Reporting of adverse events in systematic reviews

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Background (1)

- 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.

Background (2)

- 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).

Background (3)

- 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

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In response to overwhelming 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 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 harms-related data from RCTs also needs improvement. Members of the CONSORT Group, including journal editors and scientists, 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 harms-related issues, accompanying explanation, 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 harms-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.

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For author affiliations, see end of text.

For definitions of terms, see Glossary.

*For a list of members of the CONSORT Group, see Appendix 1, available at www.annals.org.

Reporting harms may cause more trouble and discredit than the fame and glory associated with successful reporting of benefits (1).

The CONSORT (Consolidated Standards of Reporting Trials) statement, a checklist (Table 1) flow diagram first published in 1996 and revised 5 years later (2, 3), is an effort to standardize, and thereby improve, published reports of randomized, controlled trials (RCTs). One of the additions to the 2001 revision was an item about reporting adverse events. This single item did not do full justice to the importance of harms-related issues. The CONSORT Group met in September 2001 to discuss how to correct this deficiency. We aimed to provide evidence-based guidance on the reporting of harms in RCTs. First, we searched MEDLINE, EMBASE, Web of Science, and the Cochrane Library using a wide array of terms related to harms and identified pertinent evidence. We also communicated with experts and reviewed bibliographies of identified articles to find additional studies. At a meeting in Montebello, Quebec, Canada, in May 2003, CONSORT Group members, including several journal editors and additional experts in related fields, held a structured discussion of recommendations about reporting of harms-related issues in RCTs. The discussions led to a written document that we circulated among the team members for comment. The present manuscript describes our recommendations on the appropriate reporting of harms in RCTs.

The terminology of harms-related issues in RCTs is confusing and often misleading or misused (see Glossary) (4, 5). "Safety" is a reassuring term that may obscure the real and potentially major "harms" that drugs and other interventions may cause. We encourage authors to use the term "harms" instead of "safety." In addition to misused terminology, reporting of harms in RCTs has received less attention than reporting of efficacy and effectiveness and is often inadequate (6–14). In short, both scientific evidence and ethical necessity call for action to improve the quality of reporting of harms in RCTs (15, 16). Here, we present a set of recommendations and accompanying explanations for the proper reporting of harms in RCTs. These recommendations should complement the existing CONSORT statement (Table 2). Examples are presented on the *Annals* (www.annals.org) and CONSORT (www.consort-statement.org) Web sites.

RECOMMENDATIONS

Title and Abstract

Recommendation 1. If the study collected data on harms and benefits, the title or abstract should so state.

The title should mention harms if the study of harms was a key trial objective. Many phase I and phase II trials, some phase II/III trials, and most phase IV trials (17, 18) target harms as primary outcomes. Yet, the title and abstract seldom contain the word "harm." Among 375 143 entries in the Cochrane Central Register of Controlled Trials (Cochrane Library, issue 3, 2003), searching titles with the search terms *harm** or *harms* yielded 337 references (compared with 55 374 for *efficacy* and 23 415 for *safety*). Of the 337, excluding several irrelevant articles on self-harm or harm reduction, only 3 trial reports and 2 abstracts contained the word "harm" in their titles.

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Cochrane Handbook for Systematic Reviews of Interventions 4.2.4

Updated March 2005

THE COCHRANE COLLABORATION®

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*.

