

Chapter 14: Adverse effects

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Key points

- To achieve a balanced perspective, all reviews should try to consider the adverse aspects of the interventions.
- A detailed analysis of adverse effects is particularly relevant when evidence on the potential for harm has a major influence on treatment or policy decisions.
- Interventions may have many different adverse effects, and reviews may need to focus on a few important ones in detail, together with a broader, more general summary of other potential adverse effects.
- As adverse effects data are often handled with less rigour than the primary outcomes of a study, the intensity of the monitoring of adverse effects and the clarity of reporting them need careful scrutiny.
- Data on adverse effects are often sparse, but the absence of information does not mean that the intervention is safe.

14.1 Introduction

14.1.1 The need to consider adverse effects

Every healthcare intervention comes with the risk, great or small, of harmful or adverse effects. A Cochrane review that considers only the favourable outcomes of the interventions that it examines, without also assessing the adverse effects, will lack balance and may make the intervention look more favourable than it should. This source of bias, like others, should be minimized. All reviews should try to include some consideration of the adverse aspects of the interventions.

This chapter addresses special issues relating to adverse effects in Cochrane reviews, with an emphasis on reviews in which adverse effects might be addressed using methods differing from those for other

outcomes. Although in principle adverse effects are most reliably assessed using randomized trials, in practice many adverse events are too uncommon or too long-term to be observed within randomized trials, or may not have been known when the trials were planned. A Cochrane review may use one of several strategies for addressing adverse effects, which differ in the extent to which the same methods are used to evaluate intended (beneficial) and unintended (beneficial or adverse) effects. The present chapter focuses on adverse effects that are usually taken to be unintended (Miettinen 1983). The different strategies for a review are discussed in Section 14.2.

14.1.2 Concepts and terminology

Many terms are used to describe harms associated with healthcare interventions. This can confuse review authors, particularly as published papers often use terms loosely and interchangeably. Some common related terms include ‘adverse event’ (an unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it), ‘adverse effect’ (an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility), ‘adverse drug reaction’ (an adverse effect specific to a drug), ‘side effect’ (any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment), and ‘complications’ (adverse events or effects following surgical and other invasive interventions).

14.1.3 When it is most important to consider adverse effects

The resources devoted to including adverse outcomes in reviews should be considered in relation to the importance of the intervention itself. If an intervention clearly does not work, or has little potential benefit and is not widely used, it may not be worth devoting resources towards a detailed evaluation of adverse effects. On the other hand, a detailed analysis of adverse effects would be warranted if the information on potential harm appears to be essential in guiding decisions of clinicians, consumers and policymakers.

Table 14.1.a exemplifies situations where analysis of adverse effects has an important role in treatment decisions.

Table 14.1.a: Contexts and examples warranting detailed examination of adverse effects

When the margin between benefits and adverse effects is narrow	
Treatment is of modest or uncertain benefit, with an important possibility of adverse effects.	<ul style="list-style-type: none"> Aspirin for prevention of cardiovascular events in a healthy patient; increase in haemorrhage. Antibiotics for acute otitis media in children; risk of rash and diarrhoea. Urgent direct current cardioversion in patients with new atrial fibrillation who are cardiovascularly stable; risk of stroke from cardioversion.
Treatment is potentially highly beneficial, but there are major safety concerns.	<ul style="list-style-type: none"> Aspirin for patient with a stroke, but who has a past history of gastrointestinal haemorrhage. Carotid endarterectomy in older patients with ischaemic heart disease who present with stroke.
Treatment is potentially beneficial in long-term, or to community, but no immediate direct benefit to individual.	<ul style="list-style-type: none"> Improving uptake of a vaccine to promote herd immunity, while trying to assuage fears about early serious neurological adverse effects.

When a number of efficacious treatments differ in their safety profiles

Treatments are of equivalent efficacy, but they have different safety profiles.

- Antiepileptic drugs for women of childbearing age with epilepsy.
- A new insulin injection device is thought to cause less pain than the existing device.
- Disease-modifying drug in erosive rheumatoid arthritis, e.g. using hydroxychloroquine (relatively safe) or methotrexate (potentially more effective, but less safe).
- Polychemotherapy versus sequential single agent chemotherapy for metastatic breast cancer.

The balance of benefits and adverse effects differs substantially, e.g. the most efficacious intervention may have serious adverse effects, while the less effective intervention is potentially safer.

