JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

THE COCHRANE COLLABORATION®

Multiple data sources exist for systematic reviews: The most important ones are hidden

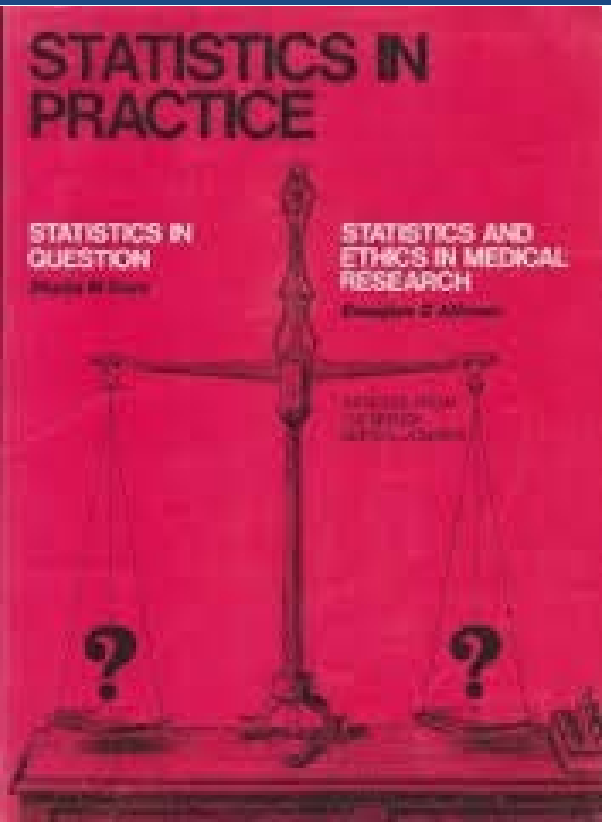
Kay Dickersin, MA, PhD

Methods Symposium to Honor Doug Altman

Québec City

Sept 24, 2013

My introduction to Doug



1982

1986


746 BRITISH MEDICAL JOURNAL VOLUME 292 15 MARCH 1986

Statistics in Medicine

Confidence intervals rath
hypothesis testing

MARTIN J GARDNER, DOUGLAS G

Abstract

Overemphasis on hypothesis testing—and the use o dichotomise significant or non-significant results— from more useful approaches to interpreting study as estimation and confidence intervals. In me investigators are usually interested in determinin difference of a measured outcome between groups, simple indication of whether or not it is statistical Confidence intervals present a range of values, on tl sample data, in which the population value for suc may lie. Some methods of calculating confidence means and differences between means are given, information for proportions. The paper also gives su graphical display

1990

1987

ACADEMIA AND CLINIC

A Proposal for More Informative Abstracts of Clinical Articles

AD HOC WORKING GROUP FOR CRITICAL APPRAISAL OF THE MEDICAL LITERATURE*

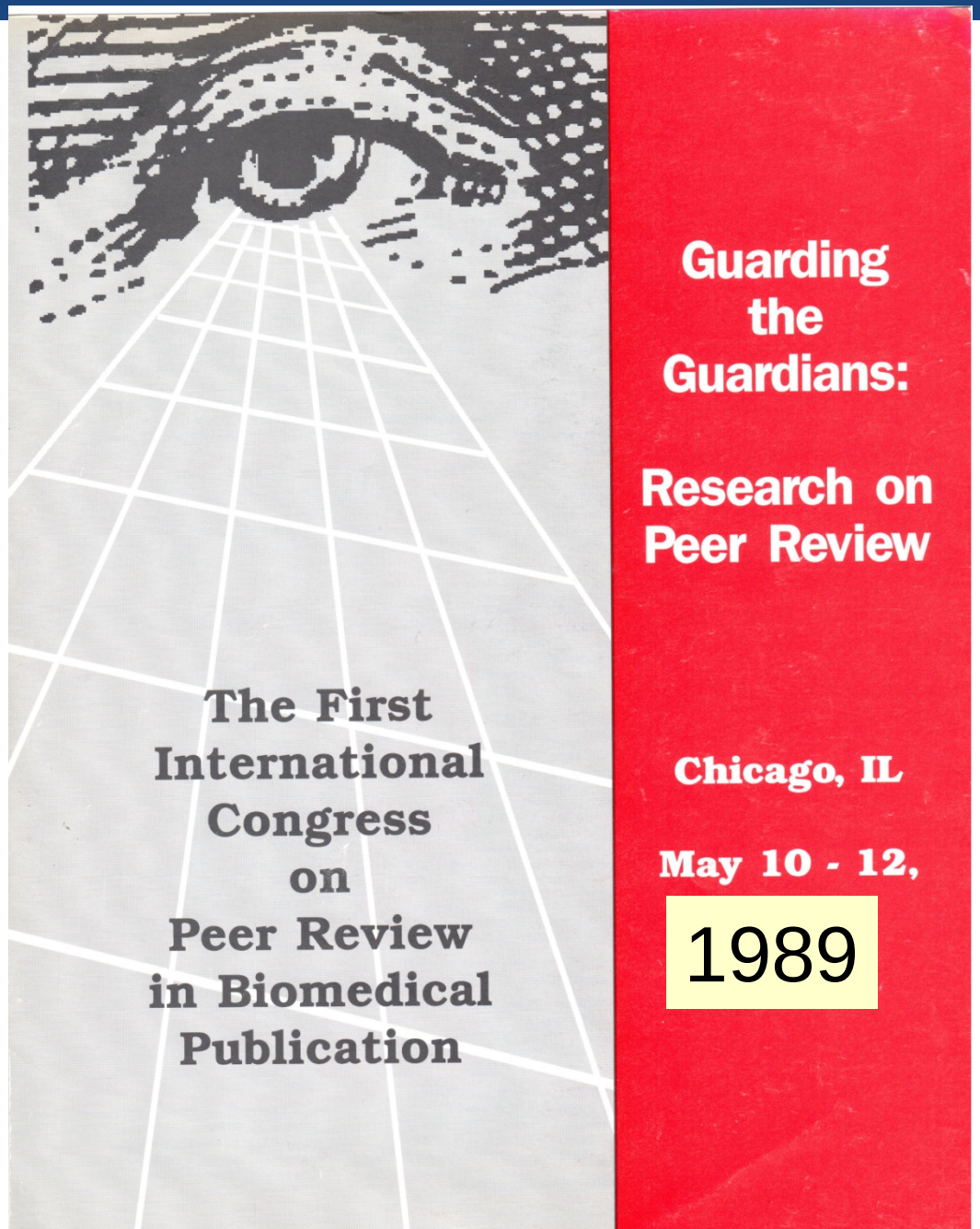
Medical journals are a principal source of new knowledge for clinicians. Unfortunately, articles containing valid and valuable information are often buried among others of less value. Innovations are needed to assist clinicians in finding articles that are both scientifically sound and applicable to their practices. An easily implemented, although partial, solution is for authors of articles that have clinical implications to structure their abstracts so that key aspects of purpose, methods, and results are reported with a partly controlled vocabulary and in a standardized format. This would assist clinical readers to select appropriate articles more quickly, allow more precise computerized literature searches, and facilitate peer review before publication.

