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ORIGINAL ARTICLE

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

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Abstract

Objectives: 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 article 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 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 text words 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 nondatabase sources.

Conclusion: This article 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; Bibliographic databases; MEDLINE; Embase; Search filters

1. Introduction

The objective of this article was 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 article arises from the major challenges in searching for adverse effects in systematic reviews [1]. First, adverse effects are not always prespecified, 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 [2–5].

In addition, it is not always appropriate to limit the searches to randomized 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), whereas other study types (for instance, case–control) will be needed for very rare, long-term adverse effects [6–8]. Searching for these non-RCT study types can be problematic due to inconsistent

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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 adds to what was known?

- Adverse effects search strategies should aim to maximize sensitivity over precision 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. Although 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.

use of terminology and poor indexing, which has led to search filters with poor sensitivity.

Finally, there is no single comprehensive source for adverse effects data, and unpublished data may be of particular importance [8–13].

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

1.1. Question formulation

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

1.1.1. 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 articles because of 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 despite the drugs being used in patients with diabetes.

1.1.2. 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 [8,14,15]. For example, systematic reviews of pharmacologic interventions should not assume that all drugs in a class will have the same potential to cause adverse effects [16].

1.1.3. 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. Although a placebo-controlled approach has greater internal validity, there is a loss of generalizability to healthcare areas if the relative harms of two or more existing interventions are being considered.

1.1.4. Outcome [O]

Review questions may incorporate all potential adverse effects (exploratory approach) or be focused on a set of prespecified 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; therefore, 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 [6,17,18].

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 [FDA]), 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.

1.1.5. 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 [6,8,19,20]. 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 comorbidities or

frail older adults), and the duration of follow-up may not capture long-term adverse effects [20]. Observational cohorts, case–control studies, case series, postmarketing surveillance, or case reports may potentially provide more relevant information for certain types of adverse effects [6,8,19–21]. If the review is using a confirmatory approach, it is more appropriate to prioritize stronger RCT evidence [19]. 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.

1.2. 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 without restriction to certain outcomes or populations [13,18,20,22]. 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 [13,14,23] and peer review of search strategies is advised [24]. The PRESS guidelines are helpful in carrying out the peer review process [24].

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 [8]. Multiple database and platform-specific search strategies should be piloted during the design stage [13,17,18,21,22,25]. An iterative approach to generating search strategies will enable structured comparisons of retrieved results to evaluate optimum approaches [22].

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 to identify a single eligible record [18,22]. The scale of resources required can often be determined using careful scoping exercises when drafting the review question.

1.3. 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," "haemorrhage," or "dysphagia") [26]. 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).

1.3.1. 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

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/	
Nondrug interventions	
	complication/
Hazards	
risk assessment/	

for drug interventions is the use of "adverse effects (ae)" as a floating subheading [25], for surgery, it is the search term "complication*" (where * represents a wildcard) in the title and abstract [27,28], and for medical devices, it is "complicat*" in the title and abstract [29]. In EMBASE, the search term that the achieves highest sensitivity for drug interventions is the floating subheading "adverse drug reaction (ae)", for surgery it is "complication*' in the title and abstract [27,28], and for medical devices, it is the floating subheading "complication (co)" [29]. Note that the generalizability of these sensitivity results is unknown although they provide useful indications to review teams.

1.3.2. Subheadings

The most useful search method for retrieving adverse effects results is to use subheadings (sometimes referred to as qualifiers) [4,27,30]. Although rarely recommended in reviews of treatment benefit, in reviews incorporating adverse effects, they are particularly useful in augmenting sensitivity and precision of searches [4,13,17,18,26]. Relevant adverse effects subheadings in MEDLINE and EMBASE are listed in Table 2.

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," which is used without a thesaurus indexing term [13,17,31]. 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) [17,18,26,31].

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.

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)	

1.3.3. 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 [22]. 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 analyzed the sensitivity of free-text terms and again indicate that the most useful terms are dependent on the type of intervention [13,18,25,27–29].

