by publication status and adjusted for differences between studies. **Misclassification**: Handsearch of FDA documents, then compared drug, dose, indication and duration against published papers to arrive at correct classification. **External validity:** Limited to NSAIDs only.
Ross et al 1997 [469]	Meta-analysis of serious adverse events in hypertensive patients receiving isradipine.	Published trials from MEDLINE, Current Contents and checking bibliographies. Unpublished trials from manufacturer. There were 32 published trials and 33 unpublished trials but not all trials were included in meta-analysis of adverse effects.	**Major adverse events** 2 published trials (N=414) OR 0.92 (0.49-1.72) 8 unpublished trials (N=1988) OR 1.04 (0.64-1.71) combined OR 0.99 (0.67-1.46) **Angina** 2 published trials (N=414) OR 0.92 (0.49-1.72) 8 unpublished trials (N=1105) OR 0.99 (0.50-1.97) combined OR 0.95 (0.60-1.51)	**Confounding**: The authors acknowledge that the unpublished trials were all from industry. **Misclassification**: Compared number of patients included, treatment regimens used and duration of trial to identify duplicate studies. In cases where studies were published subsequent to reports, only the published study was included in the analysis. **External validity:**

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
				Limited to isradipine only.
Tramer et al 1997 [283]	Systematic review of propofol and bradycardia	Published studies from MEDLINE, reference lists, scientific abstracts. Unpublished case reports from 12 national drug monitoring centres. 17 published case reports and 187 unpublished case reports.	**Bradycardia** 16 published case reports 95 spontaneous reports **Asystole** 14 published case reports 65 spontaneous reports **Death** 1 published case reports 25 Spontaneous reports	**Confounding**: Not assessed as this study looked principally at case reports with regard to publication status. **Misclassification**: Not clear how authors identified duplicate case reports. **External validity:** Limited to propofol only.
Wallace et al 2006 [470]	Meta-analysis of serious adverse events with SSRIs	Published trials from MEDLINE, CINAHL, Biosis, Cochrane Library, reference checking, journal table of contents and experts. Unpublished UK Committee on Safety of Medicine (CSM) website. 7 published and 4 unpublished trials	**Serious adverse events for SSRIs** 7 published trials (N=1303) Treatment 56/657 Placebo 28/646 RR 2.0 (1.3 – 3.0) 4 unpublished trials (N=842) Treatment 52/472 Placebo 20/370 combined : RR 1.97 (1.42 – 2.75)	**Confounding**: Although characteristics of the studies were described, there was no discussion of adjustment for any study differences between published and unpublished **Misclassification**: Not clear how authors distinguished published from unpublished **External validity**: Limited to SSRIs only.
Whittington et al 2004 [471]	Meta-analysis of serious adverse events attributable to SSRIs.	Published trials sought from EMBASE, MEDLINE, PsycINFO, CINAHL, the	**Serious adverse events** 1 published trial (N=180) Treatment 11/93 Placebo 2/87 RR 5.15 (1.17 –	**Confounding**: Although characteristics of the studies were described, there was no discussion of

Table 15.9 Characteristics of included studies in Chapter 7

Reference	Design	Data Sources	Main Outcome Measures	Quality Assessment
		Cochrane Library, reference checking, journal table of contents and contacting experts. Unpublished data from a report by the UK Committee on Safety of Medicine (CSM). Comparable unpublished and published data identified for paroxetine only.	22.56) 1 unpublished trial (N=275) 22/182 Placebo 6/93 RR 1.87 (0.79 – 4.46) combined RR 2.55 (1.23 – 5.30) **Suicide attempt or ideation** 1 published trial (N=180) Treatment 5/93 Placebo 0/87 RR 10.30 (0.58 – 183.53) 1 unpublished trial (N=484) 9/285 Placebo 7/198 combined RR 1.51 (0.62 – 3.69)	adjustment for any study differences between published and unpublished **Misclassification**: Not clear how authors distinguished published from unpublished **External validity**: Limited to SSRIs only.

Table 15.10 Excluded studies in Chapter 7

Study	Reason for Exclusion
Barbui et al 2008[472]	Compares suicidal tendencies in patients who received paroxetine or placebo. States that there is no difference between drug and placebo groups in published and unpublished trials. No further information given.
Bohlius et al 2005[473]	Compares the reporting of adverse effects from the same study when published or made available in FDA reports to that of data submitted to FDA.
Hochberg et al 2009[474]	Compares agreement in adverse event count rates from the US FDA Adverse Event Reporting System with published studies. Does not present any numerical rates or frequencies but makes comparisons using the following classifications; 'favours drug A', favours drug B' and no difference detected.
MacLean et al 1999[475]	Conference abstract containing preliminary analysis of data in MacLean et al 2003.[468]
Nissen et al 2007[476]	Includes 27 unpublished trials out of 42. Concludes if exclude unpublished trials, precision would decrease. No further details given.
Psaty et al 2004[197]	Describes the evidence (published and unpublished) which led to the removal of a drug from the market.
Rising et al 2008[477]	Compares the presence or absence of an 'adverse events table' in the unpublished and published studies. No further details given.
Scharf et al 2006[455]	Compares adverse effects in published reports and adverse effects in the National Cancer Institute (NCI) Clinical Data Update System (CDUS). CDUS is a primary resource for clinical trial data.
Steinberg et al 1997[478]	Compares the protective effect of oral contraceptives on ovarian cancer using a meta-analysis of observational studies and Individual Patient Data (IPD).[674]

Table 15.11 Characteristics of included studies in Chapter 8

Reference	Design	Main Outcome Measures	Quality Assessment
Als-Nielsen et al 2003 [496, 497]	370 trials - 146 funded by Profit organisations, 67 from non- profit organisations, 51 mixed funding and 106 no reported funding. Trials were randomly selected from 25 Cochrane Reviews across broad range of medical topics and adverse effects.	Compared number of trials reporting adverse effects in experimental and control arms according to funding. Complete absence of any AE data was more common in nonprofit (35/67, 52.3%) vs. profit (18/146, 12.3%). Higher frequency of adverse effects in experimental group was noted in 33/146 (23%) studies funded by for-profit organisations compared to 3/67 (4%) of non-profit funded studies. Occurrence of adverse effects was not associated significantly with conclusions (logistic regression – no statistics given).	**Confounding**: Adverse effects data taken from Cochrane reviews; rigorous inclusion criteria used in systematic reviews suggests that trials would be reasonably homogenous. Logistic regression was used to assess confounding factors (such as treatment effect, adverse effects and other potentially confounding trial variables (methodological quality, sample size, whether preset sample size was estimated and reached, meta-analysis, year of publication and journal impact factor). The results of logistic regression were not given though. **Misclassification**: funding source unclear for 106 (29%) of the included studies, results given separately (data excluded from this review) **Blinding**: Mainly unblinded, but authors carried out blinded assessment in 60 trials, with good intraclass coefficient between blinded and unblinded assessment at 0.93 (95% CI 0.89-0.96). **External validity**: Good, covered wide range of topics in 2001.
Juni et al 2004 [99]	11 observational studies (2 funded by Merck, 8 non-Merck funded and 1 mixed funding) in meta-analysis of MI with Naproxen	Substantial heterogeneity found in meta-analysis of the cardiovascular adverse events with naproxen. Meta-regression showed that heterogeneity was largely due to three Merck funded studies that showed substantial cardioprotective effects of naproxen(P=0.001 and P=0.056). Any rise in cardiovascular risk with rofecoxib in trials against naproxen could then be attributed to the protective effect of	**Confounding**: authors used meta-regression to explore effects of variables (case-control or cohort, and aspirin use) on estimates of cardiovascular risk. However, only 2 of the 11case-control studies were solely Merck funded, and it is hard to draw robust conclusions based on regression analysis of only 2 studies. **Misclassification**: one study had mixed funding

Table 15.11 Characteristics of included studies in Chapter 8

Reference	Design	Main Outcome Measures	Quality Assessment
		naproxen rather than harm from rofecoxib (Merck's product).	(Merck, Pharmacia, National Institute for Health (NIH), but was categorised as industry funded. **Blinding**: not reported **External validity**: poor - considers only one drug within systematic review.
Kemmeren et al 2001 [498]	10 observational studies (5 non-industry funded and 4 Industry sponsored) in meta-analysis of venous thrombosis with 2nd and 3rd generation oral contraceptives	Pooled odds ratio of venous thrombosis with 3rd generation oral contraceptives was 1.3 (95% CI 1.0 to 1.7) in studies (N=4) funded by pharmaceutical companies while odds ratio in other studies (N=5) was 2.3 (95% CI 1.7 to 3.2) when compared to 2nd generation oral contraceptives.	**Confounding**: compared adjusted and unadjusted odds ratios and presented stratified analysis by first time users, age, duration of use, confirmed cases and funding source. **Misclassification**: Not reported **Blinding**: Not reported **External validity**: Poor, only a few studies of a single class.
Nieto et al 2007 [499]	504 studies (trials and observational studies) of inhaled corticosteroids identified from MEDLINE. 275 with pharmaceutical funding, 142 with no pharmaceutical funding and 87 with no declared funding.	Statistically significant differences in adverse effects more commonly reported by non-pharmaceutical funded studies (73.0% of 74) as compared to those funded solely by drug manufacturer (26.5% of 226) Crude and multivariate association showed that pharmaceutical funded studies were less likely to report significant differences in adverse effects - crude prevalence ratios 0.53 (95% CI 0.44 to 0.64) but this was non-significant after adjustment for confounding 0.94 (95% CI 0.77 to 1.15) more likely to conclude drug is safe despite statistically significant increase in adverse effects Prevalence Ratio 3.68 (95% CI 2.14 to 6.33)	**Confounding**: The authors conducted multivariate analysis which controlled for study design variables, including studying beclomethasone versus other corticosteroids, bronchial administration versus intranasal, medium or high daily dose versus low dose, studying children, studying healthy adults, studying patients with asthma, studying patients with rhinitis, studying corisol, studying growth, studying bone metabolism, studying non-specific clinical adverse effects, studying non-specific laboratory results, studying efficacy as an aim, studying safety as an aim, randomised study, multi-centre study, and randomized clinical trial. Industry studies were more likely to be efficacy trials, while non-industry funded studies were aimed at adverse effects.Adjustment for confounding factors

Table 15.11 Characteristics of included studies in Chapter 8

Reference	Design	Main Outcome Measures	Quality Assessment
			indicated that the observed difference in adverse effects data may be mediated by factors other than funding source. **Misclassification**: source of funding for 87 (17.3%) studies was unknown and these studies were classed as non pharmaceutical funded. **Blinding**: Not reported **External validity**: Poor, limited to inhaled corticosteroids
Rochon et al 1994 [500]	56 randomised controlled trials of NSAIDs from MEDLINE. All trials had an association with a pharmaceutical manufacturer.	Description of toxicity of manufacturer drug. 22/54 trials (40.7%) reported that one drug was less toxic than the competitor drug (10 provided evidence of statistical significance). In 19 of 22 trials (86.4%) report favoured manufacturer's drug rather than competitor's drug. In 3/ 22 trials (13.6%), manufacturers' drug was reported as more toxic than the comparison (placebo). 32/54 trials (59.2%) reported comparable toxicities.	**Confounding**: not discussed – for instance manufacturer may have deliberately chosen to use a comparator drug with poor safety profile, and the trial findings reflect a true difference. **Misclassification**: original aim of study was to evaluate non-industry funded research, but authors changed their aims posthoc as they could not identify any non-industry studies **Blinding**: not reported **External validity:** poor, limited to NSAIDs only
Stelfox et al 1998 [501]	69 authors of articles on calcium channel blockers (original research, reviews and letters) were surveyed on their financial ties. 43 had financial relationship with manufacturers of calcium-channel antagonists, 40 with competing product and 47 with any manufacturer.	Blinded researchers classified tone of the articles as 'supportive, neutral or critical'. There was a financial relationship with manufacturer of calcium channel antagonists for 23/24 (96%) authors of supportive articles compared to 11/30 (37%) of authors of critical articles. There was a financial relationship with manufacturer of competing drug for 21/24 (88%) authors of supportive articles compared to 11/30 (37%) of authors of critical articles.	**Confounding**: temporal sequence of sponsorship is unclear; authors who are known to write positive articles may then be offered sponsorship, while established critics are seldom offered funding. Also, supportive authors were just as likely to receive funding from competing manufacturers. **Misclassification**: There were 20/89 authors who did not respond to survey and had to be excluded. No way of establishing accuracy of

Table 15.11 Characteristics of included studies in Chapter 8

Reference	Design	Main Outcome Measures	Quality Assessment
		For the supportive articles, 24/24 (100%) authors had financial relationship with any manufacturer. Whereas for the critical articles, 13/30 (43%) authors had financial relationship with any manufacturer.	declared sponsorship status. **Blinding**: Yes, but there may have been information in the articles which could have led the researchers to become aware of potential pharmaceutical funding for a particular author. **External validity**: Poor, limited to calcium channel blockers only.

Table 15.12 Excluded studies in Chapter 8

Study	Reason for exclusion
Chou et al 2006,[247] 2007[248]	Compares 'mostly government' with 'other'. Other was non-governmental but also non-industry source (for example, insurance company, non-profit organisation).
Vandenbroucke JP et al 2000[502] (letter)	Duplicate information in Kemmeren et al 2001[498]

Table 15.13 Characteristics of included studies in Chapter 9

Reference	Study Design	Results	Quality Assessment
Chou et al 2006,[247] 2007[248]	9 RCTs and 102 observational studies on stroke and death with Carotid Endarteectomy 16 RCTs on myocardial Infarction with Rofecoxib	**Pooled Rate of stroke or death in surgical data (95% CI)** **Author** At least one non-surgeon author: 5.6% (4.6% to 6.5%) Multiple surgeon authors: .2% (3.5% to 4.9%) Single surgeon author: 2.8% (1.7% to 3.8%) (p=0.0327 single versus multiple surgeons, p<0.0001 single surgeon versus non-surgeon, p=0.0181 multiple surgeons versus non-surgeon) **Published in high Journal Impact Factor journal** Journal Impact Factor: >7, 7.8% (4.8% to 10.8%) Journal Impact Factor: < or = 7, 4.3% (3.8% to 4.9%) (p=0.0262) **Setting** Europe: 5.7% (4.2% to 7.3%) Other, not reported or unclear or international 5.3% (3.6% to 6.9%) North America or Canada 4.2% (3.6% to 4.8%) (p=0.0771, North America versus	**1. Confounding factors by study design:** Analysed 8 quality criteria, study design factors, severity of adverse effects and demographic or risk factor variables as well as author affliation, journal impact factor, year of publication and country setting separately using univariate analyses. **2. Blinding:** Not reported. **3. Validity and Representativeness:** Limited to one surgical intervention and 2 adverse effects or one drug and one adverse effect.

Table 15.13 Characteristics of included studies in Chapter 9

Reference	Study Design	Results	Quality Assessment
		Europe, p=0.2395, North America versus other, p=0.8560, Europe versus other) **Pooled odds ratio for myocardial infarction, rofecoxib versus control** **Published in high Journal Impact Factor journal** Journal Impact Factor: >7, 4.99 (2.28, 10.93) Journal Impact Factor < or = 7, 1.39 (0.86, 2.25) (P=0.0164) **Setting** Other: 2.22 (1.05, 4.70) North America: 1.41 (0.63, 3.15) (p=0.4306) **Publication year** After 2001: 2.71 (0.99, 7.40) Before or during 2001: 1.72 (0.97, 3.06) (p=0.4563)	
Jorgensen et al 2007[509, 510]	143 studies on the harms of mammography screening	**Harms Mentioned** Authors working with screening 29% Authors not working with screening: 40% **Acknowledge overdiagnosis (unblended, blinded, and**	**1. Confounding factors by study design:** Compared the type of article (original research, editorial etc) by author group and found little difference. **2. Blinding:** Blinded data extraction to author names of affiliation. **3. Validity and Representativeness:** Limited to one diagnostic screening test with a range of adverse effects.

Table 15.13 Characteristics of included studies in Chapter 9

Reference	Study Design	Results	Quality Assessment
		combined analysis) Authors with no apparent conflict of interest: 40% (17/43), 30% (9/30), 27% (13/48) Authors in screening-affiliated speciality or funded by cancer charities: 11% (4/37), 12% (6/50), 19% (5/27) Authors working with screening: 8% (5/63), 8% (5/63), 13% (9/68) **Downplay or reject overdiagnosis (unblended, blinded, and combined analysis)** Authors with no apparent conflict of interest: 0% (0/1), 0% (0/9), 7% (1/14) Authors in screening-affiliated speciality or funded by cancer charities: 33% (2/6), 33% (3/9), 17% (1/6) Authors working with screening: 62% (8/13), 58% (7/12), 40% (6/15)	
Rothwell et al 1996[301]	51 studies on stroke and death with carotid endarterectomy	**Mortality risk (95% CI)** Neurologist author: 1.8 (1.2 to -2.5) Multiple-surgeon authors: 1.7 (95% CI 1.4-1.9) Neurologist assessor: 1.4 (95% CI 0.2-2.7) Single surgeon author: 0.7 (95% CI 0.4-1.0)	**1. Confounding factors by study design:** Author affliction, year of publication and whether studies were performed prospectively or retrospectively were analyzed in a multiple regression analysis. **2. Blinding:** Not reported **3. Validity and Representativeness:** Limited to one surgical intervention and 2 adverse effects.

Table 15.13 Characteristics of included studies in Chapter 9

Reference	Study Design	Results	Quality Assessment
		Risk of stroke and/or death Neurologist assessor: 7.7 (95% CI 5.0-10.2) Neurologist author: 6.4 (95% CI 4.6-8.1) Multiple-surgeon authors: 5.5 (95% CI 4.8-6.1) Single surgeon author: 2.3 (95% CI 1.8-2.7) **Year of Publication** 1980 to 1984: 4.3% (95% CI 2.26-6.42) 1985 to 1989: 5.28% (95% CI 4.40-6.16) 1990 to 1994: 6.08% (95% CI 5.30-6.86)	

Appendix C: **Tables for overview of methods used to search for adverse effects data in systematic reviews in Chapter 10**

Table 15.14 Systematic reviews by type of intervention 1994 to 2011

Year of publication	Type of intervention				
	Drug	Surgical/ dental	Physical	Diagnostic/ screening	Other
1994 (N=5)	5 (100%)	1 (20%)	1 (20%)	0	0
1995 (N=13)	10 (77%)	0	0	0	3 (23%)
1996 (N=21)	10 (48%)	6 (29%)	2 (10%)	0	4 (19%)
1997 (N=24)	16 (67%)	2 (8%)	1 (4%)	0	6 (25%)
1998 (N=24)	19 (79%)	2 (8%)	0	0	4 (17%)
1999 (N=29)	21 (72%)	1 (3%)	2 (7%)	1 (3%)	4 (14%)
2000 (N=19)	14 (74%)	3 (16%)	1 (5%)	0	2 (11%)
2001 (N=31)	21 (68%)	3 (10%)	2 (6%)	0	9 (29%)
2002 (N=46)	23 (50%)	7 (15%)	4 (9%)	0	12 (26%)
2003 (N=56)	32 (57%)	2 (4%)	6 (11%)	1 (2%)	16 (29%)
2004 (N=31)	26 (84%)	6 (19%)	1 (3%)	0	3 (10%)
2005 (N=77)	68 (88%)	7 (9%)	4 (5%)	0	3 (4%)
2006 (N=72)	56 (78%)	6 (8%)	6 (8%)	1 (1%)	3 (4%)
2007 (N=78)	61 (78%)	10 (13%)	7 (9%)	1 (1%)	0
2008 (N=94)	65 (69%)	18 (19%)	9 (10%)	2 (2%)	3 (3%)
2009 (N=110)	85 (77%)	19 (17%)	4 (4%)	2 (2%)	4 (4%)
2010 (N=104)	75 (72%)	15 (14%)	9 (9%)	2 (2%)	6 (6%)
Jan-Jun 2011 (N=15)	14 (93%)	1 (7%)	0	0	0
Total	**621 (73%)**	**109 (13%)**	**59 (7%)**	**10 (1%)**	**82 (10%)**

*The sum of reviews by intervention is greater than the total number of reviews because 32 reviews examined more than one type of intervention (e.g. drug and non-drug antihypertensive therapy).