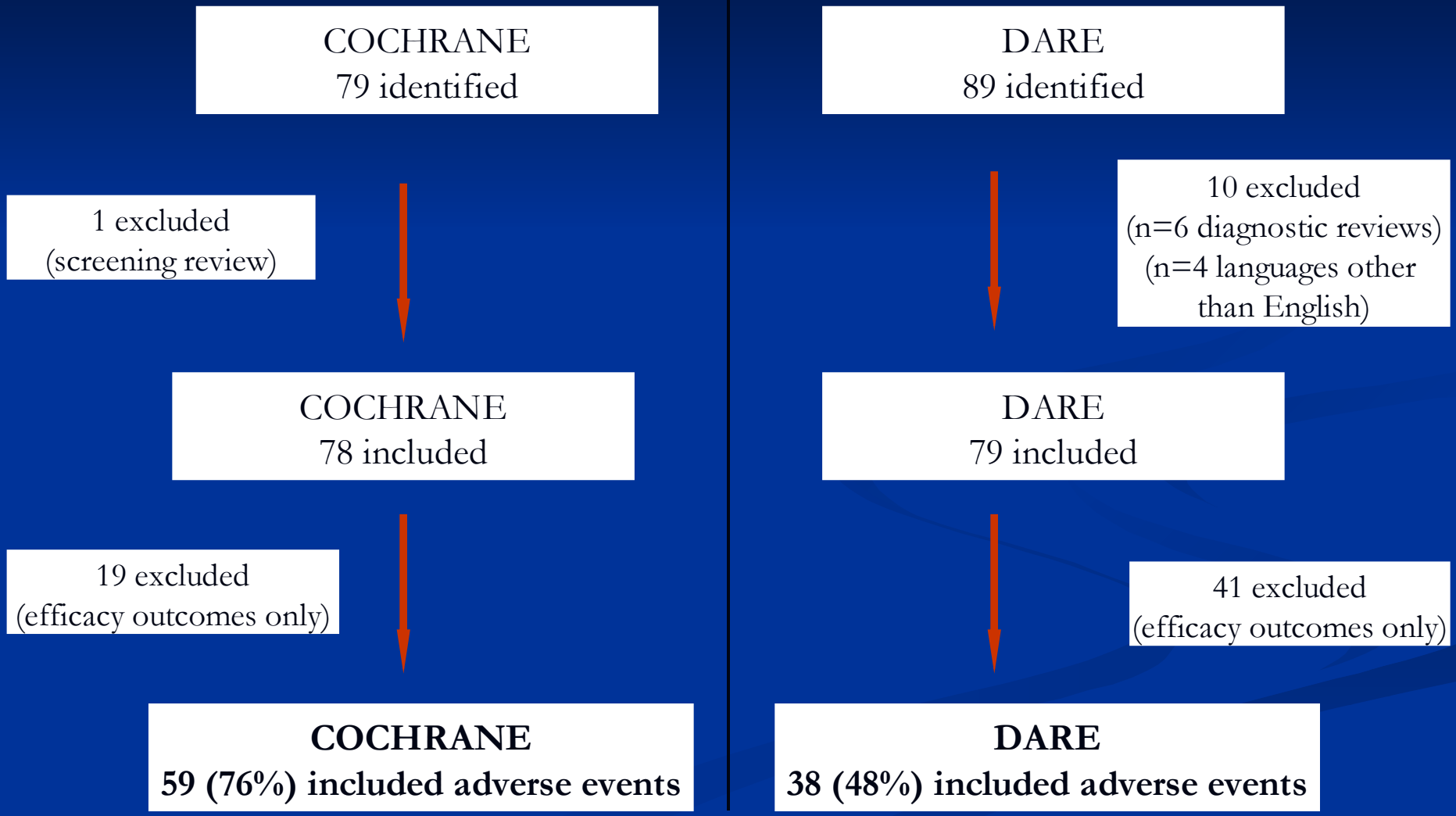
Data extraction

- 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.

