Path Forward, as Envisioned by the NRC

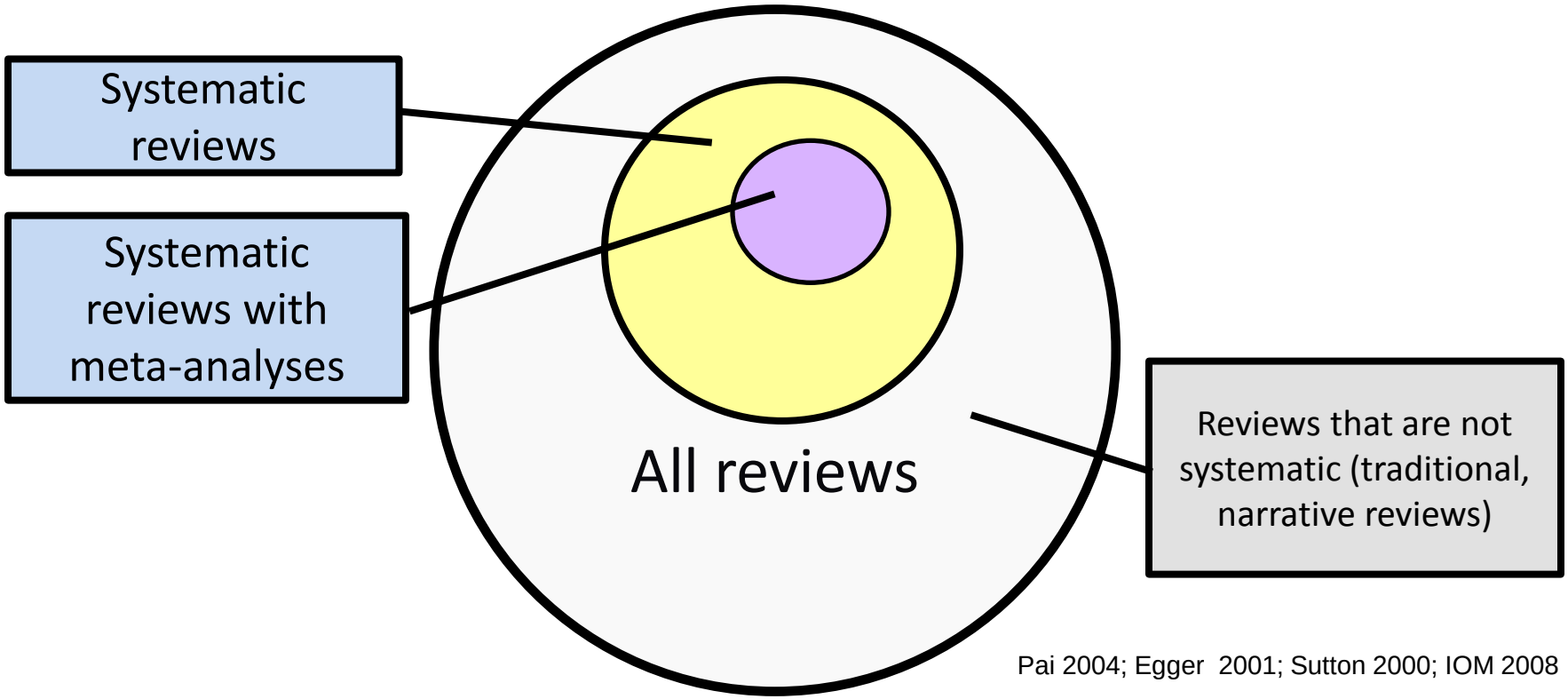
Kay Dickersin, MA, PhD

EPA IRIS Workshop on the NRC Recommendations

Arlington, Va.

