

Bias in randomised trials

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Outline

- Sources of bias in the production of evidence
- Sources of bias in the dissemination of evidence

Meta-analysis is no panacea...

- Contrasting conclusions from
 - meta-analyses of the same issue
 - meta-analyses and single large trials

- **“Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in preventing perioperative thrombosis”**

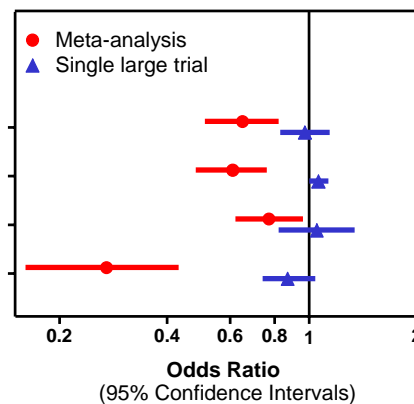
Leizorovicz BMJ 1992

- **“There is no convincing evidence that in general surgery patients LMWHs, compared with standard heparin, generate a clinically important improvement in the benefit to risk ratio”**

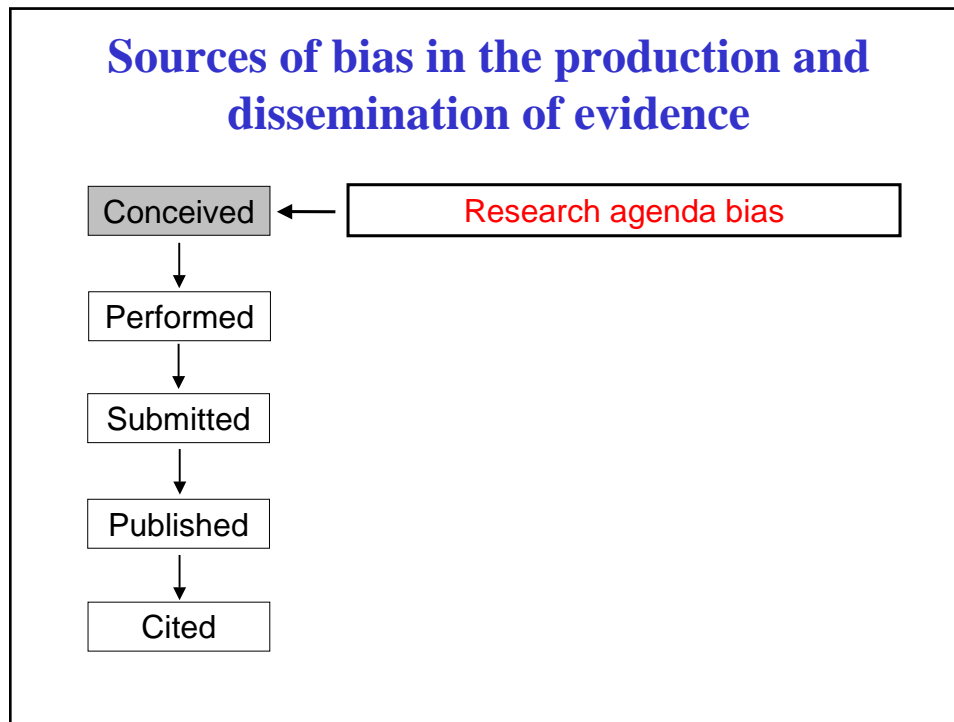
Nurmohamed Lancet 1992

Intervention:

Nitrates in myocardial infarction
Magnesium in myocardial infarction
Inpatient geriatric assessment
Aspirin for prevention of pre-eclampsia



