Pharmaceutical
STATISTICS
The Journal of Applied Statistics in the Pharmaceutical Industry

Proposed best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials

James Matcham,[a*] Steven Julious,[b] Stephen Pyke,[c] Michael O'Kelly,[d] Susan Todd,[e] Jorgen Seldrup,[f] and Simon Day[g]

James Matcham

Biostatistics Director, Amgen

Bias in Reporting Industry Sponsored Trials

Article:

Dark Side of Medical Research: Widespread Bias and Omissions

Jeremy Hsu

Date: 24 June 2010 Time: 10:16 AM ET

OPEN ACCESS Freely available online

PLoS MEDICINE

Perspective

Bias, Spin, and Misreporting: Time for Full Access to Trial Protocols and Results

An-Wen Chan

November 2008 | Volume 5 | Issue 11 | e230

Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research

An-Wen Chan, Karmela Krleža-Jerić, Isabelle Schmid, Douglas G. Altman

OPEN ACCESS Freely available online

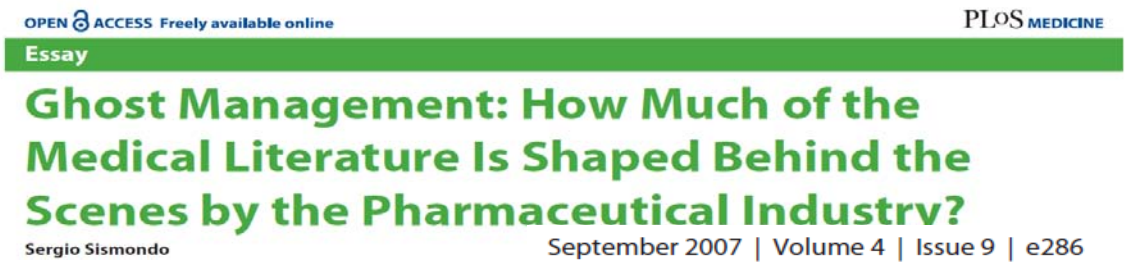
PLoS MEDICINE

Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation

Kristin Rising[1¤], Peter Bacchetti[2], Lisa Bero[3*]

1 School of Medicine, University of California San Francisco, San Francisco, California, United States of America, 2 Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, 3 Clinical Pharmacy and Health Policy, University of California San Francisco, San Francisco, California, United States of America

Bias in Reporting Industry Sponsored Trials



OPEN ACCESS Freely available online

PLoS MEDICINE

Essay

Ghost Management: How Much of the Medical Literature Is Shaped Behind the Scenes by the Pharmaceutical Industry?

Sergio Sismondo

September 2007 | Volume 4 | Issue 9 | e286

OPEN ACCESS Freely available online

PLoS MEDICINE

Editorial

Ghostwriting: The Dirty Little Secret of Medical Publishing That Just Got Bigger

The *PLoS Medicine* Editors*

September 2009 | Volume 6 | Issue 9 | e1000156

The NEW ENGLAND JOURNAL of MEDICINE

Gag Clauses in Clinical-Trial Agreements

Robert Steinbrook, M.D.

N ENGL J MED 352;21 WWW.NEJM.ORG MAY 26, 2005

Statisticians in the Pharmaceutical Industry

JAMA®
The Journal of the American Medical Association

Author Guidelines

- Authorship Criteria and Contributions
- Conflicts of Interest and Financial Disclosures
- Funding/Support and Role of Sponsor
- Data Access and Responsibility
- Duplicate/Previous Publication or Submission
- Timeliness of Data

JAMA®
The Journal of the American Medical Association

July 2004

- For industry-sponsored studies, an analysis of the data (based on the entire raw data set and evaluation of the study protocol, and prespecified plan for data analysis) must be conducted by an **independent statistician at an academic institution**, rather than by statisticians employed by the sponsor or by a commercial contract research organization.
- The independent biostatistician must be a faculty member at a medical school or academic medical center, or an employee of a government research institute, that has oversight over the person conducting the analysis and that is independent of the commercial sponsor.
- Details of this independent statistical analysis, the name and institutional affiliation of the independent statistician, and whether compensation or funding was received for conducting the analyses should be reported in the Acknowledgment section of the manuscript.
- The results of this independent statistical analysis should be the results reported in the manuscript.

