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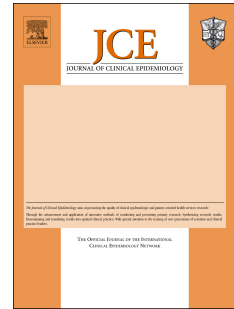
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Overview: comprehensive and carefully constructed strategies are required when conducting searches for adverse effects data

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Searching to identify adverse effects data: an overview of current evidence and guidance

Abstract

Objective: Methodological research has been undertaken to investigate the many challenges in searching for adverse effects data. It is imperative that the search approach adopted in systematic reviews is based on the best available evidence. We provide a detailed summary of the results and implications of the current evidence base to assist future searches for adverse effects.

Study Design and Setting: This paper is a narrative review from the authors of the Cochrane Handbook chapter on adverse effects.

Results: The specified search strategy must be based on the PICO (Population, Intervention, Comparator, Outcome(s)) format for question formulation and appropriate study designs for adverse effects data. Search filters and suggested search terms are available for the adverse effects of drug, medical devices and surgical interventions. The use of generic adverse effects terms (such as harms, and complications) as textwords and indexing terms and specific adverse effects terms (such as rash and wound infection) are warranted. Searching databases beyond MEDLINE has proven useful, as well as the use of non-database sources.

Conclusion: This paper provides the most up to date evidence-based guidance in identifying adverse effects data in the literature. It will support searchers and researchers evaluating the potential for harm of medical interventions in systematic reviews.

Keywords

Adverse effects; literature searching; systematic reviews; complications; information retrieval

What is new?

Key finding

- Guidance on searching for adverse effects is underpinned by methodological research and evidence based.

What this study adds to what was known?

- Adverse effects search strategies should aim to maximise sensitivity over precision in order to retrieve the totality of the evidence for appraisal.
- Published adverse effects search filters have demonstrated approaching 90% sensitivity but are unlikely to achieve a fully comprehensive list of records.

What is the implication and what should change now?

- Adverse events searching should be tailored to suit the intervention of interest. While search filters are available for drug, medical devices and surgical interventions search filters for the adverse effects of other types of interventions are now warranted.
- Searches should aim to capture adverse effects data from a broad selection of sources and not rely on a single source, such as MEDLINE.
- To reduce the potential for publication bias reviewers should attempt to search for unpublished data for relevant adverse effects information in addition to published sources.

Introduction

The objective of this paper is to assist research teams to deal with the challenges of undertaking a robust search for adverse effects data for a systematic review of medical interventions. The need for this paper arises from the major challenges in searching for adverse effects in systematic reviews. First, adverse effects are not always pre-specified and new or previously unknown adverse effects

are difficult to predict and specify in searches. Second, there can be a huge (almost limitless) range of adverse effects to consider. Third, reporting of adverse effects in studies may be inconsistent and/or less detailed when adverse effects are not the primary focus, or considered to be outcomes that are of lesser importance. This leads to poor database indexing and few relevant adverse effects terms appearing in the database record. Fourth, the terminology surrounding adverse effects is inconsistent, meaning that searchers need to use multiple synonyms in their search strategies. Fifth, different search approaches are required to identify adverse effects of different types of interventions (Farrah 2013, Golder 2014, Farrah 2016, Golder 2017).

In addition it is not always appropriate to limit the searches to randomised controlled trials (RCTs). A small short-term study (such as an RCT) may adequately capture common, immediately apparent adverse effects (such as skin reaction after injection), whilst other study types (for instance, case-control) will be needed for very rare, long-term adverse effects (Loke 2011). Searching for these non-RCT study types can be problematic due to inconsistent use of terminology and poor indexing which has led to search filters with poor sensitivity.

Lastly, there is no single comprehensive source for adverse effects data and unpublished data may be of particular importance (Golder 2010, Loke 2011, Alves 2012, Golder 2012d, Golder 2014).

With all these issues in mind, evidence based guidance to help searchers is urgently warranted.