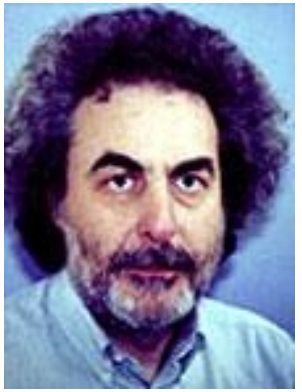
[Indexing terms: abstracting and indexing; biomedical

ly to keep up to date, few actually search it to solve problems that arise in the course of clinical practice (6). Difficulties in using journals to solve clinical problems as they present are at least partly logistical: it takes too much time to track down the appropriate information. Electronic searching makes it possible for clinicians to find applicable articles in a few minutes, from the bedside, clinic, office, and home (16-20), as well as from the library. Accurate searching, however, is hampered by limitations of indexing and lack of systematic structure in the abstracts (and full text) of published articles, so that inclusion of seemingly appropriate terms in search state-

1987 Annals Int Med

The International Congress on Peer Review





BMJ Statistics Notes

Altman DG, Bland M. Brackets (parentheses) in formulas. *BMJ* 2011; 343: d570.
Altman DG, Bland M. How to obtain the P value from a confidence interval. *BMJ* 2011; 343: d2304.
Altman DG, Bland M. How to obtain the confidence interval from a P value. *BMJ* 2011; 343: d2090.
Bland JM, **Altman DG**. Correlation in restricted ranges of data. *BMJ* 2011; 342: d556.
Bland JM, **Altman DG**. Comparisons within randomised groups can be very misleading. *BMJ* 2011; 342: d561.
Altman DG, Bland M. Parametric v nonparametric methods for data analysis. *BMJ* 2009; 339: a3167
Bland M, **Altman DG**. Analysis of continuous data from small samples. *BMJ* 2009; 338: a3166.
Altman DG, Bland M. Missing Data. *BMJ* 2007. 334: 424.
Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ* 2006; 332: 1080.
Altman DG, Bland JM. Standard deviations and standard errors. *BMJ*. 2005;331:903.
Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005; 330: 843.
Bland JM, **Altman DG.** The logrank test. *BMJ* 2004; 328: 1073.
Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ* 2004; 329: 168-169.

79.
9; 318: 1209.
1572.
).
[Reprinted :
1998; 316: 1455.
correlation
correlation

Altman DG, Bland JM. Units of analysis. *BMJ* 1997; 314: 1874.
Bland JM, **Altman DG**. Cronbach's alpha. *BMJ* 1997; 314: 572.
Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996; 313: 1200.
Matthews JNS, **Altman DG**. Interaction 3: How to examine heterogeneity. *BMJ* 1996; 313: 862.
Matthews JNS, **Altman DG**. Interaction 2: Compare effect sizes not P values. *BMJ* 1996; 313: 808.
Matthews JNS, **Altman DG**. Interaction 1: Heterogeneity of effects. *BMJ* 1996; 313: 486.
Bland JM, **Altman DG**. Measurement error proportional to the mean. *BMJ* 1996; 313: 106.

09: 188.

Bland JM, **Altman DG**. Regression towards the mean. *BMJ* 1994; 308: 1499.
Bland JM, **Altman DG**. Correlation; regression and repeated data. *BMJ* 1994; 308: 896.

1994

Review

Empirical Evidence of Bias

Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials

Kenneth F. Schulz, PhD, MBA; Iain Chalmers, MBBS, MSc; Richard J. Hayes, MSc; Douglas G. Altman

Objective.—To determine if inadequate approaches to randomized controlled trial design and execution are associated with evidence of bias in estimating treatment effects.

Design.—An observational study in which we assessed the methodological quality of 250 controlled trials from 33 meta-analyses and then analyzed, using multiple logistic regression models, the associations between those assessments and estimated treatment effects.

Data Sources.—Meta-analyses from the Cochrane Pregnancy and Childbirth Database.

Main Outcome Measures.—The associations between estimates of treatment effects and inadequate allocation concealment, exclusions after randomization, and lack of double-blinding

ditionally, they suspected that methodologically inferior trials might produce bias in both directions, thereby causing greater variability in estimates of treatment effects. In neither analysis, however, did they detect a relationship.

Using a database of systematic reviews of controlled trials in pregnancy and childbirth,[12] we sought evidence of bias related to use of inadequate methodological approaches to trial design and execution. Rather than using quality scores, we investigated specific aspects that we be-

Special Communication

Improving the Quality of Reportin
Randomized Controlled Trials

Review

OPEN ACCESS Freely available online

PLoS MEDICINE

CONSORT for Reporting Randomized Controlled Trials in Journal and Conference Abstracts: Explanation and Elaboration

Sally Hopewell[1,2*], Mike Clarke[1,3], David Moher[4,5], Elizabeth Wager[6], Philippa Middleton[7], Douglas G. Altman[2], Kenneth F. Schulz[8], and the CONSORT Group

1 UK Cochrane Centre, Oxford, United Kingdom, 2 Centre for Statistics in Medicine, Wolfson College, Oxford University, Oxford, United Kingdom, 3 School of Nursing and Midwifery, Trinity College Dublin, Dublin, Ireland, 4 Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada 5 Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada, 6 Sideview, Princes Risborough, United Kingdom, 7 Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia, 8 Family Health International, Research Triangle Park, North Carolina, United States of America

Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement

David Moher, Deborah J Cook, Susan Eastwood, Ingram Olkin, Drummond Rennie, Donna F Stroup, for the QUORO

Summary

Background The Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of randomised controlled trials (RCTs).