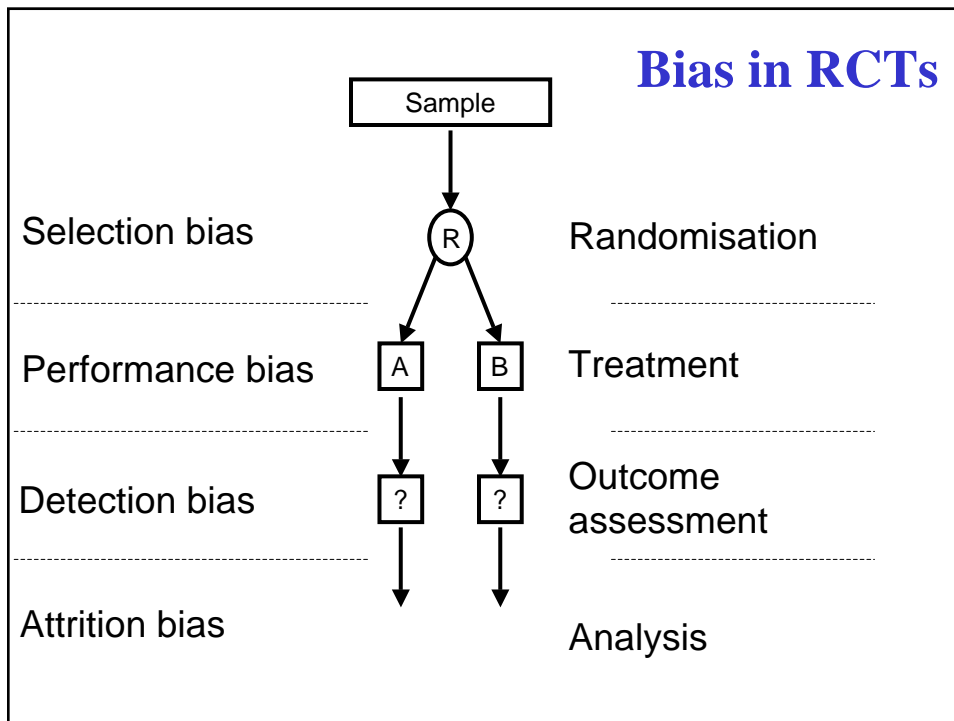
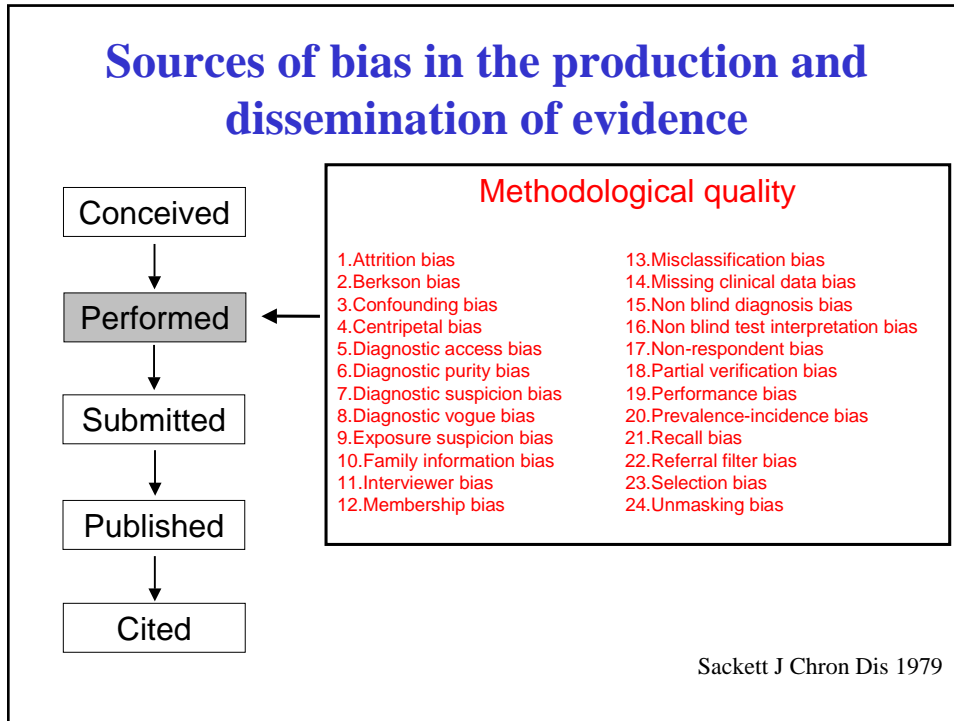
Egger BMJ 1997