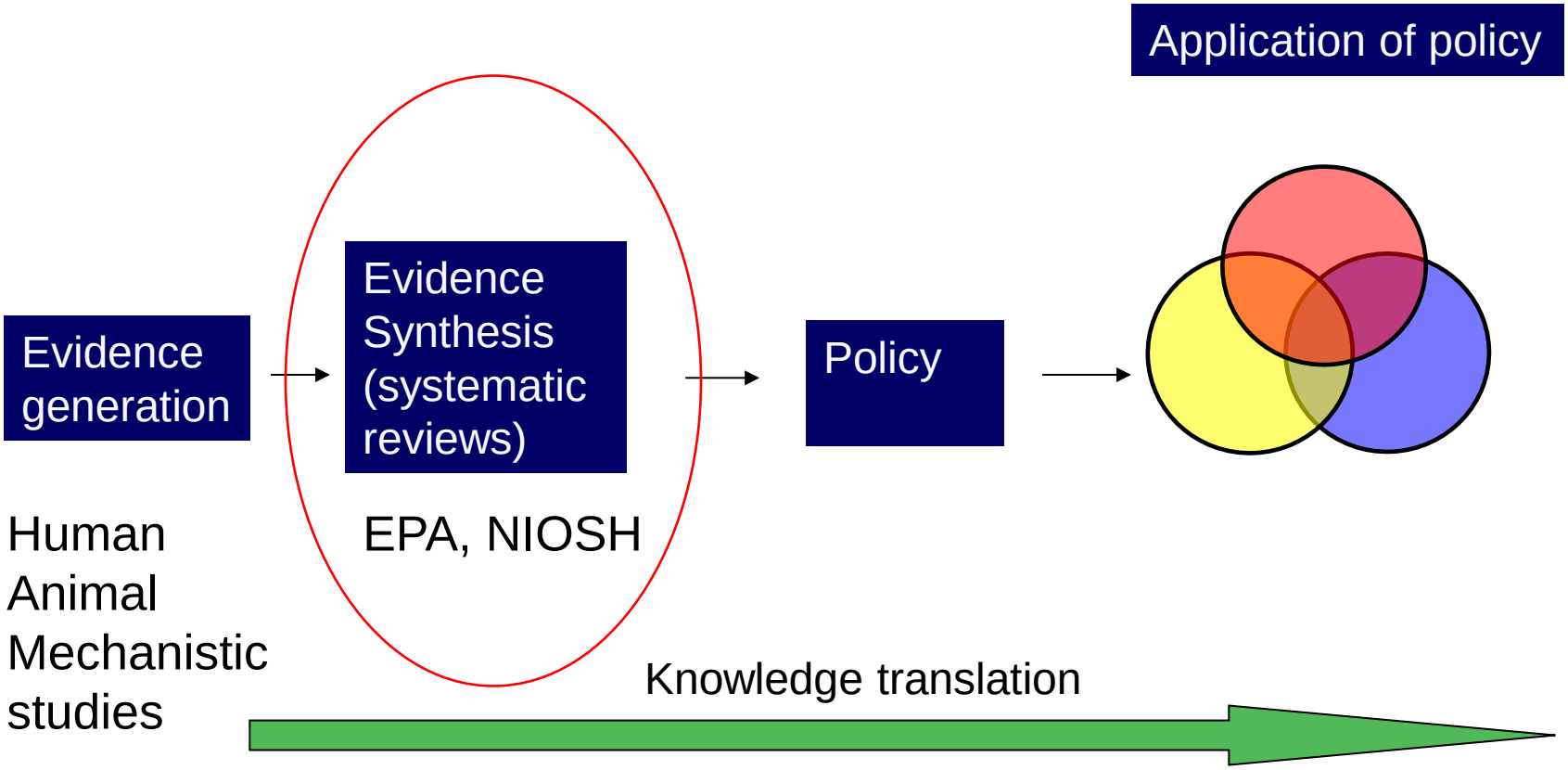
October 15, 2014

What is a systematic review?



Pai 2004; Egger 2001; Sutton 2000; IOM 2008

Knowledge translation:
From clinical research to policy decisions



I believe that SRs are the most difficult research I have ever done, primarily because of all the decisions and judgments required. **But** opinion about what to do (policy), is a separate step.

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Systematic review

From Wikipedia, the free encyclopedia

A **systematic review** is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to that

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Evidence-based Debates on Teacher Quality

By Eric A. Hanushek 03/24/2014

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Centre for Evidence Based Agriculture

Centre for Evidence-Based Agriculture (CEBA)

Centre for Evidence-Based Agriculture (CEBA)

The Centre for Evidence Based Agriculture is a reviewing, training and co-ordinating hub for the collation and synthesis of agri-food evidence in order to support decision-making.

Agri-food research is often disparate and difficult to access. Evidence syntheses aim to collate, and sometimes re-analyse, research and other

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Are top executives paid enough? The answer is clear

Conflicting viewpoints exist on the need for high executive salaries and incentives. By and large, economists conclude

Five

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http://www.thecommunityguide.org/CG-in-Action/index.html

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The Community Guide in Action: Stories from the Field

Community Guide in Action stories – ready-to-print and, in some cases, video versions – feature decision-makers, program planners, employers, and leaders from across the country who have used The Community Guide to make people safer and healthier. Use the stories in presentations, as handouts, or link to .PDF or video versions from emails or websites. [Written stories are designed to print front-and-back, head-to-head in color, on white 8.5" x 11" paper.]

