Helping to Drive the Robustness of Preclinical Research

Katrina Gore

Research Statistics, Pfizer Neusentis

Outline

- “Reducing our irreproducibility”
- The Pfizer story – Understanding Attrition
- The Assay Capability Tool (ACT)
- Conclusion

Challenges in Irreproducible Research – Nature, April 2013

- "… it has become clear that biomedical science is plagued by findings that cannot be reproduced"
- "Science as a system should place more importance on reproducibility."

Nature's Solution

- From May 2013 Nature introduced editorial methods to improve the consistency and quality of reporting
  - More space given to method sections
  - Key methodological details will be reported
  - Greater examination of statistics
  - Encourage transparency, for example by including raw data

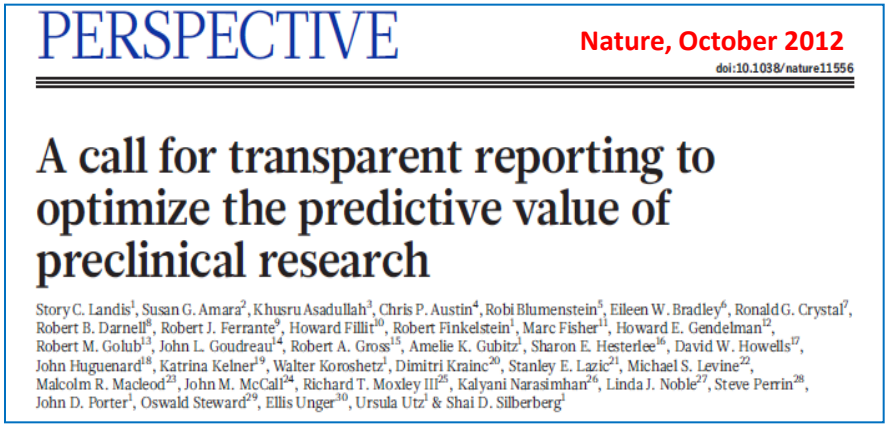
- Central to this is a new checklist prompting authors to disclose technical and statistical information

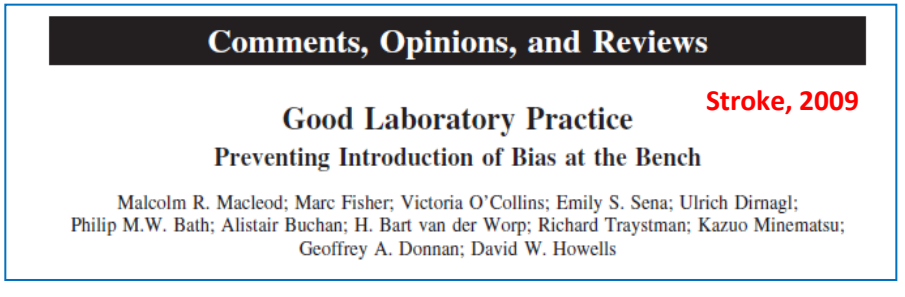
Growing Body of Evidence

Neusentis
A Pfizer research unit


Science
AAAS.ORG | FEEDBACK | HELP | LIBRARIANS
AAAS NEWS SCIENCE JOURNALS CARE
Science The World's Leading Journal of Original Scientifi
Science Home Current Issue Previous Issues Science Express
Home > Science Magazine > 22 November 2013 > Couzin-Frankel, 342 (6161): 922-925
Article Views
Summary
Full Text
Full Text (PDF)
Article Tools
Science 22 November 2013:
Vol. 342 no. 6161 pp. 922-925
DOI: 10.1126/science.342.6161.922
NEWS FOCUS
When Mice Mislead
Jennifer Couzin-Frankel
Nov 2013


OPEN ACCESS Freely available online
June 2010
PLoS BIOLOGY
Perspective
Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research
Carol Kilkenny[1]*, William J. Browne[2], Innes C. Cuthill[3], Michael Emerson[4], Douglas G. Altman[5]