Clinical research in osteoarthritis of the knee

- 460 randomised controlled trials identified
- 82.6% drug trials
- Focus groups with patients and health professionals:
 - Lack of evidence / deficit of research for:
 - Physiotherapy, exercise
 - Alternative medicine
 - Indications for joint replacement

Tallon Lancet 2000



Generation of allocation sequence

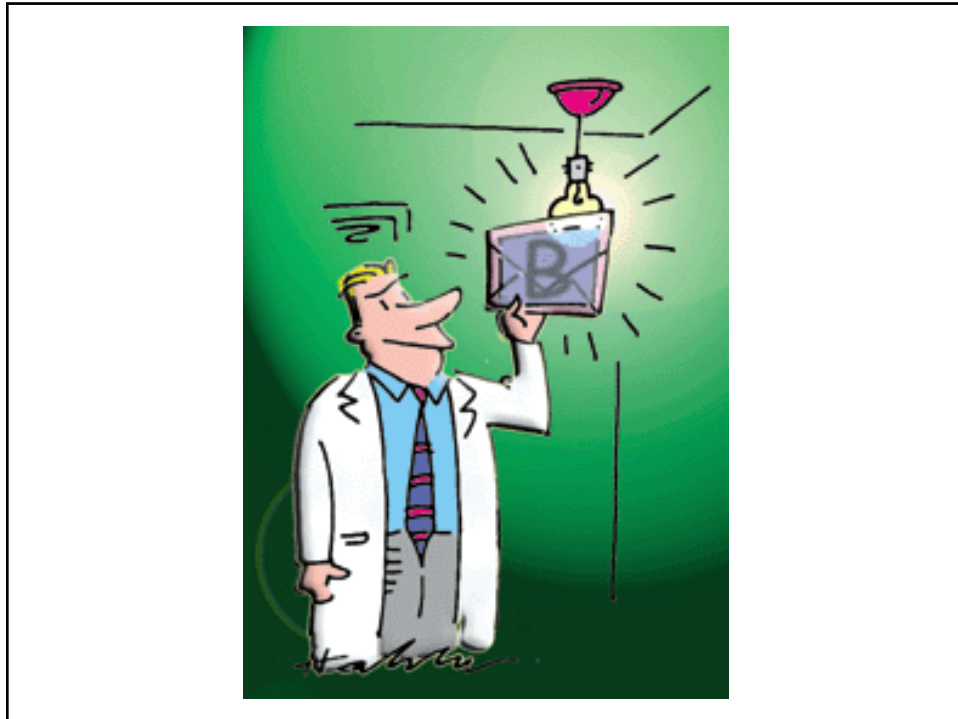
- Low risk of bias if sequence is unpredictable
- High risk of bias if sequence is predictable



Concealment of allocation sequence

- Low risk of bias if patients and enrolling physicians cannot foresee assignment
- High risk of bias if either party can foresee assignment





Envelopes

- Opaque
- Sealed
- Sequentially numbered



Schulz JAMA 1995

Note

Concealment \neq Blinding

Blinding



Single Blind



Double Blind

These terms are poorly understood and often misused

Who can be blinded?

- Participant
 - Therapist/caregiver (health care provider)
 - Outcome assessor
 - Data analyst
-
- Feasibility of blinding often dependent on intervention being assessed
 - Effect of blinding may be affected by type of outcome
 - Objective vs. subjective outcomes

