Reporting of adverse events in systematic reviews

Sally Hopewell, Luke Wolfenden, Mike Clarke

UK Cochrane Centre
Systematic reviews aim to provide an unbiased assessment of the effects of healthcare interventions. Including information about the relative effects of an intervention provides people with a balanced and realistic account of the likely outcomes. Unintended effects (adverse) of an intervention are not usually investigated as thoroughly as its intended (beneficial) effects.
Beneficial effects are usually relatively frequent and apparent in the short term.

Adverse effects are often unanticipated, uncommon and may occur in the longer term.

A study of systematic reviews indexed in MEDLINE or published in CDSR (1996 – 2000) showed only 25% included safety as an outcome measure:

- the majority focused on efficacy outcomes.
- only 4% assessed safety as the primary outcome.

(Ernst et al 2001).
Incorporating information on adverse events poses a number of methodological challenges such as the:

- type of study design, search strategy, appraisal of methodological quality, methods of analysis.

There is a lack of up-to-date information about how adverse event data are incorporated into systematic reviews.

Information is needed to guide future research and training needs.
Objectives

- To assess how information about adverse events is currently included in systematic reviews.

- To identify problematic areas and quantify the frequency of these problems.
Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement

John P.A.年年底, MD; Stephen J.W. 년, MD; Peter C. 년, MD; Dorothy 년, MD; Robert T. 년, MD; Douglas G. 년, MD; for the CONSORT Group

In response to accumulating evidence and the consequences of poor-quality reporting of randomized, controlled trials (RCTs), many medical journals and editorial groups have now endorsed the CONSORT (Consolidated Standards of Reporting Trials) statement, a 22-item checklist and flow diagram. Because CONSORT was primarily aimed at improving the quality of reporting of efficacy, only 1 checklist item specifically addressed the reporting of safety. Considerable evidence suggests that reporting of harm-related data from RCTs also needs improvement. Members of the CONSORT Group, including journal editors and scientific societies, met in Montebello, Quebec, Canada, in May 2003 to address this problem. The result is the following document: the standard CONSORT checklist with 10 new recommendations about reporting harm-related data, accompanying explanations, and examples to highlight specific aspects of proper reporting. We hope that this document, in conjunction with other CONSORT-related materials (www.consort-statement.org), will help authors improve their reporting of harm-related data from RCTs. Better reporting will help readers critically appraise and interpret trial results. Journals can support this goal by revising instructions to Authors so that they refer authors to this document.

We therefore urge all journals to make CONSORT widely available to their readers. We also encourage anyone reviewing RCTs to consult this document when assessing the quality of harm reporting. The CONSORT Group believes that the following recommendations will improve the quality of harm reporting in all RCTs.

For more information, please visit our website at www.consort-statement.org.

Recommendations

- Title and Abstract
  - Recommendation 1. If the study collected data on harms and benefits, the title or abstract should state it.
  - The title should mention harms if the study of harms was a key trial objective. Many phase I and phase II trials, some phase III trials, and most phase IV trials (17, 18) target harms as primary outcomes. Yes, the title and abstract should contain the word “harm.” Among 375 but 135 articles in the Cochrane Central Register of Controlled Trials (Cochrane Library, issue 3, 2003), searching titles with the word trauma or harms yielded 337 references (compared with 5574 for efficacy and 23,415 for safety). Of the 337, excluding several irrelevant articles on self-harm or harm reduction, only 5 trial reports and 2 abstracts contained the word “harm” in their titles.

Improve Patient Care is supported by a grant awarded by the U.S. Department of Health and Human Services (HHS), Agency for Healthcare Research and Quality (AHRQ). The opinions expressed in this article are those of the authors and do not represent the position or endorsement of AHRQ or HHS.


Updated March 2005
Selection of systematic reviews

- All new Cochrane reviews published in Issue 1 2005 of CDSR in The Cochrane Library.