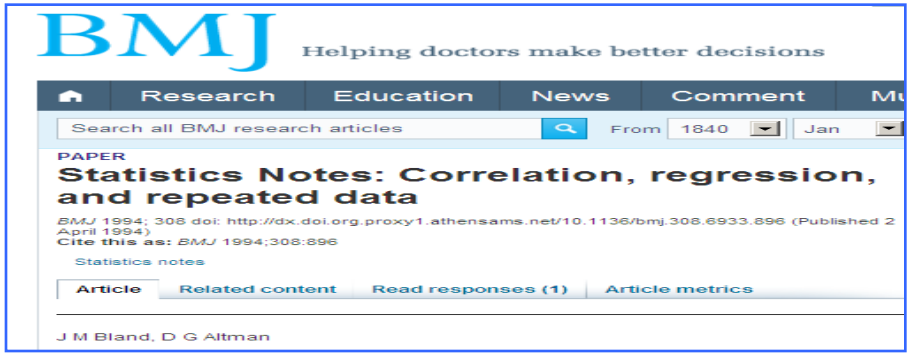

PERSPECTIVE
Nature, October 2012
doi:10.1038/nature11556
A call for transparent reporting to optimize the predictive value of preclinical research
Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert M. Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm R. Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]


Comments, Opinions, and Reviews
Stroke, 2009
Good Laboratory Practice
Preventing Introduction of Bias at the Bench
Malcolm R. Macleod; Marc Fisher; Victoria O'Collins; Emily S. Sena; Ulrich Dirnagl; Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Traystman; Kazuo Minematsu; Geoffrey A. Donnan; David W. Howells


Raise standards for preclinical cancer research
C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.
Nature, March 2012

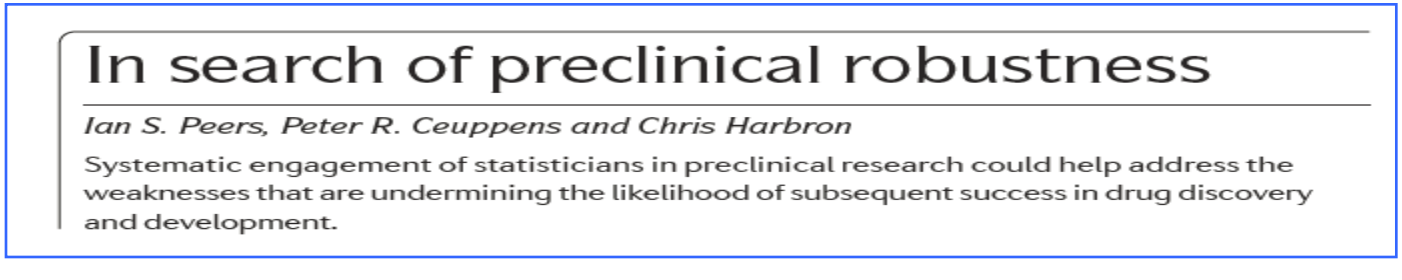

ELSEVIER
Pharmacology & Therapeutics
Volume 115, Issue 1, July 2007, Pages 148–175
July 2007
Clinical attrition due to biased preclinical assessments of potential efficacy
Mark D. Lindner

