Where to find information on adverse effects

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Structure of my presentation

- Why adverse effects matter?
- Why include adverse effects in systematic reviews?
- Where do authors of systematic reviews currently search for information on adverse effects?
- What evidence is available on where we should search for information on adverse effects?

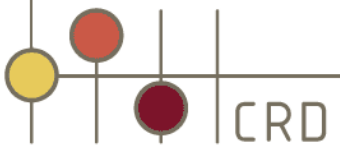
Why do adverse effects matter?

- **Definition**
  - ‘A harmful or undesirable outcome that occurs during or after the use of a drug or intervention for which there is at least reasonable possibility of a causal relation’ (Chou 2010)

- **Why adverse effects matter**
  - Unpleasant, often serious – hospitalisation, disability, death (USA: 4th to 6th leading cause of death) (Lazarou 1998)
  - Worsen quality of life, make people stop treatment
  - Cost (estimates of cost to UK NHS of £2 billion per year) (Compass 2008)

Why include adverse effects in systematic reviews?

- **Need to assess benefit/ harm balance**
- **Detailed evaluation of safety needed when:**
  - Narrow margin between benefit and harm (aspirin/ CVD)
  - A number of equally effective treatments with different safety profiles
  - When adverse effects cause withdrawal from treatment



Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

- **849 systematic reviews**

- **Study designs included**
  - RCTs (61%) (Included **only** RCTs 33%)
  - Cohort studies (37%)
  - Case-control studies (25%)
  - Case series (8%)
  - Case reports (6%)

Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

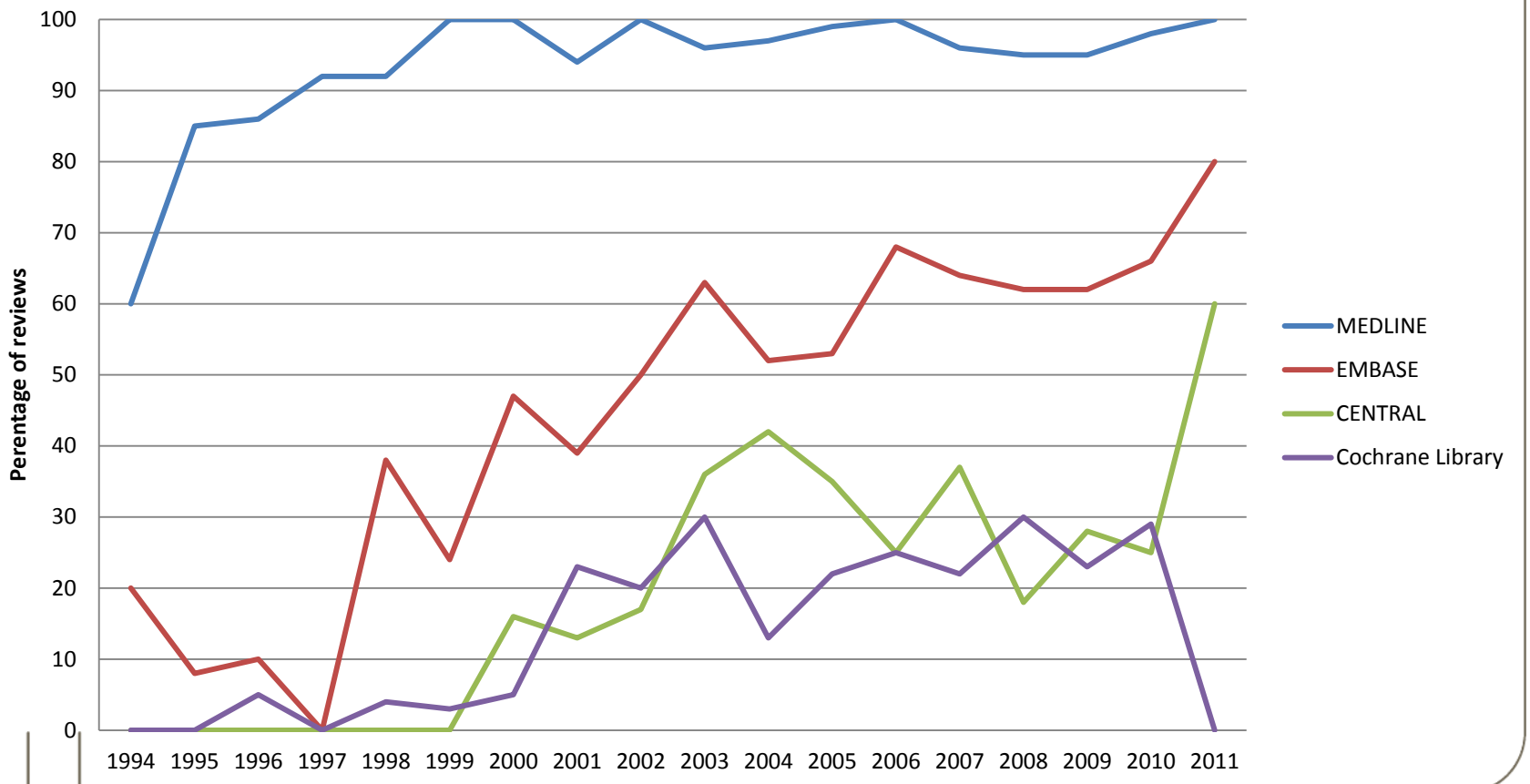
- **Median number of databases**
  - 2 (range 0 to 25)
- **Number of sources**
  - Increasing over time
  - Greater if information professional involved

Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

Top 5 most popular sources

1. MEDLINE (96%)
2. Reference checking (76%)
3. EMBASE (54%)
4. CENTRAL or Cochrane Library (45%)
5. Contacting experts (22%)

Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)



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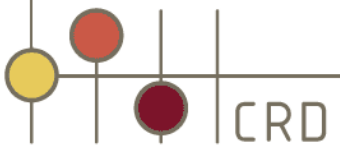
Where do authors of systematic reviews currently search for adverse effects? (Golder et al 2013, Golder et al 2014)

- **Unpublished data searches**
  - Contacting experts (18%)
  - Scanned conference reports (17%)
  - Sought industry data (13%)
  - Clinical trial registries (6%)
  - FDA website (6%)
  - Surveillance data (3%)
  - Databases of unpublished data (3%)



What the evidence suggests we should do

- Search for unpublished data?
- Which sources to search?
- Which study designs to search for?

Should we search for unpublished data?

- **Systematic review of the methodological literature**
  - 10 included studies
- **Availability of unpublished data**
  - **Case Reports**
    - Two out of three studies found more unpublished than published case reports of adverse effects
  - **Trials**
    - A higher percentage of unpublished trials report adverse effects than published trials

Should we search for unpublished data?

- **Differences in unpublished and published data**
  - **Case reports**
    - Unpublished case reports will generate a different picture of the relative frequencies of specific adverse effects
  - **Trials**
    - No clear evidence that data on adverse effects from published and unpublished trials differed
    - Inclusion of unpublished data could provide information on adverse effects earlier and give more precise risk estimates

Where to search?

The Evidence

A. Systematic review comparing sources of information on adverse effects (Golder et al 2010)

B. Case study systematic review of glitazones and fractures (Golder et al 2012a)

C. Case study systematic review of the safety of spinal fusion (unpublished)

A: Systematic review of previous research (Golder et al 2010)

- ***Objective***
  - Summarise all the literature comparing 2 or more sources to identify adverse effects

- ***Results***
  - ***EMBASE vs MEDLINE***
    - In eight out of ten cases searching EMBASE retrieved more relevant references than MEDLINE
  - ***Industry Submissions***
    - In two out of four cases data retrieved from industry submissions retrieved the highest number of relevant records and in each case many records were unique

A: Systematic review of previous research (Golder et al 2010)

- **Limitations**
  - Over 50 information sources evaluated with little overlap between each study
  - 12 of the 19 studies were published before 1999
  - Many based on poor searches with few evaluations reporting number of relevant records indexed on the databases at time of searching (i.e. potentially missed studies)