Reactions to the JAMA Requirement

- The integrity of the publication process is protected by the peer-review process including disclosure of financial (and other) interests. Where is the evidence that his has broken down?
- Are we not to trust trial reports until all perceived biases are purged?
- Who would pay the independent statistician? The journal? The Industry Sponsor?
- Should we question the independence of all involved in the trial process?

Rockhold FW. Requiring 'independent 'statistical analysis for industry sponsored clinical trials? PharmStat (2006), 5, 5-6

Reactions to the JAMA Requirement

- Why did JAMA chose to address the potential for conflict of interest by requiring independent statistical analysis? This is the least likely area for conflict of interest.
- Would an independent statistician know how to process the 'entire raw dataset', and at what cost?
- Would an independent statistician's view on the most appropriate analysis undermine the value of pre-specification?

Snapinn S. Commentary.PharmStat (2011), 10, 83-84

PSI Working Group

- Set up to discuss the direction of journal guidelines
- Provide a discussion of potential for bias in the reporting of industry trials
- Make recommendations for the role of the statistician in the reporting of industry trials

PSI Working Group

The potential for bias in reporting of industry-sponsored clinical trials

Stephen Pyke,[a*] Steven A. Julious,[b] Simon Day,[c] Michael O'Kelly,[d] Susan Todd,[e] James Matcham,[f] and Jorgen Seldrup[g]

Pharmaceut. Statist. **2011**, 10 74–79

Discusses

- Potential for Bias
- Factors that Mitigate against these biases
- Efficacy of the JAMA requirements

PSI Working Group

Making available information from studies sponsored by the pharmaceutical industry: some current practices

Michael O'Kelly,[a*] Steven A. Julious,[b] Stephen Pyke,[c] Simon Day,[d] Sue Todd,[e] Jorgen Seldrup,[f] and James Matcham[g]

Pharmaceut. Statist. **2011**, 10 60–69

- Reviews the history and current practice
- Guide to registries
- Investigates consistency of information

PSI Working Group

Proposed best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials

James Matcham,[a*] Steven Julious,[b] Stephen Pyke,[c] Michael O'Kelly,[d] Susan Todd,[e] Jorgen Seldrup,[f] and Simon Day[g]

Pharmaceut. Statist. **2011**, 10 70–73

- Proposes 8 best practices for statisticians
- Suggests a few more for discussion
- Intent is to generate discussion

Best Practice Guidelines

1. **The statistical author should be responsible for the statistical aspects of the paper**

- Statistical author should take responsibility for the content
- Include objectives, endpoints, sample size justification, analysis sets, patient flows, interpretation etc..
- Identify planned methods and explain any deviations

Best Practice Guidelines

2. **The person responsible for the statistical aspects of the paper should be recognised as an author**

- Identify and name the responsible statistician
- They should be appropriately qualified and experienced
- Provide justification is if no statistician involved
- Outline contributions of other statisticians (e.g. DMC)

Best Practice Guidelines

3. **Protocols should be published and/or made publicly available in a timely manner**

- Allows conformation of pre-defined design and analysis
- Trial statisticians to ensure that protocol information includes statistical methods for key trial outcomes
- A subsequent reviewer should be able to readily identify pre-defined design and analysis

Best Practice Guidelines

4. Financial and other conflicts of interest should be disclosed

- Along with all authors, declare financial interests and other conflicts of interest regarding employment status
- The study sponsor should be identified

Best Practice Guidelines

5. The authors should have freedom to act

- All authors should have no impediment to presenting the results as they feel appropriate
- Contractually or otherwise
- This includes the trial statistician who has professional responsibility for the accurate reporting of the trial and the ent the results

Best Practice Guidelines

6. All authors should have full access to trial data

- Access to the data used in the analysis and results of all analyses that were conducted
- Trial statistician should ensure timely presentation of the results to each author and that they have a good understanding of the results
- Facilitate communication among authors to address questions

Best Practice Guidelines

7. The trial results should be published

- In a timely manner, in trial registries
- Statisticians should ensure that all results are declared so that others can use the results in further research
- Results should be linked to trial protocol

Best Practice Guidelines

8. Independent statistical review should be highlighted

- The nature and scope of any independent review should be described
- If the review is paid for, the relationship between the sponsor and the expert should be declared

For Further Consideration

- Electronic access to CV of each author
- Best practices for *industry and non-industry trials* should be discussed and published by a suitably qualified group
- All clinical trials submitted for publication should undergo statistical review by a suitably qualified and experienced statistician

For further discussion

- Anonymized individual patient data could be made publicly available
- Regulatory bodies could publish their reviews in a more publicly accessible way