1.3.4. Search filters

A search filter is a predefined combination of search terms designed to retrieve information on a particular topic [17,22,31].

Although high sensitivity can be achieved with published drug adverse effects search filters, the full complement of relevant records is unlikely to be retrieved [17,31]. For reviews of drug interventions, the published search filter that displays the best sensitivity is by Golder et al. [25]. Research has also been undertaken to develop search filters for medical device adverse effects and surgical complications in MEDLINE and EMBASE [27,28]. 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) [27,28]. The sensitivity achieved with search filters varies. Although 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.

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 Website at https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/adverse-events-filters.

1.4. Adverse effects data sources

It is essential to not restrict adverse effect review searches to a single source or a limited combination of databases [11]. Performing a search in MEDLINE alone is not

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

Ovid MEDLINE	Ovid EMBASE
Medical devices [29]	
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 [27,28]	
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 [25]	
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.

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, abstract,.fs. is floating subheading, and adj is adjacency.

recommended, and a broad selection of database and non-database sources is required [7,9,11,12].

A case study reviewing adverse effects of thiazolidinedione use in patients with type II diabetes mellitus tested over 60 sources and demonstrated that a wide range of sources were required [11]. Searching MEDLINE alone would have failed to retrieve 66% of relevant references, whereas using MEDLINE, EMBASE, and CENTRAL would have failed to retrieve 57% of relevant references [11]. 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, EMBASE, CENTRAL, and either MEDLINE or PubMed, in addition to author contact, reference checking, and use of current awareness services (e.g., establishing alerts in Zetoc) [4]. The choice of viable sources should always be guided by the subject area and the review question [11].

1.4.1. Unpublished data sources

For the purposes of this guidance, unpublished sources are defined as sources that do not appear in a peer-reviewed journal [12,30] including Clinical Study Reports, trial registries, conference proceedings, PhD theses, and spontaneous reporting resources (Table 3). To reduce selective reporting bias that may prioritize 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 [8,19,31]. However, approximately less than half of systematic reviews incorporating adverse effects data currently search for unpublished data [30]. Failing to do this can lead to false-negative errors in estimates of harm [12,30,32–36].

Mandatory changes applied to trials regulated by the FDA regarding the submission of adverse events data to Clinicaltrials.gov [37] 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) [38].

When unpublished data are identified, researchers can never be clear whether all relevant studies have been located or how representative it is [39,40]. Accessing unpublished data can be problematic in terms of delays in

Table 3. A nonexhaustive list of sources that include adverse effects data

Source category	Source examples
Primary databases	MEDLINE, EMBASE, Central Register of Controlled Trials (CENTRAL), Science Citation Index (SCI), Social Science Citation Index (SSCI)
Specialized databases	TOXLINE, Drug Adverse Reaction Target (DART), PsycINFO, Physiotherapy Evidence Database (PEDro), Cumulative Index to Nursing and Allied Health Literature (CINAHL Complete)
Gray literature	Clinical trial registries: ClinicalTrials.gov International Clinical Trials Registry Platform (ICTRP) *Industry Trial Registries and Regulatory authorities:* Manufacturer trial registries Medicines and Healthcare products Regulatory Agency www.mhra.gov.uk/ Food and Drug Administration www.fda.gov/medwatch[i] European Medicines Agency http://www.ema.europa.eu/ema/ Online portals: Open Gray http://www.opengrey.eu/ Conference proceedings: Conference Proceedings Citation Index (CPCI) Conference Papers Index (CPI) Individual Conference Web sites Theses: Proquest Dissertation and Theses British Library EThOS
Industry clinical study report requests	Clinical Study Reports (CSR) requests can be made via the Wellcome Trust sponsored data sharing resource: https://www.clinicalstudydatarequest.com/ Current sponsors include Astellas, Bayer, Boehringer, Ingelheim, Daiichi Sankyo, Eisai, GlaxoSmithKline, Lilly, Novartis, Roche, Sanofi, Takeda, UCB, and ViiV Healthcare. Yale Open Access Data that has results available for >200 trials http://yoda.yale.edu/ 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/ 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/