Empirical evidence of bias

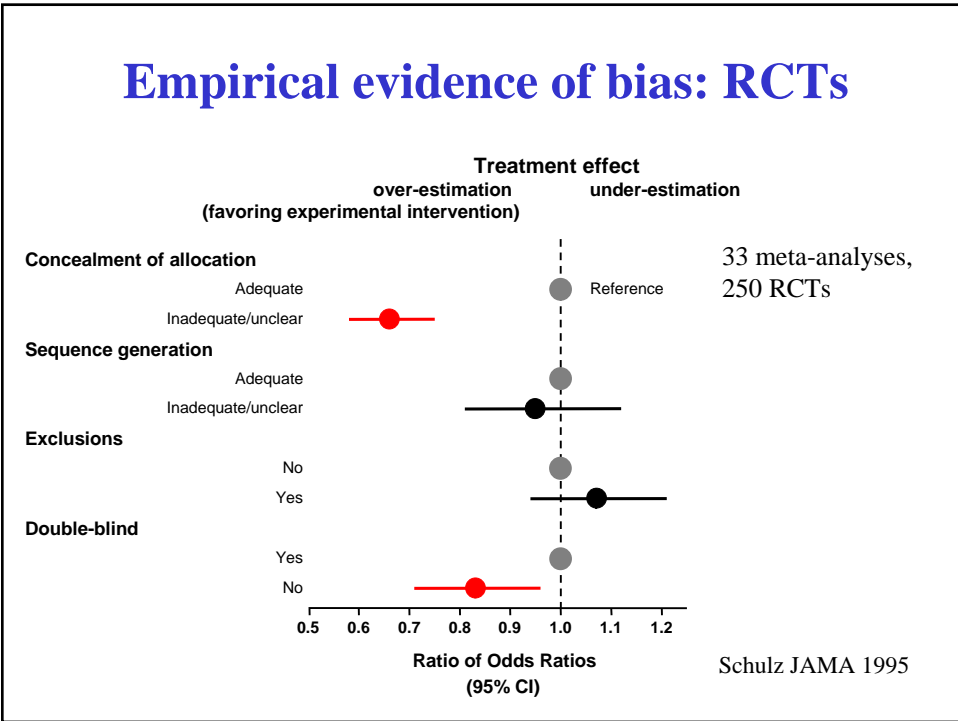


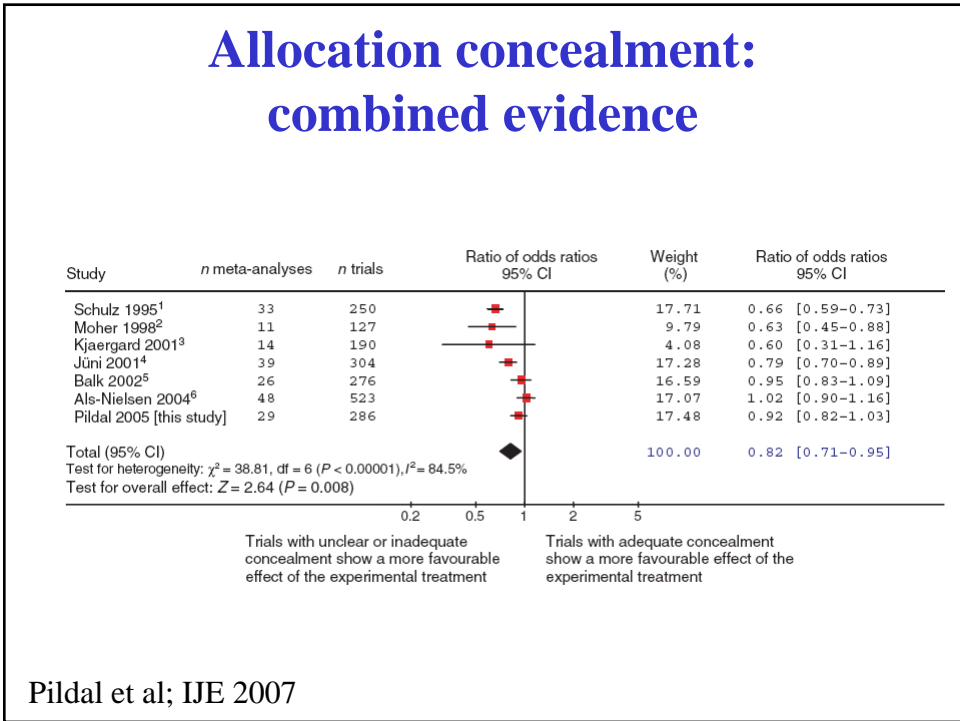
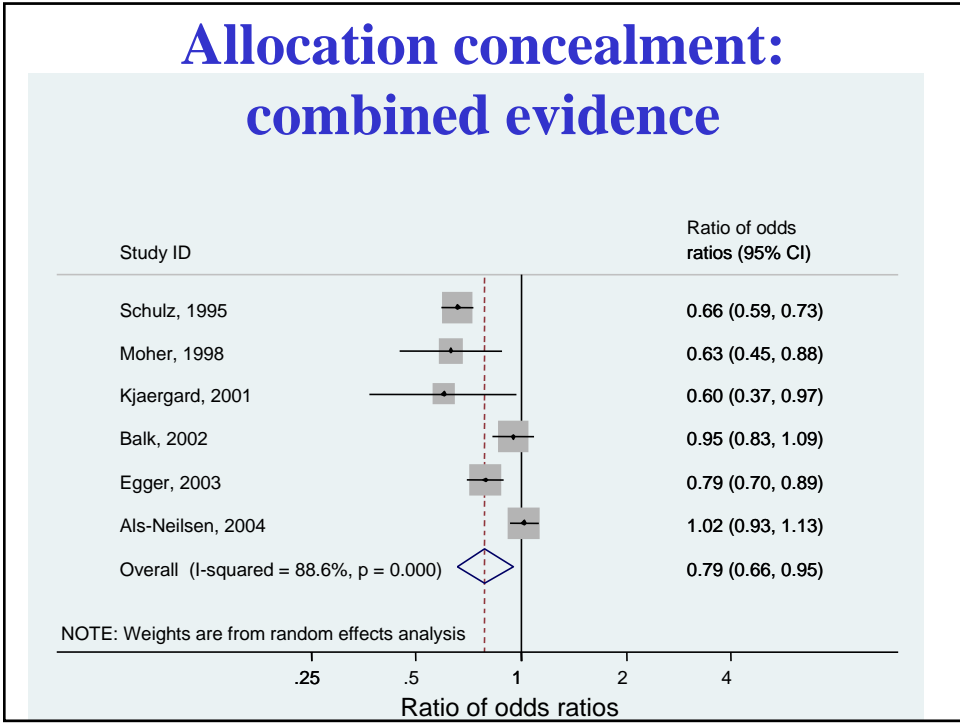