Table 15.15 Systematic reviews by types of study designs included 1994-2011

Year	Only RCTs	RCTs	CCTs	Uncontrolled trials	Cohort	Case-control studies	Cases series	Case reports	Surveillance or registry	Cross-sectional	Ecological studies	Any unclear	No study designs reported
1994	1 (20%)	2 (40%)	1 (20%)	0	1 (20%)	0	0	1 (20%)	0	0	1 (20%)	2 (40%)	2 (40%)
1995	3 (23%)	6 (46%)	1 (8%)	0	4 (31%)	7 (54%)	0	0	0	0	0	4 (31%)	1 (8%)
1996	1 (5%)	5 (24%)	1 (5%)	1 (5%)	6 (29%)	6 (29%)	2 (10%)	4 (19%)	0	1 (5%)	0	7 (33%)	1 (5%)
1997	7 (29%)	13 (54%)	3 (13%)	0	5 (21%)	5 (21%)	3 (13%)	1 (4%)	1 (4%)	0	0	7 (29%)	2 (8%)
1998	7 (29%)	13 (54%)	1 (4%)	1 (4%)	7 (29%)	7 (29%)	2 (8%)	2 (8%)	1 (4%)	2 (8%)	0	7 (29%)	1 (4%)
1999	10 (34%)	16 (55%)	3 (10%	0	8 (28%)	8 (28%)	1 (3%)	0	0	6 (21%)	1 (3%)	8 (28%)	1 (3%)
2000	6 (32%)	10 (53%)	2 (11%)	0	7 (37%)	8 (42%)	3 (16%)	5 (26%)	0	3 (16%)	0	2 (11%)	0
2001	13 (42%)	16 (52%)	2 (6%)	1 (3%)	8 (26%)	6 (19%)	1 (3%)	2 (6%)	1 (3%)	1 (3%)	2 (6%)	8 (26%)	0
2002	11 (24%)	28 (61%)	4 (9%)	1 (2%)	15 (33%)	11 (24%)	3 (6%)	6 (9%)	1 (2%)	5 (11%)	0	16 (35%)	2 (4%)
2003	15 (27%)	31 (55%)	7 (13%)	2 (4%)	21 (38%)	15 (27%)	9 (16%)	7 (13%)	2 (4%)	5 (9%)	2 (4%)	14 (25%)	3 (5%)
2004	10 (33%)	22 (71%)	4 (13%)	1 (3%)	12 (39%)	6 (19%)	2 (6%)	2 (6%)	0	0	0	11 (35%)	0
2005	34 (44%)	52 (68%)	5 (6%)	3 (4%)	31 (40%)	16 (21%)	7 (10%)	7 (10%)	1 (%)	3 (4%)	0	7 (10%)	1 (1%)
2006	20 (28%)	43 (60%)	5 (7%)	1 (1%)	31 (43%)	25 (35%)	7 (10%)	4 (6%)	0	7 (10%)	0	14 (19%)	0
2007	39 (50%)	61 (78%)	4 (5%)	1 (1%)	26 (33%)	15 (19%)	4 (5%)	3 (4%)	1 (1%)	3 (4%)	0	5 (6%)	1 (1%)
2008	32 (34%)	56 (60%)	9 (10%)	4 (4%)	34 (36%)	22 (23%)	1 (1%)	2 (2%)	0	3 (4%)	0	15 (16%)	6 (6%)
2009	36 (33%)	64 (58%)	15 (14%)	5 (5%)	42 (38%)	28 (25%)	14 (13%)	4 (4%)	0	8 (7%)	0	14 (13%)	4 (4%)
2010	27 (26%)	68 (65%)	11 (11%)	2 (2%)	47 (45%)	28 (27%)	9 (9%)	5 (5%)	0	5 (5%)	0	23 (22%)	0
2011	8 (53%)	11 (73%)	2 (13%)	0	5 (33%)	3 (20%)	0	0	0	2 (13%)	0	1 (7%)	0
Total	**280 (33%)**	**517 (61%)**	**80 (9%)**	**23 (3%)**	**310 (37%)**	**216 (25%)**	**68 (8%)**	**55 (6%)**	**8 (1%)**	**54 (6%)**	**6 (1%)**	**165 (19%)**	**25 (3%)**

Table 15.16 Databases and other sources searched in systematic reviews of adverse effects 1994-2011

Year of publication (number of reviews*)	Databases searched Median (range)	Other sources Median (range)	Total sources Median (range)
1994 (N=3)	2 (2 – 8)	1 (0 – 1)	3 (3 – 8)
1995 (N=12)	1 (1 – 5)	1 (1 – 2)	2.5 (2 – 6)
1996 (N=20)	1 (0 – 3)	1 (0 – 3)	3 (1- 5)
1997 (N=23)	1 (0 - 3)	1 (0 – 4)	2 (1 – 6)
1998 (N=23)	2 (1 – 9)	2 (0 – 5)	3 (1 – 11)
1999 (N=29)	1 (1 – 7)	2 (0 – 4)	3 (1 – 9)
2000 (N=19)	2 (1 – 7)	2 (0 – 4)	4 (2 – 10)
2001 (N=30)	2 (1 – 25)	2 (0 – 5)	4 (2 – 27)
2002 (N=46)	3 (1 – 8)	1 (0 – 4)	4 (2 – 11)
2003 (N=55)	4 (1 – 10)	2 (0 – 48)	6 (2 – 58)
2004 (N=31)	3 (1 – 9)	2 (0 – 5)	4 (1 – 13)
2005 (N=77)	3 (1 – 14)	1 (0 – 10)	4 (2 – 24)
2006 (N=72)	3 (1 – 12)	1 (0 – 4)	5 (2 – 14)
2007 (N=78)	3 (0 – 13)	1 (0 - 37)	2 (5 -50)
2008 (N=93)	3 (0 – 18)	1 (0 – 6)	4 (1 – 21)
2009 (N=108)	3 (1 – 15)	1 (0-7)	5 (2-18)
2010 (N=103)	3 (1-17)	1 (0-6)	4 (2-20)
2011 (N=15)	3 (1-9)	2 (0-6)	5.5 (2-14)

*only reviews in which the number of sources are reported were included.

Table 15.17 Systematic reviews searching the top four databases 1994-2011

Year of publication	MEDLINE	EMBASE	CENTRAL	Cochrane Library
1994 (N=5)	3 (60%)	1 (20%)	0 (0%)	0 (0%)
1995 (N=13)	11 (85%)	1 (8%)	0 (0%)	0 (0%)
1996 (N=21)	18 (86%)	2 (10%)	0 (0%)	1 (5%)
1997 (N=24)	22 (92%)	0 (0%)	0 (0%)	0 (0%)
1998 (N=24)	22 (92%)	9 (38%)	0 (0%)	1 (4%)
1999 (N=29)	29 (100%)	7 (24%)	0 (0%)	1 (3%)
2000 (N=19)	19 (100%)	9 (47%)	3 (16%)	1 (5%)
2001 (N=31)	29 (94%)	12 (39%)	4 (13%)	7 (23%)
2002 (N=46)	46 (100%)	23 (50%)	8 (17%)	9 (20%)
2003 (N=56)	54 (96%)	35 (63%)	20 (36%)	17 (30%)
2004 (N=31)	30 (97%)	16 (52%)	13 (42%)	4 (13%)
2005 (N=77)	76 (99%)	41 (53%)	27 (35%)	17 (22%)
2006 (N=72)	72 (100%)	49 (68%)	18 (25%)	18 (25%)
2007 (N=78)	75 (96%)	50 (64%)	29 (37%)	17 (22%)
2008 (N=94)	89 (95%)	58 (62%)	17 (18%)	28 (30%)
2009 (N=110)	105 (95%)	68 (62%)	31 (28%)	25 (23%)
2010 (N=104)	102 (98%)	69 (66%)	26 (25%)	30 (29%)
2011 (N=15)	15 (100%)	12 (80%)	9 (60%)	0 (0%)

Table 15.18 Systematic reviews searching the top four non-database sources 1994-2011

Year of publication	Reference lists	Contacting experts	Industry data	Scanned conference reports
1994 (N=5)	2 (40%)	0 (0%)	0 (0%)	0 (0%)
1995 (N=13)	10 (77%)	1 (8%)	0 (0%)	0 (0%)
1996 (N=21)	13 (62%)	3 (14%)	3 (14%)	0 (0%)
1997 (N=24)	17 (71%)	4 (17%)	3 (13%)	0 (0%)
1998 (N=24)	18 (75%)	8 (33%)	3 (13%)	0 (0%)
1999 (N=29)	20 (69%)	9 (31%)	7 (24%)	3 (10%)
2000 (N=19)	15 (79%)	4 (21%)	4 (21%)	4 (21%)
2001 (N=31)	26 (84%)	9 (29%)	4 (13%)	2 (6%)
2002 (N=46)	39 (85%)	10 (22%)	6 (13%)	1 (2%)
2003 (N=56)	45 (80%)	15 (27%)	6 (11%)	8 (14%)
2004 (N=31)	26 (84%)	7 (23%)	7 (23%)	7 (23%)
2005 (N=77)	63 (82%)	9 (12%)	12 (16%)	16 (21%)
2006 (N=72)	58 (81%)	16 (22%)	6 (8%)	13 (18%)
2007 (N=78)	62 (79%)	12 (15%)	9 (12%)	19 (24%)
2008 (N=94)	69 (73%)	14 (15%)	12 (13%)	20 (21%)
2009 (N=110)	76 (69%)	18 (16%)	13 (12%)	19 (17%)
2010 (N=104)	74 (71%)	14 (13%)	11 (11%)	27 (26%)
2011 (N=15)	9 (60%)	3 (20%)	4 (27%)	3 (20%)

Table 15.19 Systematic reviews with reproducible search strategies 1994-2011

Year of publication	Number and percentage of reviews with reproducible search strategies
1994 (N=5)	0 (0%)
1995 (N=13)	0 (0%)
1996 (N=21)	0 (0%)
1997 (N=24)	0 (0%)
1998 (N=24)	0 (0%)
1999 (N=29)	1 (3%)
2000 (N=19)	1 (5%)
2001 (N=31)	1 (3%)
2002 (N=46)	8 (17%)
2003 (N=56)	7 (13%)
2004 (N=31)	1 (3%)
2005 (N=77)	4 (5%)
2006 (N=72)	4 (6%)
2007 (N=78)	7 (9%)
2008 (N=94)	3 (3%)
2009 (N=110)	11 (10%)
2010 (N=104)	22 (21%)
2011 (N=15)	4 (27%)

Table 15.20 Systematic reviews with date or language restrictions 1994-2011

Year of publication	Reviews with date restrictions (N=219) of those with dates stated (N=661)	Reviews with language restrictions (N=146) of those with language stated (N=480)
1994 (N=5)	75% (3/4)	100% (2/2)
1995 (N=13)	70% (7/10)	63% (5/8)
1996 (N=21)	60% (9/15)	50% (3/6)
1997 (N=24)	56% (9/16)	27% (3/11)
1998 (N=24)	45% (9/20)	36% (4/11)
1999 (N=29)	32% (6/19)	33% (5/15)
2000 (N=19)	41% (7/17)	30% (3/10)
2001 (N=31)	67% (16/24)	17% (3/18)
2002 (N=46)	22% (7/33)	19% (6/31)
2003 (N=56)	26% (12/46)	21% (7/34)
2004 (N=31)	35% (9/26)	14% (2/14)
2005 (N=77)	29% (16/55)	37% (19/51)
2006 (N=72)	30% (16/54)	16% (6/37)
2007 (N=78)	18% (11/62)	35% (15/43)
2008 (N=94)	36% (25/69)	42% (18/43)
2009 (N=110)	25% (22/88)	28% (18/65)
2010 (N=104)	35% (31/89)	36% (26/73)
2011 (N=15)	31% (4/13)	13% (1/8)

Appendix D: **Protocol for case study systematic review evaluating fractures with rosiglitazone and pioglitazone for Chapters 11 and 12**

Objective

Primary objective: To determine systematically the relative and absolute risks of fractures with long term use of rosiglitazone or pioglitazone for type 2 diabetes.
Secondary objective: To review the effect of rosiglitazone or pioglitazone on bone mineral density to ascertain its biological plausibility.

Background

There are over 2 million people with diabetes mellitus in the UK. Type 2 diabetes is the most common form accounting for around 90% of cases,[675] and the number is increasing rapidly due to an ageing population and rapidly rising numbers of overweight and obese people.
The costs to people's quality of life, the economy, society, and the NHS are high.[676] Diabetes can also lead to serious complications such as heart disease, blindness, kidney failure, stroke and nerve damage leading to amputation.

Treatment for diabetes tends to consist of lifestyle changes and medication. Thiazolidinediones or glitazones are one of the medicines available to patients. There are two glitazones available in the UK pioglitazone and rosiglitazone (since conducting this review rosiglitazone has been withdrawn from the UK market). Both of these are recommended by NICE. Glitazones are hypoglycaemic drugs used to lower blood glucose levels and glycated haemoglobin levels. They lower blood glucose by increasing the sensitivity of the body's cells to insulin (so more glucose is taken into cells for the same amount of insulin in the bloodstream). They are not usually used alone, but are taken in addition to metformin or a sulphonylurea.

Several problems, such as myocardial infarction, heart failure, cardiovascular mortality, weight gain, upper respiratory tract infection, injury, headache, hypoglycaemia, hepatotoxicity, hyperglycaemia, diarrhoea, anaemia, edema, anemia and weight gain, have been identified with glitazones. Some adverse effects have been studied as secondary outcomes in systematic reviews of effectiveness. [677-685] However, recently systematic reviews have tended to focus on the adverse effects of glitazones as a primary outcome particularly on cardiovascular effects[279, 476, 620, 686-695] and edema.[600, 696] However, other adverse effects which had been the focus of systematic reviews include weight gain,[697] cancer[692] and fractures.[265, 698]

This systematic review will update and expand on a systematic review by Loke et al 2009[265] on fractures as an adverse effect of thiazolidinediones.

The searches for the systematic review proposed here will include a large number of sources searches to enable analysis of how searching each data source affects the numbers of retrieved relevant papers. The search will include many non-databases source and retrieve data from unpublished data sources and industry.

Sources

In addition to the sources listed in Box 1 published and unpublished data will be sought from:
contacting industry, authors and experts,
checking the reference lists of all included studies and relevant systematic reviews;

citation searches on all included studies using Google Scholar (http://scholar.google.com/), Scopus (www.scopus.com/) and Web of Science (scientific.thomsonreuters.com/products/wos/).

Box 1: Sources to be searched

Internet Search Engines
General
AltaVista
Google

Academic
Google Scholar
Intute

Bibliographic Databases
Adverse effects databases
TOXLINE (Toxicology Literature Online)

Pharmaceutical databases
ADIS Clinical Trials Insight
Derwent Drug File (previously RingDoc)
Thomson Reuters Integrity
Iowa Drug Information Service (IDIS)
International Pharmaceutical Abstracts (IPA)

Generic databases
BIOSIS Previews
British Library Direct
CENTRAL
CINAHL
EMBASE
MEDLINE
Medscape DrugInfo
PASCAL
Science Citation Index (SCI)
Scirus
Conference Databases
Conference Papers Index (CPI)
Conference Proceedings Citation Index- Science (CPCI-S)
Inside Conferences

Synthesized Database
Medical Evidence Matters

Referenced Summary Databases
ADIS R&D Insight
Lexi-Comp Database
Reactions PharmacoVigilance Insight (previously PharmaNewsFeed)
XPharm

Internet Reference Collections
The Drug Safety Research Unit (DSRU) Prescription-Event Monitoring (PEM)
MedWatch FDA

Spontaneous Reporting Systems/Post-marketing Monitoring Data
Internet

ADR_{OM}™ portal
Canada's Adverse Drug Reaction Database
UK Yellow Card scheme: Drug Analysis Prints (DAPs)

Databases
PharmaPendium

Request services
FDA's Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS)

Registries of Clinical Trials
Individual Drug Companies
GlaxoSmithKline

Company Portals
Clinical Study Results Database
International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) clinical trials portal
Lead Discovery

Other Portals
Australian New Zealand Clinical Trials Registry (ANZCTR)
ClinicalTrials.gov
Current Controlled Trials
NIH Clinical Research Studies
Trials Central
WHO International Clinical Trials Registry Platform (ICTRP)

Books and Journals
Bulletins/Newsletters
Adverse Drug Reaction Bulletin
Canadian Adverse ReactionNewsletter (CARN)
Clin-Alert
Drug Safety Update (previously Current Problems in Pharmacovigilance)
Drugs and Therapy Perspectives
Medicines Safety Update (previously Australian Adverse Drug Reactions Bulletin)
Reactions Weekly

Specialist Journals
Drug Safety
Pharmacoepidemiology and Drug Safety

Generic Journals (with highest number of articles on adverse effects)[31]
Lancet
New England Journal of Medicine
BMJ
Annals of Pharmacotherapy

Diabetes Journals
Diabetes
Diabetes Care
Diabetes Research and Clinical Practice
Diabetic Medicine

Referenced Monographs
Adverse Drug Reactions
AHFSFirst Professional Medicines Compendium
Clinical Pharmacology
Davies Textbook of Adverse Drug Reactions
Emedicine

General Practice Notebook
Martindale: the complete drug reference
Meylers's Side Effects Of Drugs
Side Effects of Drugs annual (SEDA)
ToxEd

Partially-Referenced Monographs
Drug Safety Portal
The Merck Manual

Non-Referenced Monographs
ABPI electronic Medicines Compendium (eMC)
Drugs.com
Mosby's Medical Drug Reference
Physicians' Desk Reference (PDR)
RxList
Rxmed

Referenced Lists of Adverse Effects
Litt's Drug Eruption Global Database

Non-referenced Lists of Adverse Effects
British National Formulary (BNF)
Davis's Drug Guide
Epocrates Online
Modell's Drugs in current use and new drugs

The search strategies will be developed in order to assess the comparative value of different databases and the effectiveness of published search strategies in retrieving information on adverse effects.

Search Strategies for Database Comparisons
In order to compare the results from multiple data sources, the search strategies used will be as similar as possible allowing for differences in indexing and search interface.

Search terms for the intervention (thiazolidinedione) and outcome (fractures) only will be used to create a search string (Box 2). Disease terms will not be used as thiazolidinediones are rarely prescribed for other conditions and there may be relevant papers which do not mention diabetes in the title, abstract or indexing.

No date or language restrictions will be applied to the database search strategies. However, due to logistical restraints only English language papers or papers for which a translation is readily available will be included. No restriction will be placed on the search strategies regarding type of study design (Box 3).

Box 2: Search Facets

P (population) – Type 2 diabetes
I (intervention) – Thiazolidinediones
C (comparators) – Any
O (outcome) – Fractures (adverse effect)

Box 3: Proposed Search Strategies

MEDLINE
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

EMBASE
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af. OR bmd OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

Eligibility criteria
Primary outcome - fractures
Randomized controlled trials (RCTs) and controlled observational studies will be selected that reported on fracture risk with thiazolidinedione exposure as compared to those without exposure.
The specific inclusion criteria for RCTs are (1) parallel group randomized trial of any thiazolidinedione (rosiglitazone or pioglitazone) of at least 12 months duration; (2) study participants with impaired glucose tolerance or type 2 diabetes mellitus; (3) control arm which could be placebo or oral active comparators, with the only difference between the treatment groups being the use of thiazolidinediones; and (4) clear reporting of fracture outcomes.

For the observational studies, controlled studies assessing fracture risk with thiazolidinedione exposure versus non-exposure will be selected, so long as the presented data allows extraction or calculation of odds ratio/relative risk or hazard ratios.

Secondary outcome – effects on bone mineral density
RCTs and controlled observational studies of any duration which reported on change in bone mineral density with thiazolidinedione exposure compared to non-exposure will be included.

Validity assessment
The reporting of allocation concealment and the use of blinding in RCTs will be assessed. In accordance with the Cochrane handbook of systematic reviews, the strength of adverse effects data in both the RCTs and the observational studies will be checked by recording how the investigators monitored and recorded adverse effects.