Adapted from the study by Relevo and Balshem [21].

access, and once received, the data itself may be in nonstandard formats so that a robust meta-analysis is difficult to undertake, and it may place heavy demands on the project's resources [30,35,36,38]. 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 with unpublished data (83%), and a wider range of named adverse effects are listed in unpublished data [32]. When published and unpublished data originate from the same study, the unpublished version is more likely to contain adverse effects data (95%) compared with the published version (46%) [30]. Similarly, in other research, inconsistencies were evident with adverse effects in published documents coded to appear less severe with reduced incidence when compared with the unpublished CSRs. Adverse events reported in the published article were in a range of 3–33% of those reported in the corresponding CSR summaries [35]. When discrepancies between published and unpublished data are discovered, it is recommended to attempt a sensitivity analysis to determine the potential impact on review findings and 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 [32,41]. It is recommended that review authors specify the number of unpublished studies identified and document where details of adverse effects data were inaccessible [30].

1.5. 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 guidelines or the PRISMA harms extension [15,42]. 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 [22]. It is particularly important to report all the sources used—both published and unpublished—to enable its comprehensiveness to be judged.

2. 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 [14,23,26]. Research must continue to inform practice and lead to further improvement in the quality of searches [1]. 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.

CRediT authorship contribution statement

Su Golder: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Guy Peryer:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Yoon K. Loke:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing.

References

[1] Golder S, Loke YK, Zorzela L. Some improvements are apparent in identifying adverse effects in systematic reviews from 1994 to 2011. J Clin Epidemiol 2013;66:253–60.

[2] Farrah K, Mierzwinski-Urban M, Cimon MK. Playing it safe: validating search filters for adverse events 2013: Poster presented at: 2013 Annual Meeting and Exhibition of the Medical Library Association, the 11th International Congress on Medical Librarianship (ICML), the 7th International Conference of Animal Health Information Specialists (ICAHIS), and the 6th International Clinical Librarian Conference (ICLC) One Health: Information in an Interdependent World. Boston, MA: Available at http://www.cadth.ca/media/is/MLA-Poster_Kelly.pdf. Accessed June 10, 2019.

[3] Farrah K, Mierzwinski-Urban M, Cimon K. Effectiveness of adverse effects search filters: drugs versus medical devices. J Med Libr Assoc 2016;104:221–5.

[4] Golder S, Loke YK, Zorzela L. Comparison of search strategies in systematic reviews of adverse effects to other systematic reviews. Health Info Libr J 2014;31:92–105.

[5] Golder S, Wright K, Loke YK. The feasibility of a search filter for the adverse effects of nondrug interventions in MEDLINE and Embase. Res Synth Methods 2017;8:506–13.

[6] Golder S, 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.

[7] Golder S, Loke YK, Bland M. Comparison of pooled risk estimates for adverse effects from different observational study designs: methodological overview. PLoS One 2013;8:e71813.

[8] Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Ther Adv Drug Saf 2011;2(2):59–68.

[9] Golder S, Loke YK. Sources of information on adverse effects: a systematic review. Health Info Libr J 2010;27:176–90.

[10] Alves C, Batel-Marques F, Macedo AF. Data sources on drug safety evaluation: a review of recent published meta-analyses. Pharmacoepidemiol Drug Saf 2012;21(1):21–33.

[11] Golder S, Loke YK. The contribution of different information sources for adverse effects data. Int J Technol Assess Health Care 2012;28(2):133–7.

[12] Golder S, Loke YK, Bland M. Unpublished data can be of value in systematic reviews of adverse effects: methodological overview. J Clin Epidemiol 2010;63:1071–81.

[13] Golder S, Wright K, Rodgers M. Failure or success of search strategies to identify adverse effects of medical devices: a feasibility study using a systematic review. Syst Rev 2014;3:113.

