Nonclinical Statistics & The Assay Capability Tool

Cambridge Discussion Group, Oct 2016

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Based on work performed at Pfizer Neusentis:

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

Presentation Structure

- Role of nonclinical 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

Nonclinical Statisticians

- What is the most common perception of statisticians in the Pharma Industry?
  - Clinical statisticians, designing and analysing clinical studies

- Statisticians support 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 drug target identification through to drug candidate selection for clinical trials
  - Design, randomisation, analysis, reporting of experiments
  - Assay development, characterisation and monitoring
  - Training in basic statistical methods
  - Software support and provision
  - Publication support
  - Protocol reviews
- Point of contact for discipline group (e.g. in vivo team), platform line (e.g. Medicinal Chemistry) or member of drug project team
- Remit to influence statistical awareness, research conduct, data quality and decision making

Challenges Supporting Research

- By the time a drug (compound) enters clinical trials, its effectiveness or other issues are already “baked in”
- Statistical resources should be focused 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 and the challenges are numerous:
  - No requirement for statistical involvement at any stage
  - Expectation on scientists to perform the work themselves
  - Many scientists have bad past experiences with statistics at University
  - Demonstrating “added value” can be tricky when it’s more than just ↓N
- Research statisticians need many “tools” in their support toolkit

What is the Underlying Problem?
External Research Perspective = Reproducibility

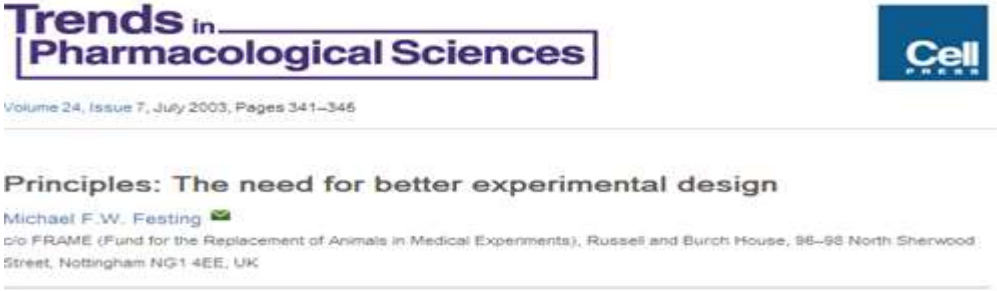
Challenges in Irreproducible Research [Nature, April 2013]

- "… 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."

What is the Underlying Problem? External Research Perspective = Reproducibility

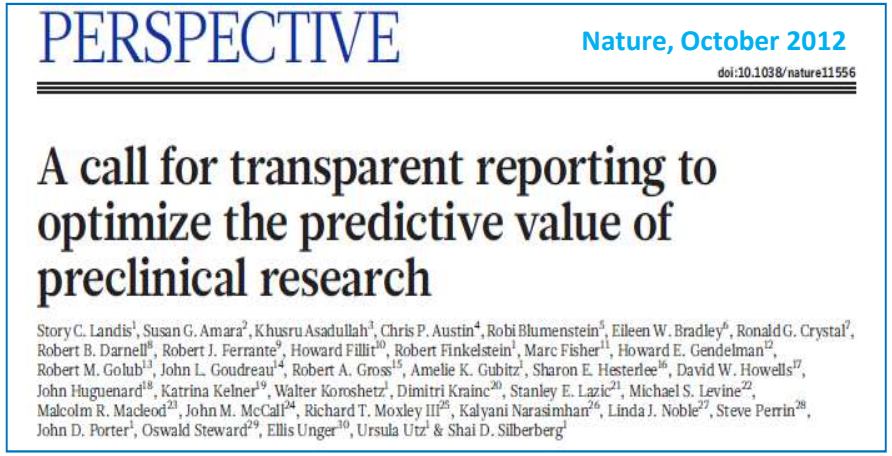
The past 10-15 years have seen a large increase in publications on the need for improved experimental design, conduct and statistical analysis

- 2003: Principles: The need for better experimental design



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

What is the Underlying Problem?
External Research Perspective = Reproducibility



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:
Vol. 342 no. 6161 pp. 922-925
DOI: 10.1126/science.342.6161.922

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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

- Article highlights issues with "miniscule" sample sizes and lack of randomisation & blinding
- During 2014, Science brought in a new statistical editorial board