When adverse effects deter a patient from continuing on an efficacious treatment

Treatment is of considerable benefit but adverse effects threaten patients' adherence, and evidence is needed to guide further management.

- An effective intervention has well-recognized adverse effects, which can make it difficult for the patient to continue therapy. Evidence is needed on whether reducing the intensity of the intervention (e.g. lower dose or duration) will help avoid the adverse effects, or whether there is a treatment strategy that can prevent adverse effects (e.g. proton pump inhibitor for peptic ulcers caused by aspirin).

14.2 Scope of a review addressing adverse effects

14.2.1 Identical methods for beneficial and adverse effects

In this section, and in Sections 14.2.2 and 14.2.3, we describe three broad strategies that a Cochrane review may use to address adverse effects. The first strategy is to assess intended (beneficial) and unintended (adverse) effects together using the same methodology, applying common eligibility criteria (in terms of types of studies, types of participants and types of interventions).

This approach implies that a single search strategy may be used. A critical issue is how review authors deal with the three datasets that may potentially arise:

- (a) Studies that report both the beneficial effects and adverse effects of interest.
- (b) Studies that report beneficial effects but not adverse effects.
- (c) Studies that report adverse effects, but not the beneficial outcomes of interest.

Studies of type (a) have the important advantage that benefits and adverse effects can be compared directly, since the data are derived from the same population and setting. Furthermore, evidence on benefits and adverse effects arises from studies with similar designs and quality. However, data on adverse effects may be very limited and in particular may be restricted to short-term harms because of the relatively short duration of included studies.

Evaluation of benefits and adverse effects using some combination of the three types of study (rather than (a) alone) will increase the amount of information available. For instance, datasets (a) and (b) could be used to evaluate beneficial effects, while (a) and (c) could be used to assess adverse effects.

However, as the studies addressing adverse effects differ from those addressing beneficial effects, authors should note that it is difficult to compare benefits and adverse effects directly.

14.2.2 Different methods for beneficial and adverse effects

The second strategy is to use different eligibility criteria for selecting studies that address unintended (adverse) effects compared with studies that address intended (beneficial) effects.

Different types of studies may be needed to evaluate different outcomes (Glasziou 2004). The use of different eligibility criteria specifically addresses the problem that most experimental studies (such as randomized trials) are insufficient to evaluate rare, long-term or previously unrecognized adverse effects (see Section 14.4). This approach allows a more rigorous evaluation of adverse effects, but takes more time and resources, and means that benefits and adverse effects can often not be compared directly. While randomized trials have the advantage that the allocation of interventions is made by the randomization process, non-randomized studies involve different mechanisms for allocating interventions, and these should be scrutinized during the review.

14.2.3 Separate review for adverse effects

The third strategy is to undertake a separate review of adverse effects alone. This might be appropriate for an intervention that is given for a variety of diseases or conditions, yet whose adverse effect profile might be expected to be similar in different populations and settings. For example, aspirin is used in a wide variety of patients, such as those with stroke, or peripheral vascular disease, and also in those with coronary artery disease. The main effects of aspirin on outcomes relevant to these different conditions would typically be addressed in separate Cochrane reviews, but adverse effects (such as bleeding into the brain or gut) are sufficiently similar within the different disease groups that an independent review might address them together. Indeed, unless trials exist on combined populations, such a question would be difficult to address in any other way.

Similarly, there may be limited adverse effects data for an intervention in a sub-population, such as children. It may be worth analysing all available data for this sub-population (e.g. adverse effects of selective serotonin reuptake inhibitors in children), even if the trials were aimed at different disease conditions.

Authors of reviews of adverse effects alone must aim to provide adequate cross referencing (preferably through electronic links) to related reviews of intended effects of the intervention. If new safety concerns are identified when an efficacy review is updated, then the adverse effects review should be updated as soon as possible.

14.3 Choosing which adverse effects to include

14.3.1 Narrow versus broad focus

The selection of adverse outcomes to include in a review can be difficult. Specific adverse effects associated with an intervention may be known in advance of the review; others will not. Which effects will be most relevant to the review may be uncertain beforehand. The following general strategies may be used depending on the study question and the therapeutic or preventive context.

Narrow focus

A detailed analysis of one or two known or a few of the most serious adverse effects that are of special concern to patients and health professionals.