Stories listed by location and public health topics

We welcome your comments. Contact Us to let us know how you use these stories. We also encourage you to send us your own Community Guide in Action stories!

Black Corals: A Gem of a Cancer Screening Program in South Carolina
In rural South Carolina, where many African American women have limited access to lifesaving medical screenings, the risk of cancer-related death is a complex public health problem. The St. James-Santee Family Health Center launched Black Corals to increase cancer screening among women. The Community Guide served as a resource to help the Black Corals program dramatically increase breast and cervical cancer screenings in their community.
(Video – 10:21)

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What's this?

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1st Cochrane Colloquium

1993: 70 people from 9 countries
2013: >31,000 active contributors in 102 countries

>6,011completed systematic reviews of healthcare published in *The Cochrane Library as of June 2014*

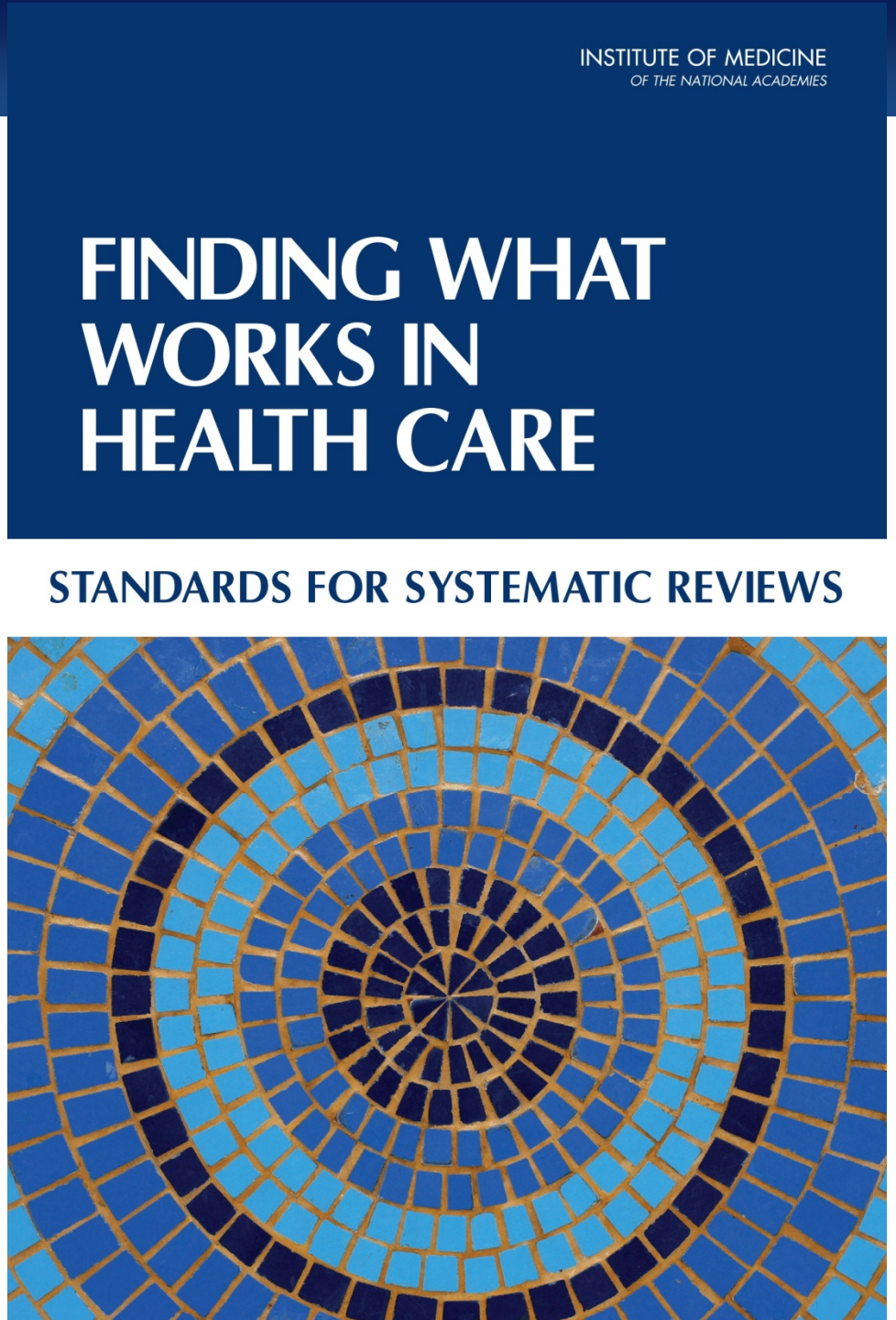
It's about collaboration

Working together toward a common goal

Society for Research Synthesis Methods

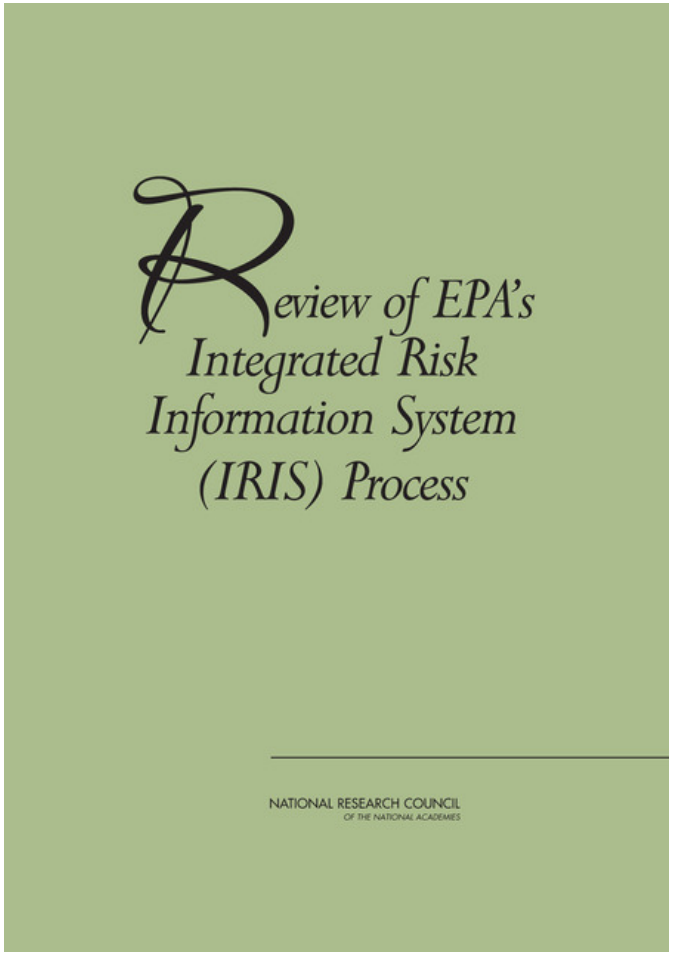
- A society of methodologists from many disciplines who are working on systematic review methods and meet annually to keep abreast of new developments
- This photo is from the 2014 meeting

IOM Standards for systematic reviews 2011



BEST

Board on Environmental Studies and Toxicology



Review of EPA's Integrated Risk Information System (IRIS) Process

Committee to Review the IRIS Process
Board on Environmental Studies and Toxicology
Division on Earth and Life Studies
National Research Council

The Committee recommended that systematic review methods be applied to the IRIS process

