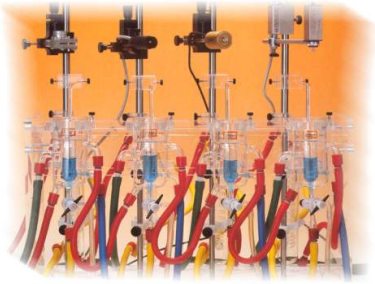
- Role of statisticians within the pharmaceutical industry
- Challenges facing nonclinical statisticians
- The Assay Capability Tool (ACT)
  - Brief creation history
  - Structure and potential for influence on scientists and projects
  - Internal adoption and external promotion

- 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

- 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, …

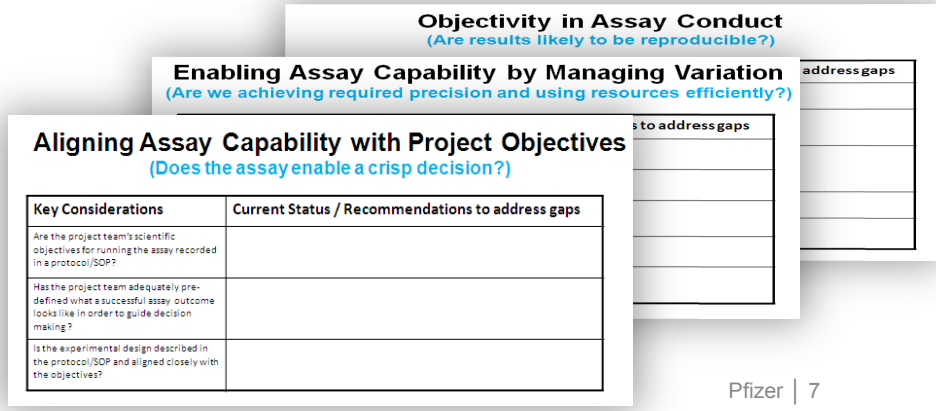


- By the time a drug (compound) enters clinical trials, its effectiveness or other issues are already “baked in”
- Resources should be focusing on adding value whilst we are searching for the candidate compound
  - It’s too late (and costly) by the time we are in the clinic
- Traditionally, the numbers 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

- 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?

- 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

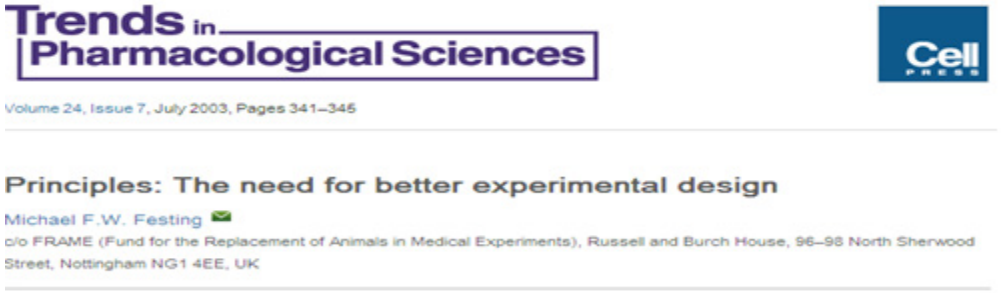


Challenges in Irreproducible Research [Nature, April 2013]

- "… 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."

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

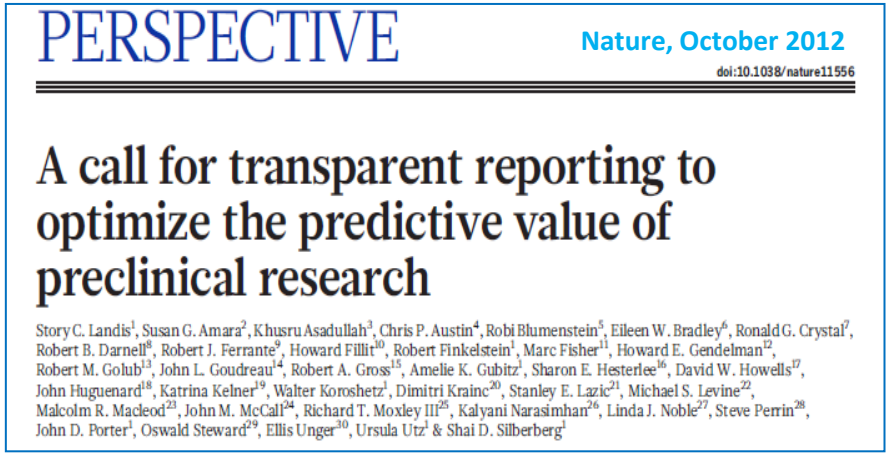


  - "Many scientists ignore the basic principles of experimental design, analyse the resulting data badly, and in some cases reach the wrong conclusions"


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
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


PERSPECTIVE
Nature, October 2012
doi:10.1038/nature11556
A call for transparent reporting to optimize the predictive value of preclinical research
Story C. Landis, Susan G. Amara, Khusru Asadullah, Chris P. Austin, Robi Blumenstein, Eileen W. Bradley, Ronald G. Crystal, Robert B. Darnell, Robert J. Ferrante, Howard Fillit, Robert Finkelstein, Marc Fisher, Howard E. Gendelman, Robert M. Golub, John L. Goudreau, Robert A. Gross, Amelie K. Gubitz, Sharon E. Hesterlee, David W. Howells, John Huguenard, Katrina Kelner, Walter Koroshetz, Dimitri Krainc, Stanley E. Lazic, Michael S. Levine, Malcolm R. Macleod, John M. McCall, Richard T. Moxley III, Kalyani Narasimhan, Linda J. Noble, Steve Perrin, John D. Porter, Oswald Steward, Ellis Unger, Ursula Utz & Shai D. Silberberg


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

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

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Science 22 November 2013:
Vol. 342 no. 6161 pp. 922-925
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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.