Advantages: Easiest approach, especially with regard to data collection. Can focus on important adverse effects and reach a meaningful conclusion on issues that have a major impact on the treatment decision (McIntosh 2004).

Disadvantages: Scope may be too narrow. Method is only really suitable for adverse events that are known in advance.

Broad focus

To detect a variety of adverse effects, whether known or previously unrecognized.

Advantages: Wider coverage, and can evaluate new adverse effects that we may not have previously been aware of.

Disadvantages: Potentially large volume of work with particular difficulties in the data collection process. Some researchers have found broad, non-specific evaluations to be very resource-intensive, with little useful information to show for the effort expended (McIntosh 2004). These researchers also point out that previously unrecognized adverse effects may be best detected through primary surveillance, rather than in a systematic review.

In order to address adverse effects in a more organized manner, review authors may choose to narrow down the broad focus into some of the following areas:

- The five to ten most frequent adverse effects.
- **All** adverse effects that either the patient or the clinician considers to be serious.
- By category, for example:
 - Diagnosed by lab results (e.g. hypokalaemia); or
 - Patient-reported symptoms (e.g. pain).

14.3.2 Withdrawal or drop-out as an outcome measure for adverse effects

Withdrawal or drop-out is often used as an outcome measure in trial reports. Review authors should hesitate to interpret such data as surrogate markers for safety or tolerability because of the potential for bias:

- The attribution of reason(s) for discontinuation is complex and may be due to mild but irritating side effects, toxicity, lack of efficacy, non-medical reasons, or a combination of causes (Ioannidis 2004).
- The pressures on patients and investigators under trial conditions to keep the number of withdrawals and drop-outs low can result in rates that do not reflect the experience of adverse events within the study population.
- Unblinding of intervention assignment often precedes the decision to withdraw. This can lead to an over-estimate of the intervention's effect on patient withdrawal. For example, symptoms of patients in the placebo arm are less likely to lead to discontinuation. Conversely, patients in the active intervention group who complained of symptoms suggesting adverse effects may have been more readily withdrawn.

14.4 Types of studies

Most Cochrane reviews focus on randomized trials, which provide the most reliable estimates of effect. However, rare adverse events or long-term adverse effects are unlikely to be observed in clinical trials, and a thorough investigation may require the inclusion of cohort studies, case-control studies and even case reports or case series. In particular, the strategies outlined in Sections 14.2.2 and 14.2.3 are likely to be chosen specifically so that different study designs are included to address adverse effects. For more detailed discussion of issues in the inclusion of non-randomized studies (including case-control and cohort studies) in a Cochrane review, see Chapter 13 (Section 13.2). Some issues to consider in the inclusion of case reports appear in Section 14.6.3.

14.5 Search methods for adverse effects

14.5.1 Sources of information on adverse effects of drugs

In addition to the usual sources of evidence, described in Chapter 6, review authors who are planning an exhaustive search for adverse effects of a drug may wish to consider checking the following sources:

- Standard reference books on adverse effects such as Meyler's Side Effects of Drugs, the Side Effects of Drugs Annuals (SEDA), Martindale: The Complete Drug Reference, Davies Textbook of Adverse Drug Reactions and the papers they summarize.
- Regulatory authorities may issue safety alerts for a variety of commercial products based on information submitted to them by the manufacturer (which have not been published or made available elsewhere). Examples of safety bulletins can be found:
 - in the UK: Current Problems in Pharmacovigilance (www.mhra.gov.uk);
 - in Australia: the Australian Adverse Drug Reactions Bulletin (www.tga.gov.au/adr/aadrb.htm);
 - in the European Public Assessment Reports from the European Medicines Evaluation Agency (www.emea.eu);
 - in the US: Food and Drug Administration FDA Medwatch (www.fda.gov/medwatch).
- Specialist drug information databases such as full-text databases (e.g. Pharmanewsfeed and Iowa Drug Information Service (IDIS)), bibliographic databases (e.g. Derwent Drug File, TOXLINE, Pharmline) and referenced summary databases (e.g. Drugdex, XPhram). However, review authors will have to consider the subscription costs to these specialist databases, particularly as their usefulness or additional yield have yet to be formally evaluated in the systematic review setting.