Question Formulation

As with other systematic reviews, the first step to informing a search strategy is to establish a PICO (Population, Intervention, Comparator, Outcome(s)) format for the adverse effects review question.

Population [P]: If study is population specific then relevant terms will need to be included to identify population of interest but if evaluating adverse effects across all conditions then population specific terms can be omitted. When searching with specific population terms the review team need to be careful to try not to miss papers due to a lack of description of the population in the title, abstract or indexing fields. For example, a paper on '*Fracture risk with rosiglitazone and pioglitazone compared*' did not mention diabetes in the bibliographic record.

Intervention [I]: It is almost always necessary to include intervention terms in the search. When defining the intervention, reviewers will need to consider the clinical heterogeneity across related studies in their mode of action and their potential to cause harm (Loke 2011, CIOMS 2016, Zorzela 2016). For example, systematic reviews of pharmacological interventions should not assume that all drugs in a class will have the same potential to cause adverse effects (Centre for Reviews and Dissemination 2009).

Comparator [C]: Including search terms for comparators is rarely done, partly because there is a very diverse range of potential comparators. Incorporating studies with a placebo group or a no active treatment group in the systematic review is more straightforward because observed adverse effects can then be more reliably attributed to the intervention. While a placebo-controlled approach has greater internal validity there is a loss of generalisability to healthcare areas if the relative harms of two or more existing interventions are being considered.

Outcome [O]: Review questions may incorporate all potential adverse effects (exploratory approach) or be focused on a set of pre-specified adverse effect (confirmatory approach) or a hybrid between the two. In the past, database records contained few specific terms relating to adverse effects in the title, abstract or database indexing. However, significant improvements have occurred in adverse effects reporting in database records so recent literature is more likely to be retrieved

using adverse effects search terms, and there is less need for scanning the full text of papers (Golder 2011, Golder 2012b, Golder 2018a).

Named adverse effects can be identified from: clinicians' observations in published reports, patients' reports (such as internet forums), scoping reviews, regulatory agencies (such as Food and Drug Administration) or tertiary sources (such as British National Formulary, Meyler's Side Effects of Drugs). Reviewers could opt to limit the adverse effects of interest based on severity, timing, or plausibility of the intervention's effect.

Study Design [S]: When carrying out reviews of adverse effects authors may opt for a wide range of included study designs because rare adverse events observed over the longer term may not be detected as part of a traditional prospectively designed RCT (Loke 2007, Chou 2010, Golder 2011, Loke 2011). Inclusion criteria in controlled trials may exclude participants of increased risk of harm, which may not be representative of everyday practice (such as children, women of childbearing age, people with co-morbidities or frail older adults), and the duration of follow-up may not capture long-term adverse effects (Loke 2007). Observational cohorts, case-control studies, case series, post-marketing surveillance, or case reports may potentially provide more relevant information for certain types of adverse effects (Loke 2007, Chou 2010, Golder 2011, Loke 2011, Relevo 2011). If the review is using a confirmatory approach it is more appropriate to prioritize stronger RCT evidence (Chou 2010). Search terms based on study design are reasonable for identifying RCTs. However, the diverse range of study designs used in assessing adverse effects (cohort, case-control, cross-sectional) creates major challenges in developing a reliable search string to pick out these specific types of studies.

Designing adverse effects search strategies

It is unlikely that a search for efficacy or effectiveness studies will be broad enough to incorporate adverse effects in a comprehensive manner unless the original search was restricted to a search for the intervention alone (Loke 2007, Golder 2009, Golder 2012b, Golder 2014). Thus, generally a search for adverse effects will need to be carried out alongside the search for effectiveness. As with all searches, the involvement of an information specialist (Golder 2014, Zorzela 2014, CIOMS 2016) and peer review of search strategies is advised (McGowan 2016). The PRESS guidelines are helpful in carrying out the peer review process (McGowan 2016).