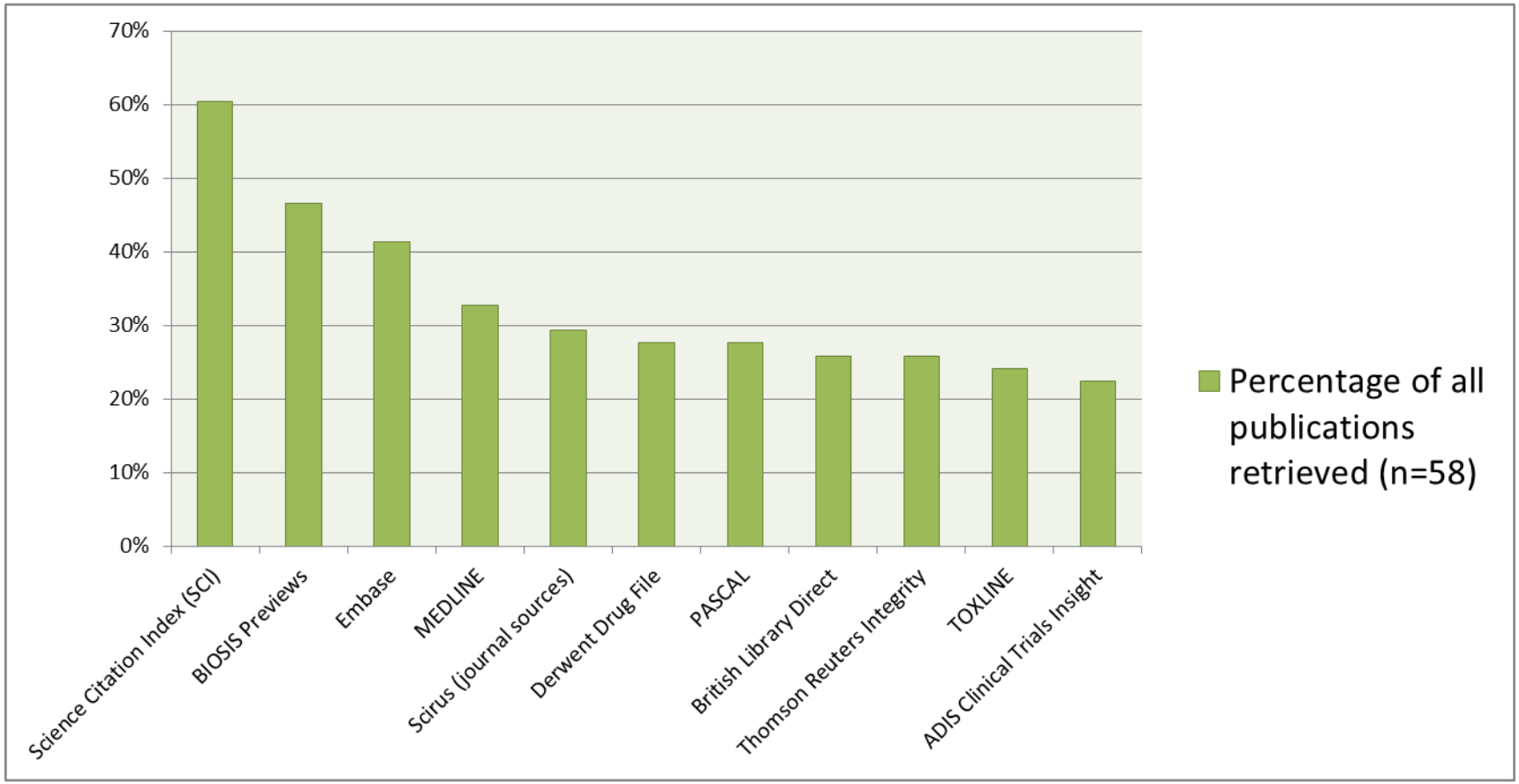
- **More research needed**

B: Case study with a drug intervention (Golder et al 2012)

Long-term use of glitazones and fractures in type 2 diabetes

- Searched over 60 sources (beyond usual practice)
- Used intervention (glitazones) and outcome (fractures) search terms
- No diabetes or study design terms used
- Multiple textwords and indexing

B: Case study with a drug intervention – top databases (Golder et al 2012)