Methods The

Introduction

Health-care

CONSORT Statement for Reporting Randomiz
Explanation and Elaboration

Douglas G. Altman, DSc; Kenneth F. Schulz, PhD; David Moher, MSc; Matthias Egger, MD; Frank Davidoff, MD; Diana
Peter C. Gøtzsche, MD; and Thomas Lang, MA, for the CONSORT

ACADEMI

porting of their trials.
This explanatory and elaboration
hance the use, understanding,
ORT statement. The mean

RESEARCH METHODS AND REPORTING

SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials

An-Wen Chan,[1] Jennifer M Tetzlaff,[2] Peter C Gøtzsche,[3] Douglas G Altman,[4] Howard Mann,[5] Jesse A Berlin,[6] Kay Dickersin,[7] Asbjørn Hróbjartsson,[3] Kenneth F Schulz,[8] Wendy R Parulekar,[9] Karmela Krleža-Jeric,[10] Andreas Laupacis,[11] David Moher[2 10]

[1]Women's College Research Institute at Women's College Hospital, Department of Medicine, University of Toronto, Toronto, Canada M5G 1N8

High quality protocols facilitate proper conduct, reporting, and external review of

mittees/institutional review boards, regulatory agencies, medical journals, systematic reviewers, and other groups rely on protocols to appraise the conduct and reporting of

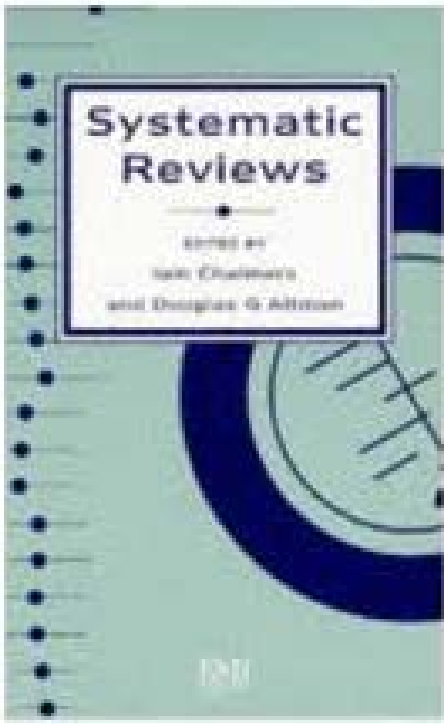
OPEN ACCESS Freely available online

Guidelines and Guidance

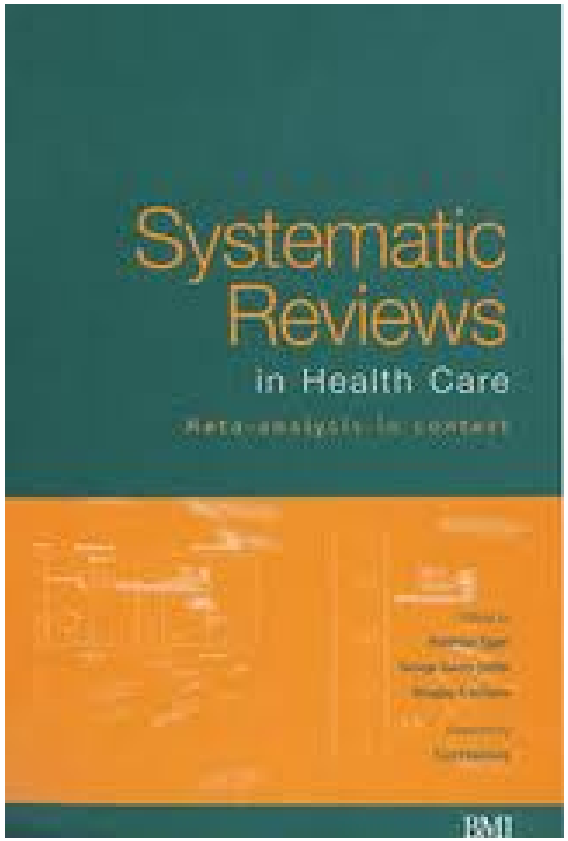
The PRISMA Statement for R
and Meta-Analyses of Studi
Interventions: Explanation

Alessandro Liberati[1,2*], Douglas G. Altman[3], Je
John P. A. Ioannidis[7], Mike Clarke[8,9], P. J. Dev

Systematic reviews



1999



2008

1993 Cochrane Colloquium

2009 SPIRIT

2007 CONSORT

OPEN ACCESS Freely available online

PLOS | ONE

Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review

Kerry Dwan*, Carrol Gamble, Paula R. Williamson, Jamie J. Kirkham, for the Reporting Bias Group¶

Department of Biostatistics, University of Liverpool, Liverpool, England

Abstract

Background: The increased use of meta-analysis in systematic reviews of healthcare interventions has highlighted several types of bias that can arise during the completion of a randomised controlled trial. Study publication bias and outcome reporting bias have been recognised as a potential threat to the validity of meta-analysis and can make the readily available evidence unreliable for decision making.

Transparency declaration

The manuscript's guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

2013 BMJ Altman & Moher

2008 BMJ Awards Dinner

2013

Multiple data sources exist for systematic reviews

- There is considerable unreported and misreported information about the effectiveness and safety of drugs
- The impact of these data on a single systematic review can
  - Reveal new safety concerns,
  - Show a lack of effectiveness for certain outcomes
  - Expose other shenanigans.
- The “true” study data remain difficult to access.
- Restorative authorship of abandoned studies is an approach that solves some problems
- BUT, it is difficult to find unpublished or other source data

Looking under the hood

- Reporting guidelines cannot influence those studies where no report is published at all.
- Evidence that the report does not represent what was done or learned from the trial
  - FDA
  - CT.gov
  - Internal company documents

The gabapentin story

- Recognizing that Neurontin earnings were limited with FDA-approved indication (epilepsy), Pfizer/Parke-Davis performed trials for the purpose of publishing them as a form of marketing off label uses:
  - Migraine
  - Bipolar disorders
  - Neuropathic pain
  - Nociceptive pain