Searches need to be as sensitive as possible to reduce the potential risk of bias and a false negative error (Type II error), whereby an intervention is judged incorrectly as having no significant evidence of harm (Loke 2011). Multiple database and platform-specific search strategies should be piloted during the design stage (Golder 2006, Golder 2009, Relevo 2011, Golder 2012a, Golder 2012b, Golder 2014). An iterative approach to generating search strategies will enable structured comparisons of retrieved results in order to evaluate optimum approaches (Golder 2009).

A highly sensitive search strategy is likely to be associated with poor precision. A search with high sensitivity search will typically generate several thousand abstracts to screen for eligibility, with potentially high numbers of results needing to be read in full in order to identify a single eligible record (Golder 2009, Golder 2012b). The scale of resources required can often be determined using careful scoping exercises when drafting the review question.

Adverse effects search terms

Both specific and generic search techniques have strengths and limitations. Recommended practice is to *consider* the use of the two search methods in combination: **generic** adverse effects terms (such as ‘side effects’, ‘harms’ and ‘adverse reactions’) using the ‘OR’ function along with **specific** adverse effects terms (such as ‘headache’, ‘blood loss’, or ‘dysphagia’) (Golder 2014). It is also advisable to combine index terms and free-text searching to increase search sensitivity and reduce the chance of missing relevant material. However, this method may still lack the high sensitivity required for systematic reviews due to poor reporting and indexing of adverse effects in bibliographic records. In addition, some compromise in this approach may be required in situation where unmanageable numbers of records for screening are retrieved.

Search fields that can be searched using generic adverse effects terms are: index terms (such as MeSH or Emtree), subheadings (linked to indexing terms or not), and text words (such as in the title or abstract).

Index terms

The index terms relevant to search strategy development for adverse effects in MEDLINE and Embase are listed in Table 1. Many of these terms can be exploded (whereby narrower index terms are included) to achieve increased sensitivity. The most relevant indexing terms for adverse effects are dependent on the type of intervention evaluated. In MEDLINE the top performing search term in relation to sensitivity for drug interventions is the use of ‘adverse effects (ae)’ as a floating subheading (Golder 2006), for surgery it is the search term ‘complication*’ (where * represents a wildcard) in the title and abstract (Golder 2018a, Golder 2018b) and for medical devices it is ‘complicat*’ in the title and abstract (Golder 2018c). In Embase, the search term that achieves highest sensitivity for drug interventions is the floating subheading ‘adverse drug reaction (ae)’, for surgery it is ‘complication*’ in the title and abstract (Golder 2018a, Golder 2018b) and for medical devices it is the floating subheading ‘complication (co)’ (Golder 2018c). Note that the generalisability of these sensitivity results is unknown although they provide useful indications to review teams.

Table 1: Index terms for adverse effects in MEDLINE and Embase

MEDLINE MeSH Index Terms	Embase Emtree Index Terms
Drug Intervention	
abnormalities, drug induced/	adverse drug reaction/
adverse drug reaction reporting systems/	drug hypersensitivity/
drug hypersensitivity/	drug monitoring/
drug monitoring/	drug recall/
drug recalls/	drug safety/
drug related side effects and adverse reactions/	drug surveillance program/
long term adverse effects/	drug toxicity/
poisoning/	intoxication/
safety-based drug withdrawals/	side effect/
substance-related disorders/	

Drug Intervention/Medical Device	
product surveillance postmarketing/	postmarketing surveillance/
	product recall/
Surgical Procedure	
intraoperative complications/	perioperative complication/
postoperative complications/	postoperative complication/
postoperative pain/	surgical risk/
Medical Device	
equipment contamination/	adverse device effect/
equipment failure/	device recall/
equipment failure analysis/	device safety/
equipment safety/	equipment safety/
medical device recalls/	medical device complication/
safety-based medical device withdrawals/	
Non-drug Interventions	
	complication/
Hazards	
risk assessment/	

Subheadings

The most useful search method for retrieving adverse effects results is to employ subheadings (sometimes referred to as qualifiers) (Golder 2006, Golder 2014, Golder 2018a). Although rarely recommended in reviews of treatment benefit, in reviews incorporating adverse effects they are particularly useful in augmenting sensitivity and precision of searches (Golder 2012a, Golder 2012c, Golder 2014, Golder 2014, Golder 2014). Relevant adverse effects subheadings in MEDLINE and Embase are listed in table 2.