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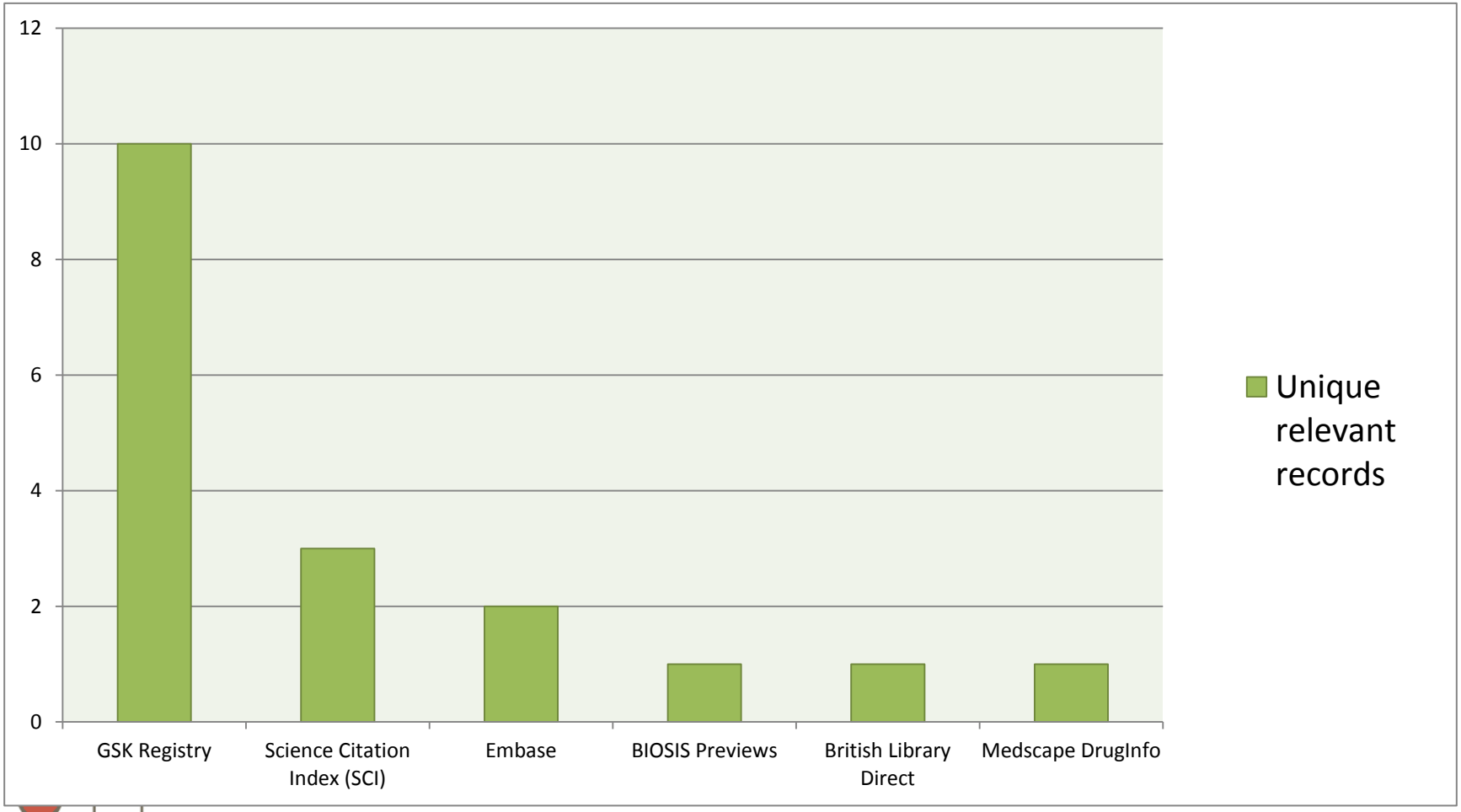
B: Case study with a drug intervention – unique records (Golder et al 2012)



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B: Case study with a drug intervention - sources required (Golder et al 2012)

Minimum combination of sources

Science Citation Index
BIOSIS Previews
Medscape DrugInfo
Thomson Reuters Integrity*
AHFS First
Reference checking

Embase
GSK website
British Library Direct
Conference Papers Index*
Handsearching**