Review authors can also apply (usually on payment of a fee) to the WHO Uppsala Monitoring Centre (UMC; www.who-umc.org) for special searches of their spontaneous reporting database (Vigibase); this was for example done for a Cochrane review on melatonin (Herxheimer 2002). However, the rank order of the most common adverse effects reported for one particular drug in the UMC database was found to differ from the data derived from a meta-analysis of double-blind, randomized trials (Loke 2004): the UMC data on amiodarone showed thyroid problems to have the highest frequency, with skin reactions coming second, whereas the meta-analysis showed heart problems to be most common, followed by thyroid disorders.

Primary surveillance data (in the form of spontaneous case reports) are also freely available via the web sites of the regulatory authorities in Canada, USA, UK, and The Netherlands. However, the format of the information varies considerably, and interpretation and analysis of these databases require specialist skills (see also Section 14.6.3).

14.5.2 Search strategy for adverse effects

The optimal search strategy for specifically identifying reports of adverse effects has yet to be established (Golder 2006). Two main approaches can be used: using index terms and free-text searching. Both of these have limitations; it is advisable to combine them to maximize sensitivity (the likelihood of not missing studies that might be relevant). The development of a search strategy is likely to require several iterations. For instance, it may be necessary to repeat the electronic search incorporating additional index terms, subheadings and free-text terms derived from the terms used to index and describe the studies initially identified as relevant. In deciding which combination of terms to use, authors will need to balance comprehensiveness (sensitivity) against precision. Some considerations in the use of index terms and free text terms follow.

14.5.2.1 Searching electronic databases for adverse effects using index terms

Index terms (also called controlled vocabulary or thesaurus terms) such as Medical Subject Headings (MeSH) in MEDLINE and Emtree in EMBASE are assigned to records in electronic databases to describe the studies. MEDLINE and EMBASE employ few useful indexing terms for adverse effects; they include DRUG TOXICITY/ and ADVERSE DRUG REACTION SYSTEMS in MEDLINE and DRUG TOXICITY/ and ADVERSE DRUG REACTION/ in EMBASE. However, the most useful way to search for adverse effects is by using subheadings (Golder 2006). Subheadings can be attached to index terms to describe specific aspects, for example 'side effects' of drugs, or 'complications' of surgery, or they can be used where they are searched for attaching to any index term (floating subheadings). The subheadings used to denote data on adverse effects differ in the major databases MEDLINE and EMBASE, for example:

Aspirin/adverse effects (MEDLINE)

Acetylsalicylic-acid/adverse-drug-reaction (EMBASE)

In the above example, Aspirin is the MeSH term and adverse effects is the subheading; Acetylsalicylic-acid is the Emtree term and adverse-drug-reaction is the subheading.

Within a database, studies may be (i) indexed under the name of the intervention together with a subheading to denote that adverse effects occurred, for example, Aspirin/adverse effects or Mastectomy/complications; or (ii) the adverse event itself may be indexed, together with the nature of the intervention, for example, Gastrointestinal Hemorrhage/ and Aspirin/ , or Lymphedema/ and Surgery/; or (iii) occasionally, an article may be indexed only under the adverse event, for example, Hemorrhage/chemically-induced.

Thus, no single index or subheading search term can be relied on to identify all data on adverse effects, but a combination of index terms and subheadings is useful in detecting reports of major adverse effects which the indexers are likely to regard as significant (Derry 2001).

Subheadings that can be used with the intervention or with all interventions (floated) and which may prove useful in MEDLINE are:

/adverse effects (NB if this subheading is exploded it will include the subheadings /poisoning and /toxicity)

/poisoning

/toxicity

/contraindications

Subheadings that can be used with the adverse outcome or with all outcomes (floated) and which may prove useful in MEDLINE are:

/chemically induced

/complications

Subheadings that can be used with the intervention or with all interventions (floated) and which may prove useful in EMBASE are:

/adverse drug reaction

/drug toxicity

Subheadings that can be used with the adverse outcome or with all outcomes (floated) and which may prove useful in EMBASE are:

/complication

/side effect

14.5.2.2 Searching electronic databases for adverse effects using free-text terms

Free-text terms (also called text words) are used by authors in the title and abstract of their studies when published as journal articles; these terms are then searchable in the title and abstract of electronic records in databases. Two important problems severely limit the usefulness of free-text searching:

1. The wide range of terms authors use to describe adverse effects, both in a general sense (toxicity, side effect, adverse effects) and more specifically (for example, lethargy, tiredness, malaise may be used synonymously).
2. The free-text search does not detect adverse effects that are not mentioned in the title or abstract of the study and are, therefore, not included in the electronic record (even though the full report describes them) (Derry 2001).