[14] CIOMS. Evidence Synthesis and Meta-Analysis: Report of CIOMS Working Group X. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS); 2016.

[15] Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ 2016;352:i157.

[16] Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2009.

[17] 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;29:28–38.

[18] Golder S, Loke YK. Failure or success of electronic search strategies to identify adverse effects data. J Med Libr Assoc 2012;100:130–4.

[19] Chou R, Aronson N, Atkins D, Ismaila AS, Santaguida P, Smith DH, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol 2010;63:502–12.

[20] Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 2007;7:32.

[21] Relevo R, Balshem H. Finding evidence for comparing medical interventions: AHRQ and the effective health care program. J Clin Epidemiol 2011;64:1168–77.

[22] Golder S, Loke Y. Search strategies to identify information on adverse effects: a systematic review. J Med Libr Assoc 2009;97:84–92.

[23] Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ 2014;348:f7668.

[24] McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol 2016;75:40–6.

[25] Golder S, McIntosh HM, Duffy S, Glanville J. Developing efficient search strategies to identify reports of adverse effects in MEDLINE and EMBASE. Health Info Libr J 2006;23:3−12.
[26] Golder S, Wright K, Rodgers M. The contribution of different information sources to identify adverse effects of a medical device: a case study using a systematic review of spinal fusion. Int J Technol Assess Health Care 2014;30(4):423−9.
[27] Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in medline and Embase. Health Info Libr J 2018;35:121−9.
[28] Golder S, Wright K, Loke YK. The development of search filters for adverse effects of surgical interventions in MEDLINE and Embase. Edinburgh, UK: 25th Cochrane Colloquium; 2018:16−8.
[29] Golder S, Farrah K, Mierzwinski-Urban M, Wright K, Loke YK. The development of search filters for adverse effects of medical devices in MEDLINE and Embase. Edinburgh, UK: 25th Cochrane Colloquium; 2018:16−8.
[30] Golder S, Loke YK, Wright K, Norman G. Reporting of adverse events in published and unpublished studies of health care interventions: a systematic review. PLoS Med 2016;13:e1002127.
[31] Golder S, Loke YK. The performance of adverse effects search filters in MEDLINE and EMBASE. Health Info Libr J 2012;29:141−51.
[32] Golder S, Loke YK, Wright K, Sterrantino C. Most systematic reviews of adverse effects did not include unpublished data. J Clin Epidemiol 2016;77:125−33.
[33] Gorrell LM, Engel RM, Brown B, Lystad RP. The reporting of adverse events following spinal manipulation in randomized clinical trials—a systematic review. Spine J 2016;16(9):1143−51.
[34] Rosati P, Porzsolt F, Ricciotti G, Testa G, Inglese R, Giustini F, et al. Major discrepancies between what clinical trial registries record and paediatric randomised controlled trials publish. Trials 2016;17:430.
[35] Schroll JB, Penninga EI, Gøtzsche PC. Assessment of adverse events in protocols, clinical study reports, and published papers of trials of Orlistat: a document analysis. PLoS Med 2016;13(8):e1002101.
[36] Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, et al. Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. PLoS Med 2013;10(10):e1001526.
[37] Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov — the final rule. N Engl J Med 2016;375(20):1998−2004.
[38] Strom BL, Buyse ME, Hughes J, Knoppers BM. Data sharing — is the juice worth the squeeze? N Engl J Med 2016;375(17):1608−9.
[39] Song F, Hooper L, Loke YK. Publication bias: what is it? How do we measure it? How do we avoid it? Rep Med Imaging 2012;5(1):71−81.
[40] Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess 2010;14(8):1−193.
[41] Golder S, Loke YK. Is there evidence for biased reporting of published adverse effects data in pharmaceutical industry-funded studies? Br J Clin Pharmacol 2008;66(6):767−73.
[42] Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R. Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates. Methodological standards for the conduct of Cochrane Intervention Reviews (Version 1.07 - last update November 2018). Available at https://community.cochrane.org/mecir-manual. Accessed June 10, 2019.