Table 2: Subheadings in MEDLINE and Embase

OVID MEDLINE	OVID Embase
/adverse effects (ae)	/adverse device effect (am)
/chemically induced (ci)	/adverse drug reaction (ae)
/complications (co)	/complication (co)
/contraindications (ct)	/drug toxicity (to)
/poisoning (po)	/side effect (si)

/toxicity (to)

Indexed subheadings can be searched attached to an indexing term or used independently. An example search string in MEDLINE is 'Aspirin/adverse effects' where 'Aspirin' is the MeSH term and 'adverse effects' is the subheading. In Embase, an example search string is: 'Acetylsalicylic-acid/adverse-drug-reaction' where 'Acetylsalicylic-acid' is the Emtree term and 'adverse-drug-reaction' is the subheading.

Subheadings can also be 'free floating' i.e. used without a thesaurus indexing term (Golder 2012a, Golder 2012c, Golder 2014,). OVID MEDLINE examples are 'ae.fs' (adverse effects), 'co.fs' (complications), 'po.fs' (poisoning), 'de.fs' (drug effects) - where '.fs' denotes a floating search. If required, in OVID MEDLINE the subheading 'adverse effects' can be exploded to include other subheadings (poisoning and toxicity) (Golder 2012a, Golder 2012b, Golder 2012c, Golder 2014).

In OVID MEDLINE the search string 'Aspirin/ae' will retrieve results that have been indexed with the combination 'Aspirin' as a subject heading with 'adverse effects' attached as a subheading. Inputting the two search terms independently and combining with the AND search operator, for example, 'Aspirin/ AND ae.fs.' will increase the sensitivity of the search strategy.

Free-text terms

Free-text terms searches (such as in the title or abstract) alone are unreliable at retrieving comprehensive results and should be used alongside thesaurus terms and/or subheadings (Golder 2009). Relevant free-text terms include (but is not limited to): 'safe', 'safety', 'side effect*', 'undesirable effect*', 'treatment emergent', 'tolerability', 'toxicity', 'adverse drug reaction*', 'adrs', 'adverse effect*', 'adverse drug effect*', 'adverse reaction*', 'adverse event*', 'adverse outcome*', 'complication*', 'harm', 'harmful', 'harms', 'risk' (where * represents a wildcard). However, care needs to be exercised with some of these terms because of the potential for a substantial amount of noise and irrelevant records, for example, articles containing phrases such as 'risk of bias', 'relative risk', 'patient safety' and 'self-harm'. Case studies have analysed the sensitivity of free-text terms and again indicate that the most useful terms are dependent on the type of intervention (Golder 2006, Golder 2012b, Golder 2014, Golder 2018a, Golder 2018b, Golder 2018c).

Search Filters

A search filter is a predefined combination of search terms designed to retrieve information on a particular topic (Golder 2009, Golder 2012a, Golder 2012c).

Although high sensitivity can be achieved with published drug adverse effects search filters, the full complement of relevant records are unlikely to be retrieved (Golder 2012a, Golder 2012c). For reviews of drug interventions the published search filter that displays the best sensitivity is by Golder et al 2006. Research has also been undertaken to develop search filters for medical device adverse effects and surgical complications in MEDLINE and Embase (Golder 2018a, Golder 2018b). These filters have demonstrated the different terminology and indexing used for the adverse effects of different types of interventions (Box 1). For example, the term 'complications' is more frequently used with surgical procedures and terms related to 'failure' and 'recall' with medical devices (Box 1) (Golder 2018a, Golder 2018b). The sensitivity achieved with search filters varies. Whilst drug adverse effects search filters tend to achieve the highest sensitivity, adverse medical device effects filters achieve the lowest sensitivity. However, generally a sensitivity approaching at least 90% is achieved.