- All reviews, with the publication year 2003 and 2004, included in DARE for the first time in Issue 1 2005 of The Cochrane Library.
Data extraction

- Review details
- Title
- Abstract
- Participants
- Disease area
- Intervention
- Outcome measures
- Study design

- Searching for studies
- Assessment of methodological quality
- Collecting data
- Data analysis
- Interpreting results and conclusions
Data extraction and analysis

- Data extraction was carried out by one author.
- Where there was uncertainty regarding a particular review, this was checked by a second and third author where necessary.
- Data were collated in Excel and analysed using STATA (v8.2) for each data variable.
Inclusion criteria

**COCHRANE**
- 79 identified
- 1 excluded (screening review)
- 78 included
- 19 excluded (efficacy outcomes only)
- 59 (76%) included adverse events

**DARE**
- 89 identified
- 10 excluded (n=6 diagnostic reviews) (n=4 languages other than English)
- 79 included
- 41 excluded (efficacy outcomes only)
- 38 (48%) included adverse events
Definitions

- **Efficacy outcomes were defined as:**
  - those showing intended (beneficial) effects of an intervention.

- **Adverse outcomes were defined as:**
  - those showing unintended (adverse) effects of an intervention.
Number of Cochrane reviews reporting adverse events (76%)
Number of DARE reviews reporting adverse events (48%)
The terminology used varied - the most commonly used terms were:

- adverse event
- adverse effect
- side effect
- safety
- complications
## Type of intervention

<table>
<thead>
<tr>
<th></th>
<th>COCHRANE (n=78)</th>
<th>DARE (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All reviews:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>COCHRANE (n=59/78: 76%)</th>
<th>DARE (n=38/79: 48%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reviews reporting adverse events:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>41 (93%)</td>
<td>29 (63%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>11 (92%)</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (32%)</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>
## Type of study design

<table>
<thead>
<tr>
<th></th>
<th>COCHRANE (n=59)</th>
<th>DARE (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT (including quasi)</td>
<td>56 (95%)</td>
<td>21 (55%)</td>
</tr>
<tr>
<td>RCT and non-RCT</td>
<td>1 (2%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Non-RCT</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><em>(Efficacy not assessed)</em></td>
<td>1 (2%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td><strong>Adverse outcomes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT (including quasi)</td>
<td>56 (95%)</td>
<td>22 (58%)</td>
</tr>
<tr>
<td>RCT and non-RCT</td>
<td>2 (3%)</td>
<td>13 (34%)</td>
</tr>
<tr>
<td>Non-RCT</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Unclear</td>
<td></td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
## Type of data analysis

<table>
<thead>
<tr>
<th>Analysis of efficacy outcomes:</th>
<th>COCHRANE (n=59)</th>
<th>DARE (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51 (86%)</td>
<td>30 (79%)</td>
</tr>
<tr>
<td>1 = harms reviews</td>
<td></td>
<td>8 = harms reviews</td>
</tr>
<tr>
<td>7 = no trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descriptive analysis</td>
<td>16 (31%)</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>35 (69%)</td>
<td>19 (63%)</td>
</tr>
<tr>
<td>Analysis of adverse outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 = not reported</td>
<td></td>
<td>1 = not reported</td>
</tr>
<tr>
<td>6 = no trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descriptive analysis</td>
<td>23 (53%)</td>
<td>20 (54%)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>20 (47%)</td>
<td>17 (46%)</td>
</tr>
</tbody>
</table>
Implications (1)

- Most Cochrane reviews of drug and surgical interventions considered adverse events:
  - the amount of detailed information varied greatly.
  - nearly all relied only on evidence from randomized trials – this may well be inadequate.

- Two-thirds of DARE reviews of drug and surgical interventions considered adverse events:
  - the amount of detailed information varied greatly.
  - these reviews were more likely to include evidence from non-randomized studies.
Implications (2)

- Few Cochrane or DARE reviews of other types of interventions considered adverse events.

- Appendix 6b: Including Adverse Events - the Cochrane Handbook:
  - should improve reporting of adverse events at a systematic review level.

- Better Reporting of Harms in Randomized Trials - an extension of the CONSORT Statement:
  - should improve reporting of adverse events at a trial level.
Lansdowne