Role of the Trial Statistician

The role of the trial statistician is to play a full and pro-active part in the

- design,
- conduct,
- analysis,
- reporting, and
- interpretation of the trial

and to be accountable for reporting the statistical aspects of the trial

Response to the Best Practices Proposal

- Authorship
  - If statisticians were authors would they provide more critical thought about the publication?
- Access
  - Is providing access to the data really useful? Would access to the statistician be more useful?
- Re-analysis
  - Given the SAS code and the dataset, does it matter where the programs are run?
  - Making the data available for re-analysis could be useful if subsequent events cast doubt on the original interpretation

Campbell MJ. Commentary. PharmStat (2011), 10, 80-81

Response to the Best Practices Proposal

- Fraud
  - Status quo means that fraudulent investigators are free to participate in future trials
- Reporting
  - Statisticians may report the result honestly, but marketing departments may 'spin' the results in the companies favour

….the potential for reporting bias exists in all trials, commercial or non-commercial. We need to try to minimise this potential and the best way to do this is to educate people to the right level of skepticism

Campbell MJ. Commentary. PharmStat (2011), 10, 80-81

Response to the Best Practices Proposal

- The professional responsibilities of statisticians in ensuring the quality of publications of clinical trial results are arguably greater than those of medical writers.
- The statistical aspects of a clinical trial paper are often crucial for the overall interpretation, so the statistician has an important role in ensuring that they are accurately described.
- Being an author of a paper should emphasize the important point that the statistician must take professional responsibility for the scientific accuracy of the paper. Taking that professional responsibility seriously is undoubtedly an important step towards more reliable publications.

Jacobs A. Commentary. PharmStat (2011), 10, 82

Response to the Best Practices Proposal

ROYAL STATISTICAL SOCIETY

Royal Statistical Society statement in support of the guideline issued by Statisticians in the Pharmaceutical Industry (PSI)

The Royal Statistical Society welcomes the initative taken by PSI in issuing a proposal 'best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials,'[1] and endorses the recommendations. The RSS also considers that many of the recommendations will be appropriate for medical statisticians more widely to consider and not just those employed with the pharmaceutical industry.

Clinical Trials Research

New Data from J. Matcham et al Illuminate Research in Clinical Trials Research

Published in **Clinical Trials Week**, *April 11th, 2011*

Pharmaceutical
STATISTICS
The Journal of Applied Statistics in the Pharmaceutical Industry

Proposed best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials

James Matcham,[a*] Steven Julious,[b] Stephen Pyke,[c] Michael O'Kelly,[d] Susan Todd,[e] Jorgen Seldrup,[f] and Simon Day[g]

James Matcham
Biostatistics Director, Amgen

Pharmaceutical
STATISTICS
The Journal of Applied Statistics in the Pharmaceutical Industry

Proposed best practice for statisticians in the reporting and publication of pharmaceutical industry-sponsored clinical trials

James Matcham,[a*] Steven Julious,[b] Stephen Pyke,[c] Michael O'Kelly,[d] Susan Todd,[e] Jorgen Seldrup,[f] and Simon Day[g]

Stephen Pyke
GlaxosmithKline

Citations and downloads @ May 2012

- *Proposed best practice* …
  - Available online in Early View from Feb 2010
- How do we measure impact of this paper?
  - Downloads: 1291 (2011), 466 (to end April 2012)
  - Citations: 3 + 2
- It seems the paper has been noticed
- Among citations
  - Snappin & Jiang Amgen
  - Zoog & Chang Amgen
  - Ibia et al Merck, Novartis, Amgen, GSK
- Fontanarosa et al, JAMA 2005
  - Cited by 97 papers (Google scholar)

Will it make a difference?

- Undeniable consensus around the benefits of greater transparency
  - Detailed conflict of interest statements
  - Tighter rules on authorship
  - Clinical trial registries
  - Trial results DB's
  - Online publication (earlier, negative as well as positive trials)
  - Author access to data
  - Independent analysis
  - Financial disclosure
- *Proposed best practice …* is of that spirit

What next?

- Methodological quality of meta-analyses: comparisons over time and between industry-sponsored and academic-sponsored reports
  - Lane et al, 2011: submitted for publication
  - *"Conclusions*: Academic meta-analysis papers are generally of higher quality than industry-supported meta-analysis papers. This is largely due to less detailed reporting in industry-supported meta-analyses and a tendency for them to take the included studies at face value rather than to critique them."
- More work to do …