Evidence-based critical appraisal

Meta-epidemiology

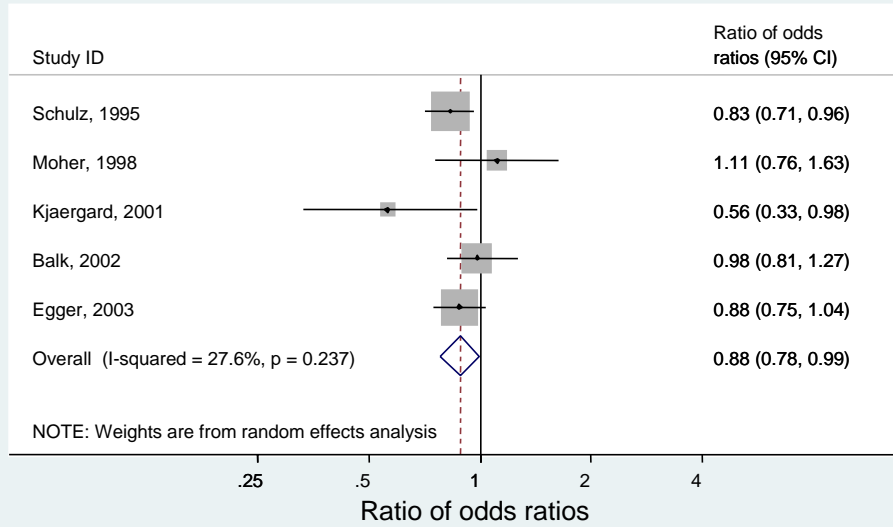
(Naylor, *BMJ* 1997; 315: 617-619)