- EPA was viewed as incorporating systematic review principles as it implements changes in the IRIS process.
- The committee agrees with EPA that the systematic-review standards provide an approach that would substantially strengthen the IRIS process.

How do you do a systematic review?

- Step 1 – Gather together your team (content and methods experts), develop your processes for gathering stakeholder input, formulating your research question, minimizing bias and conflicts of interest
- Step 2 – **Formulate the problem**
- Step 3 – **Develop your protocol and make it available for peer review**
  - Eligibility criteria, search, data abstraction, quality assessment, qualitative and quantitative (if appropriate) synthesis
- Step 4 – Identify/locate the evidence, screen and collect studies
- Step 5 – Abstract data and appraise risk of bias in the individual studies
- Step 6 – Integrate the evidence - Synthesize findings, interpret, & assess overall body of evidence (quantitative and qualitative)
- Step 7 – Write report (which is peer reviewed)
- Step 8 – Update the systematic review as needed

Formulate problem

- IRIS committee suggested a three-step process for problem formulation:
  - *Perform broad literature search* to identify possible health outcomes
  - Construct table to help *formulate specific questions*.
  - Examine table to determine which *adverse outcomes* warrant systematic review and how to define systematic-review questions.
    - e.g., does exposure to chemical x result in neurotoxic effects?

Develop protocol

- Provides transparency to methods and process of the review
  - e.g., changes made after the protocol is in place should be transparent (i.e., amendments noted), and the rationale for each should be stated.
- Provides the opportunity for peer review of the methods
- Stands as a record of the review.