Box 1: Search filters for medical devices, surgical procedures and drug interventions

Ovid MEDLINE	Ovid Embase
Medical Devices (Golder 2018c)	
complicat*.ti,ab. OR ae.fs. [adverse effects] OR safe*.ti,ab. OR exp postoperative complications/ OR failure*.ti,ab. OR adverse.ti,ab. OR co.fs. [complications] OR failed.ti,ab. OR exp equipment failure/ OR removal.ti,ab. OR equipment safety/ OR problem*.ti,ab. OR side effect*.ti,ab. OR harmful.ti,ab. OR tolerated.ti,ab. OR loosen*.ti,ab. OR Intraoperative complications/ OR migration.ti,ab. OR breakag*.ti,ab. OR discomfort.ti,ab. OR displacement.ti,ab. OR detrimental adj2 effect*.ti,ab. OR untoward effects.ti,ab.	co.fs. [Complication] OR complicat*.ti,ab. OR safe*.ti,ab. OR failure*.ti,ab. OR exp medical device complication/ OR adverse.ti,ab. OR failed.ti,ab. OR exp postoperative complication/ OR problem*.ti,ab. OR side effect*.ti,ab. OR discomfort.ti,ab. OR loosen*.ti,ab. OR removal*.ti,ab. OR complications.kw. OR migration.ti,ab. OR ae.fs. [adverse drug reaction] OR device related events.ti,ab. OR adverse effects/ OR device safety/ OR safety/ OR peroperative complication/ OR tolerated.ti,ab. OR failing.ti,ab.
Surgical Procedures (Golder 2018a, Golder 2018b)	
complication*.ti,ab. OR ae.fs. [adverse effects] OR safe*.ti,ab. OR co.fs. [complications] OR postoperative complications/	complication*.ti,ab. OR co.fs. [Complication] OR safe*.ti,ab. OR ae.fs. [adverse drug reaction] OR postoperative morbidity.ti,ab. OR surgical risk/ OR complication/ OR postoperative complication/ OR procedure related.ti,ab.
Drug interventions (Golder 2006)	
ae.fs. [adverse effects] OR co.fs. [complications] OR de.fs. [drug effects] OR safe.ti,ab. OR safety.ti,ab. OR side-effect*.ti,ab. OR undesirable effect*.ti,ab. OR treatment emergent.ti,ab. OR tolerability.ti,ab. OR toxicity.ti,ab. OR adrs OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)).ti,ab.	("DRUG"/ae, to) [adverse drug reaction, drug toxicity] OR safe.ti,ab. OR safety.ti,ab. OR side-effect*.ti,ab. OR undesirable effect*.ti,ab. OR treatment emergent.ti,ab. OR tolerability.ti,ab. OR toxicity.ti,ab. OR adrs.ti,ab. OR (adverse adj2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)).ti,ab.

N.B. All search filters provided higher sensitivity when ORed with specific named adverse effect terms. "DRUG" refers to where searches need to insert the specific drug(s), * represents a wildcard, / indicates indexing term, .ti,ab. is title and abstract, .fs. is floating subheading and adj is adjacency.

If search filters are used it is very important to ensure they are specifically designed and validated according to the data sources being used (such as MEDLINE via OVID), and that they are up to date. Published search filter resources for adverse effects are provided by the InterTASC Information Specialists' Sub-Group (ISSG) website at <https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/adverse-events-filters>.

Adverse effects data sources

It is essential to not restrict adverse effect review searches to a single source, or a limited combination of databases (Golder 2012d). Performing a search in MEDLINE alone is not recommended and a broad selection of database and non-database sources are required (Golder 2010, Golder 2012d, Golder 2013).

A case study reviewing adverse effects of thiazolidinedione use in patients with type 2 diabetes mellitus tested over 60 sources and demonstrated that a wide range of sources were required (Golder 2012d). Searching MEDLINE alone would have failed to retrieve 66% of relevant references while using MEDLINE, Embase and CENTRAL would have failed to retrieve 57% of relevant references

(Golder 2012d). To identify all the included studies for this review multiple databases needed to be searched along with reference checking and industry sources.

