

Driving the Robustness of Preclinical Research

RSS PSF Webinar

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Neuroscience & Pain

A **Pfizer** Research Unit

Presentation Structure

- Role of statisticians within the pharmaceutical industry
- Challenges facing nonclinical statisticians
- The Assay Capability Tool (ACT)
 - Brief creation history
 - Structure and potential for influence on scientists and projects
 - Internal adoption and external promotion

Statisticians at Pfizer

- What is the common perception of statisticians in the Pharma Industry?
 - Clinical statisticians, designing and analysing clinical studies
- There are 200+ statisticians at Pfizer covering all phases of drug discovery, development, manufacturing & commercialisation
 - Specialist “nonclinical” groups supporting scientists within **early Research**, Drug Safety, Pharmaceutical Sciences, Manufacturing
 - “Clinical” groups supporting Phase I to IV trials, health economics
 - Unified purpose of promoting statistical excellence, championing statistical influence, and ensuring statistical support for all projects and products

Nonclinical Statisticians Supporting Research

- Provide statistical support to all research activities from initial drug target identification through to drug candidate nomination
- Point of contact for discipline group (e.g. in vivo team) or platform line (e.g. Medicinal Chemistry), or member of drug project team
 - Influencing data quality and decision making (ACT)
- Ensuring quality throughout assay development, characterisation and monitoring
 - “Estimation”: optimisation, uniformity, variation assessment, replication strategy, monitoring
 - “Comparative”: design, conduct, endpoints, analysis methods
 - In vivo protocol review (UK studies)
- Individual ad-hoc queries, Training, Publications, ...



Challenges Supporting Research

- By the time a drug (compound) enters clinical trials, its effectiveness or other issues are already “baked in”
- Resources should be focusing on adding value whilst we are searching for the candidate compound
 - It’s too late (and costly) by the time we are in the clinic
- Traditionally, the numbers of statisticians focused on early research are very low
 - No requirement for statistical involvement at any stage
 - Expectations on scientists to be capable of performing work themselves
 - Many scientists have bad experiences with statistics at University

Challenges Supporting Research

- Ratio of statistician to scientist is unbalanced
 - Enable scientists to design, run and analyse experiments themselves
 - Need to balance grass roots vs highly technical support
 - Identify the projects with potential for higher impact
- There's no requirement for statistical involvement
 - Increase visibility and awareness (within resource constraints)
- Demonstrating “added value” can be tricky
 - Simple when talking about reducing “n” in a single study, or increasing “n” to reduce risk of a study needing to be re-run
 - How do you measure an increase in statistical awareness across an organisation?

What is the Assay Capability Tool?

- A set of thirteen questions guiding scientists and project teams during the development and use of in vitro and in vivo assays
 - Promotes easy to follow but absolutely essential experimental design and analysis strategies
 - Documents strengths, weaknesses and precision of an assay
 - Provides transparency on appropriate interpretation of an assay's results in the light of its current capabilities
- Represents distilled experience of >3 decades of statistical support to Pfizer lab scientists packaged into a user friendly format targeting:
 - Data generation process
 - Decision making process

Aligning Assay Capability with Project Objectives (Does the assay enable a crisp decision?)	
Key Considerations	Current Status / Recommendations to address gaps
Are the project team's scientific objectives for running the assay recorded in a protocol/SOP?	
Has the project team adequately pre-defined what a successful assay outcome looks like in order to guide decision making?	
Is the experimental design described in the protocol/SOP and aligned closely with the objectives?	

Enabling Assay Capability by Managing Variation (Are we achieving required precision and using resources efficiently?)	
	address gaps

Objectivity in Assay Conduct (Are results likely to be reproducible?)	
	address gaps

What is the Underlying Problem?