- Identify a large number of meta-analyses
- Record characteristics of individual studies (e.g., quality, type of publication, language etc.)
- Compare treatment effects *within* each meta-analysis (e.g., high-quality vs. low-quality according to some dimension of trial quality)
- Estimate **ratio of odds ratios** comparing high quality and low quality trials (“meta-meta-analysis”)

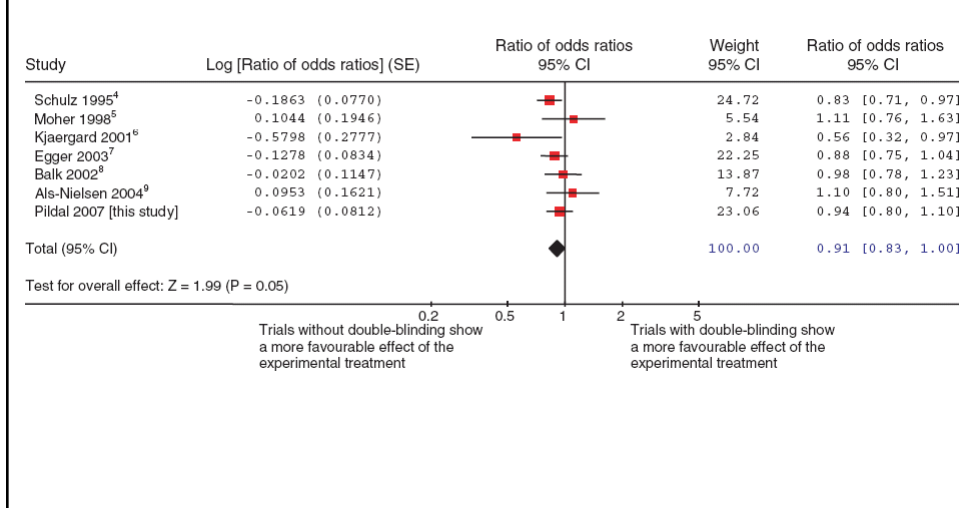




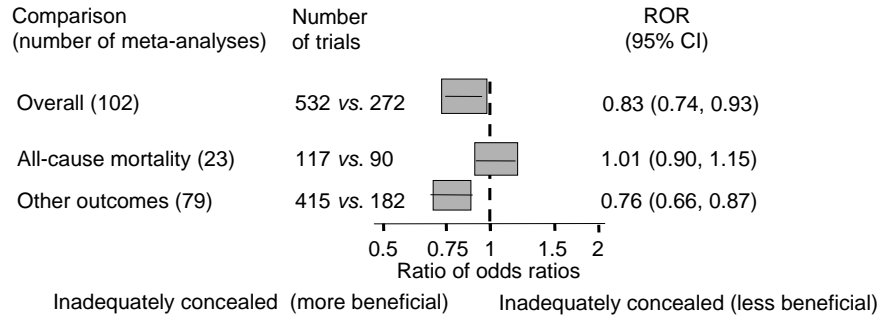
Blinding: combined evidence



Blinding: combined evidence

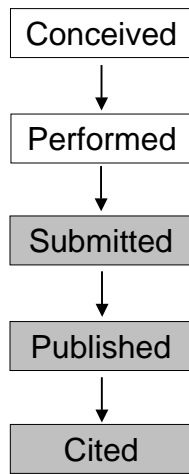


Variability in the effect of inadequate allocation concealment



Wood et al., Cochrane Colloquium 2006

Sources of bias in the production and dissemination of evidence



Reporting Biases:
 Publication Bias
 Time Lag Bias
 Language Bias
 Multiple Publication Bias
 Outcome reporting bias
 Citation bias

The dissemination of evidence ...

unavailable
(unpublished)

available in principle
(e.g. thesis, obscure journal)

easily available
(Medline-indexed)

actively
disseminated
(e.g. reprint from
drug company)