Data extraction strategy
Two reviewers will assess the eligibility and quality of studies for adverse event reporting. Data will be extracted independently by one reviewer using a standardised data extraction form and checked by one other reviewer. The reviewers will obtain full consensus on inclusion of the studies and data extraction after resolving any discrepancies though discussion with a third reviewer. Authors will be contacted if any items require clarification.

Study characteristics
The dose and duration of thiazolidinedione therapy, and baseline characteristics of participants in the RCTs will be recorded. For the observational studies, the data sources, study participants, ascertainment of exposure and outcomes will be recorded.

Assessment of risk of bias
In accordance with the recommendations of the Cochrane Adverse Effects Methods Group, participant selection (including baseline characteristics), nature of follow-up, ascertainment of exposure, and definition and monitoring of adverse outcomes will be assessed. Confounders that were adjusted for, as well as the adjusted and unadjusted estimates of effect size, will be recorded where available.

Data analysis
RevMan 5.024 (Nordic Cochrane Centre) will be used to conduct random effects meta-analysis using M-H fixed effects model for the clinical trial data, and inverse variance method for pooled odds ratios from the observational studies (OR). Similarity between the risk ratio and odds ratio is assumed because fractures are uncommon events.

For the observational studies, where possible pool adjusted odds ratios from the primary studies will be calculated, otherwise raw outcome data will be used to yield unadjusted odds ratios (which may be particularly susceptible to confounding).

In view of the potential diversity of study designs, the analysis will be stratified based on the groupings:

- using unadjusted odds ratios for the relevant outcomes, with no correction for baseline differences or confounding
- using odds ratios adjusted for potential confounders

Exclusion Criteria
Animal models, preclinical and biological studies, editorials and opinions will be excluded.

Statistical heterogeneity,
Statistical heterogeneity will be assessed using I^2 statistic, with I^2 values of 30-60% representing a moderate level of heterogeneity.

Appendix E: **Search strategies for case study systematic review in Chapters 11 and 12:**

Internet Search Engines

General

AltaVista

Host: www.altavista.com/
Date searched: 24/08/10
Number of records retrieved: 8,340,000 results, browsed first 3 pages (30 results)
Search strategy: (rosiglitazone OR rosiglitazones OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone OR glitazones OR thiazolidinedione OR thiazolidinediones OR tzd OR pioglitazone OR pioglitazones OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

Google

Host: www.google.com/
Date searched: 24/08/10
Number of records retrieved: 1,430,000 results, browsed first 3 pages (30 results, one link did not work)
Search strategy: (rosiglitazone OR rosiglitazones OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone OR glitazones OR thiazolidinedione OR thiazolidinediones OR tzd OR pioglita7zone OR pioglitazones OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

Academic

Google Scholar

Host: http://scholar.google.co.uk/
Date searched: 24/08/10
Number of records retrieved: 120,000 records, browsed first 3 pages (30 results)
Search strategy: (rosiglitazone OR rosiglitazones OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone OR glitazones OR thiazolidinedione OR thiazolidinediones OR tzd OR pioglitazone OR pioglitazones OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

Intute

Host: http://www.intute.ac.uk/
Date searched: 24/08/10
Number of records retrieved: 0
Search strategy: (rosiglitazone OR rosiglitazones OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone OR glitazones OR thiazolidinedione OR thiazolidinediones OR tzd OR pioglitazone OR pioglitazones OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

Bibliographic Databases

Adverse effects databases

TOXLINE (Toxicology Literature Online)

Host: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE
Date range: 1965 to present
Date searched: 21/07/10
Number of records retrieved: 141 (only 8 not in Pubmed)

Search strategy: (rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR “ppar gamma agonist*” OR “peroxisome proliferator activated receptor gamma agonist*” OR pioglitazone* OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture* OR bone* OR bmd OR osteoporo*)

Pharmaceutical databases

ADIS Clinical Trials Insight

Host: Wolters Kluwer Pharma Solutions: http://bi.adisinsight.com/Login/Login.aspx
Date range: Version 7.3.1, 16 Feb 2010
Date searched: 21/07/10
Number of records retrieved: 70
Search strategy: Drug is Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandaryl OR Avandia OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/glimepiride OR Pioglitazone/metformin OR Pioglitazone/TAK-536 OR Actos OR Actoplus-Met OR Duetact OR Nyracta OR Venvia AND
Text contains ‘"fracture*" OR "bone*" OR "osteoporo*"’
OR
Drug is Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandaryl OR Avandia OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/glimepiride OR Pioglitazone/metformin OR Pioglitazone/TAK-536 OR Actos OR Actoplus-Met OR Duetact OR Nyracta OR Venvia AND
Text contains ‘"bmd"’

Derwent Drug File (previously RingDoc)
Host: Dialogweb
Date range: 1983-2010/Aug
Date searched: 03/09/10
Number of records retrieved: 141
Search strategy:
s rosiglitazone?
s avandia
s avandaryl
s avaglim
s avandamet
s glitazone?
s thiazolidinedion?
s tzd
s ppar(w)gamma(w)agonist?
s peroxisome(w)proliferator(w)activated(w)receptor(w)gamma(w)agonist?
s pioglitazone?
s actos
s actoplus
s duetact
s competact
s glustin
s nyracta
s venvia
s RN=111025-46-8
s RN=122320-73-4
s s1:s20

s fracture?
S bone?
S bmd
S osteoporo?
s s22:s25
s s26 and s21

Thomson Reuters Integrity
Host: http://integrity.prous.com/integrity/xmlxsl/pk_home.util_home
Date range: 1988 – 20/08/10
Date searched: 20/08/10
Number of Records Retrieved: 96 records
Search strategy:
Title/text = bone* or bmd or osteoporo* or fracture*
AND
Product > Drug Name = rosiglitazone or pioglitazone

Iowa Drug Information Service (IDIS)
Host: http://www.uiowa.edu/~idis/idisweb.htm/
Date range*:* 1966 to 2010
Date searched: 15/07/10
Number of records retrieved: 60 (Indexes over 200 journals, plus FDA, NICE and AHRQ material Links to the full-text but searches are of title, abstract and descriptors. (Descriptors are assigned by trained pharmacists)).
Search strategy:
(rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR "ppar gamma agonist*" OR "peroxisome proliferator activated receptor gamma agonist*" OR pioglitazone* OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) [drug field]
AND
(fracture* OR bone* OR bmd OR osteoporo*) [all fields]

International Pharmaceutical Abstracts (IPA)
Host: Dialogweb
Date range*:* 1970-2010/Aug
Date searched: 03/09/10
Number of records retrieved: 28
Search strategy:
s rosiglitazone?
s avandia
s avandaryl
s avaglim
s avandamet
s glitazone?
s thiazolidinedion?
s tzd
s ppar(w)gamma(w)agonist?
s peroxisome(w)proliferator(w)activated(w)receptor(w)gamma(w)agonist?
s pioglitazone?
s actos
s actoplus
s duetact
s competact
s glustin
s nyracta

s venvia
s RN=111025-46-8
s RN=122320-73-4
s s1:s20
s fracture?
S bone?
S bmd
S osteoporo?
s s22:s25
s s26 and s21

Generic databases
BIOSIS Previews
This search required a 2 stage approach as the University of York subscription only runs from 1969-2008.
Stage 1
Host: ISI web of science
Date range: 1969-2008
Date searched: 21/07/10
Number of records retrieved: 702
Search strategy:
TS=(rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR (ppar SAME gamma SAME agonist*) OR (peroxisome SAME proliferator SAME activated SAME receptor SAME gamma SAME agonist*) OR pioglitazone* OR actos OR actoplus ORduetact OR competact OR glustin OR nyracta OR venvia) AND TS=(fracture* OR bone* OR bmd OR osteoporo*)

Stage 2
Host: Dialogweb
Date range: 1993-2010/Aug
Date searched: 03/09/10
Number of records retrieved: 178 additional records
Search strategy:
s rosiglitazone?
s avandia
s avandaryl
s avaglim
s avandamet
s glitazone?
s thiazolidinedion?
s tzd
s ppar(w)gamma(w)agonist?
s peroxisome(w)proliferator(w)activated(w)receptor(w)gamma(w)agonist?
s pioglitazone?
s actos
s actoplus
s duetact
s competact
s glustin
s nyracta
s venvia
s RN=111025-46-8
s RN=122320-73-4
s s1:s20

s fracture?
S bone?
S bmd
S osteoporo?
s s22:s25
s s26 and s21
s py=2007:2011
s s27 and s28

British Library Direct
Host: http://direct.bl.uk/bld/SearchResults.do
Date range: Last 5 years
Date searched: 15/07/10
Number of records retrieved: 117
Search strategy:
(rosiglitazone OR rosiglitazones OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone OR glitazones OR thiazolidinedione OR thiazolidinediones OR tzd OR pioglitazone OR pioglitazones OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) AND (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

CENTRAL
Host: The Cochrane Library
Date Range: Issue 7, 2010
Date Searched: 21/07/10
Number of Records Retrieved: 12
Search strategy:
#1 MeSH descriptor Thiazolidinediones
#2 rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR “ppar gamma agonist*” OR “peroxisome proliferator activated receptor gamma agonist*” OR pioglitazone* OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia
#3 MeSH descriptor Fractures, Bone explode all trees
#4 MeSH descriptor Bone Density
#5 MeSH descriptor Osteoporosis explode all trees
#6 fracture* OR bone* OR bmd OR osteoporo*
#7 (#1 OR #2) AND (#3 OR #4 OR #5 OR #6)

CINAHL
Interface: EBSCOhost www.ebscohost.com/
Date range: 2006-2010
Date searched: 21/07/10
Number of records retrieved: 70
Search strategy:
(MH "Thiazolidinediones") OR (MH "Rosiglitazone") OR (MH "Pioglitazone") OR Rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedione* OR tzd OR pioglitazone* OR actos OR actoplus ORduetact OR competact OR glustin OR nyracta OR venvia
AND
(MH "Fractures+") OR fracture* OR (MH "Bone Density") OR bone* OR bmd OR (MH "Osteoporosis+") OR osteoporosis

EMBASE
Interface: Wolters Kluwer Health OvidSP http://www.ovid.com/
Date range: 1996 to 2010 Week 28

Date searched: 21/07/10
Number of records retrieved: 1017
Search strategy:
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af. OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

MEDLINE
Interface: Wolters Kluwer Health OvidSP http://www.ovid.com/
Date range: 1996 to July Week 1 2010
Date searched: 21/07/10
Number of records retrieved: 251
Search strategy:
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

Medscape
Host: http://www.medscape.com/
Date range: January 1990 – 9th July 2010
Date searched: 09/07/10
Search results: 115 records
Search Strategy: Terms are automatically ANDed and searching with terms such as fracture and bone also retrieves fractures and bones
rosiglitazone fracture 44
rosiglitazone bone 56
rosiglitazone bmd 5
rosiglitazone osteoporosis 20
rosiglitazones 0
avandia fracture 44
avandia bone 56
avandia bmd 5
avandia osteoporosis 20
avandaryl fracture 1
avandaryl bone 1
avandaryl bmd 0
avandaryl osteoporosis 1
avaglim 0
avandamet fracture 3
avandamet bone 1
avandamet bmd 0
avandamet osteoporosis 2
glitazone fracture 4

glitazone bone 4
glitazone bmd 0
glitazone osteoporosis 2
glitazones fracture 6
glitazones bone 11
glitazones bmd 1
glitazones osteoporosis 4
thiazolidinedione fracture 25
thiazolidinedione bone 32
thiazolidinedione bmd 0
thiazolidinedione osteoporosis 7
thiazolidinediones fracture 32
thiazolidinediones bone 44
thiazolidinediones bmd 1
thiazolidinediones osteoporosis 13
tzd fracture 18
tzd bone 15
tzd bmd 0
tzd osteoporosis 9
pioglitazone fracture 34
pioglitazone bone 49
pioglitazone bmd 1
pioglitazone osteoporosis 15
pioglitazones 0
actos fracture 34
actos bone 49
actos bmd 1
actos osteoporosis 15
actoplus fracture 0
actoplus bone 0
actoplus bmd 0
actoplus osteoporosis 0
duetact fracture 0
duetact bone 0
duetact bmd 0
duetact osteoporosis 0
competact fracture 0
competact bone 0
competact bmd 0
competact osteoporosis 0
glustin 0
nyracta 0
Venvia 0

PASCAL
Interface: http://stanalyst.inist.fr/
Date range: 1973 - present
Date searched: 20/08/10
Number of records retrieved: 64
Search strategy :
mc=(rosiglitazone ou pioglitazone ou ''thiazolidinedione derive'' ou ''derive de la thiazolidinedione'') ou (mc=agoniste et mc=''recepteur ppar*'') ou (glitazone* ou thiazolidinedione* ou avandaryl ou avandia ou avaglim ou avandamet ou actos ou actoplus ou duetact ou competact ou glustin ou nyracta ou venvia) et (mc=(fracture*

ou "densite minerale osseuse" ou osteoporo* ou "pathologie du systeme osteoarticulaire" ou "systeme osteoarticulaire*") ou fractur*)

Science Citation Index (SCI)
Host: http://scientific.thomsonreuters.com/products/sci/
Date range: 1899-present
Host: ISI Web of Knowledge, Web of Science
Date searched: 21/07/10
Number of records retrieved: 312
Search strategy:
TS=(rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR (ppar SAME gamma SAME agonist*) OR (peroxisome SAME proliferator SAME activated SAME receptor SAME gamma SAME agonist*) OR pioglitazone* OR actos OR actoplus ORduetact OR competact OR glustin OR nyracta OR venvia) AND TS=(fracture* OR bone* OR bmd OR osteoporo*)

Scirus
Date range: 1900-2011 (limited to journal articles only)
Host: http://www.scirus.com/
Date searched: 23/09/10
Number of records retrieved: 2152 (1928 after within database deduplication)
Search strategy:
(rosiglitazon* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazon* OR thiazolidinedion* OR tzd OR pioglitazon* OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia) (fracture OR fractures OR bone OR bones OR bmd OR osteoporosis)

Conference Databases
Conference Papers Index (CPI)
Host: http://www.proquest.co.uk/en-UK/catalogs/databases/detail/cpi-set-c.shtml
Date range: 1982 – current (updated bimonthly)
Date searched: 15/07/10
Number of records retrieved: 31
Search strategy:
The searches were not restricted to any field but searched 'anywhere' which includes all fields including a keyword field.
rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR "ppar gamma agonist*" OR "peroxisome proliferator activated receptor gamma agonist*" OR pioglitazone* OR actos OR actoplus OR duetact OR competact OR glustin OR nyracta OR venvia
AND
fracture* OR bone* OR bmd OR osteoporo*

Conference Proceedings Citation Index- Science (CPCI-S)
Host: ISI Web of Knowledge, Web of Science
Date range: 1990-present
Date searched: 15/07/10
Number of records retrieved: 45
Search strategy:
TS=(rosiglitazone* OR avandia OR avandaryl OR avaglim OR avandamet OR glitazone* OR thiazolidinedion* OR tzd OR (ppar SAME gamma SAME agonist*) OR (peroxisome SAME proliferator SAME activated SAME receptor SAME gamma SAME agonist*) OR pioglitazone* OR actos OR actoplus ORduetact OR competact

OR glustin OR nyracta OR venvia) AND TS=(fracture* OR bone* OR bmd OR osteoporo*)

Inside Conferences
Host: Dialogweb
Date range: 1993-2010/Sep
Date searched: 03/09/10
Number of records retrieved: 7
Search strategy:
s rosiglitazone?
s avandia
s avandaryl
s avaglim
s avandamet
s glitazone?
s thiazolidinedion?
s tzd
s ppar(w)gamma(w)agonist?
s peroxisome(w)proliferator(w)activated(w)receptor(w)gamma(w)agonist?
s pioglitazone?
s actos
s actoplus
s duetact
s competact
s glustin
s nyracta
s venvia
s RN=111025-46-8
s RN=122320-73-4
s s1:s20
s fracture?
S bone?
S bmd
S osteoporo?
s s22:s25
s s26 and s21

Synthesized Databases
Medical Evidence Matters
Host: http://proquest.umi.com/login
Searched: 24/11/10
Search results: References to Nissen and Scheen, 2 RCTs on fractures. Presents data from papers.

Referenced Summary Databases
ADIS R&D Insight
Host: Wolters Kluwer Pharma Solutions http://bi.adisinsight.com/Login/Login.aspx
Date Range: Version 7.3.1, 16 Feb 2010
Date Searched: 21/07/10
Number of Records Retrieved: 1 Monograph for rosiglitazone refers to BARI-2D conference paper. No included references.
Search strategy:
Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandia® OR Avandamet® OR Avandamet® XR OR Peroxisome proliferator-activated receptor agonists research programme - Eli Lilly OR Pioglitazone OR Pioglitazone/alogliptin

OR Pioglitazone/glimepiride OR Pioglitazone/metformin OR Pioglitazone/TAK 536 OR Actos® OR ACTOplus met® OR ACTOplus met® XR OR Duetact™ OR Competact® OR Glustin™ OR Avaglim® OR Avandaryl® AND Text contains "fracture*" OR "bone*" OR "osteoporo*"
OR
Drug is Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandaryl OR Avandia OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/glimepiride OR Pioglitazone/metformin OR Pioglitazone/TAK-536 OR Actos OR Actoplus-Met OR Duetact OR Nyracta OR Venvia AND Text contains '"bmd"'

DRUGDEX
Host: MICROMEDEX 2.0
Interface: http://www.thomsonhc.com/
Date Searched: 07/10/10
Number of records retrieved: 6 monographs with 5 references in total. 1 included reference - 1 RCT fracture

monographs for rosiglitazone, ROSIGLITAZONE MALEATE/METFORMIN HYDROCHLORIDE and ROSIGLITAZONE MALEATE/GLIMEPIRIDE

Lexi-Comp Database
Date range: June 2010
Interface: http://www.crlonline.com/
Date searched: 18/08/10
Number of Records retrieved: Lexi-comp mongraph for rosiglitazone and pioglitazone refer to fractures as adverse effects (contains references at end of text). 6 included references 3 RCT fractures, 1 observational study of fractures and 2 observational studies of bone mineral density Also contains monographs from AHFS Information and Martindales. 21 references including those from AHFS Information and Martindales. In totals 7 included references (representing 6 studies), 4 RCT fractures (representing 3 studies), 1 observational study of fractures and 2 observational studies of bone mineral density

XPharm
Host: www.xpharm.com/
Date Range: 2007
Interface: http://www.sciencedirect.com/science/referenceworks/9780080552323.
Date searched: 27/10/10
Number of Records retrieved: 3 referenced monographs (rosiglitazone, pioglitazone, thiazolidinediones). No mention of fractures in text on adverse effects.