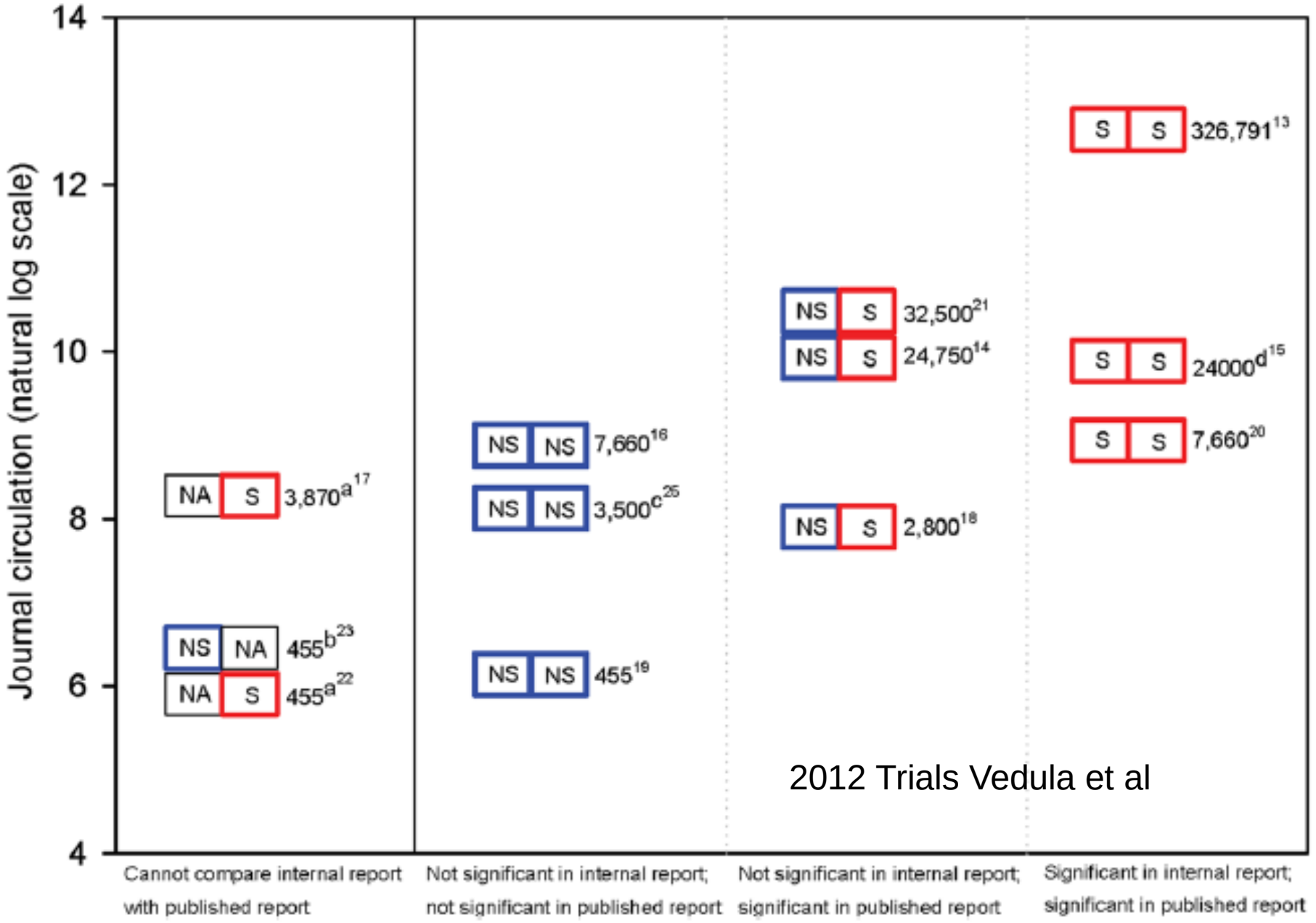
Vedula SS et al. N Engl J Med 2009;361:1963-1971

Findings from review of gabapentin documents

- Selective outcome reporting
- Changes between protocol and publication
  - Definition of primary outcome
  - Number randomized
  - Efficacy analysis (who would be included)
  - How ITT defined
- Role of publication in marketing

2009 (NEJM), 2012 (Trials), 2013 (PLoS Med) Vedula et al

Journal circulation of main publication, by primary outcome statistical significance in internal vs published reports