Identify evidence

- Use standardized search strategy and reporting format (e.g., line-by-line search strategy, date of the searches)
- Work with an evidence-based information specialist trained in systematic-review methods
- Screen and select eligible studies using two independent reviewers

Extract evidence from reports

Extracted evidence allows EPA to:

- Compare similarities and differences among relevant studies on study characteristics (e.g., population, exposures, dose, outcomes), including potential confounding variables
- Assess exposure effect (hazard identification and dose response effect)

Extract information about internal validity of the study (risk of bias)

- *"Risk of bias"* reflects study design characteristics that can introduce a systematic error that might affect the magnitude and even the direction of the apparent effect
  - NB: I am using "bias" as a statistical term, not one indicating prejudice on any person's part. Wikipedia says: "A statistic is **biased** if it is calculated in such a way that it is systematically different from the population parameter of interest".
- Develop ROB tools for animal and mechanistic studies

Risk of bias of observational studies-examples

- Selection bias
  - Definitions of exposed/unexposed
  - Choice of cases/controls
- Information bias
  - Definition exposure
  - Definition outcome
  - How information obtained
- Analysis

Integrate evidence

- Several qualitative and quantitative options are available for overall evidence integration and are described in committee's report.

- Transparency
  - Include search process and what was identified
  - Risk of bias
  - Findings
  - How the study characteristics, ROB and other factors may have influenced the findings

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By Review Group

Intervention Review

Exercise for improving balance in older people

Database Title

Tracey E Howe[1,*], Lynn Rochester[2], Fiona Neil[3], Dawn A Skelton[4], Claire Ballinger[5]

Editorial Group: Cochrane Bone, Joint and Muscle Trauma Group

Published Online: 9 NOV 2011

Assessed as up-to-date: 31 MAR 2011

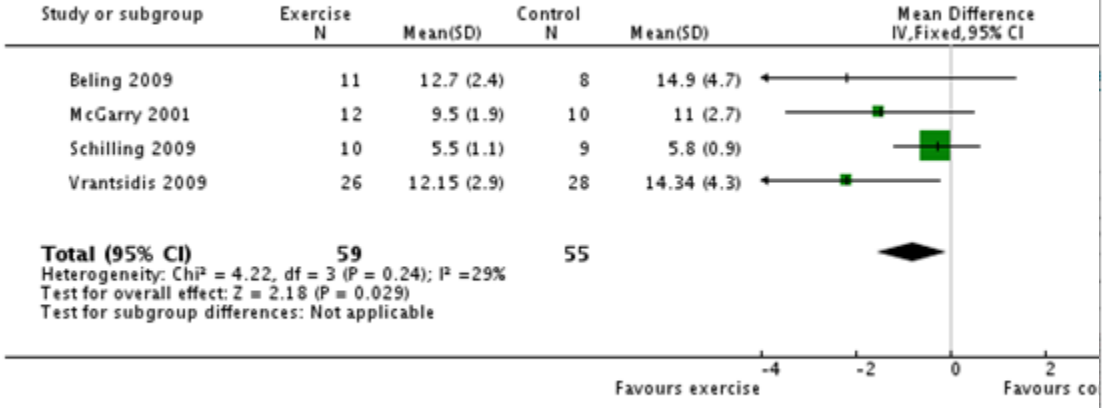
DOI: 10.1002/14651858.CD004963.pub3

SEARCH

Title, Abstra

Analysis 1.1. Comparison 1 Gait, balance, co-ordination, fu

Review: Exercise for improving balance in older people
Comparison: 1 Gait, balance, co-ordination, functional tasks exercise versus control
Outcome: 1 Timed Up & Go Test (s): lower values indicate better balance ability



Analysis 1.1. Comparison 1 Gait, balance, co-ordination, functional tasks exercise versus control, Outcome 1 Tim
balance ability.