External Research Perspective = Reproducibility

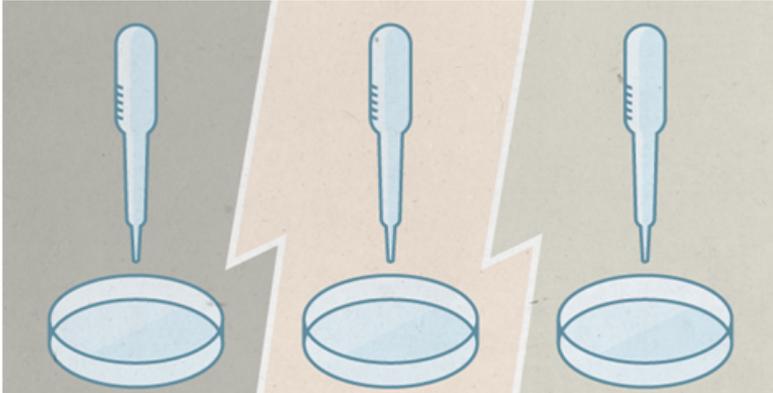


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CHALLENGES IN IRREPRODUCIBLE RESEARCH

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.

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.”



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NATURE | COLUMN: WORLD VIEW

حربي



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

What is the Underlying Problem?

External Research Perspective = Reproducibility

The past 10-15 years have seen a large increase in publications on the need for improved experimental design, conduct and statistical analysis

- 2003: Principles: The need for better experimental design

Trends in
Pharmacological Sciences

Volume 24, Issue 7, July 2003, Pages 341–345



Principles: The need for better experimental design

Michael F.W. Festing 

c/o FRAME (Fund for the Replacement of Animals in Medical Experiments), Russell and Burch House, 96–98 North Sherwood Street, Nottingham NG1 4EE, UK

- “Many scientists ignore the basic principles of experimental design, analyse the resulting data badly, and in some cases reach the wrong conclusions”



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What is the Underlying Problem?

External Research Perspective = Reproducibility



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  

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

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

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 Finkelstein¹¹, Marc Fisher¹¹, Howard E. Gendelman¹², Robert M. Golub¹³, John L. Goudreau⁴, Robert A. Gross¹³, Amelie K. Gubitzi², Sharon E. Hesterlee¹⁶, David W. Howells¹⁷, John Huguenard¹⁸, Katrina Kelner¹⁹, Walter Koroshetz², 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

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



Science 22 November 2013:
Vol. 342 no. 6161 pp. 922–925
DOI: 10.1126/science.1246192

NEWS FOCUS

When Mice Mislead
Jennifer Couzin-Frankel

Nov 2013

What is the Underlying Problem?

External Research Perspective = Reproducibility

Science The World's Leading Journal of Original Scientific Research, Global News, and Commentary.

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Home > Science Magazine > 22 November 2013 > Couzin-Frankel, 342 (6161): 922-925

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Science 22 November 2013:
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DOI: 10.1126/science.342.6161.922

NEWS FOCUS

When Mice Mislead

Jennifer Couzin-Frankel

Tackling a long-standing disconnect between animal and human studies, some charge that animal researchers need stricter safeguards and better statistics to ensure their science is solid.

Three mice had vanished. And Ulrich Dirnagl had a hunch about where they'd ended up: in the metaphorical dustbin housing animals—and there are lots of them—that line up at an experiment's starting line but are discarded before the finish. The paper that Dirnagl, director of the Center for Stroke Research at Charité University Medicine Berlin, was reviewing described how a new drug protected a rodent's brain after a stroke. The authors used 20 mice, half of which got the therapy. But mysteriously, only seven of the 10 treated animals appeared in a graph analyzing the results.