In another case study of a review of a medical device the sources required to identify the evidence included: Science Citation Index (SCI), Embase, CENTRAL, and either MEDLINE or PubMed, in addition to author contact, reference checking and use of current awareness services (for example, establishing alerts in Zetoc) (Golder 2014). The choice of viable sources should always be guided by the subject area and the review question (Golder 2012d).

Table 3: A non-exhaustive list of sources that include adverse effects data (adapted from Relevo 2011)

Source category	Source examples
Primary databases	MEDLINE, Embase, Central Register of Controlled Trials (CENTRAL), Science Citation Index (SCI), Social Science Citation Index (SSCI)
Specialised databases	TOXLINE, Drug Adverse Reaction Target (DART), PsycINFO, Physiotherapy Evidence Database (PEDro), Cumulative Index to Nursing and Allied Health Literature (CINAHL Complete)
Grey Literature	<p><i>Clinical trial registries:</i> ClinicalTrials.gov International Clinical Trials Registry Platform (ICTRP)</p> <p><i>Industry Trial Registries and Regulatory authorities:</i> Manufacturer trial registries Medicines and Healthcare products Regulatory Agency www.mhra.gov.uk/ Food and Drug Administration www.fda.gov/medwatch European Medicines Agency: http://www.ema.europa.eu/ema/</p> <p><i>Online portals:</i> Open Grey http://www.opengrey.eu/</p> <p><i>Conference proceedings:</i> Conference Proceedings Citation Index (CPCI); Conference Papers Index (CPI) Individual Conference websites</p> <p><i>Theses:</i> Proquest Dissertation and Theses British Library EThOS</p>
Industry Clinical Study Report Requests	<p>Clinical Study Reports (CSR) requests can be made via the Wellcome Trust sponsored data sharing resource: https://www.clinicalstudydatarequest.com/</p> <p>Current sponsors include: Astellas, Bayer, Boehringer, Ingelheim, Daiichi Sankyo, Eisai, GlaxoSmithKline, Lilly, Novartis, Roche, Sanofi, Takeda, UCB, and ViiV Healthcare.</p> <p>Yale Open Access Data that has results available for >200 trials http://yoda.yale.edu/</p> <p>Requests from companies external to the data sharing agreement can be made by direct contact. For example: MERCK - www.merck.com/mrl/clinical_trials/ AstraZeneca - www.astrazenecaclinicaltrials.com/</p>

	Pfizer - www.pfizer.com/research/clinical_trials
Forward citation search	Example interfaces include: Scopus, Web of Science, Google Scholar
Backward citation search	Target specific references identified in key research articles
Corresponding with researchers/authors	Contact corresponding authors of key articles identified in search results for further information
Hand search	Target specific journals out of scope of previously searched databases
Spontaneous reporting	Adverse Drug Reactions http://ww1.adverse-drug-reaction.net/ UK Yellow card scheme https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/ Food and Drug Administration- Adverse Event Reporting System https://open.fda.gov/data/faers/

Unpublished data sources

For the purposes of this guidance unpublished sources are defined as sources that do not appear in a peer-reviewed journal (Golder 2010, Golder 2016) including: Clinical Study Reports, trial registries, conference proceedings, PhD theses, and spontaneous reporting resources (Table 3). To reduce selective reporting bias that may prioritise evidence of benefit it is **strongly encouraged** that reviewers search unpublished sources in parallel to published sources and contact study authors to request further information if published data could be incomplete. (Chou 2010, Loke 2011, Wieseler 2013). However, approximately less than half of systematic reviews incorporating adverse effects data currently search for unpublished data (Golder 2016). Failing to do this can lead to false-negative errors in estimates of harm (Golder 2010, Wieseler 2013, Golder 2016, Golder 2016, Gorrell 2016, Rosati 2016, Schroll 2016).