**either database*
*** ten key journals*

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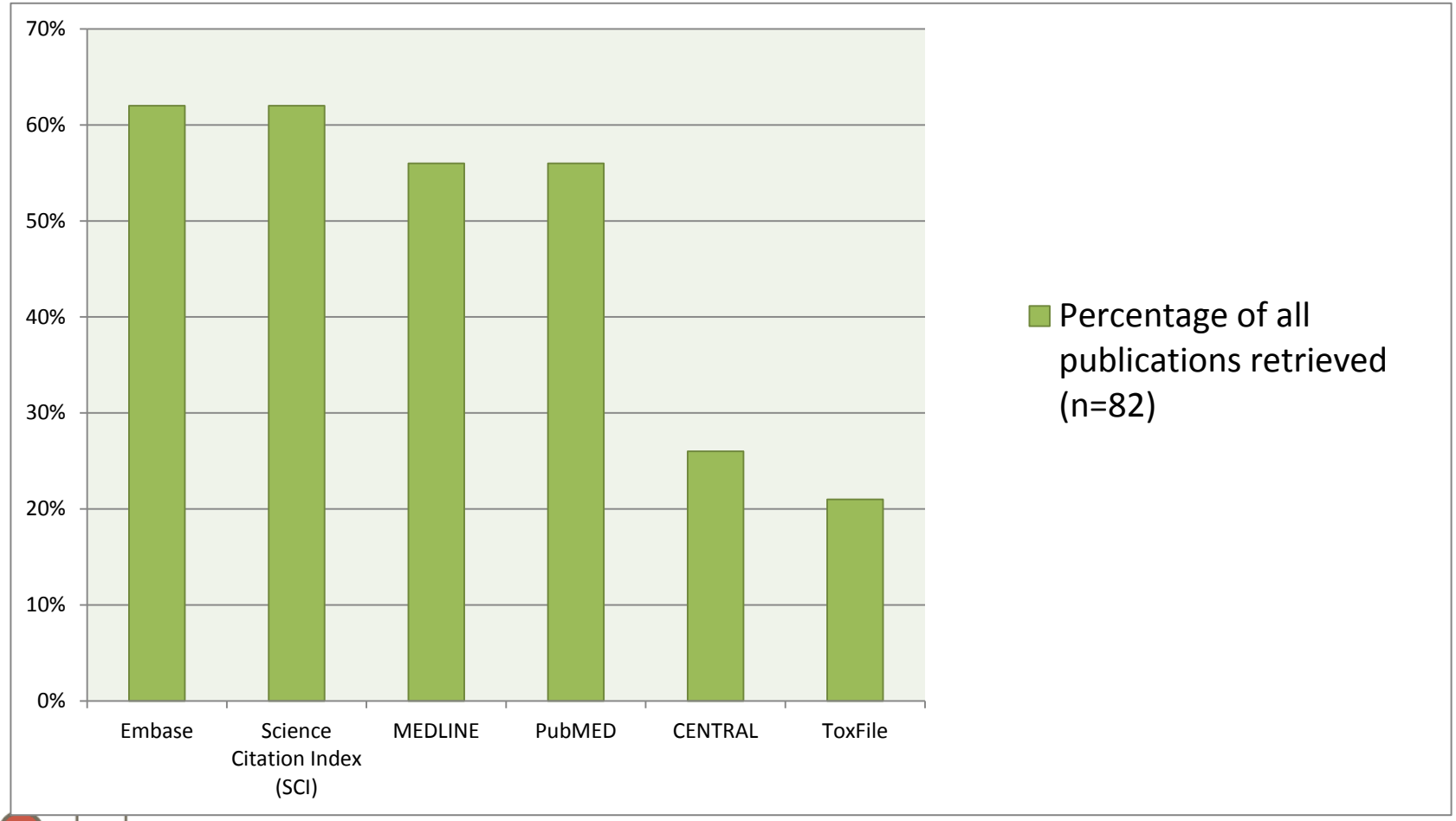
C: Case study with a medical device (unpublished)