View larger version:

Nov 2013

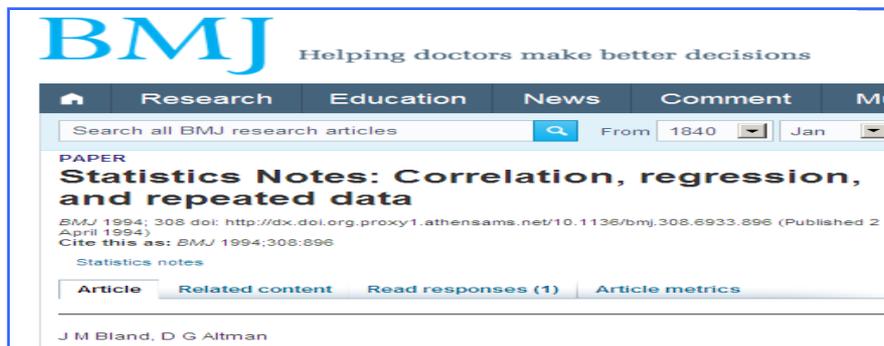
- “Many animal studies are poorly done, they say, and if conducted with greater rigor they'd be a much more reliable predictor of human biology”
- “Sometimes the fundamentals get pushed aside – the basics of experimental design, the basics of statistics”

Lawrence Tabak, Principal Deputy Director of the NIH

- During 2014, Science brought in a new statistical editorial board

What is the Underlying Problem?

External Research Perspective = Reproducibility



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 > v.163(2); May 2011 > PMC3087124



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)

**Multiple Journals
May 2011 onwards**

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

WEB COLLECTION

Statistics for biologists

Home | Practical guides | Statistics in biology | Points of Significance | Other resources

Since September 2013 *Nature Methods* has been publishing a monthly column on statistics called "Points of Significance." This column is intended to provide researchers in biology with a basic introduction to core statistical concepts and methods, including experimental design. Although targeted at biologists, the articles are useful guides for researchers in other disciplines as well. A continuously updated list of these articles is provided below.

Nature Methods, Sept 2013 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 | CORRESPONDENCE

Can you trust your animal study data?

Ian S. Peers, Marie C. South, Peter R. Ceuppens, Jonathan D. Bright & Elizabeth Pilling



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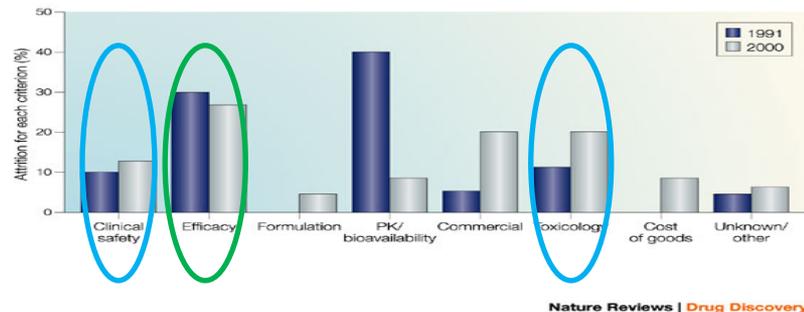
Nature Reviews, Drug Discovery October 2012 & June 2014

What is the Underlying Problem?

Pharmaceutical Industry Perspective = Attrition

Risk of a compound progressing to FIH and through later stage Clinical Trials supported by insufficient, weak or biased evidence

- 2004 Nature article: ~ 60% of attrition during clinical trials in 2000 was attributed to lack of efficacy and safety



- Pfizer had already launched its Attrition Taskforce teams initially focussed on late stage trials
- By 2009 the internal teams were focussing on data underpinning the transition of a project into the clinic
 - Research Statistics asked to assess the risk of progressing late stage discovery assets to First in Human studies

What is the Underlying Problem?

2009 Research Statistics review recommendations

- 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

- 2010 ACT created: understand an assay's capability to meet the requirements of a drug project, explicitly stating its limitations to ensure appropriate interpretation of the data

It's all about **Data Quality** and **Decision Making**

- Scientists want:
 - To produce data that can be used with confidence to make informed decisions
- Drug Project Teams need:
 - To understand the context in which the data were generated
 - Understand the limitations and appropriate interpretation of the data
- Senior Leaders require assurance that:
 - Appropriate and integral data are collected and used
 - The data have been interpreted appropriately
 - The risks associated with the interpretation of the data are understood and explicitly stated

Three Domains of the ACT

1. **Aligning Assay Capability with Project Objectives:**

- Does the assay enable decision making?
- 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 & rules for outlier exclusion?
- Has an analysis that is appropriate for the design been identified?