2012 Trials Vedula et al

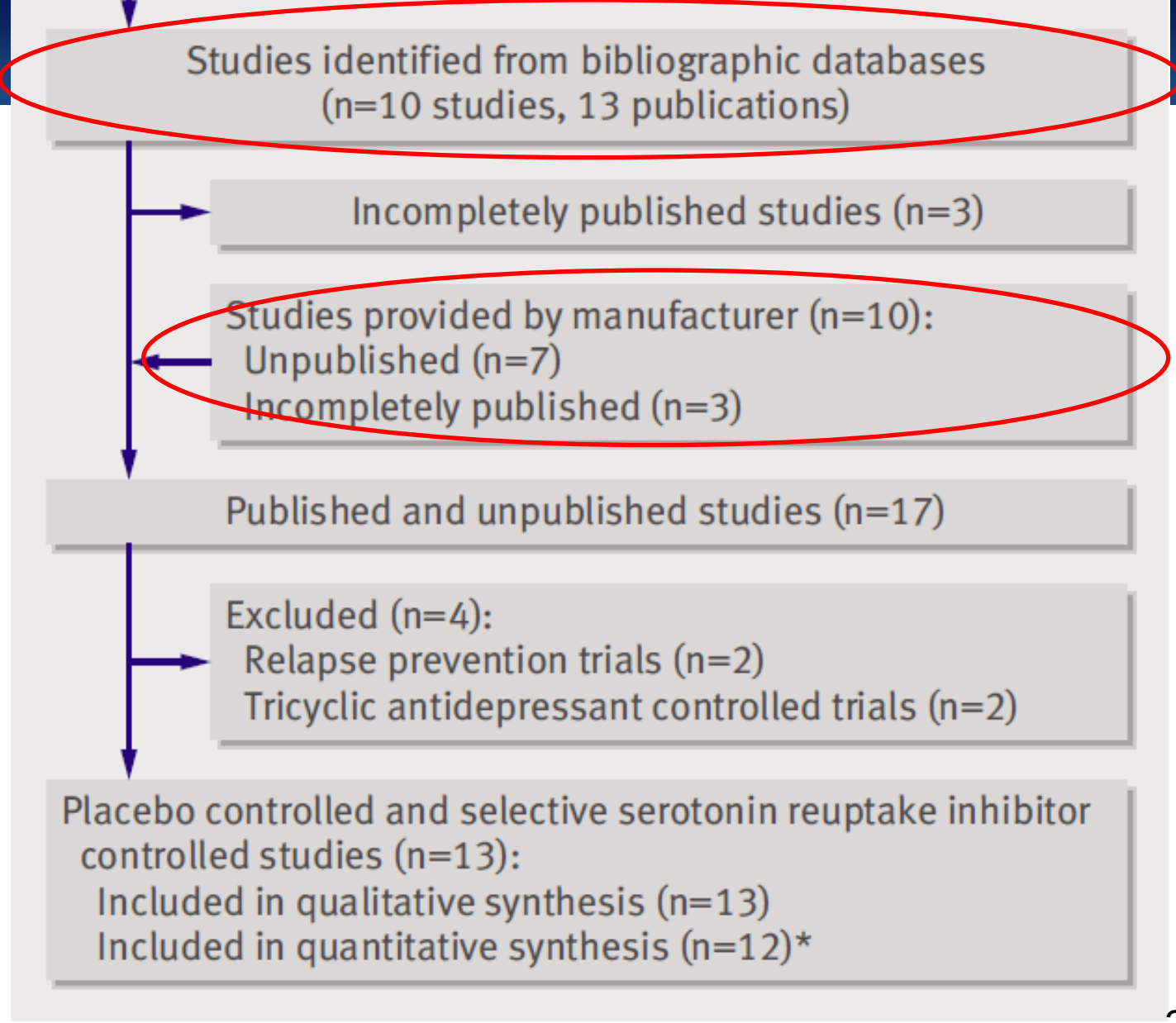


Fig 1 | Flowchart of study selection. *Excluding long term acute treatment trial

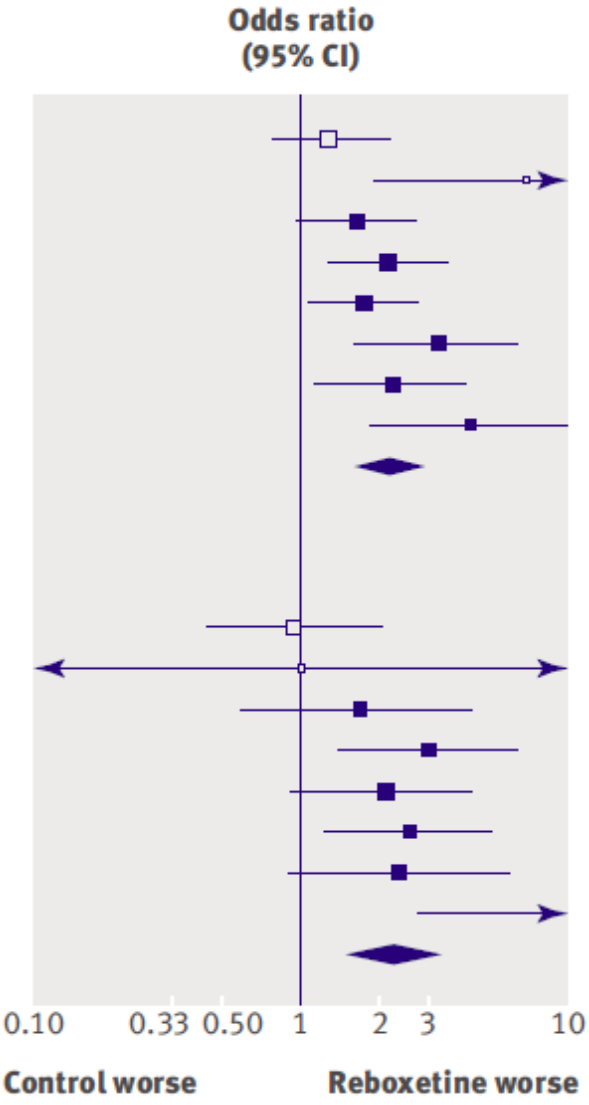
Reboxetine vs placebo and/or SSRI RCTs for major depression

2010 BMJ Edying et al

Reboxetine vs placebo and/or SSRIs for depression

■ Unpublished □ Published

Trial	Reboxetine (n/N)	Placebo (n/N)
Patients with adverse events		
014	84/126	78/128
091	24/28	13/28
015	71/112	58/112
046	239/264	208/254
047	225/258	201/252
050	138/150	117/150
045	68/89	52/87
049	98/106	77/104
Total	947/1133	804/1115
Total heterogeneity: I^2=44.0%, P=0.085; total effect: P<0.001		
Withdrawal owing to adverse events		
014	14/126	15/128
091	1/28	1/28
015	11/112	7/112
046	26/264	9/254
047	20/258	10/252
050	27/150	12/150
045	15/89	7/87
049	23/106	3/104
Total	137/1133	64/1115
Total heterogeneity: I^2=38.4%, P=0.124; total effect: P<0.001		