Internet Reference Collections
The Drug Safety Research Unit (DSRU) Scientific Publications
Host: http://www.dsru.org/
Date Range: 1979- present
Date Searched: 21/07/10
Number of Records Retrieved: 3
Search strategy:
Rosiglitazone 1 record, 0 potentially relevant
Rosiglitazones 0
Avandia 0
Avandaryl 0
avaglim 0

avandamet 0
glitazone 0
glitazones 0
thiazolidinedione 0
thiazolidinediones 0
tzd 0
pioglitazone 3 records, 0 potentially relevant
pioglitazones 0
actos 0
actoplus
duetact
competact 0
glustin 0
nyracta 0
venvia 0

MedWatch FDA
Host: http://www.fda.gov/medwatch/safety.htm
Date Range:
Date Searched: 21/07/10
Number of Records Retrieved: 9 records after dedup, 2 potentially relevant letters. No included references.
Search strategy:
rosiglitazone fracture 4 records, 1 potentially relevant letter, 2 links to potentially relevant letter
rosiglitazone fractures 4 records, 1 potentially relevant letter, 2 links to potentially relevant letter
rosiglitazone bone 3 records, 1 potentially relevant letter
rosiglitazone bmd 0
rosiglitazone osteoporosis 1 record, 1 potentially relevant letter
rosiglitazones 0
avandia fracture 4 records, 1 potentially relevant letter, 2 links to potentially relevant letter
avandia fractures 4 records, 1 potentially relevant letter, 2 links to potentially relevant letter
avandia bone 3 records, 1 potentially relevant letter
avandia bmd 0
avandia osteoporosis 1 record, 1 potentially relevant letter
avandaryl 0
avaglim 0
avandamet fracture 2 records, 1 potentially relevant letter, 1 link to potentially relevant letter
avandamet fractures 2 records, 1 potentially relevant letter, 1 link to potentially relevant letter
avandamet bone 1 record, 1 potentially relevant letter
avandamet bmd 0
avandamet osteoporosis 1 record, 1 potentially relevant letter
glitazone 0
glitazones 0
thiazolidinedione fracture 0
thiazolidinedione fractures 0
thiazolidinedione bone 0
thiazolidinedione bmd 0
thiazolidinedione osteoporosis 0
thiazolidinediones fracture 1 record, 1 potentially relevant letter

thiazolidinediones fractures 1 record, 1 potentially relevant letter
thiazolidinediones bone 2 records, 1 potentially relevant letter
thiazolidinediones bmd 0
thiazolidinediones osteoporosis 0
tzd 0
pioglitazone fracture 3 records, 1 potentially relevant letter, 2 links to potentially relevant letter
pioglitazone fractures 3 records, 1 potentially relevant letter, 2 links to potentially relevant letter
pioglitazone bone 2 records, 1 potentially relevant letter
pioglitazone bmd 0
pioglitazone osteoporosis 0
pioglitazones 0
actos fracture 3 records, 1 potentially relevant letter, 2 links to potentially relevant letter
actos fractures 3 records, 1 potentially relevant letter, 2 links to potentially relevant letter
actos bone 2 records, 1 potentially relevant letter
actos bmd
actos osteoporosis 0
actoplus
duetact
competact 0
glustin 0
nyracta 0
venvia 0

Internet
ADR$_{OM}$™ portal (Information from the FDA's Adverse Event Reporting System (AERS))
Host: https://www.prosoftedc.com/aers/aers.html
Date Range: Q1 2004 to Q3 2009
Date Searched: 19/08/10
Search Results:
Rosiglitazone – 14 reports (Ankle fracture 1 female, Foot: 1 female, forearm: 1 female, hip 3 females, osteoporotic: 2 females, spinal compression: 2 males, spinal: 2 females, unspecified: 1 female, wrist: 1 female)
Pioglitazone – 4 reports (Ankle: 2 females, Fibula: 2 females)

Canada's Adverse Drug Reaction Database
Host: http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php
Date Range: 1965 to **2010-03-31**
Date Searched: 19/08/10
Number of Records Retrieved: 2
Search strategy:
Controlled index so searched for rosiglitazone and pioglitazone and all cases of fracture or bone or osteoporosis
Rosiglitazone fracture 18 patients with fractures (some patients had more than one fracture)
Ankle fracture 1 (1 male), Femur fracture 1 (1 female), Foot fracture 5 (4 females and 1 male), Hip fracture 1 (1 female), Humerus fracture 1 (1 female), Lumber vertebral fracture 1 (1 female), Multiple fractures 2 (2 female), Pathological fracture 4 (4 female), Rib fracture 1 (1 female), Unspecified fracture 2 (2 female), Upper limb fracture 2 (2 females), Wrist fracture 1 (1 female)
pioglitazone fracture 0

UK Yellow Card scheme: Drug Analysis Prints (DAPs)
Host: http://www.mhra.gov.uk
Date Range: 01 June 1963- 28 June 2010
Date Searched: 18/08/10
Number of Records Retrieved: DAPS for rosiglitazone and pioglitazone.
Rosiglitazone 27 reports (Unspecified fracture 3, ankle fracture 5, fibula fracture 1, foot fracture 4, hip fracture 2 lower limb fracture 1, spinal fracture 1, forearm fracture 1, hand fracture 1, humerus fracture 2, radius fracture 1, ulna fracture 1, wrist fracture 4)
Pioglitazone 8 reports (Ankle fracture 1, femur fracture 1, foot fracture 1, tibia fracture 1, lumber vertebral fracture 1, thoracic vertebral fracture 1, humerus fracture 1, wrist fracture 1)

Databases
PharmaPendium
Host: http://www.info.pharmapendium.com/
Date Range: 1938 – July 2010
Date Searched: 27/10/10
Number of Records Retrieved: 13 EMEA approval documents and one FDA approval package document. 576 post-marketing reports (AERS)
Metformin Hydrochloride; Rosiglitazone Maleate 43 reports, 8 male and 35 female, Foot fracture (8), Wrist fracture (7), Ankle fracture (5), Fracture (5), Fibula fracture (4), Radius fracture (4), Upper limb fracture (4), Hip fracture (3) ,Humerus fracture (3), Hand fracture (2), ,Lower limb fracture (2), Multiple fractures (2), Stress fracture (2), Tibia fracture (2), Compression fracture (1), Forearm fracture (1), Osteoporotic fracture (1), Pathological fracture (1), Thoracic vertebral fracture (1)
Rosiglitazone Maleate 296 reports, 78 male and 214 female. Fracture (64), Foot fracture (51), Upper limb fracture (31), Ankle fracture (26), Hip fracture (20), Humerus fracture (19), Multiple fractures (19), Lower limb fracture (16), Wrist fracture (15), Femur fracture (13), Hand fracture (11), Pathological fracture (8), Rib fracture (8), Spinal fracture (7), Stress fracture (7), Patella fracture (6), Pelvic fracture (6), Radius fracture (6), Ulna fracture (5), Osteoporotic fracture (4), Bone fissure (3), Femoral neck fracture (3), Forearm fracture (3), Fracture nonunion (3), Lumbar vertebral fracture (3), Tibia fracture (3), Clavicle fracture (2), Fractured sacrum (2), Scapula fracture (2), Compression fracture (1), Facial bones fracture (1), Fibula fracture (1), Fractured coccyx (1), Pubic rami fracture (1), Sternal fracture (1)
Rosiglitazone Maleate; Glimepiride 13 reports, 0 male and 13 female Hip fracture (3), Osteoporotic fracture (2), Spinal fracture (2), Ankle fracture (1), Foot fracture (1), Forearm fracture (1), Fracture (1), Humerus fracture (1), Upper limb fracture (1), Wrist fracture (1)
Pioglitazone Hydrochloride 224 reports, 42 male and 179 female. Ankle fracture (23), Foot fracture (20), Hip fracture (19), Upper limb fracture (19), Spinal fracture (18), Tibia fracture (18), Rib fracture (17), Fracture (14), Humerus fracture (14), Lower limb fracture (14), Fibula fracture (13), Radius fracture (13), Femoral neck fracture (11), Pathological fracture (11), Pelvic fracture (11), Compression fracture (10), Hand fracture (10), Stress fracture (10), Wrist fracture (10), Lumbar vertebral fracture (8), Ulna fracture (8), Femur fracture (7), Multiple fractures (5), Facial bones fracture (4), Thoracic vertebral fracture (4), Clavicle fracture (3), Forearm fracture (3), Fractured coccyx (3), Ilium fracture (3), Pubic rami fracture (3), Acetabulum fracture (2), Bone fissure (2), Greenstick fracture (2), Patella fracture (2), Avulsion fracture (1), Cervical vertebral fracture (1), Fractured sacrum (1), Skull fracture (1), Ankle fracture (23), Foot fracture (20), Hip fracture (19), Upper limb fracture (19), Spinal fracture (18), Tibia fracture (18), Rib fracture (17), Fracture (14), Humerus

fracture (14), Lower limb fracture (14), Fibula fracture (13), Radius fracture (13), Femoral neck fracture (11), Pathological fracture (11), Pelvic fracture (11), Compression fracture (10), Hand fracture (10), Stress fracture (10), Wrist fracture (10), Lumbar vertebral fracture (8), Ulna fracture (8), Femur fracture (7), Multiple fractures (5), Facial bones fracture (4), Thoracic vertebral fracture (4), Clavicle fracture (3), Forearm fracture (3), Fractured coccyx (3), Ilium fracture (3), Pubic rami fracture (3), Acetabulum fracture (2), Bone fissure (2), Greenstick fracture (2), Patella fracture (2), Avulsion fracture (1), Cervical vertebral fracture (1), Fractured sacrum (1), Skull fracture (1)

Request services

FDA's Adverse Event Reporting System (AERS) and Spontaneous Reporting System (SRS)

Host: http://www.foiservices.com/brochure/ADR_search.cfm or
http://www.ntis.gov/products/adverse.aspx or
http://www.fda.gov/cder/aers/extract.htm
Date range: 01 Nov 1997-31 Dec 2009
Rosiglitazone fractures 72 reports (Ankle Fracture 6 (1 male and 5 females), femur fracture 2 (2 females), foot fracture 9 (8 females, 1 unknown), forearm fracture 1 (1 female), unspecified 7 (3 males, 3 females, 1 unknown), fracture nos 1 (1 female), hand fracture 3 (2 female, 1 unknown), hip fracture 4 (4 female), humerus 2 (2 female), lower limb fracture 7 (4 female, 2 male, 1 unknown), osteoporotic fracture 3 (3 female), pathological fracture 1 (1 female), radius fracture 4 (4 female), rib fracture 6 (3 females and 3 males), skull fracture nos 3 (3 males), spinal compression fracture 3 (2 males and 1 female), spinal fracture 4 (2 females, 1 male, 1 unknown), upper limb fracture 3 (2 female, 1 unknown), upper limb fracture nos 1 (1 female), wrist fracture 2 (2 female))

Pioglitazone Fractures, 95 reports
Acetabulum fracture 2 (2 males), ankle fracture 13 (12 females and 1 male), avulsion fracture 1 (1 male), compression fracture 2 (2 female), femoral neck fracture 2 (1 male and 1 unknown), femur fracture 9 (3 female and 6 male), fibula fracture 5 (4 female and 1 male), foot fracture 7 (6 female and 1 male), unspecified fracture 2 (2 females), unspecified fracture nos 1 (1 female), hand fracture 3 (2 females and 1 male), hip fracture 10 (5 male, 4 females, 1 unknown), humerus fracture 1 (1 male), ilium fracture 2 (2 males), lower limb fracture 3 (2 females and 1 male), multiple fractures 1 (1 female), pelvic fracture 8 (6 males and 2 females), radius fracture 3 (2 male and 1 female), rib fracture 6 (5 males and 1 female), skull fracture 1 (1 female), spinal fracture 1 (1 female), spinal fracture nos 1 (1 female), tibia fracture 2 (2 males), ulna fracture 2 (1 male and 1 female), upper limb fracture 1 (1 female), upper limb fracture nos 1 (1 female), wrist fracture 5 (3 females and 2 males)

Registries of Clinical Trials

Individual Drug Companies

GlaxoSmithKline

Host: http://www.gsk-clinicalstudyregister.com
Date Range:
Date Searched: 23/08/10
Number of Records Retrieved: 147 results, 39 protocols (117 phase III and IV studies and 38 protocols. 30 observational studies and 1 protocol)
Description: Searched for rosiglitazone in phase III and IV studies and observational studies.
Ongoing studies RCT - GSK TIDE study not due for completion until 2015

RCT – GSK RECORD follow-up study due for completion 2012

Takeda Pharmaceuticals (https://www.takeda.co.uk/)
Emailed if have register on several occasions. No response.

Drug Company Portals
Clinical Study Results Database
Host: http://www.clinicalstudyresults.org/
Date Searched: 23/08/10
Number of Records Retrieved: 229 records
Search strategy:
Series of searches were undertaken;
avandamet 15
Avandamet,Avandamet XR 1
Avandia 5
Avandia XR 10
Avandia:avandia 189
actos 7
actos, fortamet 2

International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) clinical trials portal
Host: clinicaltrials.ifpma.org/
Date searched: 24/08/10
Number of records retrieved: 84 records - Gaasbeek, BMD 48 weeks RCT in Kidney disease
Search strategy:
rosiglitazone AND fracture 11 (use synonyms selected includes avandia)
rosiglitazone AND fractures 8
rosiglitazone AND bone 33
rosiglitazone AND bmd 6
rosiglitazone AND osteoporosis 8
avandaryl 0
avaglim 0
avandamet AND fracture 0
avandamet AND fractures 0
avandamet AND bone 2
avandamet AND bmd 1
avandamet AND osteoporosis 0
glitazone AND fracture 1
glitazone AND fractures 1
glitazone AND bone 2
glitazone AND bmd 0
glitazone AND osteoporosis 1
glitazones AND fracture 14 (use synonyms selected includes thiazolidinediones)
glitazone AND fractures 10
glitazones AND bone 31
glitazones AND bmd 6
glitazones AND osteoporosis 10
thiazolidinedione AND fracture 7
thiazolidinedione AND fractures 6
thiazolidinedione AND bone 9
thiazolidinedione AND bmd 1
thiazolidinedione AND osteoporosis 6
tzd AND fracture 10

tzd and fractures 4
tzd AND bone 13
tzd AND bmd 2
tzd AND osteoporosis 5
pioglitazone AND fracture 13 (use synonyms selected includes actos)
pioglitazone AND fractures 7
pioglitazone AND bone 38
pioglitazone AND bmd 6
pioglitazone AND osteoporosis 17
actoplus AND fracture 0
actoplus AND fractures 0
actoplus AND bone 0
actoplus AND bmd 0
actoplus AND osteoporosis 0
duetact AND fracture 0
duetact AND fractures 0
duetact AND bone 0
duetact AND bmd 0
duetact AND osteoporosis 0
competact 0
glustin AND fracture 0
glustin AND fractures 0
glustin AND bone 0
glustin AND bmd 0
glustin AND osteoporosis 0
nyracta 0
Venvia 0

Lead Discovery
Host: http://www.leaddiscovery.co.uk
Date searched: 24/08/10
Number of records retrieved: 36 records after deduplicaton. All from clinicaltrials.gov. 0 potentially relevant.
Search strategy:
Rosiglitazone 4 records, 0 potentially relevant
Rosiglitazones 0
Avandia 1, 0 potentially relevant
Avandaryl 0
avaglim 0
avandamet 0
glitazone 0
glitazones 0
thiazolidinedione 5 records, 0 potentially relevant
thiazolidinediones 0
tzd 0
pioglitazone 27 records, 0 potentially relevant
pioglitazones 0
actos 0
actoplus 0
duetact 0
competact 0
glustin 0
nyracta 0
venvia 0

Other Portals

Australian New Zealand Clinical Trials Registry (ANZCTR)

Host: http://www.anzctr.org.au/
Date range: Last updated 12/07/10
Date searched: 15/07/10
Number of records retrieved: 15 records retrieved after duplicates removed. 1 potentially relevant record. Grey (BMD 1 year rct, registered in 2007 = emailed author – replied no publication yet)
Search strategy:
Rosiglitazone 5 records, 1 potentially relevant
Rosiglitazones 0
Avandia 0
Avandaryl 0
avaglim 0
avandamet 0
glitazone 3 records, 1 potentially relevant
glitazones 2 records,0 potentially relevant
thiazolidinedione 8 records, 2 potentially relevant
thiazolidinediones 8 records, 2 potentially relevant
tzd 0
pioglitazone 6 records, 1 potentially relevant
pioglitazones 0
actos 0
actoplus 0
duetact 0
competact 0
glustin 0
nyracta 0
venvia 0

ClinicalTrials.gov

Host: http://www.clinicaltrials.gov/
Date range: Last updated 13/07/10
Date searched: 15/07/10
Number of records retrieved: Series of searches carried out. 25 trials retrieved after deduplication
rosiglitazone AND fracture 4
rosiglitazone AND bone 11
rosiglitazone AND bmd 4
rosiglitazone AND osteoporosis 2
avandia AND fracture 4
avandia AND bone 11
avandia AND bmd 4
avandia AND osteoporosis 2
avandaryl 0
avaglim 0
avandamet AND fracture 0
avandamet AND bone 1
avandamet AND bmd 1
avandamet AND osteoporosis 0
glitazone AND fracture 6
glitazone AND bone 9
glitazone AND bmd 4

glitazone AND osteoporosis 4
thiazolidinedione AND fracture 6
thiazolidinedione AND bone 9
thiazolidinedione AND bmd 4
thiazolidinedione AND osteoporosis 4
tzd AND fracture 3
tzd AND bone 3
tzd AND bmd 0
tzd AND osteoporosis 1
pioglitazone AND fracture 4
pioglitazone AND bone 15
pioglitazone AND bmd 6
pioglitazone AND osteoporosis 2
actos AND fracture 4
actos AND bone 15
actos AND bmd 6
actos AND osteoporosis 2
actoplus
duetact
competact 1
glustin AND fracture 4
glustin AND bone 15
glustin AND bmd 6
glustin AND osteoporosis 2
nyracta AND fracture 4
nyracta AND bone 11
nyracta AND bmd 4
nyracta AND osteoporosis 2
venvia AND fracture 4
venvia AND bone 11
venvia AND bmd 4
venvia AND osteoporosis 2

Current Controlled Trials
Host: http://www.controlled-trials.com
Date range: Last updated 14/07/10
Date searched: 15/07/10
Number of records retrieved: Series of searches carried out. Excluded clincialtrials.gov as this database was searched directly. 0 records retrieved
Search strategy:
rosiglitazone* AND fracture* 0
rosiglitazone* AND bone 0
rosiglitazone* AND bmd 0
rosiglitazone* AND osteoporo* 0
avandia 0
avandaryl
avaglim
avandamet 0
glitazone* AND fracture* 0
glitazone* AND bone 0
glitazone* AND bmd 0
glitazone* AND osteoporo* 0
thiazolidinedione* AND fracture* 0
thiazolidinedione* AND bone 0
thiazolidinedione* AND bmd 0

thiazolidinedione* AND osteoporo* 0
tzd 0
pioglitazone* AND fracture* 0
pioglitazone* AND bone 0
pioglitazone* AND bmd 0
pioglitazone* AND osteoporo* 0
actos 0
competact 0
glustin 0
nyracta 0
Venvia 0

NIH Clinical Research Studies
Host: http://clinicalstudies.info.nih.gov
Date range: Last updated 15/07/10
Date searched: 16/07/10
Search results: Series of searches carried out. 2 records after duplicate records removed. No relevant records identified.
Search strategy:
rosiglitazone 0
rosiglitazones 0
avandia 0
avandaryl 0
avaglim 0
avandamet 0
glitazone
glitazones
thiazolidinedione 0
thiazolidinediones 0
tzd 0
pioglitazone 2
pioglitazones 0
actos 1
actoplus 0
duetact 0
competact 0
glustin 0
nyracta 0
Venvia 0

Trials Central
Host: http://www.trialscentral.org
Date Range: NS
Date Searched: 16/07/10
Search Results: Browse Find Clinical and Medical Drug Interventions for Hypoglycemic Agents, Rosiglitazone, pioglitazone. 133 entries for rosiglitazone, 141 entries for pioglitazone. Entries browsed – 6 potentially relevant.

WHO International Clinical Trials Registry Platform (ICTRP)
Host: http://apps.who.int/trialsearch
Date Range: Last updated 13/07/10
Date Searched: 16/07/10
Number of Records Retrieved: Series of searches carried out. 15 records retrieved after duplicates removed.
Search strategy:

rosiglitazone* AND fracture* 0
rosiglitazone* AND bone 5
rosiglitazone* AND bmd 1
rosiglitazone* AND osteoporo* 0
avandia AND fracture* 0
avandia AND bone 1
avandia AND bmd 0
avandia AND osteoporo* 0
avandaryl 0
avaglim 0
avandamet AND fracture* 0
avandamet AND bone 0
avandamet AND bmd 0
avandamet AND osteoporo* 0
glitazone* AND fracture* 0
glitazone* AND bone 1
glitazone* AND bmd 1
glitazone* AND osteoporo* 0
thiazolidinedione* AND fracture* 1
thiazolidinedione* AND bone 3
thiazolidinedione* AND bmd 0
thiazolidinedione* AND osteoporo* 2
tzd AND fracture* 1
tzd AND bone 1
tzd AND bmd 0
tzd AND osteoporo* 1
pioglitazone* AND fracture* 0
pioglitazone* AND bone 6
pioglitazone* AND bmd 2
pioglitazone* AND osteoporo* 1
actos AND fracture* 0
actos AND bone 0
actos AND bmd 0
actos AND osteoporo* 0
actoplus 0
duetact 0
competact 0
glustin 0
nyracta 0
Venvia 0

Books and Journals

Bulletins/Newsletters

Adverse Drug Reactions Bulletin
Host: http://www.ovid.com/site/catalog/Journal/3145.jsp
Date Range: Volume 38 February 1973 - Volume 262 June 2010.
Date Searched: 14/07/2010
Search Results: No articles on rosi or pio. Bulletin on Drug-induced bone disease. (Dec 2005 pg. 903-906) but no mention of rosiglitazone or pioglitazone

Canadian Adverse ReactionNewsletter (CARN)
Host: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php
Date Range: January **1991; 1:1 -** July 2010;3(2)
Date Searched: 14/07/10

Search Results: 3 articles on rosiglitazone but not in relation to fractures. No articles on pioglitazone.