Statistician's Perspective



Doug Altman & Martin Bland series in BMJ 1994 onwards

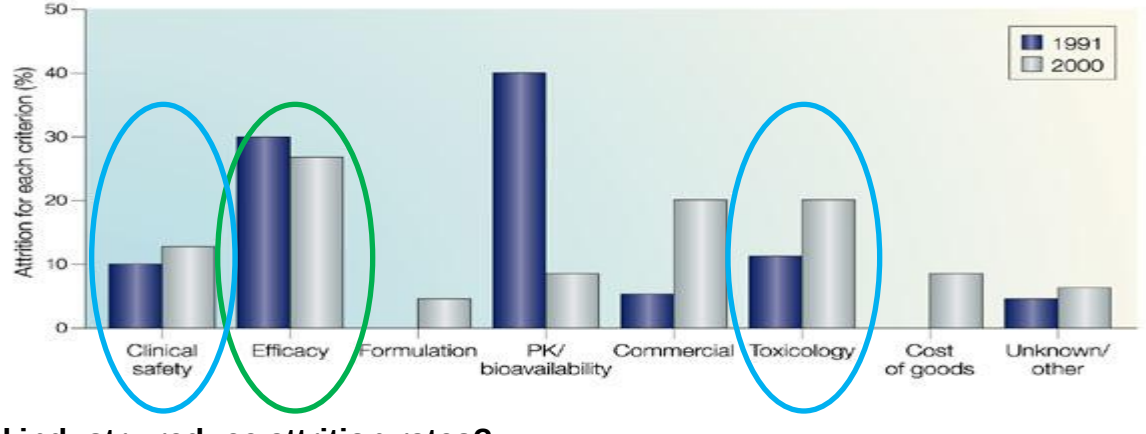
Multiple Journals May 2011 onwards



Nature Reviews, Drug Discovery October 2012

Investigating Attrition in the Pharma Industry

- During 1991-2000 average success rate in clinical development was 11%
- By early 2000s cost of discovering & developing a drug was ~$900m, yet top-line growth was <10%
- In 2000 approximately 60% of attrition during clinical trials was attributed to **lack of efficacy** and **safety**



Can the pharmaceutical industry reduce attrition rates?
Nature Perspectives – August 2004

Investigating Attrition at Pfizer

- Pfizer was also internally investigating attrition
- Internal groups were created to focus on the robustness and reproducibility of *in vivo* models
  - *In vivo* assays were carried out to industry standard
  - Insufficient awareness of the impact deficiencies can have on the quality of decision-making
- Two key recommendations were:

1) Greater transparency: in assay design and execution, and increased communication of assay characteristics

2) A cultural shift: projects/scientists should consider how pre-clinical assay package informs subsequent development in terms of quantitative risk evaluation

The Assay Capability Tool

Neusentis
A Pfizer research unit

13 item *checklist* assisting the scientist and statistician in designing and conducting preclinical assays (experiments)

Warranty facilitating informed use of assay results by decision makers

Ensures that the scientist has considered:

- What the drug project team needs to make crisp decisions
- Which important sources of variability need to be controlled
- How to safeguard from unintended biases

The Assay Capability Tool
Three Domains

Neusentis
A Pfizer research unit

1) Aligning Assay Capability with Project Objectives:

- Does the assay enable a crisp decision?
- What does a successful result look like?

2) Enabling Assay Capability by Managing Variation:

- Was the assay soundly developed, does it deliver consistent results and is it tracked over time?
- Have we identified/removed/controlled sources of variability and understood the impact on sample size and precision of results?

3) Objectivity in Assay Conduct:

- Have randomisation/blocking/blinding been used and potential for subjectivity in assay conduct, data handling/analysis considered?
- Are there inclusion/exclusion criteria and rules for outlier exclusion?
- Has an analysis that is appropriate for the design been identified?

ACT Summary Page

Example Model A [Project B]	Aligning Study Capability with Project Objectives	Enabling Assay Capability by Managing Variation	Objectivity in Assay Conduct
Confidence in Decision Making using Data from this Assay (Low/Medium/High)	**Medium** Model of inflammatory pain, but size of a meaningful effect is in this model not fully known. **Recommendation:** further benchmark meaningful effect sizes to establish target value and move from drug success being defined by a significant difference to vehicle.	**Medium** Sources of variation identified, but not all quantified and impact on sample size & precision not fully assessed; detailed protocol allows for reproducible experiment. **Recommendation:** assess impact of additional sources; create QC chart to monitor assay over time.	**High** Randomisation, blocking & blinding routinely used; clearly defined inclusion / exclusion criteria exist; analysis method appropriate for design.

	Technical Specification
Target Value	40% reduction in key response compared with vehicle **Recommendation:** further benchmarking of meaningful effect size
Required Precision	>80% power to detect a 40% reduction in key response (required SED=0.1 on log scale)
Required Replication	N=16 per group **Recommendation:** revisit calculations once additional work complete

What Next?

- Independent sources are converging on the same potential solution
  - Pfizer are developing the ACT
  - Nature launched their checklist
  - National Institute of Environmental Health Sciences (RTP, North Carolina) are investigating 15 “risk of bias” questions

- All solutions highlight the importance of the basics of experimental design / statistical principles
- Issues with lack of translation can only be properly addressed when it is based on trustworthy data, generated from a process where quality is built in

Acknowledgements

- Global ACT development & launch team
  - Ed Kadyszewski (lead), Maya Hanna, Phillip Yates, Yanwei Zhang, Yao Zhang
- My (initial) ACT co-developers
  - Phil Stanley & Phil Woodward
- My pilot groups
  - The many scientists at Pfizer Neusentis!