Chapter 19: Adverse Effects
Guidance on searching for adverse effects

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My background

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   https://methods.cochrane.org/adverseeffects/
❖ Research interests: systematic reviews, literature searching, adverse effects, unpublished data, social media research
Structure for today’s webinar

1. Importance of adverse effects
2. Issues with searching for adverse effects
3. Approaches to searching for adverse effects
Importance of adverse effects
What is an adverse effect?

An unfavourable or harmful outcome that occurs during or after the use of a drug or other intervention for which there is at least a reasonable possibility of a causal relationship between the intervention and the event.
Types of interventions in systematic reviews of adverse effects

Section 19.1

Drugs

Surgery

Physical interventions

Other

Diagnostic tests
“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.”
Issues with searching for adverse effects
Special issues for searching for adverse effects

- **Poor reporting** in titles and abstracts and indexing

- **Inconsistent terminology and indexing**

- May wish to identify **all** adverse effects. Hard to predict/plan.

- **Range of study designs**, not just RCTs

Section 19.1.2 and section 19.1.2.3
Approaches to searching for adverse effects
Search method

- **Single search**
  - Retrieves studies evaluating both benefits and harms
  - Not recommended
  - Study designs to evaluate adverse effects may be different to those reporting efficacy.
  - Adverse effects are not necessarily limited to the condition or types of participant.
  - More likely need separate searches
Sources to search

- Performing a search in MEDLINE alone is not recommended.
- **Wide breadth of sources** needed to ensure identification of relevant data.
- **Unpublished sources** particularly important for adverse effects data.
- Examples include **clinical study reports (CSR), trials registers** and **regulatory agency websites**.
Planning a search

<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population/Problem</td>
<td>Intervention/Exposure</td>
<td>Comparison</td>
<td>Outcome</td>
</tr>
<tr>
<td>Population characteristics or health issue of interest</td>
<td>Drug, surgery, policy, community program, etc.</td>
<td>No intervention, common practice, control group</td>
<td>Health outcomes of interest</td>
</tr>
</tbody>
</table>

Outcome = adverse effects
Which adverse effects to look for

- **Confirmatory approach**
  - Review authors list one or more adverse effects as outcomes of interest in their review protocol

- **Exploratory approach**
  - Involves extracting any, or all, of the adverse event data found within the included studies.

- **Hybrid approach**
  - Combines elements of both confirmatory and exploratory approaches to capture anticipated and previously unrecognized adverse effects
Example Cochrane Reviews

Confirmatory approach
- Combined oral contraceptives: venous thrombosis
- Progestin-only contraceptives: effects on weight

Exploratory approach
- Adverse side effects of dexamethasone in surgical patients
- Adverse events in people taking macrolide antibiotics versus placebo for any indication
Searching on outcomes

**Specific** adverse effects terms (headache, death)
- Textwords (Title/Abstract)
- Indexing terms (MeSH/EMTREE)

**Generic** adverse effects terms (harms, side effects)
- Textwords (Title/Abstract)
- Indexing terms (MeSH/EMTREE)
- Subheadings/qualifiers
- Search filters/hedges
Title: Adverse events associated with prolonged antibiotic use.


MeSH Subject Headings:
- Adolescent
- Adult
- Adverse Drug Reaction Reporting Systems
- Aged
- Amoxicillin / ad [Administration & Dosage]
- Amoxicillin / ae [Adverse Effects]
- Anthrax / pc [Prevention & Control]
- *Anti-Bacterial Agents / ae [Adverse Effects]
Free text adverse effects terms

❖ Examples

adrs, adverse drug effect*, adverse drug reaction*, adverse effect*, adverse event*, adverse outcome*, adverse reaction*, complication*, harm, harmful, harms, risk, safe, safely, safety, side effect*, tolerability, toxicity, treatment emergent, undesirable effect*, undesirable event*, unexpected effect*, unexpected event*

❖ Warning!

False hits; ‘relative risk’, ‘risk of bias’, ‘self-harm’, ‘patient safety’, ‘adverse effects were not considered’
Generic MeSH terms

- **Hazards**
  - risk assessment/

- **Surgery**
  - intraoperative complications/
  - postoperative complications/
  - postoperative pain/

- **Device**
  - equipment contamination/
  - equipment failure/
  - equipment failure analysis/
  - equipment safety/
  - medical device recalls/
  - safety-based medical device recalls/
  - safety-based medical device withdrawals/

- **Drugs**
  - abnormalities, drug induced/
  - adverse drug reaction reporting systems/
  - drug recalls/
  - drug hypersensitivity/
  - drug monitoring/
  - drug related side effects and adverse reactions/
  - poisoning/
  - safety-based drug withdrawals/
  - substance-related disorders/

- **Drug/device**
  - product surveillance postmarketing/

Many of these terms can be exploded to include narrower indexing terms.
MEDLINE
Attached to intervention
‘Aspirin/ae’
Aspirin is the MeSH term and adverse effects is the subheading

Attached to adverse effect
‘headache/ci’
Headache is the MeSH term and chemically induced is the subheading

Embase
‘Acetylsalicylic-acid/ae’
Acetylsalicylic-acid is the EMTREE term and adverse-drug-reaction is the subheading

‘headache/si’
Headache is the EMTREE term and side effect is the subheading
How to use subheadings (2)

- **Free floating subheadings**
  
  Subheadings attached to any indexing term

- **Examples for OVID MEDLINE**
  
  `ae.fs.` (adverse effects)
  (or exploded `ae.xs.` to include toxicity and poisoning)
  `ci.fs.` (chemically induced)
  `co.fs.` (complications)
  `ct.fs.` (contraindications)
  `de.fs.` (drug effects)
  `po.fs.` (poisoning)
  `to.fs.` (toxicity)
Summary

- Likely require *separate search* for adverse effects and efficacy
- The search process needs to be *reported* for all searches
- Searching on *generic* and/or *specific adverse effects* terms may be necessary depending on the question
- Different search approaches are required for adverse effects of *drugs, medical devices and surgical procedures*
Guidance

- **Cochrane Handbook**

- **Overview Paper**

- **Search Filters**


Welcome to the Cochrane Adverse Effects Methods Group (CAEMG)

The Cochrane Adverse Effects Methods Group (AEMG) was formally registered with Cochrane on the 14th June 2007. The Group aims to develop the methods for producing high quality systematic reviews and to advise Cochrane on how the validity and precision of systematic reviews can be improved.

The main purposes of the group are;
• to raise awareness of the adverse effects of interventions, and to promote the inclusion of adverse effects data in Cochrane reviews;
• to provide educational help to reviewers and users of reviews to spread and deepen understanding of the principles involved in assessing adverse effects;
• to provide methodological guidance on specific aspects of evaluating adverse effects;
• to identify areas of methodological uncertainty, and to develop a toolbox for the assessment of adverse effects.
Questions
Further Reading


Section 19.7