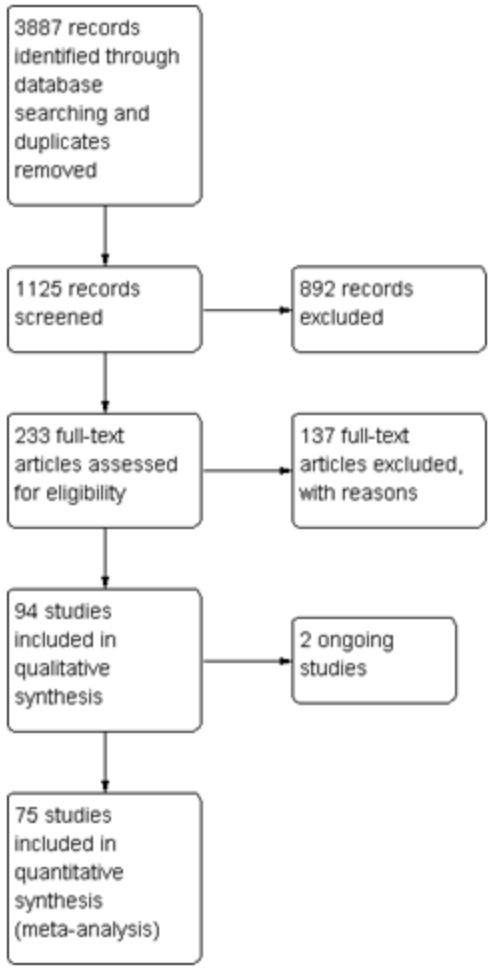


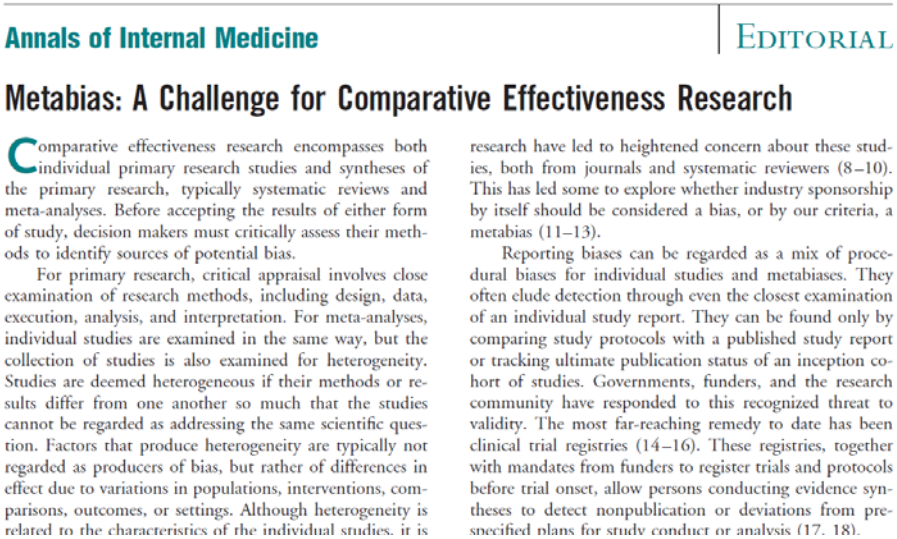
Figure 1. Study flow diagram.

Bias in systematic reviews

- Bias can be introduced multiple ways when doing a systematic review
  - Bias in the methods used in the included studies
  - Bias in the methods used in the systematic review

("metabias")

- Selection biases
- Information bias
- Analysis bias



Annals of Internal Medicine | EDITORIAL

Metabias: A Challenge for Comparative Effectiveness Research

Comparative effectiveness research encompasses both individual primary research studies and syntheses of the primary research, typically systematic reviews and meta-analyses. Before accepting the results of either form of study, decision makers must critically assess their methods to identify sources of potential bias.

For primary research, critical appraisal involves close examination of research methods, including design, data, execution, analysis, and interpretation. For meta-analyses, individual studies are examined in the same way, but the collection of studies is also examined for heterogeneity. Studies are deemed heterogeneous if their methods or results differ from one another so much that the studies cannot be regarded as addressing the same scientific question. Factors that produce heterogeneity are typically not regarded as producers of bias, but rather of differences in effect due to variations in populations, interventions, comparisons, outcomes, or settings. Although heterogeneity is related to the characteristics of the individual studies, it is

research have led to heightened concern about these studies, both from journals and systematic reviewers (8–10). This has led some to explore whether industry sponsorship by itself should be considered a bias, or by our criteria, a metabias (11–13).

Reporting biases can be regarded as a mix of procedural biases for individual studies and metabiases. They often elude detection through even the closest examination of an individual study report. They can be found only by comparing study protocols with a published study report or tracking ultimate publication status of an inception cohort of studies. Governments, funders, and the research community have responded to this recognized threat to validity. The most far-reaching remedy to date has been clinical trial registries (14–16). These registries, together with mandates from funders to register trials and protocols before trial onset, allow persons conducting evidence syntheses to detect nonpublication or deviations from prespecified plans for study conduct or analysis (17, 18).