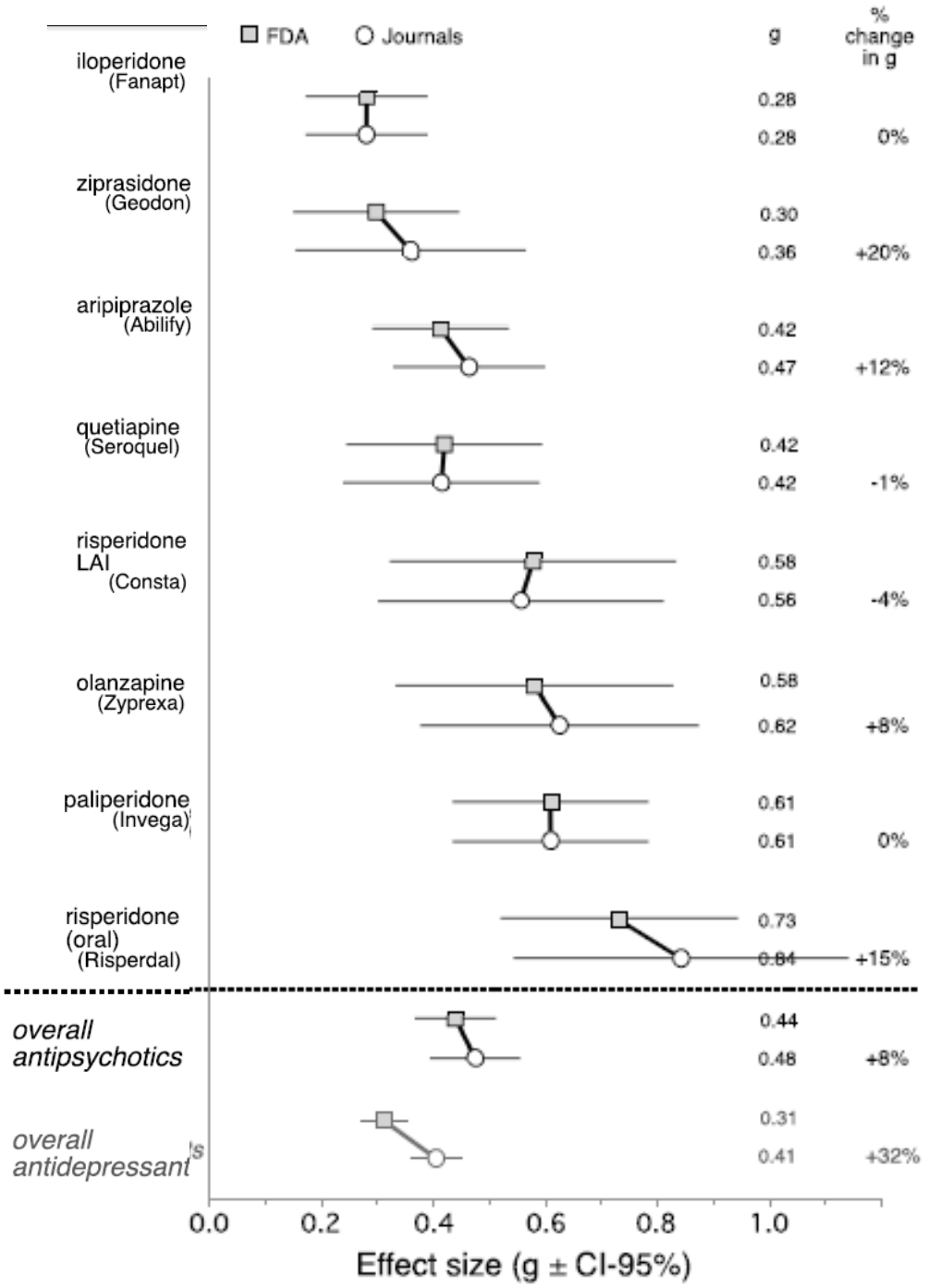


Edying et al BMJ 2010

FDA data included in meta-analysis

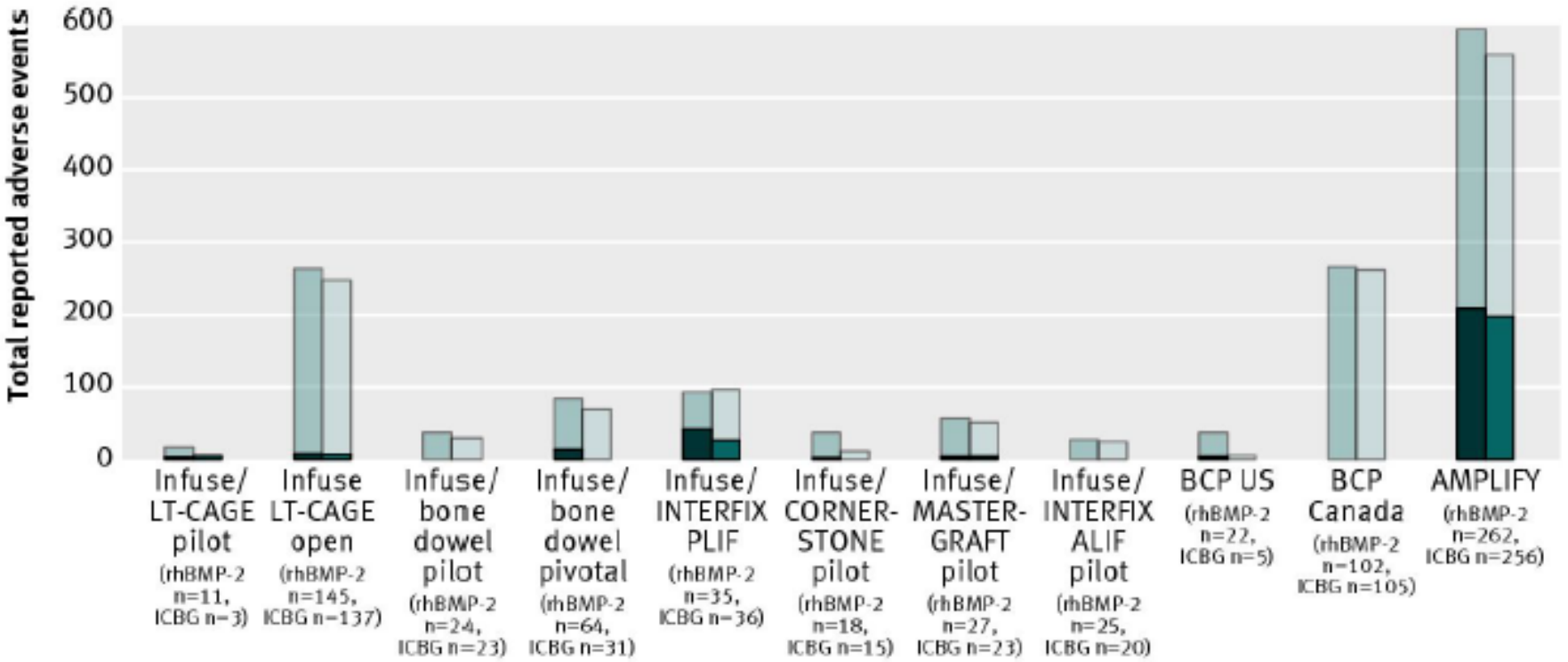
Published data only included in meta-analysis

Meta-analysis with and without unpublished data



2012 PLoS Med Turner et al

Adverse events in Medtronic RCTs: IPDs vs publications



Two methods of spinal fusion rhBMP-2 vs ICBG

Rodgers et al. BMJ 2013

Drugs for which negative outcomes (adverse events or lack of efficacy) were discovered using company data

Drug name	What happened
Rosiglitazone	Unpublished trials revealed serious adverse effects , especially cardiovascular
Oseltamivir	Authors concluded that previous effectiveness claims were not supported by the available evidence.
Gabapentin	Outcome reporting bias, changes in participants included in analysis, plans to delay publication, ghostwriting all revealed by internal company documents.
Rofecoxib	FDA documents indicated that there might be increased CVD events caused by the drug.

Adapted from Doshi 2012 PLoS Med

Information that was missed without access to internal company files on oseltamivir/Tamiflu

- Total number of trials done on topic
- Adverse events not reported in articles
- Adverse events classified as “complications”
- Trials published 10 years after completion
- Trial details vital to interpretation
- Authorship of reports

Source: Doshi et al PloS Med 2012

The protocol and data are not enough for assessment of reporting biases

Conclusions from Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion systematic review and meta-analysis (YODA)

- "Although we had unusual access to protocols and documents submitted by the manufacturer to the FDA, other information, such as operative notes and internal correspondence, might have helped assess the extent of design and reporting bias. Internal correspondence is essential to evaluating selective analysis reporting, ghostwriting, timelag-bias, and misrepresentation of facts".