Clin-Alert
Host: http://cla.sagepub.com
Date range: 1990:28**:1-** 30 June 2010;48:9
Date searched: 14/07/10
Search results: 4 articles. Thiazolidinediones: Bone fractures. Volume 47, number 4 February 28, 2009, Thiazolidinediones: fracture risk. Volume 46, number 10, May 31 2008, Pioglitazone: FDA safety alert: increased risk of fractures. Volume 45 number 1 2007, Rosilitazone: FDA safety alert: increased risk of fractures. Volume 42 number 1 2007. 4 articles (two for Thiazolidinediones, one for pio and one for rosi). 4 references. 1 included reference, 1 fracture obs

Drug Safety Update (previously Current Problems in Pharmacovigilance)
Host:
http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm
Date Range: Current Problems in Pharmacovigilance 01 May 1990 - 01 May 2006, Drug Safety Update 01 Aug 2007 –Volume 3, Issue 12, July 2010
Date Searched: 14/07/10
Search Results: Rosiglitazone and pioglitazone: cardiovascular safety and fracture risk Drug Safety Update: Volume 1, Issue 3, October 2007 References Letters to healthcareprofessionals were sent in March and April, 2007. See http://www.mhra.gov.uk/mhra/HealthcareProfessionalLetters

Drugs and Therapy Perspectives
Host: http://www.ingentaconnect.com/content/adis/dtp
Date Range: 1993;1:1 –Volume 26 Number 8, 1 August 2010
Date Searched: 14/07/10
Search Results: 1 referenced article – “Glitazones accelerate bone loss and increase the risk of fracture in patients with type 2 diabetes mellitus. Drugs & Therapy Perspectives: 1 January 2010 - Volume 26 - Issue 1 - pp 22-23 doi: 10.2165/11203640-000000000-00000” containing 11 references of which 7 were included references/studies. 2 fracture RCTs, 2 bone RCTs, 1 observational study on fractures, 2 observational study on fractures.

Medicines Safety Update (previously Australian Adverse Drug Reactions Bulletin)
Host: http://www.tga.gov.au/adr/aadrb.htm
Date Range: Australian Adverse Drug Reactions Bulletin 1995;14:1-2009;28:6. Medicines Safety Update 1:2010- 3:2010
Date Searched: 14/07/10
Search Results: “Thiazolidinediones and reduced bone density. Australian Adverse Drug Reactions Bulletin. Volume 26, Number 5, October 2007”. Contains 4 references. 2 included references, 1 fracture RCT, 1 bone RCT.

Reactions PharmacoVigilance Insight (previously PharmaNewsFeed)
Host: Wolters Kluwer Pharma Solutions http://bi.adisinsight.com/Login/Login.aspx
Date Range: Version 7.3.1, 16 Feb 2010
Date Searched: 21/07/10
Search results: Includes full-text of the newsletters Inpharma, Pharmacoeconomics & Outcomes News and Reactions, Medline / Embase indexed journal titles. 20 news on rosiglitazone or pioglitazone with 38 references to the literature. 4 included references, 1 RCT fracture, 2 bone obs 1 bone RCT
Search strategy:

Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandia OR Avandaryl OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/alogliptin OR Pioglitazone/candesartan-cilexetil OR Pioglitazone/glimepiride OR Pioglitazone/glimepiride/metformin OR Pioglitazone/metformin OR Pioglitazone/metformin/glimepiride Pioglitazone/sitagliptin Pioglitazone/TAK-536 Actos Actoplus-Met Duetact Nyracta Venvia
AND
Text contains '"fracture*" OR "bone*" OR "osteoporo*"
OR
Drug is Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandaryl OR Avandia OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/glimepiride OR Pioglitazone/metformin OR Pioglitazone/TAK-536 OR Actos OR Actoplus-Met OR Duetact OR Nyracta OR Venvia AND
Text contains '"bmd"'

Rosiglitazone OR Rosiglitazone-hydrochloride OR Rosiglitazone-maleate OR Rosiglitazone/glimepiride OR Rosiglitazone/metformin OR Avandia OR Avandaryl OR Avandamet OR Peroxisome-proliferator-activated-receptor-agonists OR Pioglitazone OR Pioglitazone-hydrochloride OR Pioglitazone/alogliptin OR Pioglitazone/candesartan-cilexetil OR Pioglitazone/glimepiride OR Pioglitazone/glimepiride/metformin OR Pioglitazone/metformin OR Pioglitazone/metformin/glimepiride OR Pioglitazone/sitagliptin OR Pioglitazone/TAK-536 OR Actos Actoplus-Met OR Duetact OR Nyracta OR Venvia
AND
Text contains "bmd"

Reactions Weekly
Host: http://www.ovid.com/site/catalog/Journal/615.jsp
Date Range: 11 January v383 1992 – v1309 10 July 2010
Date Searched: 14/07/10 Search Results: 19 news articles with 37 references to the literature. 4 included references, 1 RCT fracture, 2 bone obs 1 bone RCT

Specialist Journals
Drug Safety (http://www.ingentaconnect.com/content/adis/dsf) 1998;18:1-2010;33:6
Pharmacoepidemiology and Drug Safety
(http://www.pharmacoepi.org/publications/journal.cfm) 1998;7:1 – 2010;19:6

Generic Journals (with highest number of articles on adverse effects)[31]
Lancet (http://www.thelancet.com/) 1998;351:9095-2010;**375:9731**
New England Journal of Medicine (http://content.nejm.org/) 1998:338;1-2010;362:24
BMJ (www.bmj.com/) 1998;316:7124-2010;340:7759
Annals of Pharmacotherapy (www.theannals.com/) 1998;32:1- 2010:44:6

Diabetes Journals
Diabetes (http://diabetes.diabetesjournals.org/) 1998; 47:1 - 2010;59:6
Diabetes Care (http://care.diabetesjournals.org/) 1998;21:1-2010;33:6
Diabetes Research and Clinical Practice
(http://www.journals.elsevierhealth.com/periodicals/diab) 1998;39:1- 2010;89:1

Diabetic Medicine (http://www.wiley.com/bw/journal.asp?ref=0742-3071) 1998:15:1-2010:27;6

Referenced Monographs

Adverse Drug Reactions[653]
Host: Print edition/Book
Date range: 2006
Date searched: 09/07/10
Search results: Chapter on musculoskeletal disorders discusses fractures but does not refer to either rosiglitazone and pioglitazone. Brief mention of rosiglitazone and pioglitazone in respect to hypoglycaemia in chapter on endocrine and metabolic disorders.

AHFS drug information
Host: http://www.medicinescomplete.com
Date Range: June 2010
Date Searched: 09/07/10
Search results: Monographs for rosiglitazone and pioglitazone. Both contain section on fracture risk with 11 references in the rosigltiazone monograph and 7 references in the pioglitazone monograph. 12 references in total of which 4 were included references. 2 RCT fractures, 1 bone observational study, 1 fracture observational study

Clinical Pharmacology
Host: http://www.clinicalpharmacology.com
Date Range: Not stated
Date Searched: 09/07/10
Search Results: Monographs for rosiglitazone and pioglitazone. Both contain section on fractures with references. 3 references in total. 1 fracture RCT.

Davies Textbook of Adverse Drug Reactions[654]
Host: Print edition/Book
Date Range: 1998 5th edition
Date Searched: 09/07/10
Search Results: Organised by adverse effects. Chapter on muscle, bone and connective tissue disorders with section on fractures. No mention of any glitazones.

Emedicine
Host: http://www.emedicine.com
Date Range: Not stated
Date Searched: 09/07/10
Search Results: Provides clinical overviews of over 6,800 topics. Entry for diabetes. Mentions risk of fractures with glitazones and reference to Loke et al 2009 CMAJ

General Practice Notebook
Host: http://www.gpnotebook.co.uk
Date Searched: 09/07/10
Search Results: **O**nline encyclopaedia of medicine providing concise synopsis of the entire field of clinical medicine focussed on the needs of the General Practitioner.14 pages retrieved with rosiglitazone or pioglitazone in title. Monograph entries for rosiglitazone and entry for pioglitazone, text on fractures refers to Loke et al 2009 CMAJ.

Martindale: the complete drug reference

Host: http://www.medicinescomplete.com
Date Range: 22 Jun 2010: Martindale 3rd quarter 2010 update
Date Searched: 09/07/10
Search results: Evaluated information on drugs and medicines used throughout the world. Preparations summaries of more than 176,000 proprietary products from 40 countries or regions are included.Monograph entry for Rosiglitazone and Pioglitazone. Text on fractures in monograph of rosiglitazone contained 6 references and pioglitazone one reference. (7 in total), 4 included references 3 RCTs fracture (representing 2 studies), 1 bone observational study

Meylers's Side Effects Of Drugs The International Encyclopedia of Adverse Drug Reactions and Interactions. Fifteenth Edition.
Edited by: Jeffrey K. Aronson. Elsevier. 2006 and Pharmapendium
Date Searched: 20/08/10
Search results: 1 monograph for thiazolidinediones but no mention of fractures, bone density or osteoporosis

Side Effects of Drugs annual (SEDA)
Host: Book published by Elsevier
Edition: Aronson J. (editor) Side Effects of Drugs annual (SEDA) 31. 2009. San Diego, CA: Elsevier
Date searched: July 2010
Search results: Provides information relating to adverse drug reactions and interactions with references to published articles throughout text. Entry for thazolidinediones (glitazones) with section on fracture risk. Text discusses fracture risk and has 6 references. 5 included references, 2 fracture RCTs, 1 fracture observational, 2 bone RCTs

ToxEd
Host: https://members.toxed.com/login.aspx
Edition: July 2010
Date searched: 09/07/10
Search results: Monograph for thiazolidinediones with references. Section on adverse reactions but no mention of fractures.

Partially Referenced Monographs
Drug Safety Portal
Host: https://www.prosoftedc.com/aers/aers.html
Date Range:
Date Searched:
Search Results: **Contains FDA approved labeling for drugs.** Entry for rosiglitazone and pioglitazone. Fractures discussed in text. Refers to ADOPT study for rosi and PROactive study for pio. No citations for these studies given.

The Merck Manual
Host: http://www.merck.com/mmpe/index.html
Date Range: Content last modified August 2007
Date Searched: 07/07/10
Search Results: Entry for diabetes with links online to lexi-com drug information. Entry for rosiglitazone discusses possible risk of fractures, bibliography at end of text but references not cited in text, entry for pioglitazone discusses possible risk of fractures, bibliography at end of text but references not cited in text. 2 references on fracture risk, both includes bone observational studies.

Non-referenced Monographs

ABPI electronic Medicines Compendium (eMC)
Host: http://emc.medicines.org.uk
Date Searched: 09/07/10
Search Results: Package leaflet, medicines guide and summary of product characteristics for rosiglitazone and pioglitazone. Discusses evidence on fracture but text is not referenced.

Drugs.com, Drug Side Effects
Host: http://www.drugs.com/sfx
Date Searched: 09/07/10
Search results: Provides peer-reviewed information on more than 24,000 prescription drugs, over-the-counter medicines & natural products. Contains an entry for rosiglitazone and pioglitazone. Discusses possible side effects based on the literature but is not referenced. Refers to the ADOPT study.

Mosby's Medical Drug Reference[657]
Host: Print and Pharmapendium
Edition: 2006 (now discontinued)
Date Searched: August 2010
Search results: Monographs for rosiglitazone and pioglitazone but no mention of fractures.

Physicians Desk Reference (PDR)[658]
Host: Print edition: Physicians Desk Reference (PDR) 2010 64th edition. Oradell, N.J.:Medical Economics Co.
Edition: 2010, 64th edition
Date searched: 07/07/10
Search Results: Entry for rosiglitazone and pioglitazone. Fractures discussed in text. Refers to ADOPT study for rosi and PROactive study for pio. No citations for these studies given. Other references presented.

RxList: The Internet Drug Index
Host: http://www.rxlist.com
Date searched: 02/07/10
Search results: Monograph for rosiglitazone refers to the ADOPT study but the text is not referenced Monograph for pioglitazone refers to the PROACTIVE study but text is not referenced.

Rxmed: Pharmaceutical Information
Host: http://www.rxmed.com
Date searched: 02/07/10
Search Results: No entry for rosiglitazone or pioglitazone.

Referenced Lists of Adverse Effects

Litt's Drug Eruption Global Database
Host: http://www.drugeruptiondata.com/index.php
Date Range: Drugs and references added each month
Date Searched: 16/07/10
Search Strategy: Searched on drug names: rosiglitazone, pioglitazone
Search results: Entry for rosiglitazone and pioglitazone, fractures listed among adverse effects with 4 references for each drug (5 in total). 2 included studies, 1 RCT fracture, 1 observational study on fractures.

Non-referenced Lists of Adverse Effects

British National Formulary (BNF)
Host: http://www.bnf.org/
Edition: March 2010 No.58
Date Searched: 09/07/10
Search Results: Entry for rosiglitazone and pioglitazone. Lists fractures as a risk factor. No data or references presented.

Davis's Drug Guide
Host: http://www.drugguide.com/
Date Searched: 09/07/10
Search Results: Entry for rosiglitazone and pioglitazone. Adverse effects listed but not referenced.

Epocrates Online
Host: www.epocrates.com *(free trial online, subscription required)*
Date searched: 09/07/10
Search results: Monograph for rosiglitazone and pioglitazone. Lists serious and common adverse reactions. Fractures listed as serious adverse reaction for both rosiglitazone and pioglitazone. No text, data or references presented.

Modell's Drugs in current use and new drugs[656]
Edition: 2006
Date searched: 24 August 2010
Search results: Entry for rosiglitazone and pioglitazone but no mention of fractures.

Appendix F: **Included and excluded studies for case study systematic review in Chapters 11 and 12**

Table 15.21 Included studies for case study systematic review

Fracture RCTs
Study 1
DeFronzo RA. Actos Now for Prevention of Diabetes (ACT NOW). NCT00220961. Proceedings of the American Diabetes Association 68th Scientific Sessions: Late Breaking Clinical Studies. 2008 Jun 6–10; San Fransisco. Alexandria (VA) : The American Diabetes Association; 2008.
Tripathy D, Banerji MA, Bray GA, Buchanan TA, Clement S, Henry RR, et al. ACTos NOW for the Prevention of Diabetes (ACT NOW) study. Diabetologia. 2008.
Ramachandran A, Snehalatha C, Mary S, Selvam S, Kumar CKS, Seeli AC, et al. Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: Results of the Indian Diabetes Prevention Programme-2 (IDPP-2). Diabetologia. 2009 June;52(6):1019-26.
Study 2
Dormandy 2009 (PROACTIVE) Dormandy, J., M. Bhattacharya, et al. (2009). "Safety and Tolerability of Pioglitazone in High-Risk Patients with Type 2 Diabetes an Overview of Data from Proactive." Drug Safety 32: 187-202.
Dormandy J, Charbonnel B, Eckland DJ, et al (2006) Secondary Prevention of Macrovascular Events in Patients With Type 2 Diabetes in the PROactive Study (PROspective PioglitAzone Clinical Trial In MacroVascular Events): A Randomised Controlled Trial. Lancet 366: 1279-1289.
Study 3
Gerstein, H., R. Ratner, et al. (2010). "Effect of rosiglitazone on progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial." Circulation 121(10): 1176-87.
GSK (2008) A Phase III, 18 Month, Multicenter, Randomized, Double-Blind, Active Controlled Clinical Trial to Compare Rosiglitazone versus Glipizide on the Progression of Atherosclerosis in Subjects with Type 2 Diabetes Mellitus and Cardiovascular Disease (APPROACH) [study no AVD100521]. Brentford (UK): GlaxoSmithKine: 2008. http://www.gsk-clinicalstudyregister.com/
Study 4
GSK (2008) Comparison of the action of the fixed association rosiglitazone-metformin and the free association of metformin plus glicazide on B-cell function in patients suffering from type 2 diabetes not controlled by metformin alone. Open, randomised, multi-centre, parallel group study over 3 years [study no AVAF4001]. GlaxoSmithKline.
Study 5
GSK (2009) A randomized, parallel group, double-blind, multi-center study comparing the efficacy and safety of AVANDAMET and metformin after 80 weeks of treatment [study no AVT105913]. Brentford (UK): GlaxoSmithKine: 2009. http://www.gsk-clinicalstudyregister.com/
Study 6
GSK (2005) A randomised, multi-centre, phase IV, double-blind, parallel group study comparing the effects of 52 weeks administration of AVANDAMET and metformin plus sulphonylurea on change in HbA1c from baseline in overweight type 2 diabetics poorly controlled on metformin [study no AVM100264]. Brentford (UK): GlaxoSmithKine: 2006. http://www.gsk-clinicalstudyregister.com/
Study 7
GSK (2007) RAS Rosiglitazone and atherosclerosis study: A 1 year randomised, double blind, parallel group, placebo controlled study to evaluate the efficacy of rosiglitazone on the progression of intima-media thickness in the carotid artery in subjects with insulin resistance syndrome and/or type 2 diabetes mellitus [study no BRL-049653/334]. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/
Study 8
GSK (2008) Rosiglitazone and Plaque Study: A 12 Month Randomised, Double-blind,

Table 15.21 Included studies for case study systematic review

Placebo-controlled, Magnetic Resonance Imaging Study to Evaluate the Effect of Rosiglitazone on the Structure and Composition of Carotid Atherosclerotic Plaques in Subjects with Type 2 Diabetes Mellitus and Coexisting Vascular or hypertension [study no 49653/351]. Brentford (UK): GlaxoSmithKine: 2008. http://www.gsk-clinicalstudyregister.com/
Study 9
Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125-35.
GSK (2008) RECORD: Rosiglitazone evaluated for cardiac outcomes and regulation of glycaemia in diabetes: A long term, open label, randomised study in patients with type 2 diabetes, comparing the combination of rosiglitazone and either metformin or sulfonylurea with metformin plus sulfonylurea on cardiovascular endpoints and glycaemia [study no BRL-049653/231]. Brentford (UK): GlaxoSmithKine: 2008. http://www.gsk-clinicalstudyregister.com/
Study 10
Jain R, Osei K, Kupfer S, Perez AT, Zhang J. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy. 2006;26(10):1388-95.
Study 11
Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, et al. Rosiglitazone-associated fractures in type 2 diabetes - An analysis from a diabetes outcome progression trial (ADOPT). Diabetes Care. 2008 May;31(5):845-51.
GSK (2007) A randomized, double-blind study to compare the durability of glucose lowering and preservation of pancreatic beta-cell function of rosiglitazone monotherapy compared to metformin or glyburide/gibenclamide in patients with drug-naive, recently diagnosed type 2 diabetes mellitus [study no BRL-049653/048]. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/
Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. NEJM. 2006;355(23):2427-43.
Kahn SE, Haffner SM, Lachin JM, Herman WH, Zinman B, Holman RR, et al. Increased incidence of fractures in women who received rosiglitazone in ADOPT (A Diabetes Outcome Progression Trial). Diabetologia. 2007 Sep;50:0077.
Zinman B, Haffner SM, Herman WH, Holman RR, Lachin JM, Kravitz BG, et al. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. Journal of Clinical Endocrinology & Metabolism. Jan;95(1):134-42.
Study 12
Kaku K, Daida H, Kashiwagi A, Yamashina A, Yamazaki T, et al. (2009) Long-term effects of pioglitazone in Japanese patients with type 2 diabetes without a recent history of macrovascular morbidity. Current Medical Research and Opinion 25: 2925-2932.
Study 13
Nissen SE, Nicholls SJ, Wolski K, Nesto R, Kupfer S, Perez A, et al. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA : the journal of the American Medical Association. 2008;299(13):1561-73.
Study 14
Seufert J, Urquhart R. 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. Diabetes Res Clin Pract 2008;79:453-60.
Study 15
Tolman KG, Freston JW, Kupfer S, Alfonso P. Liver safety in patients with type 2 diabetes treated with pioglitazone: Results from a 3-year, randomized, comparator-controlled study in the US. Drug Safety. 2009;32(9):787-800.
Fracture Observational Studies
Study 1
Aubert R, Herrera V, Chen W, Haffner S, Pendergrass M (2010) Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes Diabetes, Obesity