Mandatory changes applied to trials regulated by the Food and Drug Administration (FDA) regarding the submission of adverse events data to Clinicaltrials.gov (Zarin 2016) and the legislated publication of clinical data by the European Medicines Agency (EMA) means that previous accessibility limitations are improving (EMA). Requests to access CSRs directly from certain industry sponsors can be made via a publicly accessible website: Clinical study data request (CSDR) (Strom 2016).

When unpublished data are identified, researchers can never be clear whether all relevant studies have been located or how representative it is (Song 2010, Song 2012). Accessing unpublished data can be problematic in terms of delays in access and once received the data itself may be in non-standard formats so that a robust meta-analysis is difficult to undertake, and it may place heavy demands upon the project's resources (Wieseler 2013, Golder 2016, Golder 2016, Schroll 2016, Strom 2016). Consequently, data access issues should be considered at the planning stage.

Including unpublished data sources can provide more detailed information on adverse events than publicly available sources. It has been demonstrated that fewer adverse effects are reported in published data (43%) compared to unpublished data (83%), and a wider range of named adverse

effects are listed in unpublished data (Golder 2016). When published and unpublished data originate from the same study the unpublished version is more likely to contain adverse effects data (95%) compared to the published version (46%) (Golder 2016). Similarly, in other research, inconsistencies were evident with adverse effects in published documents coded to appear less severe with reduced incidence when compared to the unpublished CSRs. Adverse events reported in the published paper were in a range of 3% to 33% of those reported in the corresponding CSR summaries (Schroll 2016). When discrepancies between published and unpublished data are discovered it is recommended to attempt a sensitivity analysis to determine the potential impact upon review findings, and to contact study authors to clarify potential causes of disparity.

These additional search requirements are likely to increase demands on time and resources for the review team; however, including unpublished material may modify critical conclusions regarding the safety of medicinal products and increase precision of estimates incorporated in meta-analyses (Golder 2008, Golder 2016). It is recommended that review authors specify the number of unpublished studies identified and document where details of adverse effects data were inaccessible (Golder 2016).

Reporting search strategies

If adverse effects data are reviewed in combination with data on treatment benefit, the search history identifying adverse effects data requires a separate report, presented in full. When reporting the search history for adverse effects reviewers should adhere to the Methodological Expectations for Cochrane Intervention Reviews (MECIR) guidelines or the PRISMA harms extension (Zorzela 2016, Higgins 2018). It is important to report the search strategy as it was run with exact search terms and relevant truncation, the dates of searches completed, and any limits imposed so it could be reproduced in the future and readers can assess the methods used (Golder 2009). It is particularly important to report all the sources used - both published and unpublished – to enable its comprehensiveness to be judged.

Conclusion

Searching for adverse effects data for systematic reviews is challenging but feasible and essential. How searching is carried out and which sources are used, will determine what adverse effects are found. The search phase is of critical importance and it is strongly advised to involve an information specialist (Golder 2014, Zorzela 2014, CIOMS 2016). Research must continue to inform practice and lead to further improvement in the quality of searches. Other types of interventions are not covered by the available search filters, for example, physical or psychological interventions, diagnosis or screening. Search filters for adverse effects of interventions beyond drugs, medical devices and surgical interventions are therefore required.

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What is new?**Key finding**

- Guidance on searching for adverse effects is underpinned by methodological research and evidence based.

What this study adds to what was known?

- Adverse effects search strategies should aim to maximise sensitivity over precision in order to retrieve the totality of the evidence for appraisal.
- Published adverse effects search filters have demonstrated approaching 90% sensitivity but are unlikely to achieve a fully comprehensive list of records.

What is the implication and what should change now?

- Adverse events searching should be tailored to suit the intervention of interest. While search filters are available for drug, medical devices and surgical interventions search filters for the adverse effects of other interventions are now warranted.
- Searches should aim to capture adverse effects data from a broad selection of sources and not rely on a single source, such as MEDLINE.
- To reduce the potential for publication bias reviewers should attempt to search for unpublished data for relevant adverse effects information in addition to published sources.

All authors (Su Golder, Guy Peyer and Yoon Loke) contributed to; Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing.

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Conflicts of Interest

The authors declare that they have no conflicts of interests.

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