Influencing Data Generation: ACT and Scientists

Mouse Formalin Model [Project A]	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)	<p style="text-align: center;">Medium</p> <p>Model of inflammatory pain, but size of a meaningful effect is unknown.</p> <p>Recommendation: further benchmark meaningful effect size and move from drug success being defined by a significant difference to vehicle.</p>	<p style="text-align: center;">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 Batch/initial weight; create QC chart to monitor assay over time</p>	<p style="text-align: center;">High</p> <p>Randomisation, blocking & blinding routinely used; clearly defined inclusion / exclusion criteria exist; analysis method appropriate for design.</p>

	Technical Specification
Target Value	40% reduction in flinching compared with vehicle Recommendation: further benchmarking of meaningful effect size
Required Precision	>80% power to detect a 40% reduction in total flinches in the second phase of the formalin response (required SED=0.1 on log scale)
Required Replication	N=16 per group Recommendation: revisit calculations after batch/initial weight assessed



Influencing Decision Making: ACT and Projects

- Project teams process data from multiple assays from many sources for many (thousands) compounds
- The primary objective is to select one compound to progress to clinical trials
- When considering each compound a project team balances many properties (potency, safety, selectivity, pharmacokinetics etc.), but what do we know about the assays providing the data?
- The ACT benchmarks the current capability of an assay, explicitly stating its limitations to ensure appropriate interpretation of the data

ACT Internal Adoption

- Since 2013 the ACT has been created for many assays across many projects, but it is work in progress
- It is promoted by statisticians, but it should be owned by the scientists creating assays
- With the aid of statisticians, project teams are also starting to use the ACT to influence their decision making
- There are goals in place within statistical groups and many biological groups for its use when projects are reaching key developmental milestones

ACT External Sharing and Recognition

- In 2014 we initiated a series of external presentations and publications resulting in:
 - 5 external conference presentations and 3 external publications
 - Internal 2014 3Rs team award for development of a Joint Rotation model
 - Recognition of the ACT by the National Centre for 3Rs (UK) and ABPI
 - 2015 RSS/PSI award for Statistical Excellence in Pharmaceutical Industry

2014 August: PLOS One publication

RESEARCH ARTICLE	VIEWS
A Preclinical Physiological Assay to Test Modulation of Knee Joint Pain in the Spinal Cord: Effects of Oxycodone and Naproxen	
Jason A. Miranda  , Phil Stanley, Katrina Gore, Jamie Turner, Rebecca Dias, Huw Rees	
Published: August 26, 2014 • DOI: 10.1371/journal.pone.0106108	

2015: Associate of British Pharmaceutical Industry member's guide



2015 May: Joint winners of RSS/PSI award for Statistical Excellence in the Pharmaceutical Industry



2015 June: Significance Magazine [RSS/ASA]



2015 June: PR&P publication



ORIGINAL ARTICLE

Helping to drive the robustness of preclinical research – the assay capability tool

Katrina Gore & Phil Stanley

Research Statistics, Clinical Research, Pfizer, Cambridge, United Kingdom

Conclusions

- There are many challenges facing nonclinical statisticians
 - Tools such as the ACT enable greater visibility and extend our potential for impact
- Externally there are changes that give hope for a more robust and reproducible future for preclinical research
 - Journals and funding bodies are requiring more transparency in reporting and increasing space for methods
 - Statistical articles within key biomedical journals are increasing and statisticians are more involved
 - Tools/checklists/good practice are being shared and issues highlighted
- All solutions highlight the importance of the basics of experimental design / statistical principles
 - Translation can only be properly addressed when based on trustworthy data, generated from quality processes



Acknowledgements

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