2010 Annals Intern Med Goodman & Dickersin

Methods of conducting the review should be unbiased

- **Selection bias**
- Information bias
- Analysis

Selection bias

Selecting studies for a systematic review

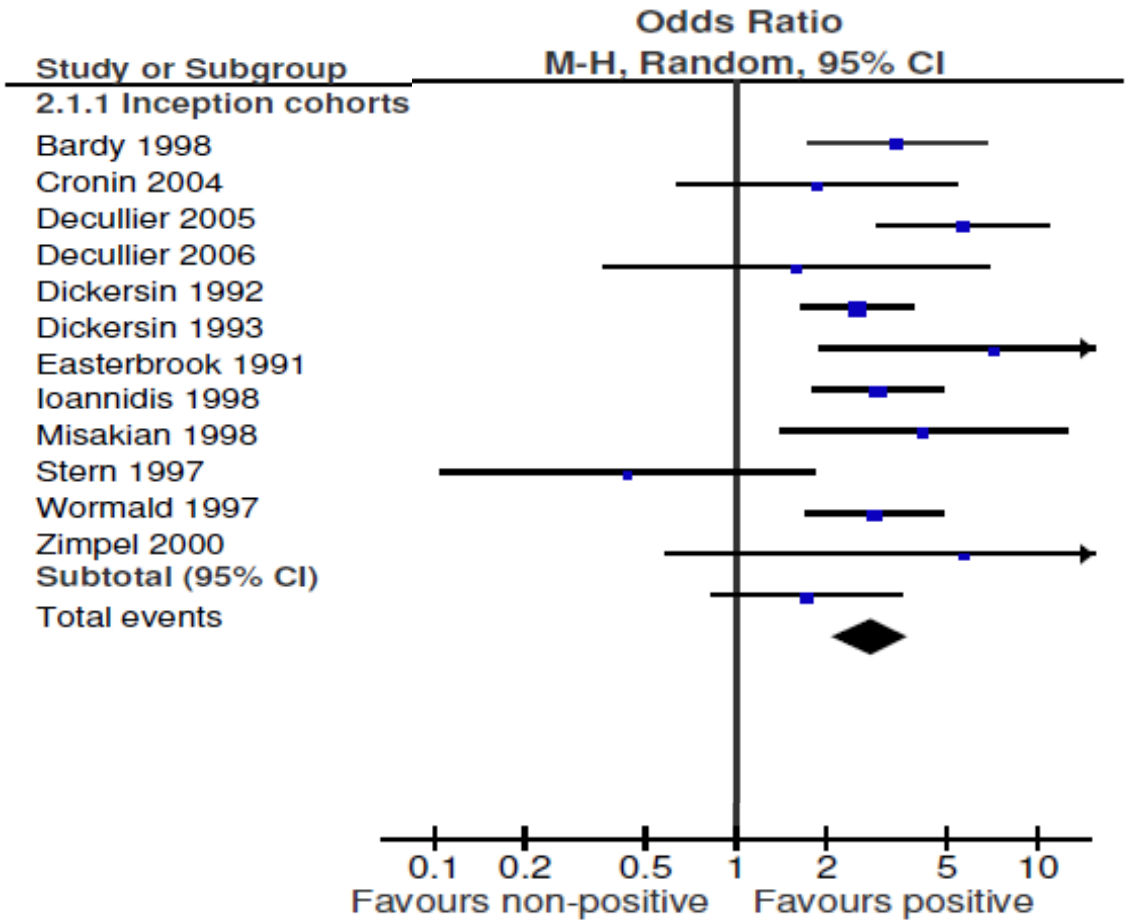
- Reporting bias
  - Publication bias - Unpublished studies tend to have different results than published studies
  - Selective outcome reporting – Even when the study is published, positive outcomes are reported over null or negative outcomes
  - Ascertainment bias – Studies that are easier to find have positive results more often than studies that are harder to find
- Inclusion bias – If study findings are known when inclusion criteria are set or data are abstracted, is outcome of meta-analysis affected?

Findings may not be published

Population	Identification	Follow-up	% Published
JHU-MED	1980	1988	81
JHU-PH	1980	1988	66
NIH trials	1979	1988	93
Oxford	1984–87	1990	73
Sydney	1979–88	1992	59
NIH AIDS trials	1986–96	1996	55
Barcelona trials	1997	2001	21
Denmark trials	1994–95	2003	63
Canada CIHR trials	1990–98	2002–03	46
France ethics	1994	2000–02	38
Bern ethics	1988-1998	2009	52
Westfalen-Lippe ethics	1996	2003-04	70

Odds ratio of publication of positive vs non-positive studies

Inception cohorts



Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 17.53$, df = 11 (P = 0.09); $I^2 = 37\%$
Test for overall effect: Z = 7.10 (P < 0.00001)

Song et al BMC Med Res Method 2009

Selective reporting of outcomes

- Nearly two-thirds of the 100+ studies approved by 2 Danish ethics committees had a change in at least one primary outcome between the protocol and publication
- Statistically significant outcomes had a higher likelihood of being reported compared to non-significant findings

Source: Chan AW et al. JAMA 2004;291:2457-2465.