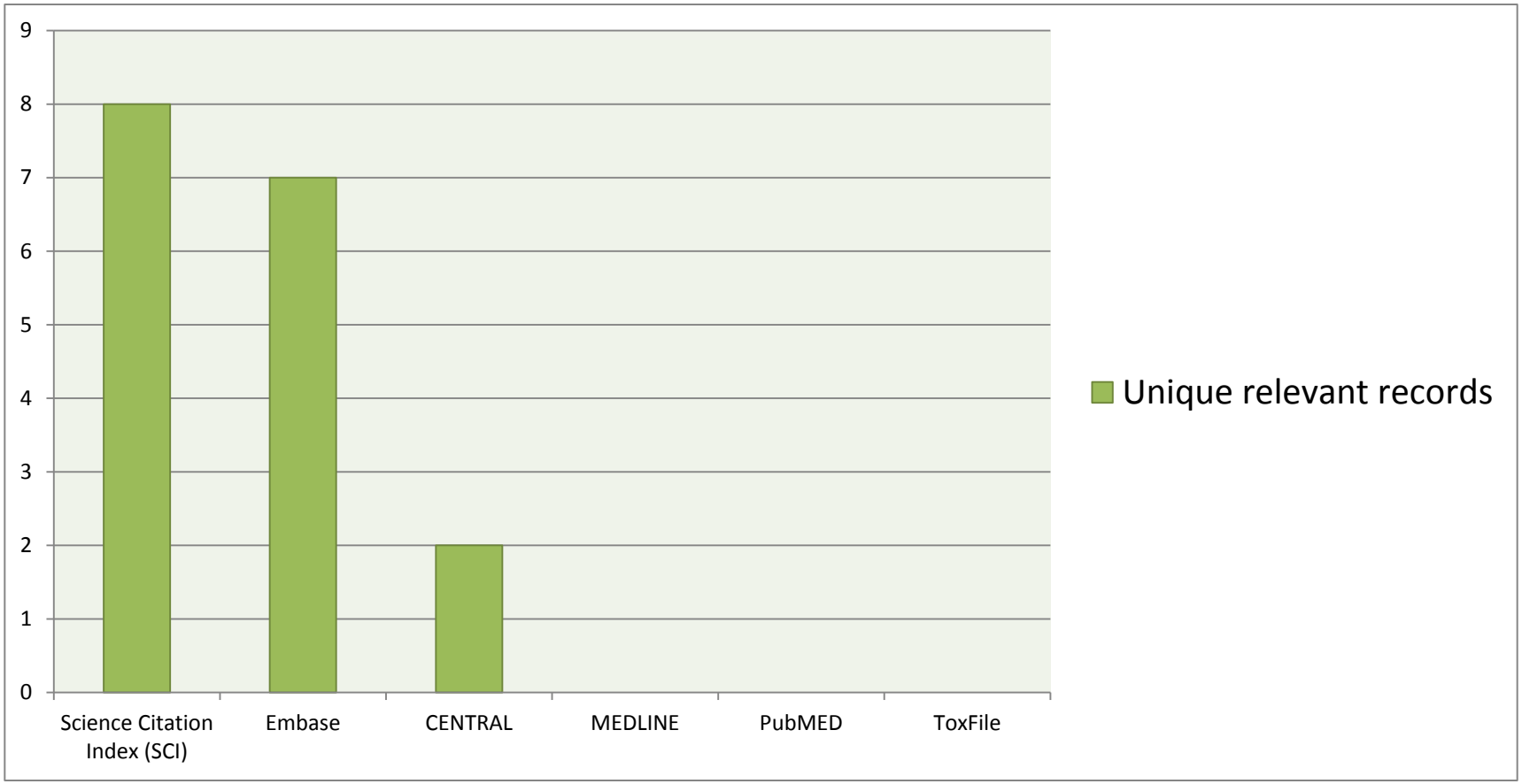
Safety of recombinant human bone morphogenetic protein-2 (rhBMP-2)

- Searched 10 databases plus reference checking, contacting authors and automated current awareness service
- Used intervention terms; recombinant human bone morphogenetic protein-2 (rhBMP-2) and spinal fusion
- Multiple textwords and indexing

C: Case study with a medical device – top databases



C: Case study with a medical device – unique records



C: Case study with a medical device – sources required

Minimum combination of sources

- Science Citation Index (SCI)
- Embase
- CENTRAL
- MEDLINE or PubMED
- Reference checking
- Contacting authors
- Automated current awareness service

