



Helping to Drive the Robustness of Preclinical Research

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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



nature

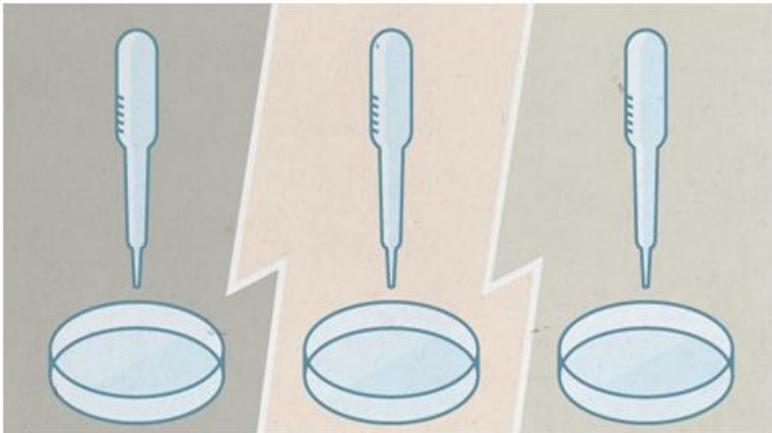
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CHALLENGES IN IRREPRODUCIBLE RESEARCH

No research paper can ever be considered to be the final word, and the replication and corroboration of research results is key to the scientific process. In studying complex entities, especially animals and human beings, the complexity of the system and of the techniques can all too easily lead to results that seem robust in the lab, and valid to editors and referees of journals, but which do not stand the test of further studies. *Nature* has published a series of articles about the worrying extent to which research results have been found wanting in this respect. The editors of *Nature* and the *Nature* life sciences research journals have also taken substantive steps to put our own houses in order, in improving the transparency and robustness of what we publish. Journals, research laboratories and institutions and funders all have an interest in tackling issues of irreproducibility. We hope that the articles contained in this collection will help.

- “... 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

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NATURE | COLUMN: WORLD VIEW

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If a job is worth doing, it is worth doing twice

Researchers and funding agencies need to put a premium on ensuring that results are reproducible, argues [Jonathan F. Russell](#).

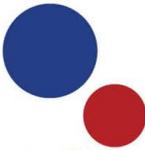
03 April 2013

- 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

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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.1226192

NEWS FOCUS

When Mice Mislead **Nov 2013**

Jennifer Couzin-Frankel

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. Browne², Innes C. Cuthill³, Michael Emerson⁴, Douglas G. Altman⁵

PERSPECTIVE **Nature, October 2012**
doi:10.1038/nature11556

A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis¹, Susan G. Amara², Khusru Asadullah³, Chris P. Austin⁴, Robi Blumenstein⁵, Eileen W. Bradley⁶, Ronald G. Crystal⁷, Robert B. Darnell⁸, Robert J. Ferrante⁹, Howard Fillit¹⁰, Robert Finkelstein¹, Marc Fisher¹¹, Howard E. Gendelman¹², Robert M. Golub¹³, John L. Goudreau¹⁴, Robert A. Gross¹⁵, Amelie K. Gubitz¹, Sharon E. Hesterlee¹⁶, David W. Howells¹⁷, John Huguenard¹⁸, Katrina Kelner¹⁹, Walter Koroshetz¹, Dimitri Krainc²⁰, Stanley E. Lazic²¹, Michael S. Levine²², Malcolm R. Macleod²³, John M. McCall²⁴, Richard T. Moxley III²⁵, Kalyani Narasimhan²⁶, Linda J. Noble²⁷, Steve Perrin²⁸, John D. Porter¹, Oswald Steward²⁹, Ellis Unger³⁰, Ursula Utz¹ & Shai D. Silberberg¹

Comments, Opinions, and Reviews

Good Laboratory Practice **Stroke, 2009**

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

Pharmacology & Therapeutics

Volume 115, Issue 1, July 2007, Pages 148-175

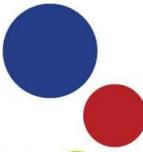
July 2007

Clinical attrition due to biased preclinical assessments of potential efficacy

Mark D. Lindner



Statistician's Perspective



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BMJ Helping doctors make better decisions

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PAPER
Statistics Notes: Correlation, regression, and repeated data

BMJ 1994; 308 doi: <http://dx.doi.org.proxy1.athensams.net/10.1136/bmj.308.6933.896> (Published 2 April 1994)
Cite this as: *BMJ* 1994;308:896

Statistics notes

Article Related content Read responses (1) Article metrics

J M Bland, D G Altman

Doug Altman & Martin Bland series in BMJ 1994 onwards

Journal List > Br J Pharmacol x v.163(2); May 2011 > PMC3087124

BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

Br J Pharmacol. May 2011; 163(2): 207.
doi: [10.1111/j.1476-5381.2011.01252.x](https://doi.org/10.1111/j.1476-5381.2011.01252.x)

Statistics: all together now, one step at a time

[Gordon B Drummond](#),¹ [David J Paterson](#),² [P McLoughlin](#),³ and [John C McGrath](#)⁴

Multiple Journals May 2011 onwards

In search of preclinical robustness

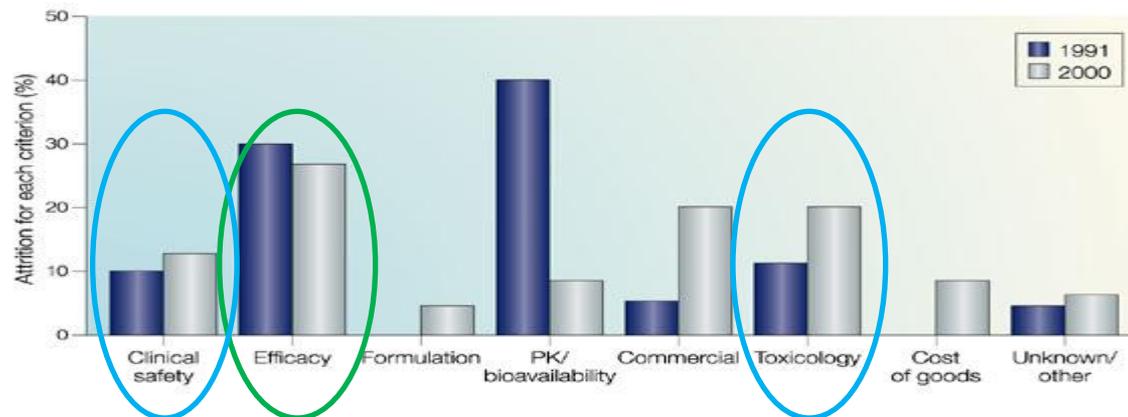
Ian S. Peers, Peter R. Ceuppens and Chris Harbron

Systematic engagement of statisticians in preclinical research could help address the weaknesses that are undermining the likelihood of subsequent success in drug discovery and development.

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**





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

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



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

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

- 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!