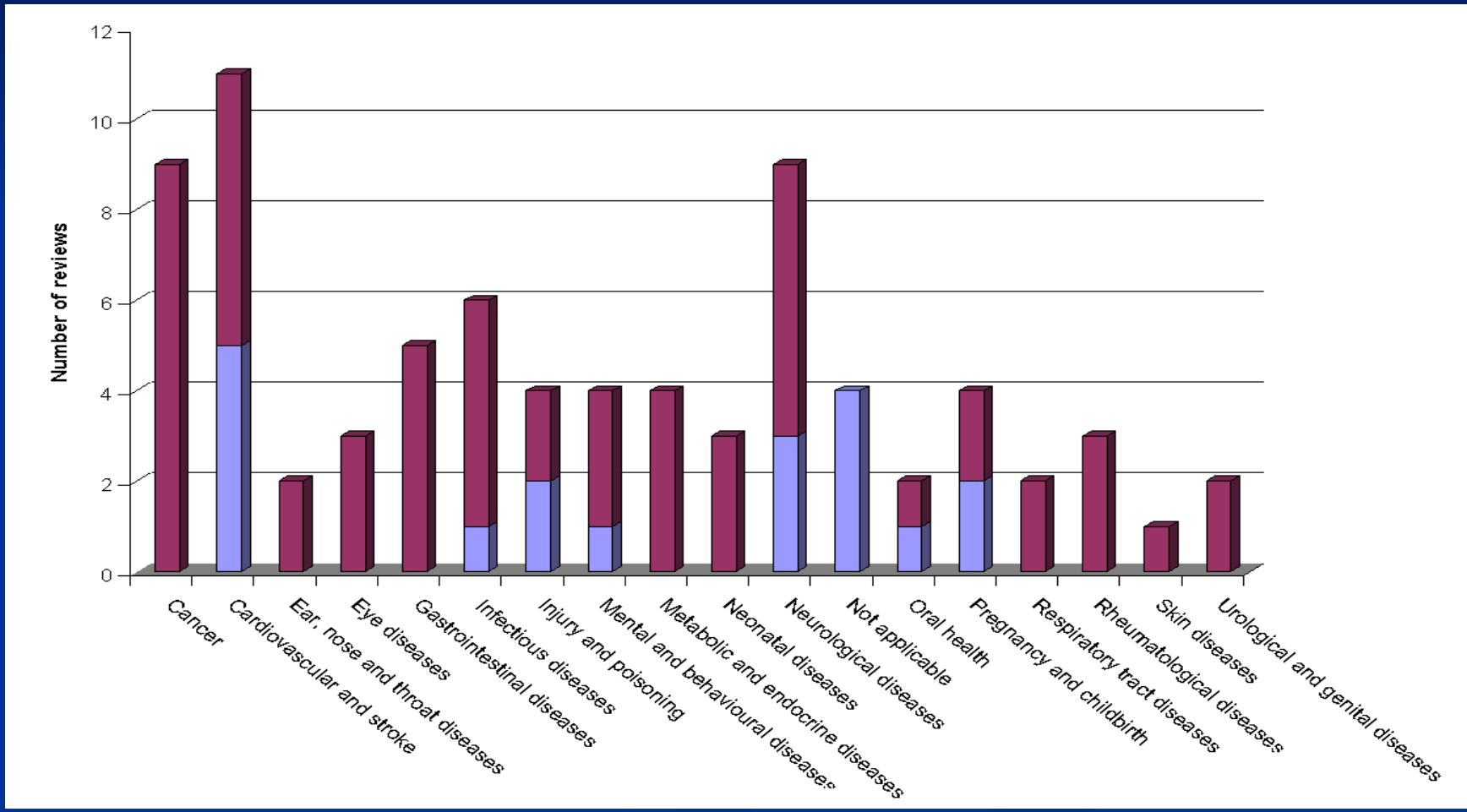
Inclusion criteria



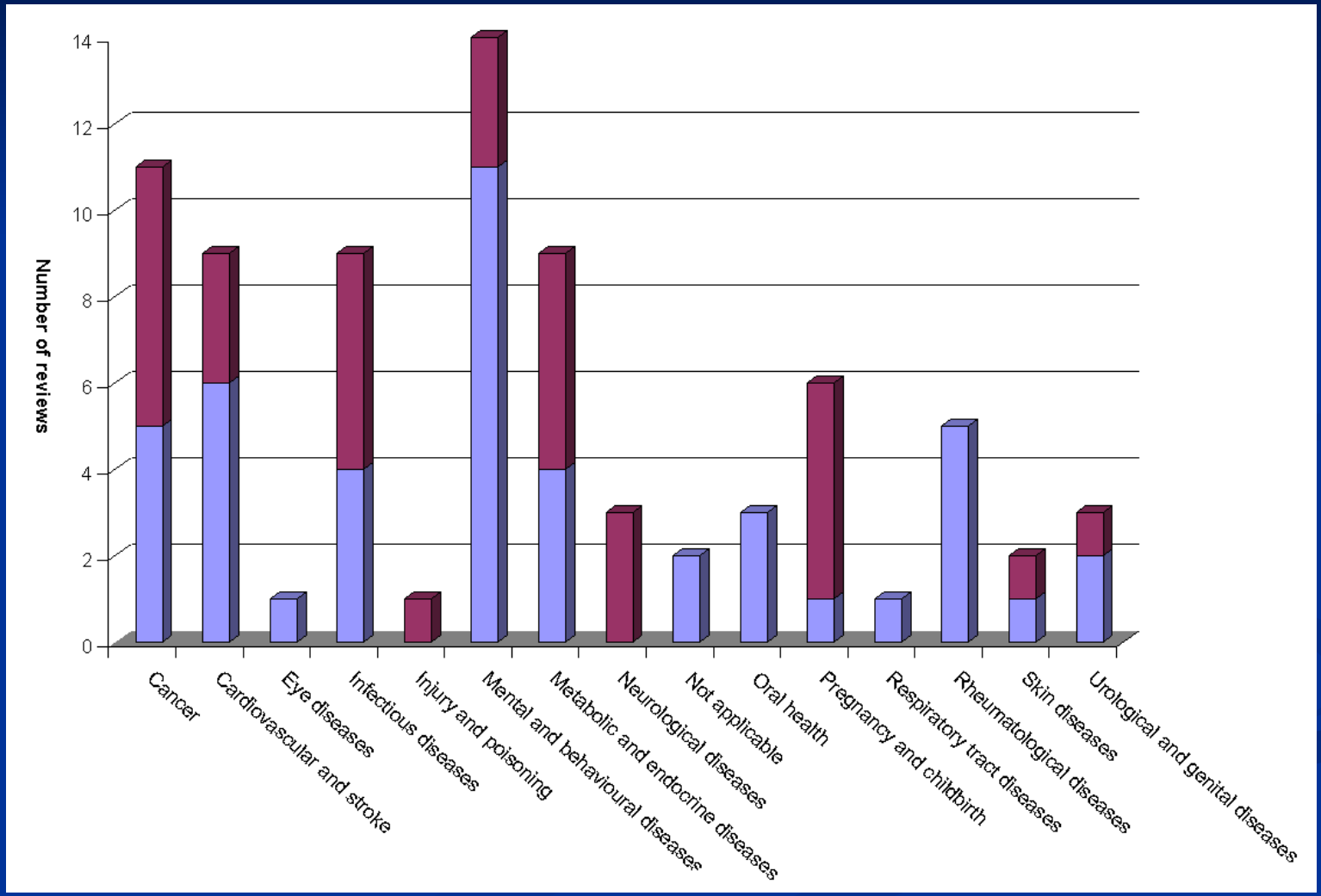
Definitions

- 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%)



Terminology

- The terminology used varied - the most commonly used terms were:
  - adverse event
  - adverse effect
  - side effect
  - safety
  - complications

Type of intervention

	COCHRANE (n=78)	DARE (n=79)
All reviews:		
Drug	44	46
Surgery	12	10
Other	22	23

	COCHRANE (n=59/78: 76%)	DARE (n=38/79: 48%)
Reviews reporting adverse events:		
Drug	41 (93%)	29 (63%)
Surgery	11 (92%)	6 (60%)
Other	7 (32%)	3 (13%)

Type of study design

	COCHRANE (n=59)	DARE (n=38)
Efficacy outcomes:		
RCT (including quasi)	56 (95%)	21 (55%)
RCT and non-RCT	1 (2%)	7 (18%)
Non-RCT	1 (2%)	1 (3%)
Unclear		1 (3%)
(Efficacy not assessed)	*1 (2%)*	*8 (21%)*
Adverse outcomes:		
RCT (including quasi)	56 (95%)	22 (58%)
RCT and non-RCT	2 (3%)	13 (34%)
Non-RCT	1 (2%)	2 (5%)
Unclear		1 (3%)

Type of data analysis

	COCHRANE (n=59)	DARE (n=38)
Analysis of efficacy outcomes:	51 (86%)	30 (79%)
	1 = harms reviews 7 = no trials	8 = harms reviews
Descriptive analysis	16 (31%)	11 (37%)
Meta-analysis	35 (69%)	19 (63%)
Analysis of adverse outcomes:	43 (73%)	37 (97%)
	10 = not reported 6 = no trials	1 = not reported
Descriptive analysis	23 (53%)	20 (54%)
Meta-analysis	20 (47%)	17 (46%)

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