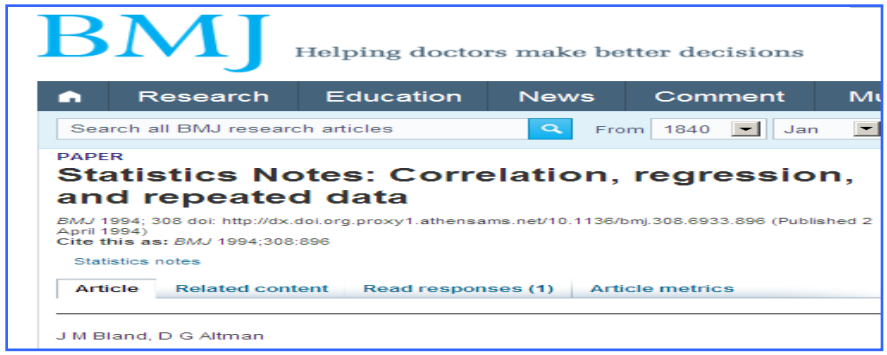
View larger version:

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"

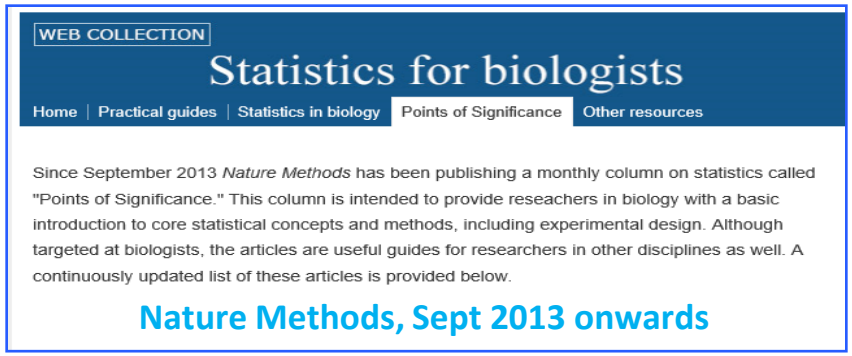
Lawrence Tabak, Principal Deputy Director of the NIH

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

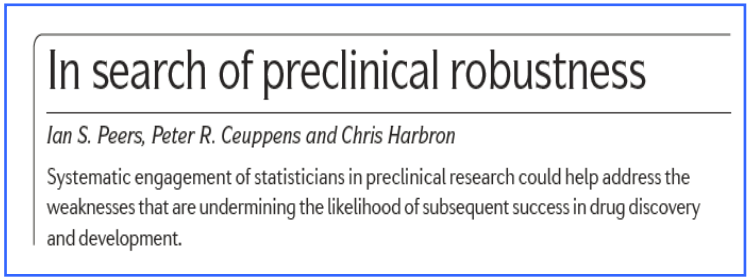


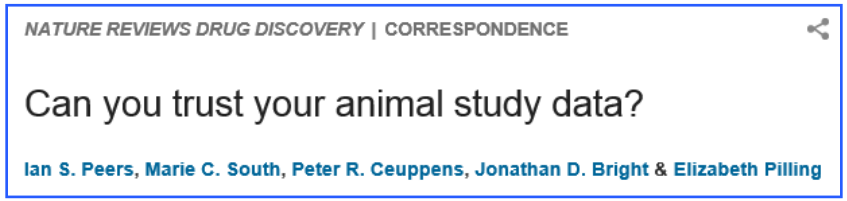
Doug Altman & Martin Bland
series in BMJ
1994 onwards

Multiple Journals
May 2011 onwards



Nature Methods, Sept 2013 onwards

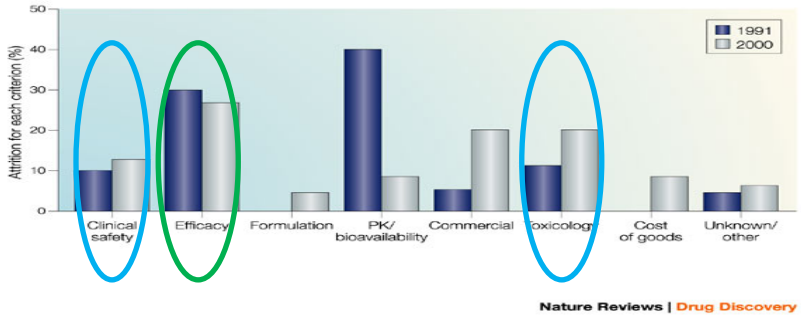




Nature Reviews, Drug Discovery October 2012 & June 2014

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

- 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

Data Quality 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

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:

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)	**Medium** Model of inflammatory pain, but size of a meaningful effect is unknown. **Recommendation:** further benchmark meaningful effect size 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 Batch/initial weight; 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 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:

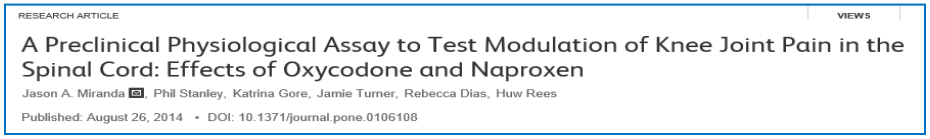
- Project teams process data from multiple assays from many sources for many (thousands) compounds
- The primary objective is to select one compound to progress to clinical trials
- When considering each compound a project team balances many properties (potency, safety, selectivity, pharmacokinetics 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

- 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

- 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


PRP Pharmacology Research & Perspectives Open Access

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

- 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

- 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!