Type of reporting bias	Definition
Publication bias	The <i>publication or non-publication</i> of research findings, depending on the nature and direction of the results
Time lag bias	The <i>rapid or delayed</i> publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The <i>multiple or singular</i> publication of research findings, depending on the nature and direction of the results
Citation bias	The <i>citation or non-citation</i> of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings <i>in a particular language</i> , depending on the nature and direction of the results
Outcome reporting bias	The <i>selective reporting</i> of some outcomes but not others, depending on the nature and direction of the results

Reporting versus conduct

- assessed the quality of 63 reports of breast cancer trials
 - chalmers (tc) index; 0 to 100, higher scores indicating superior quality
- average score = 50% (46%, 54%)
- interviewed 62 (of 63) corresponding authors
- average score = 57%

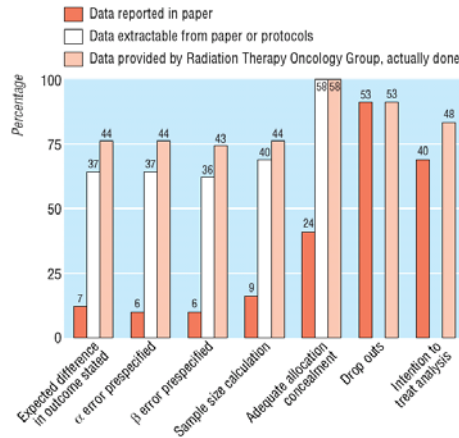
liberati a, et al. journal of clinical oncology 1986;4:942-51

Reporting versus conduct

- reviewed all terminated phase III trials conducted by the Radiation Oncology Group since 1968
- protocols undergo extensive peer review
- access to 56 protocols and 58 associated publications
- evaluated characteristics acknowledged to be important in minimizing bias:
 - allocation concealment
 - sample size calculation
 - intention to treat analysis

soares hp, et al. bmj 2004;328:22-25

Reporting versus conduct



Quality of reporting compared with actual methodological quality of 56 randomised controlled trials (58 reports) conducted by the Radiation Therapy Oncology Group, based on information from published reports, protocols, and verification by the group. Absolute numbers of reports are shown

Phases in development of a trial protocol by Radiation Therapy Oncology Group

- Approval of concept
- Review and approval of protocol among group members
- Review by headquarters, including statistics, data management, quality assurance, protocol administrator, and review by the institutional review board
- Review by National Cancer Institute
- Activation of protocol
- Revision of protocol

Reporting versus conduct

- pildal et al. *bjm* 2005;330:1049-1052
 - 96 (of 102; 94%) trial reports had unclear allocation concealment
 - according to the protocols 80 (of 96; 83%) unclear allocation concealment

Examining the quality of reports of 'older' trials

- 45 reports published in 'high' impact factor journals
 - 5 (11%) mentioned sample size calculation
 - 6 (13%) made use of confidence intervals
 - statistical analysis tended to exaggerate intervention efficacy
- reviewed 2000 randomized trials of all treatments for schizophrenia
 - only 4% (n=80) of the trials clearly described the methods of allocation

Pocock SJ, Hughes MD, Lee RJ. Statistical problems in the reporting of clinical trials. *NEJM* 1987;317:426-432.

Thornley B, Adams CE. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *British Medical Journal* 1998;317:1181-1184.

Examining the quality of reports of trials published 'today'

- Cross-sectional examination of reports of randomized trials
- Published in December 2000 and indexed on PubMed by July 2002
- Examined a number of characteristics
 - random sequence generation
 - allocation concealment
 - handling of attrition

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet* 2005;365:1159-1162

Results

- 519 reports included in sample
- random sequence generation
 - 109 (21%) reported
- allocation concealment
 - 94 (18%) reported
- handling of attrition
 - 174 (34%) reported

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet* 2005;365:1159-1162

Fussing over randomized trials

- the most expensive form of healthcare evaluation
 - can easily cost \$1 million to \$50 million
 - > 41,000 ongoing randomized trials
 - www.centerwatch.com
- accounts for less than 10% of the published healthcare literature

funai EF, et al. gynecologic and obstetric investigation. 2001;51:8-11