Information bias manifests different ways

- **Experienced vs inexperienced data extractors** (2009 JCE Horton)
  - High error rates at all experience levels (28.3% to 31.2%)
  - Error rates for omission (11.3% to 16.4%)
  - Error rates for inaccuracy (13.9% to 17.9%)
- **Methodology experts vs PhD students extracting data for standardized mean difference (SMD)** (2009 BMJ Tendal)
  - Agreement was 53% at study level
  - Important reasons for disagreement were differences in selection of time points, scales, control groups, and type of calculations; whether to include a trial in the meta-analysis; and data extraction errors made by the observers.
- Double data extraction results in fewer errors (2006 JCE Buscemi)

Features of a systematic reviews

- Facilitates efficient integration of information & a basis for rational decision making
- Provides a clear and transparent process
- Demonstrates where the effects of an exposure are consistent & where they vary
- Minimizes bias (systematic errors) & reduces chance effects
- Meta-analysis can provide more precise estimates than individual studies
- Can be readily updated, as needed.
- Allows decisions based on the totality of the available evidence

Challenges for all systematic reviews

- Require more time and effort than people expect
- Require judgments about what's in what's out
  - Studies
  - Data
- Reporting biases
- Heterogeneity

Integration of all the evidence

- Many types of studies
  - Mechanistic
  - Animal
  - Human
- "Weight of the evidence"- Overview of all the evidence and systematic review syntheses taken together (quality and strength of all evidence, together)
  - This step is not a part of the systematic review but falls somewhere between the systematic review and policy.
  - Policymakers need it
  - Judgment calls (expert opinion) involved

Quality scales

The Jadad scale places emphasis on some aspects of risk of bias assessment and does not take into account others, and also shows low consistency between different raters. So, along with other quality scoring methods, it has been rejected by most systematic reviewers, including Jadad.

Transplant International

LETTER TO THE EDITOR

The merits of measuring the quality of clinical trials: is it becoming a Byzantine discussion?

doi:10.1111/j.1432-2277.2009.00919.x

Editor: I welcome the opportunity to respond to Dr Berger, particularly because it is the second article authored by him that I have seen this year, and the fourth overall, in which he criticizes the so-called 'Jadad Scale', or 'Jadad score', as he calls it (I was not responsible for the moniker).

Although it might appear surprising, I agree with most

Alejandro R. Jadad
Centre for Global eHealth Innovation,
R. Fraser Elliott Building,
4th floor, Toronto General Hospital,
190 Elizabeth Street, Toronto,
ON M5G 2C4, Canada

Quality scores (and ranks) of 12 RCTs, included in a systematic review of antithrombotic therapy in acute ischemic stroke, using 6 published quality assessment scales

RCT no.	Andrew	Brown	Chalmers	Detsky	Gotzsche	Reisch	% Range (difference)	Rank range
1	75(5)	62(11)	30(9)	61(8)	43,57 (4,7)	61(10)	30-72(42)	4-11
2	89(3)	86(1)	80(1)	96(1)	71,71(2,3)	94(1)	71-96(25)	1-3
3	89(3)	86(1)	47(7)	73(3)	86,71)(1,3)	91(3)	47-91(44)	1-7
4	72(5)	71(10)	28(11)	68(6)	29,86(6,1)	52(12)	29-72(43)	1-12
5	56(9)	76(6)	60(5)	60(9)	29,14(6,12)	67(9)	14-76(62)	5-9
6	94(1)	86(1)	71(3)	71(4)	57,71(3,3)	79(5)	57-94(37)	1-5
7	72(5)	86(1)	65(4)	71(4)	14,43(12,11)	79(5)	14-86(72)	1-12
8	94(1)	81(5)	74(2)	77(2)	43,71(4,3)	94(1)	71-94(23)	1-5
9	50(10)	76(6)	38(8)	53(11)	14,57(10,7)	88(4)	14-88(74)	6-11
10	50(10)	76(6)	25(12)	57(10)	29,57(6,7)	73(8)	29-76(47)	6-12
11	39(12)	57(12)	28(10)	53(11)	14,57(10,7)	56(11)	14-57(43)	7-12
12	72(5)	76(6)	55(6)	64(7)	29,86(6,1)	79(5)	29-79(50)	1-7

The scale developed by Gotzsche has two parts, methods and analysis, which are scored separately

Moher,et al, 1996