2013 Annals Int Med Fu et al

RIAT: Publication of hidden trial data

Restoring invisible and abandoned trials: a call for people to publish the findings

Unpublished and misreported studies make it difficult to determine the true value of a treatment. **Peter Doshi and colleagues** call for sponsors and investigators of abandoned studies to publish (or republish) and propose a system for independent publishing if sponsors fail to respond

Well designed and well performed randomised controlled trials are considered to provide the most reliable evidence on the effects of health related interventions. However, the credibility of findings from individual trials and from summaries of trials examining a similar research question (that is, systematic reviews and meta-analyses) has been undermined by numerous reporting biases in the published medical literature.[1-14] Reporting biases are often difficult to detect, but have the potential to discredit earnest efforts towards evidence based decision making.

Two basic problems of representation are driv-

bmj.com

Read more about *BMJ*'s open data campaign at bmj.com/open-data

CLINICAL STUDY REPORTS IN OUR POSSESSION

Amgen Epoetin Alfa study 930107
AstraZeneca quetiapine study 015, 041, 049, 135, 125, 127, 126
Bristol-Myers Squibb clopidogrel study CAPRIE, CURE, CLARITY, COMMIT, PICOLO
Bristol-Myers Squibb aripiprazole study CN138135
GSK H5N1 pandemic influenza vaccine studies

thousands of pages of trial reports in the public domain. Other trial reports, such as for oseltamivir and clopidogrel, were obtained through new freedom of information policies at the European Medicines Agency (EMA) that have revolutionised the public's ability to access trial data.[20-23] The documents are a substantial resource of information about trials. We expect that other independent groups will also have access to many additional trial reports.

The documents we have obtained include trial reports for studies that remain unpublished years after completion (such as Roche's study M76001, the largest treatment trial of oseltamivir, and Pfizer's study A945-1008, the largest trial of

One full clinical study report (Roche Tamiflu study WP16263)

8545 pages
8000
7000
6000
5000
4000
3000
2000
1000

Same trial – 7 pages in a medical journal

International Journal of Antimicrobial Agents 35 (2010) 401–407

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

ELSEVIER

Safety and pharmacokinetics of oseltamivir at standard and high dosages

R. Dutkowski[a], J.R. Smith[b,*], B.E. Davies[a]

[a] Hoffmann-La Roche Inc., Nutley, NJ, USA
[b] F. Hoffmann-La Roche Ltd., PRMT Bldg 74/3D 104, CH-4070 Basel, Switzerland

ARTICLE INFO

Article history:
Received 15 October 2009
Accepted 26 December 2009

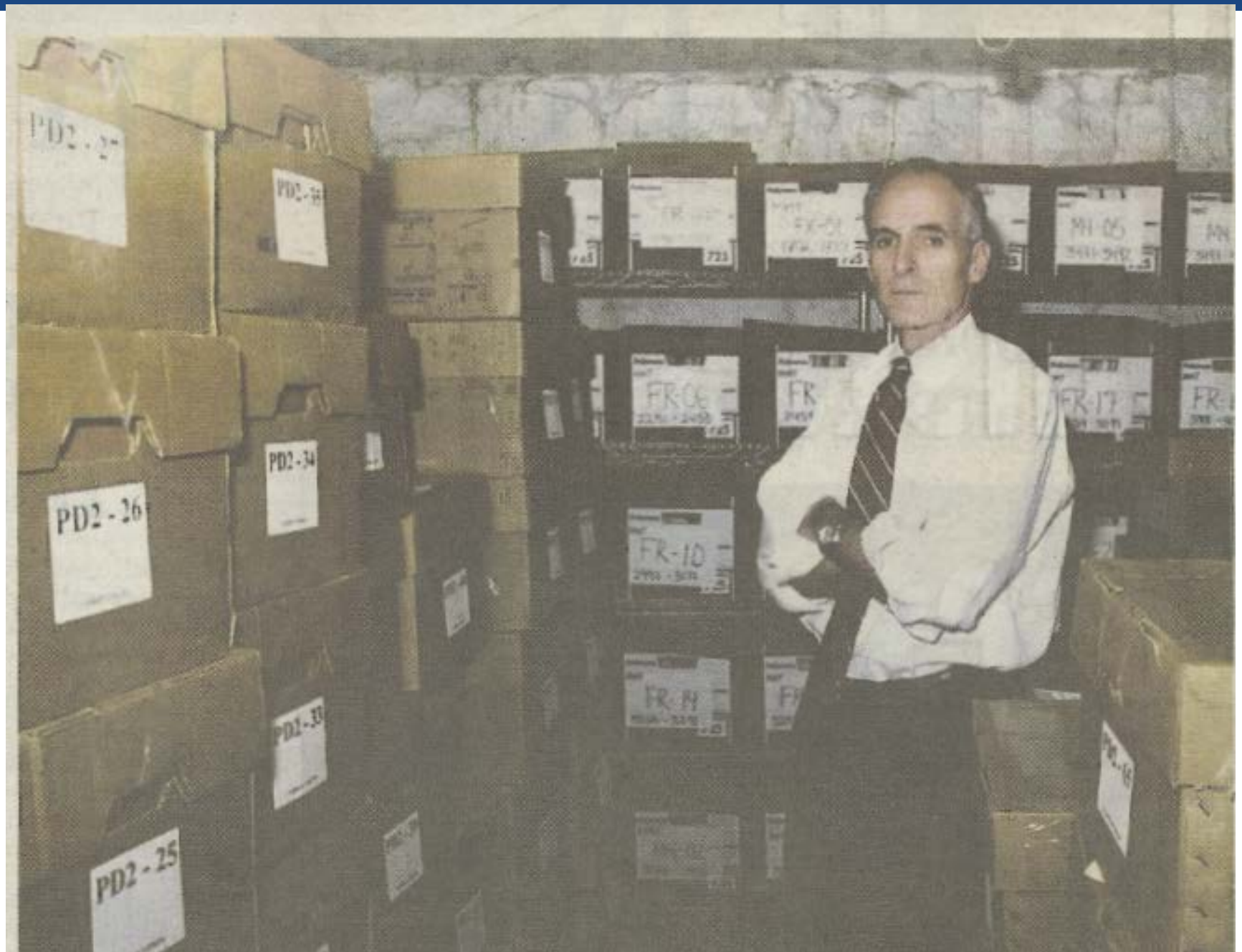
Keywords:
Oseltamivir
High dose
Safety
Pharmacokinetics