A highly sensitive free-text search should incorporate the potentially wide variety of synonymous terms while also taking into account different conventions in spelling and variations in the endings of terms to include, for example, singular and plural terms. This should then be combined with free-text terms involving the intervention of interest, for example:

(aspirin or acetylsalicylic acid) and (adverse or side or hemorrhage or haemorrhage or bleed or bleeding or blood loss).

14.6 Assessing risk of bias for adverse effects

14.6.1 Clinical trials

Although the general advice is to assess risk of bias in clinical trials as described in Chapter 8, authors must also consider other specific factors that may have a larger influence on the adverse effects data. Areas of special concern include methods for monitoring and detecting adverse effects, conflicting interests (Jüni 2004), selective outcome reporting (Chan 2004) and blinding (Schulz 2002).

The primary outcome measure of an intervention may have been studied in a placebo controlled, well-masked, adequately concealed randomized trial. In contrast, the adverse effects data may be collected retrospectively, for example via an end-of-study questionnaire sent out only to those who are known to have received the active intervention. Although a low risk of bias may be assigned to the primary outcomes, the way in which harmful effects of the interventions are monitored may not permit a similar rating. The recommended risk of bias tool, implemented in RevMan, allows for different assessments of blinding and of incomplete outcome data for each outcome, or for a class of outcomes as defined by the review author.

The methods used in monitoring or detecting adverse effects are known to have a major influence on adverse effect frequencies: studies in which adverse effects are carefully sought will report a higher frequency than studies in which they are sought less carefully. For example, in a group of hypertensive patients, passive monitoring based on spontaneous reports yielded rates of 16%, while active surveillance using specific questioning found a rate of 62% (Olsen 1999). As different methods of monitoring adverse effects will yield different results, it may be difficult to compare studies, and pointless to do a formal meta-analysis (Edwards 1999). Duration and frequency of monitoring should also be noted.

Studies with limited follow-up or infrequent monitoring may not reliably detect adverse effects; the absence of information must not be interpreted as indicating the intervention is safe. In contrast, studies with rigorous follow-up and active surveillance for pre-defined adverse effects may be able to generate evidence that the intervention genuinely has few adverse effects.

Finally, the age of an intervention and the evolution of its use are likely to be related to the types of adverse events detected and their number. This is obvious for long-term effects such as carcinogenicity, but also because some interventions, for example in surgery, change more or less subtly over time.

Examples of potentially useful questions to consider in assessing the quality of evidence on adverse effects are:

On conduct:

- Are definitions of reported adverse effects given?
- Were the methods used for monitoring adverse effects reported? Use of prospective or routine monitoring; spontaneous reporting; patient checklist, questionnaire or diary; systematic survey of patients?

On reporting:

- Were any patients excluded from the adverse effects analysis?
- Does the report provide numerical data by intervention group?
- Which categories of adverse effects were reported by the investigators?

14.6.2 Case-control and cohort studies

While the study of beneficial effects almost always necessitates randomized trials, adverse effects of treatment can often be effectively investigated in non-randomized studies (Miettinen 1983).

Vandenbroucke has proposed that observational studies of adverse effects of medical interventions offer some of the best chances for unbiased observational studies (Vandenbroucke 2004). This idea was empirically verified by a comparison of randomized and observational studies of adverse effects, which found that, if anything, risk estimates from observational studies were lower (Papanikolaou 2006)). In some instances where observational studies showed markedly higher risks, they better reflected actual patient care (Vandenbroucke 2006). Like any study, case-control and cohort studies are potentially susceptible to bias, and any limitations of the data should therefore be critically discussed. See Chapter 13 (Section 13.5) for further discussion of assessing risk of bias in such studies. Jick has drafted a taxonomy of the type of study that is most likely to detect an adverse effect, as well as the type of study that is necessary for verification (Jick 1977).

14.6.3 Case reports

Case reports of adverse events are widely found in the published literature, and are also collated by regulatory agencies. There are specific methodological problems with the evaluation of such case reports. Review authors who are potentially interested in such data will need to consider the following issues.

Do the reports have good predictive value?