Table 15.21 Included studies for case study systematic review

and Metabolism 12: 716-721.
Aubert R (2009) Thiazolidinedione Treatment Increases the Risk of Fracture. 69th Annual Scientific Sessions of the American Diabetes Association, . Morial Convention Center, New Orleans, Louisiana.
Study 2
Bilik D, McEwen L, Brown M, Pomeroy N, Kim C, et al. (2010) Thiazolidinediones and Fractures: Evidence from Translating Research into Action for Diabetes. J Clin Endocrinol Metab.
Study 3
Colhoun HM, GRP TSDRNE. Thiazolidinedione Associated Fractures Are Not Limited to Distal Fractures and Occur in Men as Well as Women; 2010 26-29 June; Orlando, Florida.
Study 4
Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM (2009) Thiazolidinediones and fractures in men and women. Arch Intern Med 169: 1395-1402.
Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM (2009) Thiazolidinediones and Fractures in Men and Women. Pharmacoepidemiology and Drug Safety 18: S193-S193.
Study 5
Douglas IJ, Evans SJ, Pocock S, Smeeth L (2009) The Risk of Fractures Associated with Thiazolidinediones: A Self-controlled Case-Series Study. Plos Medicine 6.
Study 6
Gau CS, Lin YS (2009) Use of Thiazolidinediones and the Risk of Fracture in Patients with Type II Diabetes in Taiwan. Pharmacoepidemiology and Drug Safety 18: S192-S193.
Study 7
Fracture diagnoses in patients receiving monotherapy with antidiabetic agents, including hand and foot fractures. GSK WEUSRTP2181. Brentford (UK): GlaxoSmithKine: 2008. http://www.gsk-clinicalstudyregister.com/
Study 8
Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, et al. (2010) Thiazolidinedione Use and the Longitudinal Risk of Fractures in Patients with Type 2 Diabetes Mellitus. Journal of Clinical Endocrinology & Metabolism 95: 592-600.
Study 9
Hsiao FY, Mullins CD (2010) The association between thiazolidinediones and hospitalisation for fracture in type 2 diabetic patients: a Taiwanese population-based nested case-control study. Diabetologia 53: 489-496.
Study 10
Irvine D, Wise L (2008) An analysis of glitazone use and small bone fractures using the General Practice Research Database (GPRD) database. Pharmacoepidemiology and Drug Safety 17: 397.
Study 11
Jones SG, Momin SR, Good MW, Shea TK, Patric K (2009) Distal Upper and Lower Limb Fractures Associated With Thiazolidinedione Use. American Journal of Managed Care 15: 491-496.
Study 12
Lee J, Choi NK, Jung SY, Kim YJ, Seong JM, et al. (2009) Evaluation of Thiazolidinedione Related Risk of Fracture. Pharmacoepidemiology and Drug Safety 18: S153-S153.
Study 13
Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, et al. (2009) Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone 45: 784-788.
Study 14
Meier C, Kraenzlin ME, Bodmer M, Jick SS, et al. (2008) Use of thiazolidinediones and fracture risk (ref art 594579 and 594582). Arch Intern Med 168: 820-825.
Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, et al. (2008) Thiazolidinedione use and osteoporotic fracture risk. Calcified Tissue International 82: S29.
Study 15
Rodriguez A, Cipres L, Tofe S, Polavieja P, Reviriego J (2010) Clinical evaluation of combined therapy for type 2 diabetes. Current Medical Research and Opinion 26: 1171-1183.

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Study 16
Solomon DH, Cadarette SM, Choudhry NK, Canning C, et al. (2009) A cohort study of thiazolidinediones and fractures in older adults with diabetes. J Clin Endocrinol Metab 94: 2792-2798.
Study 17
Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, et al. (2009) Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 339.
Study 18
Yamamoto M, Yamaguchi T, Yamauchi M, Yano S, Sugimoto T (2008) Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. Journal of Clinical Endocrinology & Metabolism 93: 1013-1019.
Bone Mineral Density RCTs
Study 1
BILEZIKIAN J, BORGES J, PANELO A, CHANG C, NINO A, et al. Effects of Rosiglitazone/Metformin FDC on BMD after 80 Weeks of Treatment in Drug-Naive T2DM Subjects; 2010 26-29 June; Orlando, Florida.
Study 2
Glintborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP (2008) Association of pioglitazone treatment with decreased bone mineral density in obese premenopausal patients with polycystic ovary syndrome: a randomized, placebo-controlled trial. J Clin Endocrinol Metab 93: 1696-1701.
Glintborg D, Andersen M, Hagen C, Hermann A (2007) Pioglitazone treatment significantly decreased bone mineral density in a randomised placebo-controlled study in patients with polycystic ovary syndrome. Calcified Tissue International 80: S161.
Glintborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP (2008) Association of Pioglitazone Treatment with Decreased Bone Mineral Density in Obese Premenopausal Patients with Polycystic Ovary Syndrome: A Randomized, Placebo-Controlled Trial. 10th European Congress of Endocrinology (ECE 2008), Berlin (Germany).
Study 3
Grey A, Bolland M, Gamble G, Wattie D, et al. (2007) The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial (ref art 574984). J Clin Endocrinol Metab 92: 1305-1310.
Grey A, Bolland M, Gamble G, Wattie D, Home A, et al. (2007) The peroxisome-proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: A randomized, controlled trial. Bone 40: S133-S133.
Reid IR, Grey AB (2009) TZDs and bone. 20th World Diabetes Congress : abstr 0127, . Montreal: Available from: URL: http://www.worlddiabetescongress.org/ . Odense University Hospital, Dept. of Endocrinology, Odense C, Denmark.
Study 4
GSK (2005) A six-month double-blind, randomised, parallel-group study to compare the effect of oral rosiglitazone (less than or equal to 4mg bd) versus oral glibenclamide therapy (less than or equal to 15 mg daily) on body fat distribution when administered to subjects with type 2 diabetes mellitus [study no BRL-049653/369]. GlaxoSmithKline.
Study 5
Sui HG, X.-s. Geng, X.-q. (2009) Effects of Metformin and Rosiglitazone on Bone Mineral Density in Newly Diagnosed Male Patients with Type 2 Diabetes Mellitus CHINESE JOURNAL OF PREVENTION AND CONTROL OF CHRONIC NON COMMUNICABLE DISEASES 17: 577-578.
Observational Studies on Bone Mineral Density
Study 1
Carteni B, D'Adamo M, Micchelini B, Guglielmi V, Donadel G, et al. (2008) Effect of thiazolidinediones on bone metabolism in diabetic patients. Diabetologia 51: S370-S371.
D'Adamo M, Carteni B, Micchelini B, Guglielmi V, Donadel G, et al. (2008) Effect of thiazolidinediones on bone metabolism in diabetic patients. Diabetes 57: A599-A599.

Table 15.21 Included studies for case study systematic review

Study 2
Li HC, R. Cai, H. Wu, G. Lv, Z. Sheng, C. Cheng, X. Li, F. Yu, Y. (2010) The effect of thiazolidinediones on bone mineral density in Chinese older patients with type 2 diabetes JOURNAL OF BONE AND MINERAL METABOLISM 28: 77-81.
Study 3
Schwartz A, Sellmeyer D, Vittinghoff E (2006) Thiazolidinedione Use and Bone Loss in Older Diabetic Adults. J Clin Endocrin Metab 91: 3349-3354.
Schwartz AV, Sellmeyer DE, Feingold KR, Strotmeyer E, Resnick HE, et al. (2002) Thiazolidinedione (TZD) use and bone density in older adults with diabetes. Diabetes 51: 961.
Schwartz AV, Sellmeyer DE, Vintinghoff E, Palermo L, Feingold KR, et al. (2005) Thiazolidinedione (TZD) use and change in bone density in older diabetic adults. Diabetes 54: A41-A41.
Study 4
Yaturu S, Bryant B, Jain SK (2007) Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men (ref art 576504). Diabetes Care 30: 1574-1576.
Yaturu S (2006) Decreased bone mineral density with thiazolidinediones. Journal of Bone and Mineral Research 21: S178-S178.

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
Fracture RCTs	
DeFronzo RA. Actos Now for Prevention of Diabetes (ACT NOW). NCT00220961. Proceedings of the American Diabetes Association 68th Scientific Sessions: Late Breaking Clinical Studies. 2008 Jun 6–10; San Fransisco. Alexandria (VA) : The American Diabetes Association; 2008	No data from abstract. Loke et al 2008[265] contacted authors.
Tripathy D, Banerji MA, Bray GA, Buchanan TA, Clement S, Henry RR, et al. ACTos NOW for the Prevention of Diabetes (ACT NOW) study. Diabetologia. 2008.	Not enough data
Seufert J, Urquhart R. 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. Diabetes Res Clin Pract 2008;79:453-60.	No data from abstract. Loke et al 2008[265] contacted authors.
Abe M, Okada K, Kikuchi F, Matsumoto K. Clinical investigation of the effects of pioglitazone on the improvement of insulin resistance and blood pressure in type 2-diabetic patients undergoing hemodialysis. *Clinical Nephrology* 2008;70:220-28	No fractures in both study arms
Abe M, Okada K, Maruyama T, Maruyama N, Soma M, Matsumoto K. Clinical effectiveness and safety evaluation of long-term pioglitazone treatment for erythropoietin responsiveness and insulin resistance in type 2 diabetic patients on hemodialysis. *Expert Opinion on Pharmacotherapy* 2010;11:1611-20.	No fractures in both study arms
Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, Placebo-Controlled Trial of Pioglitazone in Nondiabetic Subjects With Nonalcoholic Steatohepatitis. *Gastroenterology* 2008;135:1176-84.	No fractures in both study arms
American Diabetes Association 2010 Diabetes drug rosiglitazone not associated with increased risk of death, stroke, or heart attacks in BARI 2D study?	Compares insulin sensitising drugs with insulin providing drugs. No separate analysis for rosiglitazone or pioglitazone presented.
Beck-Nielsen. H. Results of the RECORD1 Trial. 20th World Diabetes Congress : abstr. 0125, 18 Oct 2009. Available from: URL: http://www.worlddiabetescongress.org/ . Odense University Hospital, Dept. of Endocrinology, Odense C, Denmark	Rosiglitazone group had increased upper and distal lower limb fractures (no data)
Gruntmanis U, Fordan S, Ghayee HK, Abdullah SM, See R, Ayers CR, et al. The Peroxisome Proliferator-Activated Receptor-gamma Agonist Rosiglitazone Increases Bone Resorption in Women with Type 2 Diabetes: A Randomized, Controlled Trial. *Calcified Tissue International* 2010;86:343-49.	Less than 12 months follow-up
A 16 week randomized, double-blind, parallel group study to evaluate the efficacy and safety of a new medication (GSK523338) to lower LDL-c and HbA1c in subjects with type 2 diabetes mellitus. GSK AVS101946. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/	Compares different dosages of rosiglitazone

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
A 24 week randomized, double-blind, double-dummy, multicenter study to compare the efficacy of formulation X and AVANDIA (8mg OD) in subjects with diabetes mellitus. GSK AXR100723. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/	No data on control
A 24 week randomized, double-blind, double-dummy, multicenter study to evaluate the safety, efficacy and tolerability of oral formulation X and AVANDIA (4mg BD) in patients with type 2 diabetes. GSK BRL-049653/183. Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	No data on control
A randomized, open-label, parallel group study to evaluate the management of rosiglitazone-related fluid retention by investigating the effect of diuretics on plasma volume in subjects with type 2 diabetes mellitus treated for twelve weeks with rosiglitazone 4mg bd in addition to background anti-diabetic agents. GSK BRL-049653/342. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/ Karalliedde J, Buckingham R, Starkie M, Lorand D, Stewart M, Viberti G. Effect of various diutretic treatments on rosiglitazone-induced fluid retention. J Am Soc Neph 2006;17(12):3482-90.	Adverse effects not listed by rosiglizone treatment and control
A randomized, double blind, placebo controlled, parallel group study to assess the safety and efficacy of three dose levels of rosiglitazone maleate in the treatment of chronic plaque psoriasis. GSK BRL-049653/330. Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	Compares different dosages of rosiglitazone
A randomized, double-blind, placebo-controlled, parallel group study to assess the safety and efficacy of rosiglitazone maleate in the treatment of chronic plaque psoriasis. GSK BRL-049653/331. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/	Combination of drugs used, not RSG alone
A 16 week randomized, double blind, parallel group, placebo-controlled study to evaluate the effect of rosiglitazone on myocardial glucose uptake in subjects with type 2 diabetes mellitus and stable coronary heart disease. GSK BRL-049653/352. Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	Less than 12 months follow-up
A 24-week, double blind, double dummy, randomized, parallel group study to investigate the effects of rosigliazone (extended release tablets), donepezil, and placebo as monotherapy on cognition and overall clinical response in APOE 4-stratified subjects with mild-to-moderate Alzheimer's disease (REFLECT-1). GSK AVA105640. Brentford (UK): GlaxoSmithKine: 2008. http://www.gsk-clinicalstudyregister.com/	Mild to moderate Alzheimer's disease and less than 12 months follow-up
A 54-week, double-blind, randomized, placebo-controlled, parallel-group study to investigate the effects of rosiglitazone (extended release tablets) as adjunctive therapy to acetylcholinesterase inhibitors on cognition and overall clinical response in APOE 4-stratified subjects with mild to moderate Alzheimer's disease (REFLECT-3). GSK AVA102670. Brentford (UK): GlaxoSmithKine: 2009. http://www.gsk-clinicalstudyregister.com/	Mild to moderate Alzheimer's disease
A 54-week, double-blind, randomized, placebo-controlled, parallel-group study to investigate the effects of rosiglitazone (extended release tablets) as adjunctive therapy to donepezil on cognition and overall clinical response in APOE 4-stratified subjects with mild to moderate Alzheimer's disease (REFLECT-2). GSK AVA102672. Brentford (UK): GlaxoSmithKine: 2009. http://www.gsk-clinicalstudyregister.com/	Mild to moderate Alzheimer's disease
A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Control, Clinical Evaluation of Insulin Plus Rosiglitazone (2mg and 4mg) Compared to Insulin Plus Placebo for 24 Weeks in Subjects with Type 2	Less than 12 months follow-up

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
Diabetes Mellitus Who Are Inadequately Controlled On Insulin. GSK BRL-049653/347. Brentford (UK): GlaxoSmithKine: 2006. http://www.gsk-clinicalstudyregister.com/ Hollander P, Weston WM, Huang C, Chou H, and Porter LE. Low dose rosiglitazone significantly improves glycemic control without increasing adverse events in patients with T2DM not well controlled on insulin. Diabetes 2005;54(suppl 1):A3-4. Abstract 12-OR.	
A Phase III, 24 week, multi-centre, double-blind, randomized, parallel group study comparing the effects of Avandamet (8mg/200mg). Plus insulin to placebo plus insulin on change in Hba1c, in subjects with type 2 diabetes starting insulin therapy. GSK SB-712753/009. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/ Home P, Bailey C, Donaldson J, Chen H, Stewart M. A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone+metformin therapy when starting insulin therapy in people with type 2 diabetes. Diabetic Med. 2007	Less than 12 months follow-up
A phase III, 24 week, multi-centre, randomisedm, double-blind, parallel group, dose escalation study of Advandamet (rosiglitazone/metformin) and high dose metformin monotherapy in subjects with poorly controlled type 2 diabetes mellitus. GSK SB-712753/002. Brentford (UK): GlaxoSmithKine: 2007. http://www.gsk-clinicalstudyregister.com/ Bailey C, Bagdonas A, Rubes J, McMorn S, Donaldson J, Biswas N, Stewart M. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes. Clinical Therapeutics. 2005;27(10): 1548-61.	Less than 12 months follow-up
Hamann A, Garcia-Puig J, Paul G, Donaldson J, Stewart M. Comparison of fixed-dose rosiglitazone/metformin combination therapy with sulphonylurea plus metformin in overweight individuals with Type 2 diabetes inadequately controlled on metformin alone. Exp Clin Endocrinol Diabetes 2008; 116: 6– 1 3	Related publication to GSK AVM100264 but contains no fracture data
Hedblad B, Zambanini A, Nilsson P, Janzon L, Berglund G. Rosiglitazone and carotid IMT progression rate in a mixed cohort of patients with type 2 diabetes and the insulin resistance syndrome: main results from the Rosiglitazone Atherosclerosis Study. J Intern Med. 2007 Mar;261(3):293-305.	Related publication to GSK BRL-049653/334 but contains no fracture data
Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Dargie H, Komajda M, Gubb J, Biswas N, Jones NP. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD): study design and protocol. Diabetologia. 2005 Sep;48(9):1726-35.	Related publication to GSK BRL-049653/231 but contains no fracture data
Home PD, Jones NP, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Komajda M, Curtis P; RECORD Study Group. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med. 2007 Jun;24(6):626-34.	Related publication to GSK BRL-049653/231 but contains no fracture data
Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ; RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. N Engl J Med. 2007 Jul 5;357(1):28-38.	Related publication to GSK BRL-049653/231 but

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
	contains no fracture data
Kahn SE, Zinman B, Haffner SM, O'Neill MC, Kravitz BG, Yu D, Freed MI, Herman WH, Holman RR, Jones NP, Lachin JM, Viberti GC; ADOPT Study Group. Obesity is a major determinant of the association of C-reactive protein levels and the metabolic syndrome in type 2 diabetes. Diabetes. 2006 Aug;55(8):2357-64.	Related publication to GSK BRL-049653/048 but contains no fracture data
Karalliedde 200 1. Karalliedde J, Buckingham RE. Choice of monotherapy in newly diagnosed type 2 diabetic patients: Clinical perspective of ADOPT. *Therapy* 2007;4:535-40. 2. Karalliedde J, Buckingham RE. Thiazolidinediones and their fluid-related adverse effects: Facts, fiction and putative management strategies. *Drug Safety* 2007;30:741-53.	ADOPT trial but no fracture data
Komajda M, Curtis P, Hanefeld M, Beck-Nielsen H, Pocock SJ, Zambanini A, Jones NP, Gomis R, Home PD; RECORD Study Group. Effect of the addition of rosiglitazone to metformin or sulfonylureas versus metformin/sulfonylurea combination therapy on ambulatory blood pressure in people with type 2 diabetes: a randomized controlled trial (the RECORD study). Cardiovasc Diabetol. 2008 Apr 24;7:10.	Related publication to GSK BRL-049653/231 but contains no fracture data
Mayor S. Rosiglitazone associated with slower monotherapy failure... International Diabetes Federation 19th World Diabetes Congress, Cape Town, South Africa, 3rd-7th December 2006. *British Journal of Diabetes & Vascular Disease* 2006;6:290-90	ADOPT trial but no fracture data
Nesto RW. Effect of rosiglitazone versus glipizide on pregression of coronary atherosclerosis in patients with type 2 diabetes and coronary artery disease. American Heart Association Scientific Sessions. November 12, 2008, New Orleans, LA. http://directnews.americanheart.org/extras/pdfs/approach_slides.pdf	Related publication to GSK AVD100521 but contains no fracture data
Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating patients with T2DM. *Current Medical Research and Opinion* 2009;25:2915-23.	Less than 12 months follow-up
Ratner RE, Cannon CP, Gerstein HC, Nesto RW, Serruys PW, Kolatkar NS, Kravitz BG, Zalewski A, Fitzgerald PJ; APPROACH Study Group. Assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history (APPROACH): study design and baseline characteristics. Am Heart J. 2008; 156(6): 1074-9.	Related publication to GSK AVD100521 but contains no fracture data
Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, Neuschwander-Tetri BA, Lavine JE, Tonascia J, Unalp A, Van Natta M, Clark J, Brunt EM, Kleiner DE, Hoofnagle JH, Robuck PR; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010 May 6;362(18):1675-85.	Nonalcoholic steatohepatitis
Scheen AJ, Tan MH, Betteridge DJ, Birkeland K, Schmitz O, et al. (2009) Long-term glycaemic effects of pioglitazone compared with placebo as add-on treatment to metformin or sulphonylurea monotherapy in PROactive (PROactive 18). Diabetic Medicine 26: 1242-1249.	subgroup analysis of data in Dormandy 2009
Tripathy D, Banerji MA, Bray GA, Buchanan TA, Clement S, Henry RR, et al. ACTos NOW for the Prevention of Diabetes (ACT NOW) study. *Diabetologia* 2008.	Impaired glucose intolerance (ACTos NOW)