ABSTRACT

Although clinical evidence is currently lacking, opinion in the literature on avian influenza A/H5N1 suggests that increased doses of the oral neuraminidase inhibitor oseltamivir may offer clinical benefits against highly pathogenic influenza where high levels of viral replication and disseminated infection cause severe disease. We assessed the pharmacokinetics and safety/tolerability of oseltamivir at dosages up to 450 mg twice daily. Healthy adult volunteers were randomised to receive placebo or oseltamivir 75, 225 or 450 mg every 12 h for 5 days. Volunteers were followed up to Day 7 for pharmacokinetic parameters, vital signs, adverse events and cardiac safety. In total, 391 volunteers were randomised and evaluated. Pharmacokinetics were linear and dose-proportional, with no evidence of accumulation of oseltamivir or its active metabolite at any dosage. Headache was the most common adverse event (16.8–23.7% across groups), but its incidence was unrelated to dosage. Dosage-related events with oseltamivir included nausea (up to 31.3% of volunteers) and vomiting (up to 19.2%), which generally occurred on Day 1 and lasted <1 day, and possibly dizziness (up to 11.3%). Oseltamivir had no relevant

Source: P. Doshi

Neurontin/gabapentin documents & plaintiff lawyer T. Greene



We found few research articles using internal documents from pharmaceutical industry compared with tobacco

- **Studies using tobacco documents** (n=325)
  - 324 (>99%) used documents released through litigation, and located in repositories
  - 303 (93%) examined strategic behavior by companies
  - 31 (10%) examined the research methods used
  - 278 (86%) received government funding
- **Studies using pharmaceutical documents** (n=20)
  - 18 (90%) used documents released through litigation
  - 15 (75%) examined strategic behavior
  - 9 (45%) examined methods used
  - 3 (15%) received government funding

2013 Wieland et al (submitted)

Did we find all research using internal docs?

Pharmaceuticals (n=20 articles)

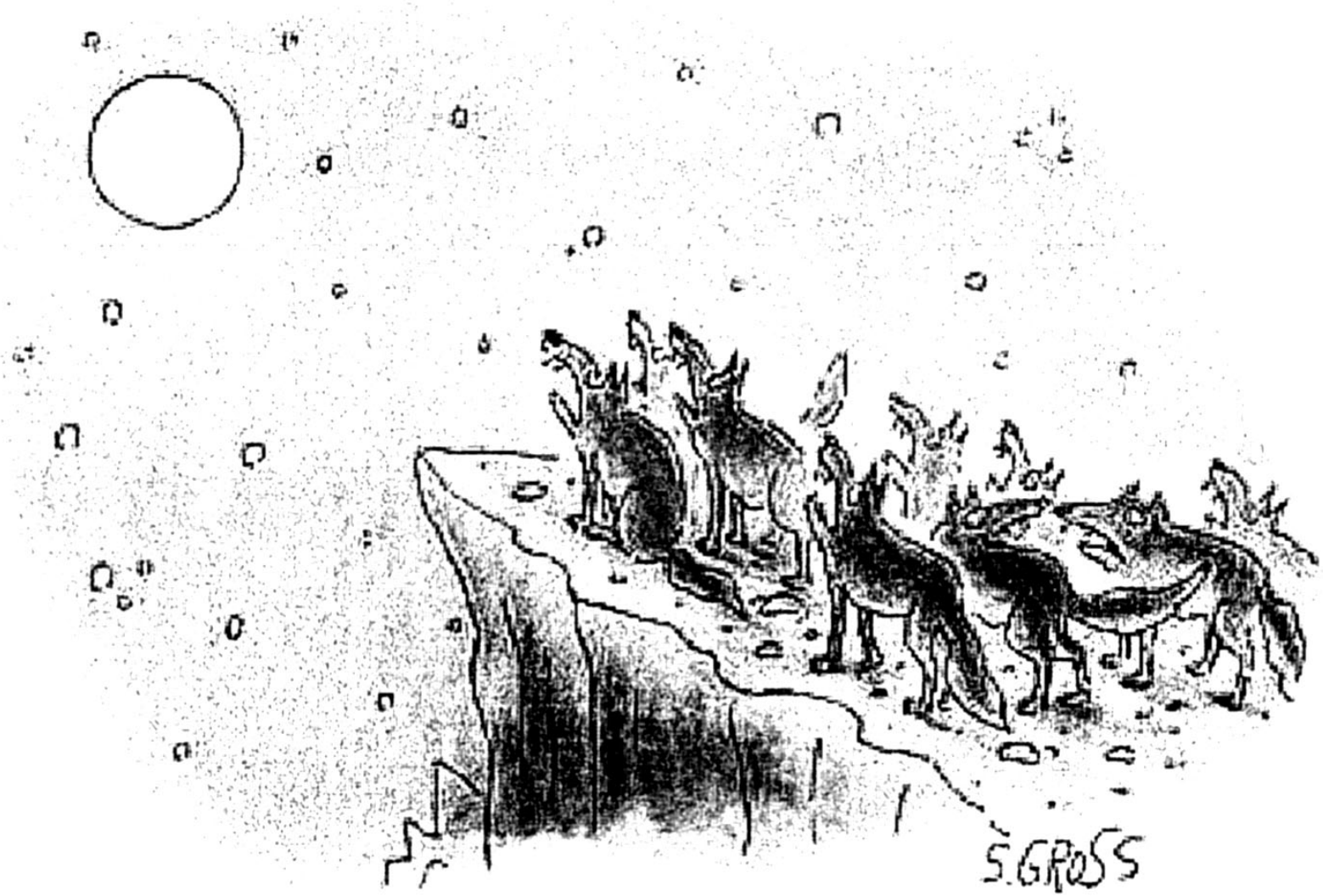
- No reference standard so we have no idea whether we found all eligible articles
- Internal pharmaceutical company documents released as a result of litigation (n=18) are not necessarily publicly available.
- Documents used in articles can be found in documents archives (DIDA) (9) ; court records only (2); and court records plus website (4 articles with active website links and 3 articles citing non-working links).
- There is substantial overlap in the litigation, authors, and/or documents used in these articles

Only a few research articles by a few authors?

2013 Wieland et al (submitted)

How can EQUATOR (and others) help?

- Guidelines for creating an open access dataset prospectively
- Guidelines for making trial information available retrospectively
- Guidelines for organizing materials in trial data repositories



"My question is: Are we making an impact?"