Anecdotal reports may turn out to be false alarms on subsequent investigation, rather than genuine indicators of the link between the intervention and adverse effect. Although one study has claimed that three quarters of a collection of anecdotal case reports from 1963 were correct (Venning 1982), a more recent systematic survey of 63 suspected adverse reactions found that most (52 of 63, 82.5%) had not yet been evaluated in more detail (Loke 2006). Controlled study data supporting the postulated link between drug and adverse event were available in only three cases, while in two cases controlled studies failed to confirm the link. Nevertheless, product information sheets or drug monographs may have been amended to include listings of these adverse events. It is thus not easy to tell whether a case report is a genuine alert or a false alarm. Still, case reports remain the cornerstone of the initial detection of new adverse effects (Stricker 2004). The removal of drugs from the market is overwhelmingly based on case reports and case series, in the past as well as in the present (Venning 1983, Arnaiz 2001). Removal of a drug from the market due to a dramatic effect does not require formal control groups (Glasziou 2007).

Determining causality

There is usually uncertainty as to whether the adverse event was caused by the intervention (particularly in patients who are taking a wide variety of treatments). Review authors must decide on the likelihood of the intervention having a causative role, or whether the occurrence of the adverse event during the intervention period was simply a coincidence. However, two independent review authors might not reach the same judgement from the same case report. Several studies have evaluated the responses of review authors who were asked to appraise reports of adverse event. In one study, complete agreement was obtained only 35% of the time between two observers who used causality criteria in an algorithm for assessing suspected adverse reactions (Lanctot 1995). In another study, three clinical pharmacologists, who evaluated 500 reports of suspected reactions, failed to agree on the culprit drug in 36% of the cases (Koch-Weser 1977).

Is there a plausible biological mechanism linking the intervention to the adverse event?

A reported adverse event is more plausible if it can be explained by a well-understood biological mechanism. For example, amiodarone has an iodine-like chemical structure, which explains the commonly seen adverse effects on thyroid function.

Do the reports provide enough information to allow detailed appraisal of the evidence?

One study looked at 1520 published case reports of suspected adverse reactions, and found substantial differences in the information provided in these reports (Kelly 2003). With regard to details of patient characteristics, only three patient variables were reported more than 90% of the time, while 12 others were reported less than 25% of the time. In assessing the culprit drug, Kelly found that only one drug variable (for instance dose or duration or frequency or exact formulation) was reported more than 90% of the time; six others were reported 14 to 74% of the time. The substantial variation in the nature of the reporting means that detailed appraisal is difficult for review authors.

Are there any potential problems from using data from the reports, which might outweigh the perceived benefit of being comprehensive?

There is a trade-off between the desire to be 'all-inclusive' and the need to avoid publicizing biased or unreliable information that may trigger a false alarm. The MMR vaccination programme was disrupted by anecdotal reports in a reputable journal, with scores of people in the UK harmed by measles outbreaks from decreased vaccine uptake (Asaria 2006). The inclusion of extra (but potentially unreliable) information on 'adverse events' can have harmful effects, and review authors will need to carefully consider the negative impact and legal ramifications of conveying such information.

14.7 Chapter information

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Box 14.7.a: The Cochrane Adverse Effects Methods Group

The Adverse Effects Methods Group (AEMG) provides methodological guidance on the appropriate techniques for the identification and systematic assessment of adverse effects. The origins of the AEMG date back almost a decade to the informal meetings of a few individuals who were involved in systematically evaluating the harmful effects of interventions. This led, in January 2001, to the formation of the Adverse Effect Subgroup as part of the Non-Randomised Studies Methods Group. In June 2007, the Adverse Effects Methods Group (AEMG) was officially registered.

The fundamental tenet of the AEMG is that every healthcare intervention carries some risk of harm. In order to reach a fully-informed decision, treatment choices need to be supported by a systematic assessment of benefits and harms. Reviews that focus mainly on treatment benefit, together with lack of information on harmful effects, would create difficulties for people who are trying to make balanced decisions. The AEMG aims to redress this imbalance, and aims to collaborate with Review Groups and Methods Groups to improve the methodology and quality of adverse effects analyses. The AEMG will be happy to look into any areas of methodological uncertainty that require further research, and hopes to develop and disseminate appropriate ways of filling any gaps that are identified.

Web site: aemg.cochrane.org

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