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, Haffner SM, Levy D, Lachin JM, Berry RA, Heise MA, Jones NP, Freed MI. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care. 2002 Oct;25(10):1737-43.	Related publication to GSK BRL-049653/048 but contains no fracture data
Viberti GC KS, Haffner S, Herman W, Holman R, Lachin J, Zinman B, Heise MJN, Kravitz B, O'Neill C, ADOPT Study Group. Results of the ADOPT trial In: *Diabetic Medicine 23 (Suppl. 4): 43 (plus oral presentation) abstr. 97, Dec 2006 . King's College London School of Medicine, London, England; GlaxoSmithKline, King of Prussia, Pennsylvania, USA* 2006.	ADOPT trial but no fracture data
Viberti G, Lachin J, Holman R, Zinman B, Haffner S, Kravitz B, Heise MA, Jones NP, O'Neill MC, Freed MI, Kahn SE, Herman WH; for the ADOPT Study Group. A Diabetes Outcome Progression Trial (ADOPT): baseline characteristics of Type 2 diabetic patients in North America and Europe. Diabet Med. 2006 Dec;23(12):1289-94.	Related publication to GSK BRL-049653/048 but contains no fracture data
Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI; ADOPT Study Group. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. Diabetes. 2004 Dec;53(12):3193-200.	Related publication to GSK BRL-049653/048 but contains no fracture data
Zinman B, Haffner SM, Herman WH, Holman RR, et al. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* 2010;95:134-42.	Combination of drugs used, not RSG alone
Fractures observational studies	
Giorgadez	No actual description of numbers of fractures
An open-label extension study of the long-term safety and efficacy of rosiglitazone extended-release (RSG XR) as adjunctive therapy to acetylcholinesterase inhibitors in subjects with mild-to-moderate Alzheimer's desease (REFLECT-4). GSK AVA102675. Brentford (UK): GlaxoSmithKine: 2009. http://www.gsk-clinicalstudyregister.com/	no control arm
An open-label extension study of the long-term safety and efficacy of rosiglitazone extended release (RSG XR) in subjects with mild to moderate Alzheimer's disease (REFLECT-5). GSK AVA102677. Brentford (UK): GlaxoSmithKine: 2009. http://www.gsk-clinicalstudyregister.com/	no control arm
AVA-177: Avandia in daily practice. GSK 49653/177 (AVA-177/2000). Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	no control arm
AVA-295: Avandia in daily practice GSK 49653/295 (AVA-295/2001). Brentford (UK): GlaxoSmithKine: 2006. http://www.gsk-clinicalstudyregister.com/	no control arm
AVANTAGE: Monitoring a patient cohort with Avandia – Evaluation of safety data. GSK ROSF4003 (101732). Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	no control arm
A 24-week open study to investigate the effectiveness, tolerability and	Crossover study

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
efficacy to reach HbA1c-goals of a new oral antidiabetic drug (Avandamet) in patients with type 2 diabetes with inadequate glycemic control under metformin monotherapy. GSK 712753/100420 (ZIEL). Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	
The association between exposure to spironolactone or amiloride and fracture risk among subjects treated with thiazolidinediones. GSK WWE113332/WEUSKOP4103. Brentford (UK): GlaxoSmithKine: 2005. http://www.gsk-clinicalstudyregister.com/	Does not have non-TZD comparator group
Influence of guidance-compliant treatment of diabetes mellitus type 2 on effectiveness and costs (LEADIT/ADIT). GSK AVA371. Brentford (UK): GlaxoSmithKine: 2006. http://www.gsk-clinicalstudyregister.com/	Compares guidelines vs. no guidelines, and not TZD vs. no TZD
Spanheimer 2007 Observation of an increased incidence of fractures in female patients who received long-term treatment with ACTOS (pioglitazone HOI) tablets for type 2 diabetes mellitus. http://www.fda.gov/medwatch/safety/ 2007/Actosmar0807.pdf	Aggregated data from Takeda RCTs - no study level data
Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia* 2005;48:1292-99.	No specific TZD data
Melton LJIII, Leibson CL, Achenbach SJ, Therneau TM, Khosla S (2008) Fracture risk in type 2 diabetes: Update of a population-based study. Journal of Bone and Mineral Research 23: 1334-1342.	Had risk data but was excluded as it was unclear what the control group was and how the risk was statistically calculated.
Monami M, Cresci B, Colombini A, Pala L, Balzi D, et al. (2008) Bone Fractures and Hypoglycemic Treatment in Type 2 Diabetic Patients A case-control study. Diabetes Care 31: 199-203	No data
Bone Mineral Density RCTs	
Sui H, Guo XS, Geng XQ. Effects of Metformin and Rosiglitazone on Bone Mineral Density in Newly Diagnosed Male Patients with Type 2 Diabetes Mellitus *Chinese Journal of Prevention and Control of Chronic Non Communicable Diseases* 2009;17:577-8.	Chinese language
BANERJI MA, SIGNAEVSKI M, LEBOVITZ HE (2010) Changes in Bone Mineral Density in Patients with Type 2 Diabetes Treated with Rosiglitazone vs. Glypizide. A Randomized Trial. American Diabetes Association 70th Scientific Session. Orlando, Florida.	Risk data available but format not suitable for meta-analysis.
Schindler KR, A. Tura, A. Gmeinhardt, B. Touzeau-Romer, V. Haider, D. Pacini, G. Ludvik, B. (2009) The Effect of Rosiglitazone on Insulin Sensitivity, Beta Cell Function, Bone Mineral Density, and Body Composition in HIV-positive Patients on Highly-active Antiretroviral Therapy (HAART) HORMONE AND METABOLIC RESEARCH 41: 573-579.	This has data but is on HIV patients receiving a variety of different drugs.
Strotmeyer ES, Boudreau RM, Marshall LM, Schwartz AV, Bauer DC, et al. (2008) Higher Bone Mineral Density Loss in Older Men with Diabetes: The Osteoporotic Fractures in Men Study. Journal of Bone and Mineral	Risk data not usable in meta-analysis

Table 15.22 Excluded studies for case study systematic review

Study	Reason for exclusion
Research 23: S59.	
Tsagareli M, Giorgadze E, Jikurauli N, Chachibaia V, Lomidze M, et al. (2009) Bone turnover and bone mineral density in type2 diabetes patients treated with rosiglitazone. Bone -New York- 44 S386.	Before and after study with no controls
Barbour KE, Zmuda JM, Strotmeyer ES, Horwitz MJ, Boudreau R, Evans RW, et al. Correlates of Trabecular and Cortical Volumetric Bone Mineral Density of the Radius and Tibia in Older Men: The Osteoporotic Fractures in Men Study. *Journal of Bone and Mineral Research* 2010;25:1017-28.	Does not actually compare TZD vs. non TZD
Glowczewski JE, Munn AL, Thomas ML, Brunner JE. Incidence and Clinical Significance of Thiazolidinedione Induced Edema and Weight Gain in Type 2 Diabetic Patients. *ASHP Midyear Clinical Meeting* 2001;36:P-427E.	No comparative data
Ing SW, Osei K, Gaillard T, Sinnott LT, Jackson RD. Rosiglitazone-induced Change in Bone Mineral Density among African Americans with Type 2 Diabetes Mellitus or Impaired Glucose Tolerance. *Journal of Bone and Mineral Research* 2008;23:S321-S21.	Does not actually compare TZD vs. non TZD

Appendix G: **MEDLINE and EMBASE searches tested in Chapter 12**

MEDLINE (OVID: 1996 to July Week 1 2010)
Searched: 21/07/10
Original Search
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

Badgett et al 1999[427, 428]
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. ((ae OR co OR po OR de).fs OR case report/) AND humans/
4. 1 AND 2 AND 3

BMJ Clinical Evidence[432]
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. (ae OR to OR po OR co).fs. OR (safe OR safety).ti,ab. OR side effect$.ti,ab. OR ((adverse OR undesirable OR harm$ OR serious OR toxic) adj3 (effect$ OR reaction$ OR event$ OR outcome$)).ti,ab. OR exp product surveillance, postmarketing/ OR exp adverse drug reaction reporting systems/ OR exp clinical trials, phase iv/ OR exp poisoning/ OR exp substance-related disorders/ OR exp drug toxicity/ OR exp abnormalities, drug induced/ OR exp drug monitoring/ OR exp drug hypersensitivity/ OR (toxicity OR complication$ OR noxious OR tolerability).ti,ab. OR exp Postoperative Complications/ OR exp Intraoperative Complications/
4. 1 AND 2 AND 3

Buckingham et al 2005a[434] Without the quick filter (hedge)
1. thiazolidinediones/ae, ct, po, to
2. exp fractures, bone/ci, ep, et OR bone density/ab, ci, ep, et, tm OR exp osteoporosis/ab, ci, ep, et,tm
3. 1 AND 2

Buckingham et al 2005b[434] With the quick filter (hedge)
1. thiazolidinediones/ae, ct, po, to
2. exp fractures, bone/ci, ep, et OR bone density/ab, ci, ep, et, tm OR exp osteoporosis/ab, ci, ep, et,tm
3. case control studies/ OR cohort studies/ OR risk/
4. 1 AND 2 AND 3

Golder et al 2006a[360] Most sensitive search strategy
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR

pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. exp Fractures, Bone/ci OR bone density/ci OR exp osteoporosis/ci
4. (ae OR co OR de).fs
5 (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab
5. 1 AND 2 AND (3 OR 4 OR 5)

Golder et al 2006b[360] Most sensitive search strategy excluding use of specified adverse effects
1. thiazolidinediones/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR glustin.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp Fractures, Bone/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. (ae OR co OR de).fs
4 (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab
5. 1 AND 2 AND (3 OR 4)
The addition of the fracture terms means that the Golder et al 2006a[360] 'most sensitive search strategy' is essentially the same as the Golder et al 2006b[360] 'most sensitive search strategy excluding use of specified adverse effects'.

Wieland et al 2005a[121, 430] Exploding MeSH term search
1. humans/ AND journal article.pt
2. exp fractures, bone/ OR bone density/ OR exp osteoporosis/
3. thiazolidinediones/
4. exp risk/ OR exp follow-up studies/ OR exp case-control studies/
5. 1 AND 2 AND 3 AND 4

Wieland et al 2005b[121, 430] Maximise Precision: MeSH term search with major topics and subheadings
1. humans/ AND journal article.pt
2. *Fractures, Bone/ OR * bone density/ OR *osteoporosis/
3. thiazolidinediones/
4. risk/ OR risk factors/ OR follow-up studies/ OR odds ratio/
5. 1 AND 2 AND 3 AND 4

Wieland et al 2005c[121, 430] MeSH term search without study methodology terms
1. humans/ AND journal article.pt
2 *Fractures, Bone/ OR * bone density/ OR *osteoporosis/
3. thiazolidinediones/
4. 1 AND 2 AND 3

Wieland et al 2005d[121, 430] Text word search with automatic term mapping
1. humans/ AND journal article.pt
2. exp fractures, bone OR fracture.tw OR fractures.tw OR exp bone and bones/ OR bone.tw OR bones.tw OR bmd.tw OR osteoporosis.tw
3. rosiglitazone.tw. OR avandia.tw. OR avandaryl.tw OR avaglim.tw. OR avandamet.tw. OR glitazone.tw. OR glitazones.tw OR thiazolidinediones.tw. OR tzd.tw OR ppar gamma agonist.tw. OR peroxisome proliferator activated receptor gamma agonist.tw. OR pioglitazone.tw. OR actos.tw. OR actoplus.tw OR duetact.tw OR competact.tw. OR glustin.tw. OR nyracta.tw. OR venvia.tw.
4. exp risk/ OR risk.tw OR follow-up.tw OR exp epidemiology/ OR epidemiology.tw OR

epidemiologic.tw
5. 1 AND 2 AND 3 AND 4

Wieland et al 2005e[121, 430] Text word search with truncation and double quotes
1. humans/ AND journal article.pt
2. fracture$.tw OR bone$.tw OR bmd.tw OR osteoporo$.tw
3. rosiglitazone$.tw. OR avandia.tw. OR avandaryl.tw OR avaglim.tw. OR avandamet.tw. OR glitazone$.tw. OR thiazolidinedion$.tw. OR tzd.tw OR ppar gamma agonist$.tw. OR peroxisome proliferator activated receptor gamma agonist$.tw. OR pioglitazone$.tw. OR actos.tw. OR actoplus.tw OR duetact.tw OR competact.tw. OR glustin.tw. OR nyracta.tw. OR venvia.tw.
4. risk.tw OR epidemiolog$.tw
5. 1 AND 2 AND 3 AND 4

Wieland et al 2005f[121, 430] Text word search without study methodology text words
1. humans/ AND journal article.pt
2. fracture$.tw OR bone$.tw OR bmd.tw OR osteoporo$.tw
3. rosiglitazone$.tw. OR avandia.tw. OR avandaryl.tw OR avaglim.tw. OR avandamet.tw. OR glitazone$.tw. OR thiazolidinedion$.tw. OR tzd.tw OR ppar gamma agonist$.tw. OR peroxisome proliferator activated receptor gamma agonist$.tw. OR pioglitazone$.tw. OR actos.tw. OR actoplus.tw OR duetact.tw OR competact.tw. OR glustin.tw. OR nyracta.tw. OR venvia.tw.
4. 1 AND 2 AND 3

EMBASE (OVID: 1996 to 2010 Week 28)
Searched: 21/07/10

Original Search
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af. OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. 1 AND 2

BMJ Clinical Evidence[432]
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. (ae OR si OR to OR co).fs. OR (safe OR safety).ti,ab. OR side effect$.ti,ab. OR ((adverse OR undesirable OR harm$ OR serious OR toxic) adj3 (effect$ OR reaction$ OR event$ OR outcome$)).ti,ab. OR exp adverse drug reaction/ OR exp drug toxicity/ OR exp intoxication/ OR exp drug safety/ OR exp drug monitoring/ OR exp drug hypersensitivity/ OR exp postmarketing surveillance/ OR exp drug surveillance program/ OR exp phase iv clinical trial/ OR (toxicity OR complication$ OR noxious OR tolerability).ti,ab. OR exp postoperative complication/ OR exp Peroperative Complication/
4. 1 AND 2 AND 3

Golder et al 2006a[360] Most sensitive search strategy
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator

activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. exp fracture/si OR exp osteoporosis/si
4. (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab
5. 1 AND 2 AND (3 OR 4)

Golder et al 2006b[360] Most sensitive search strategy excluding use of specified adverse effects
1. 2,4 thiazolidinedione derivative/ OR exp glitazone derivative/ OR rosiglitazone$.af. OR avandia.af. OR avandaryl.af OR avaglim.af. OR avandamet.af. OR glitazone$.af. OR thiazolidinedion$.af. OR tzd.af OR ppar gamma agonist$.af. OR peroxisome proliferator activated receptor gamma agonist$.af. OR pioglitazone$.af. OR actos.af. OR actoplus.af OR duetact.af OR competact.af. OR nyracta.af. OR venvia.af. OR 111025 46 8.rn. OR 122320 73 4.rn.
2. exp fracture/ OR fracture$.af OR bone density/ OR bone$.af OR bmd.af OR exp osteoporosis/ OR osteoporo$.af
3. 2,4 thiazolidinedione derivative/ae,to OR exp glitazone derivative/ae,to
4. (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab
5. 1 AND 2 AND (3 OR 4)

Legend
MEDLINE Subheadings: ab=Abnormalities, ae=Adverse Effects, co=Complications, ct=contraindications, ci=Chemically Induced, de=Drug Effects, ep=Epidemiology, et=Etiology, po=Poisoning, to=Toxicity, tm=Transmission
EMBASE Subheadings: ae=Adverse Drug Reaction, co=Complication, to=Drug Toxicity, si=Side Effect
Fields Searched: ab=abstract, af= all fields, fs=floating subheading, rn=registry number, ti=title

Appendix H: **Published adverse effects search filters for MEDLINE and EMBASE for Chapters 12 and 13**

Search Strategies excluding specified named adverse effects terms
MEDLINE
Badgett[427, 428]
(ae OR co OR po OR de).fs OR CASE REPORT/ and HUMAN/ (no need to preselect specific adverse drug reactions)

Golder[360]
Most sensitive search strategy excluding use of specified named adverse effects
(ae OR co OR de).fs OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)).ti,ab

EMBASE
Golder[360]
Most sensitive search strategy excluding use of specified named adverse effects
DRUG/ae, to OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab

Search Strategies including specified named adverse effects terms
MEDLINE
BMJ Clinical Evidence[432]
Specified named adverse effect AND (ae OR to OR po OR co).fs. OR (safe OR safety).ti,ab. OR side effect$.ti,ab. OR ((adverse OR undesirable OR harm$ OR serious OR toxic) adj3 (effect$ OR reaction$ OR event$ OR outcome$)).ti,ab. OR exp product surveillance, postmarketing/ OR exp adverse drug reaction reporting systems/ OR exp clinical trials, phase iv/ OR exp poisoning/ OR exp substance-related disorders/ OR exp drug toxicity/ OR exp abnormalities, drug induced/ OR exp drug monitoring/ OR exp drug hypersensitivity/ OR (toxicity OR complication$ OR noxious OR tolerability).ti,ab. OR exp Postoperative Complications/ OR exp Intraoperative Complications/

Buckingham[434]
Step 1. Source of harm with possible subheadings
Adverse Effects (AE), *Mortality (MO)* (not always an option), Contraindications (CT) Poisoning (PO), Toxicity (TO)
Step 2. Disease or disorder/outcome with possible subheadings
Abnormalities (AB), Chemically Induced (CI), Epidemiology (EP), *Etiology (ET)* Mortality (MO), Transmission (TM)
Step 3. Combine Previous Searches with a Quality Filter
Combine the first two search statements, using the boolean operator "and" and combine the final subject statement with the quick filter (hedge) below.
case control studies/ OR cohort studies/ OR risk/

Golder[360]
Most sensitive search strategy
Specified named adverse effects/ci OR (ae OR co OR de).fs OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)).af

Wieland[121, 430]
Exploding MeSH term search
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND breast neoplasms [mh] AND contraceptives, oral [mh] AND (risk [mh] OR follow-up studies [mh] OR case-control studies [mh])

Maximise Precision: MeSH term search with major topics and subheadings

1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast neoplasms” [majr:noexp] AND (contraceptives, oral [mh:noexp] OR contraceptives, oral/pharmacology [mh] OR contraceptives, oral/therapeutic use [mh] OR estrogens/therapeutic use [mh] OR contraceptives, oral/adverse effects [mh]) AND (risk [mh:noexp] OR risk factors [mh:noexp] OR follow-up studies [mh:noexp] OR odds ratio [mh:noexp])

MeSH term search without study methodology terms
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast neoplasms” [majr:noexp] AND (contraceptives, oral [mh:noexp] OR contraceptives, oral/pharmacology [mh] OR estrogens/therapeutic use [mh] OR contraceptives, oral/therapeutic use [mh] OR contraceptives, oral/adverse effects [mh])

Maximise Sensitivity: MeSH term search without intervention terms
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast neoplasms” [majr:noexp] AND (risk [mh:noexp] OR risk factors [mh:noexp] OR follow-up studies [mh:noexp] OR odds ratio [mh:noexp])

Text word search with automatic term mapping
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND breast cancer AND (oral contraceptive OR oral contraceptives OR estrogen OR estrogens OR hormones OR hormonal) AND (risk OR follow-up OR epidemiologic)