Which study designs to include? (Golder et al 2011)

- **Objective**
  - Summarise the literature comparing harm estimates from different study designs
- **Analysis**
  - 51 included studies
  - Measured confidence interval overlap
  - Measured occurrence of different answers (significant increase, no significant difference, significant decrease)
  - Compared odds ratios

Which study designs to include? (Golder et al 2011)

Study designs compared	Confidence interval overlap
RCTs vs all 'observational' studies	93%
RCTs vs cohort studies	100%
RCTs vs case-control studies	90%
RCTs vs 'observational' studies	91%

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Which study designs to include? (Golder et al 2011)

Study designs compared	Agreement in findings (direction and significance)	Discrepancy in findings (significance only)	Discrepancy in findings (direction)
RCTs vs all 'observational studies'	64%	34%	2%
RCTs vs cohort studies	69%	31%	0%
RCTs vs case-control studies	40%	60%	0%
RCTs vs observational studies	69%	28%	3%

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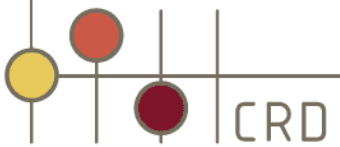
Which study designs to include? (Golder et al 2011)

Study designs compared	Pooled ratio of odds ratios (RORs) and 95% confidence intervals
RCTs vs all 'observational studies'	1.03 (0.93-1.15)
RCTs vs cohort studies	1.02 (0.82-1.28)
RCTs vs case-control studies	0.84 (0.57-1.23)
RCTs vs observational studies	1.08 (0.94-1.22)

Which study designs to include? (Golder et al 2011)

- Most confidence intervals overlap between study designs
- Most study designs agree, in terms of finding an increase, decrease or no difference, in adverse effects
- Overall meta-analyses of RCTs agree with meta-analyses of observational studies



Take home messages

- Searching unpublished data retrieves additional useful data
- Searching multiple sources is required
- Observational studies not a major threat to bias

Future

- **More reviews** are including adverse effects either as secondary outcome (in addition to effectiveness) or as primary outcome

- **Better reporting**
  - CONSORT Extension for Harms (Ioannidis et al 2004)
  - PRISMA Harms Extension (Zorzela et al 2014)

Guidance

Cochrane Handbook

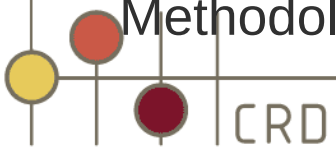
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

CRD's Guidance

Systematic Reviews: CRD's guidance for undertaking reviews in health care.
http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf

BMC Paper

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



Help and support

Cochrane Adverse Effects Methods Group
http://aemg.cochrane.org/

Discussion List
http://lists.cochrane.org/mailman/listinfo/aemg

Twitter
@CAEMG1

References

Chou R, Aronsonb N, Atkinsc D, Ismailad AS, Santaguidad 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;502-12.

Compass. *Adverse drug reactions wastes NHS £2BN reveals Compass*. Compass; London; 2008. Available from: http://www.compassonline.org.uk/news/item.asp?n=1551.

Golder S, Loke YK, Bland M. Unpublished data can be of value in systematic reviews of adverse effects: methodological overview. *J Clin Epidemiol* 2010:1071-81.

Golder S, Loke YK. Sources of information on adverse effects: a systematic review. *Health Info Libr J* 2010;176-90.

Golder SP, Loke YK, Bland M. Meta-analyses of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview. *PLOS Medicine* 2011;e1001026

Golder S, Loke YK. The contribution of different information sources for adverse effects data. *Int J Technol Assess Health Care*. 2012:133-7.

References

Golder S, Loke YK, Zorzela L. Some improvements are apparent in identifying adverse effects in systematic reviews from 1994 to 2011. *J Clin Epidemiol* 2013:253-60.

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

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.

Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004:781-788.

Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reaction in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998:1200-5.

Zorzela L, Golder S, Liu, Y, Pilkington K, Hartling L, Joffe A, Loke Y, Vohra S. Quality of reporting in systematic reviews of adverse events: systematic review. *BMJ. 2014;348.*