Text word search with truncation and double quotes
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (oral contraceptive* OR “estrogen” OR “hormones” OR “hormonal”) AND (“risk” OR “epidemiologic”)

Text word search without study methodology text words
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (oral contraceptive* OR “estrogen” OR “hormones” OR “hormonal”)

Maximise Sensitivity: Text word search without intervention text words
1966:1995 [dp] AND “human” [MESH] AND journal article [pt] AND “breast cancer” AND (“risk” OR epidemiolog*)

EMBASE
BMJ Clinical Evidence[432]
Specified named adverse effect AND (ae OR si OR to OR co).fs. OR (safe OR safety).ti,ab. OR side effect$.ti,ab. OR ((adverse OR undesirable OR harm$ OR serious OR toxic) adj3 (effect$ OR reaction$ OR event$ OR outcome$)).ti,ab. OR exp adverse drug reaction/ OR exp drug toxicity/ OR exp intoxication/ OR exp drug safety/ OR exp drug monitoring/ OR exp drug hypersensitivity/ OR exp postmarketing surveillance/ OR exp drug surveillance program/ OR exp phase iv clinical trial/ OR (toxicity OR complication$ OR noxious OR tolerability).ti,ab. OR exp postoperative complication/ OR exp Peroperative Complication/

Golder[360]
Most sensitive search strategy
Specified named adverse effects OR (safe OR safety OR side effect* OR undesirable effect* OR treatment emergent OR tolerability OR toxicity OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes))).ti,ab

Appendix I: **Adverse effects terms in database records in Chapter 13**

Table 15.23 Accepted adverse effects terms

Accepted terms in title or abstract	Accepted indexing terms, keywords and subheading terms
GENERIC: adverse effect(s), adverse drug effects, adverse event(s), adverse experiences, adverse medication effects, adverse CV events, adverse reactions, harm, safe, safety, side effect, tolerability, tolerated, toxicity, toxicities, toxic effect, untoward events, well-tolerated **SPECIFIC**: bleeding, blood loss, edema, oedema, cancer, hypokalemia, cardiac failure, heart failure, myocardial infarction, cardiovascular events, cardiovascular outcomes, cardiovascular mortality, cardiovascular risk, weight, thrombocytopenia, lymphoma, heart failure, cardiovascular outcomes, cardiovascular disease, cardiovascular event, myocardial infarction, cardiovascular disease, coronary heart disease, pneumonia	**GENERIC**: **MEDLINE**: drug toxicity/, adverse effects (ae), chemically induced (ci) **EMBASE**: drug fatality/, drug induced disease/, side effect/, unspecified side effect/, drug safety/, drug tolerability/ drug tolerance/, adverse drug reaction (ae), side effects (si) **Science Citation Index (SCI):** drug toxicity, safety, tolerability, toxicity, tolerance. **SPECIFIC**: **MEDLINE**: postoperative hemorrhage/, myocardial infarction/, heart failure/ cardiovascular diseases/, weight gain/, thrombocytopenia/, heart failure/ cardiovascular diseases/ myocardial infarction/, **EMBASE**: postoperative hemorrhage/, leg edema/, edema/, peripheral edema: cancer/, hypokalemia/ congestive heart failure/, heart failure/, heart infarction/, heart arrest/, heart muscle ischemia/, acute heart infarction/, ischemic heart disease/ cardiovascular risk, body weight/ weight change/, weight Gain/, body weight disorder/, jaw osteonecrosis/, thrombocytopenia/, heart atrium fibrillation/, heart failure/, heart infarction/, congestive heart failure/ heart death/, heart disease/ cardiovascular disease/, nonhodgkin lymphoma/, B cell lymphoma/, lymphoma/, heart failure/, heart infarction/, heart atrium fibrillation/, ischemic heart disease/, congestive heart failure/ cardiovascular risk/ cardiovascular disease, heart atrium fibrillation/, heart failure/, congestive heart failure/ heart death, heart disease/ cardiovascular disease/, pneumonia/ **Science Citation Index (SCI)**: blood-loss, acute myocardial-infarction, myocardial-infarction, coronary heart-disease, congestive-heart-failure, cardiovascular thrombotic events, weight-gain, bisphosphonate-associated osteonecrosis, thrombocytopenia, congestive-heart-failure, lymphoma, heart-failure, congestive-heart-failure.

Table 15.24 Records in each review with 'adverse effects' related terms in the title, abstract or indexing in MEDLINE or EMBASE

Reference	Topic	Adverse effects terms in title or abstract	Adverse effect indexing terms in MEDLINE or EMBASE	Retrievable by a combined search
Agbabiaka 2009[598] (N=15)	Adverse effects with serenoa repens	8 (53%)	13 (87%)	13 (87%)
Albavera-hernandez 2009[599] (N=14)	Safety of botulinum toxin A	3 (21%)	11 (79%)	11 (79%)
Alghamdi 2007[239] (N=1)	Bleeding with aspirin	1 (100%)	1 (100%)	1 (100%)
Berlie 2007[600] (N=23)	Edema with Thiazolidinediones	20 (87%)	21 (91%)	22 (96%)
Bonovas 2007[601] (N=4)	Cancer with pravastatin	2 (50%)	4 (100%)	4 (100%)
Cao 2010[602] (N=6)	Hypokalemia with cetuximab-based therapy	6 (100%)	6 (100%)	6 (100%)
Chavez-Tapia 2009[603] (N=9)	Adverse effects with rimonabant	9 (100%)	9 (100%)	9 (100%)
Chen 2007[604] (N=15)	Myocardial infarction with COX-2 inhibitors	13 (87%)	14 (93%)	14 (93%)
Correll 2007[605] (N=19)	Weight gain/metabolic effects of mood stabilizers/antipsychotics	17 (89%)	18 (95%)	18 (95%)
Dugoua 2009[606] (N=7)	Safety of probiotics	2 (29%)	1 (14%)	3 (43%)
Ford 2008[607] (N=9)	Adverse effects of bismuth salts	6 (67%	8 (89%)	8 (89%)
Gehling 2009[608] (N=8)	Side-effects of intrathecal morphine combined with spinal anaesthesia	7 (88%)	7 (88%)	8 (100%)
Johansson 2009[609] (N=20)	Adverse effects of orlistat, sibutramine and rimonabant	12 (60%)	17 (85%)	18 (90%)
Lakhdar 2008[610] (N=6)	Safety and tolerability of ACE inhibitors and angiotensin receptor blocker	3 (50%)	4 (67%)	4 (67%)
Luykx 2009[611] (N=9)	Adverse effects of topiramate	8 (89%)	9 (100%)	9 (100%)
Mauri 2009[612] (N=5)	Osteonecrosis of the jaw with bisphosphonates	4 (80%)	5 (100%)	5 (100%)
Morris 2007[613] (N=4)	Thrombocytopenia with heparin	3 (75%)	4 (100%)	4 (100%)
Phillips 2007[614] (N=4)	Adverse effects of blockers/inhibitors	3 (75%)	4 (100%)	4 (100%)
Ravindran 2009[615] (N=4)	Safety of glucocorticoid therapy	4 (100%)	4 (100%)	4 (100%)

Table 15.24 Records in each review with 'adverse effects' related terms in the title, abstract or indexing in MEDLINE or EMBASE

Reference	Topic	Adverse effects terms in title or abstract	Adverse effect indexing terms in MEDLINE or EMBASE	Retrievable by a combined search
Rodrigo 2008[616] (N=18)	Safety of B-agonists	11 (61%)	14 (78%)	16 (89%)
Rodrigo 2009[617] (N=13)	Cardiovascular events with tiotropium	5 (38%)	12 (93%)	12 (93%)
Siegel 2009[278] (N=18)	Lymphoma with anti-tumor necrosis factor and immunomodulator therapy	14 (78%)	18 (100%)	18 (100%)
Silva 2007[619] (N=4)	Adverse effects of statins	2 (50%)	4 (100%)	4 (100%)
Singh 2007[620] (N=4)	Cardiovascular events with rosiglitazone	2 (50%)	4 (100%)	4 (100%)
Singh 2008[621] (N=9)	Cardiovascular events with anticholinergics	4 (44%)	8 (89%)	8 (89%)
Singh 2009[622] (N=5)	Pneumonia with corticosteroids	4 (80%)	5 (100%)	5 (100%)
Average percentage of records	All reviews	69%	90%	92%

N = number of references from each review containing adverse effects data published in English later than 2001 and available from MEDLINE or EMBASE.

Table 15.25 Performance of individual search terms in MEDLINE and EMBASE

MEDLINE		EMBASE	
Floating Subheadings (N=231)	Number of Relevant Records (N=231)	Floating Subheadings	Number of Relevant Records (N=222)
Adverse Effects (ae)	117 (51%)	Adverse Drug Reaction (ae)	185 (83%)
Complications (co)	41 (18%)	Complication (co)	24 (11%)
Drug Effects (de)	62 (27%)	Drug Toxicity (to)	2 (1%)
Poisoning (po)	0	Side Effect (si)	185 (83%)
Toxicity (to)	0		
Subheadings attached to Intervention (N=231)		Subheadings attached to Intervention	
Adverse Effects (ae)	117 (51%)	Adverse Drug Reaction (ae)	185 (83%)
Contraindications (ct)	0	Drug Toxicity (to)	2 (1%)
Mortality (mo)	0		
Pharmacology (pd)	22 (10%)		
Poisoning (po)	0		
Therapeutic use (tu)	177 (77%)		
Toxicity (to)	0		
Subheadings attached to Disease or Disorder/Outcome (N=119)			
Abnormalities (ab)	0		
Chemically Induced (ci)	7 (6%)		
Epidemiology (ep)	2 (2%)		
Etiology (et)	0		
Mortality (mo)	3 (3%)		
Transmission (tm)	0		
MeSH Terms (N=231)		EMTREE Terms (N=222)	
Exp abnormalities, drug induced/	0	exp adverse drug reaction/	43 (19%) (0 adverse drug reaction, one chemotherapy induced emesis, eight drug eruption, 10 drug fatality, 4 drug fever, four drug hypersensitivity, six drug induced disease, seven drug induced headache, eight flu like

Table 15.25 Performance of individual search terms in MEDLINE and EMBASE

MEDLINE		EMBASE	
			syndrome, three injection site reaction, six unspecified side effect)
Exp adverse drug reaction reporting systems/	0	exp drug hypersensitivity/	4 (2%) (drug hypersensitivity)
Case control studies/	1 (0.5%)	exp drug monitoring/	0
Exp case control studies/	8 (3%)	exp drug safety/	85 (38%)
Case report/	0	exp drug surveillance program/	0
Exp clinical trials, phase iv as topic/	0	exp drug toxicity/	0
Cohort studies/	3 (1%)	exp intoxication/	0
exp drug hypersensitivity/	2 (1%) (both drug hypersensitivity/)		
Exp drug monitoring/	0		
Exp drug toxicity/	3 (1%) (1 drug toxicity/ and two Serum Sickness/)		
Exp follow-up studies/	24 (10%)		
Human/	231 (100%)		
Exp Intraoperative Complications/	3 (1%) (1 Intraoperative Complications and two Blood Loss, Surgical)		
odds ratio/	1 (0.5%)		
Exp poisoning/	4 (2%) (1 Drug-Induced Liver Injury, one drug toxicity and two Serum Sickness)		
Exp Postoperative Complications/	1 (0.5%) (1 Postoperative Hemorrhage)		
Exp product surveillance, postmarketing/	0		
Risk/	6 (3%)		
Exp Risk/	28 (12%) (6 risk, three Risk Assessment, 19 Risk Factors)		
Risk factors/	19 (8%)		

Table 15.25 Performance of individual search terms in MEDLINE and EMBASE

MEDLINE		EMBASE	
Exp Substance-related disorders/	6 (3%) (1 Substance Withdrawal Syndrome, one Substance-related disorders, one Drug-Induced Liver Injury, one drug toxicity and two Serum Sickness)		
Terms in the Title or Abstract		**Terms in the Title or Abstract**	
adrs	0	adrs	0
adverse adj2 effect	4 (2%)	adverse adj2 effect	4 (2%)
adverse adj2 effects	17 (%)	adverse adj2 effects	15 (7%)
adverse adj3 effect$	19 (8%) (4 adverse effect, 13 adverse effects, one adverse medication effects, two adverse side effects, one adverse drug effects)	adverse adj3 effect$	19 (9%) (4 adverse effect, 12 adverse effects, one adverse medication effects, one adverse side effects, one adverse side-effect, one adverse drug effects)
adverse adj2 event	14 (6%)	adverse adj2 event	13 (6%)
adverse adj2 events	67 (29%)	adverse adj2 events	63 (28%) (11 adverse event, 51 adverse events, one adverse CV events)
adverse adj3 event$	75 (32%) (12 adverse event, 66 adverse events, one adverse CV events)	adverse adj3 event$	71 (32%) (13 adverse event, 62 adverse events, one adverse CV events)
adverse adj2 outcome	0	adverse adj2 outcome	0
adverse adj2 outcomes	0	adverse adj2 outcomes	0
adverse adj3 outcome$	0	adverse adj3 outcome$	0
adverse adj2 reaction	0	adverse adj2 reaction	0
adverse adj2 reactions	3 (1%) (3 adverse reactions)	adverse adj2 reactions	3 (1%) (3 adverse reactions)
adverse adj3 reaction$	3 (1%) (3 adverse reactions)	adverse adj3 reaction$	3 (1%) (3 adverse reactions)
complication$	7 (3%) (6 complications, one complication)	complication$	7 (3%) (6 complications, one complication)

Table 15.25 Performance of individual search terms in MEDLINE and EMBASE

MEDLINE		EMBASE	
epidemiolog*	0	epidemiolog*	0
epidemiologic	0	epidemiologic	0
follow-up	29 (13%) (25 follow-up, four follow up)	follow-up	28 (13%) (25 follow-up, four follow up)
harm$ adj3 effect$	0	harm$ adj3 effect$	0
harm$ adj3 event$	0	harm$ adj3 event$	0
harm$ adj3 outcome$	0	harm$ adj3 outcome$	0
harm$ adj3 reaction$	0	harm$ adj3 reaction$	0
noxious	0	noxious	0
risk	64 (27%)	risk	61 (27%)
safe	17 (7%)	safe	17 (8%)
safety	71 (31%)	safety	63 (28%)
serious adj3 effect$	1 (0.5%) (1 serious side-effects)	serious adj3 effect$	1 (0.5%) (1 serious side-effect)
serious adj3 event$	15 (6%) (1 serious adverse event, 11 serious adverse events, one serious cardiovascular events, one serious CV thromboembolic events, one serious and non-serious adverse events, one serious symptomatic adverse event)	serious adj3 event$	12 (5%) (1 serious adverse event, nine serious adverse events, one serious cardiovascular events, one serious CV thromboembolic events, one serious and non-serious adverse events, one serious symptomatic adverse event)
serious adj3 outcome$	0	serious adj3 outcome$	0
serious adj3 reaction$	2 (1%) (2 serious adverse reactions)	serious adj3 reaction$	2 (1%) (2 serious adverse reaction)
side effect$	22 (10%) (1 side effect, 17 side effects, five side-effects)	side effect$	23 (10%) (1 side effect, 18 side effects, five side-effects)
tolerability	23 (10%)	tolerability	24 (11%)
toxic adj3 effect$	2 (1%)	toxic adj3 effect$	2 (1%) (2 toxic effects)
toxic adj3 event$	0	toxic adj3 event$	0
toxic adj3 outcome$	0	toxic adj3 outcome$	0
toxic adj3 reaction$	0	toxic adj3 reaction$	0
toxicity	11 (5%)	toxicity	11 (5%)
treatment emergent	0	treatment emergent	0
undesirable effect*	0	undesirable	0

Table 15.25 Performance of individual search terms in MEDLINE and EMBASE

MEDLINE		EMBASE	
		effect*	
undesirable adj3 effect$	0	undesirable adj3 effect$	0
undesirable adj3 event$	0	undesirable adj3 event$	0
undesirable adj3 outcome$	0	undesirable adj3 outcome$	0
undesirable adj3 reaction$	0	undesirable adj3 reaction$	0
All fields		**All fields**	
adrs	0	adrs	0
adverse adj2 effect	4 (2%)	adverse adj2 effect	4 (2%)
adverse adj2 effects	16 (7%) (13 adverse effects, one adverse medication effects, two adverse side effects, one adverse drug effects)	adverse adj2 effects	15 (7%) (12 adverse effects, one adverse medication effects, one adverse side effects, one adverse side-effects one adverse drug effects)
adverse adj2 event	12 (5%)	adverse adj2 event	70 (32%)
adverse adj2 events	67 (29%) (66 adverse events, one adverse CV events)	adverse adj2 events	63 (28%) (1 adverse cv events)
adverse adj2 outcome	0	adverse adj2 outcome	0
adverse adj2 outcomes	0	adverse adj2 outcomes	0
adverse adj2 reaction	0	adverse adj2 reaction	0
adverse adj2 reactions	3 (1%)	adverse adj2 reactions	3 (1%)
safe	17 (7%)	safe	16 (7%)
safety	72 (31%)	safety	62 (28%)
side effect*	22 (10%) (1 side effect, 17 side effects, five side-effects)	side effect*	18 (8%)
tolerability	23 (10%)	tolerability	24 (11%)
toxicity	11 (5%)	toxicity	11 (5%)
treatment emergent	0	treatment emergent	0
undesirable effect*	0	undesirable effect*	0

Appendix J: **Sensitivity of searches in case study systematic review and selection of databases in systematic reviews of adverse effects.**

Database	Sensitivity of searches in case study systematic review in Chapter 11 (N=58)	Percentage of reviews that search each source in survey in Chapter 10 (N=849)
Science Citation Index (SCI)	60%	5%
BIOSIS Previews	47%	8%
EMBASE	41%	54%
MEDLINE	33%	96%
Scirus (journal sources)	29%	0%
Derwent Drug File	28%	0%
PASCAL	28%	1%
British Library Direct	26%	0%
Thomson Reuters Integrity	26%	0%
TOXLINE	24%	2%
ADIS Clinical Trials Insight	22%	0%
Iowa Drug Information Service (IDIS)	21%	1%
Manufacturer	17%	13%
International Pharmaceutical Abstracts (IPA)	12%	3%
CINAHL	10%	13%
Conference Proceedings Citation Index-Science	10%	0%
CENTRAL	9%	24%
Medscape DrugInfo	7%	0%
Conference Papers Index (CPI)	3%	0%
Inside Conferences	0%	0%

Abbreviations

ADE – Adverse Drug Effect
ADR – Adverse Drug Reaction
AE – Adverse Event
CCIS - Micromedex Computerized Clinical Information Service
CDSR – Cochrane Database of Systematic Reviews
CHM – Commission on Human Medicines
CI – Confidence Interval
COSTART - Coding Symbols for a Thesaurus of Adverse Reaction Terms
CPI – Conference Papers Index
CPRD – Clinical Practice Research Datalink
CRD – Centre for Reviews and Dissemination
DARE – Database of Abstracts of Reviews of Effects
DDF - Derwent Drug File
EMA – European Medicines Agency
FDA – Food and Drug Administration
HRT – Hormone Replacement Therapy
IDIS - Iowa Drug Information Service
IPA - International Pharmaceutical Abstracts
IPD – Individual Participant Data
MedDRA - Medical Dictionary for Regulatory Activities
MHRA - Medicines and Healthcare products Regulatory Agency
NHS – National Health Service
NICE - National Institute for Health and Care Excellence
NNH – Number Needed to Harm
NSAIDs – Non-steroidal anti-inflammatory Drug
NTIS - National Technology Information Service
OR – Odds Ratio
PDR - Physician's Desk Reference
PEM – Prescription Event Monitoring
RAE – Routine Adverse Events
RCT – Randomised Controlled Trial
ROR – Ratio of Risk Ratios
RR – Risk Ratio
SADR – Serious Adverse Drug Reaction or Suspected Adverse Drug Reaction
SAE – Serious Adverse Event
SE – Standard Error
SEDA - Side Effects of Drugs Annuals
SCI – Science Citation Index
SSCI – Social Science Citation Index
WHO – World Health Organisation
WHO-ART - World Health Organisation Adverse Reactions Terminology
WMD – Weighted Means Difference

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