What is the Underlying Problem?
External Research Perspective = Reproducibility


BMJ
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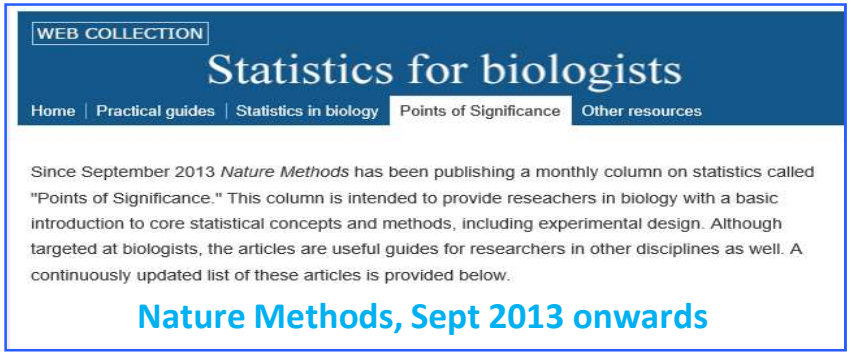
From 1840 Jan
PAPER
Statistics Notes: Correlation, regression, and repeated data
BMJ 1994; 308 doi: http://dx.doi.org.proxy1.athensams.net/10.1136/bmj.308.6933.896 (Published 2 April 1994)
Cite this as: *BMJ* 1994;308:896
Statistics notes
Article | Related content | Read responses (1) | Article metrics
J M Bland, D G Altman

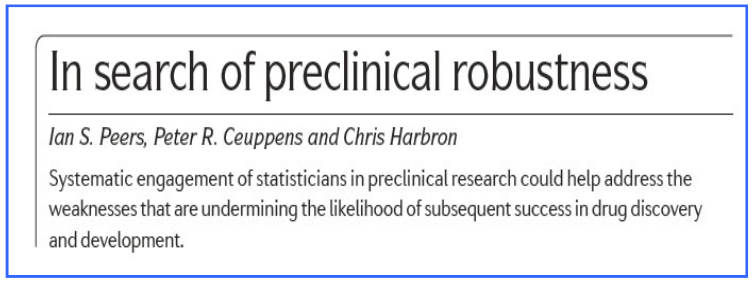
Doug Altman & Martin Bland
series in BMJ
1994 onwards


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


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 reseachers 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.

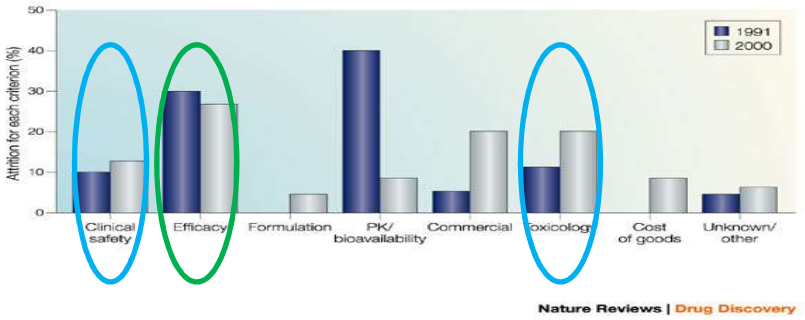

NATURE REVIEWS DRUG DISCOVERY | CORRESPONDENCE
Can you trust your animal study data?
Ian S. Peers, Marie C. South, Peter R. Ceuppens, Jonathan D. Bright & Elizabeth Pilling

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

- 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

- 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

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

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?

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?	

Three Domains of the ACT

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?

Enabling Assay Capability by Managing Variation

(Are we achieving required precision and using resources efficiently?)

Key Considerations	Current Status / Recommendations to address gaps
Are the assay's development and validation fully documented?	
Have the sources of variability present in the assay been explored?	
Is the proposed sample size/ level of replication fit for purpose?	
Is there a comprehensive protocol /SOP detailing *key assay characteristics*?	
How is assay performance monitored over time? What is the plan for reacting to signs of instability?	

Three Domains of the ACT

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?

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

Key Considerations	Current Status / Recommendations to address gaps
Are inclusion/exclusion criteria for the assay specified in the protocol/SOP?	
Is the management of subjectivity in data collection and reporting defined in the assay protocol/SOP?	
If the raw data are processed (e.g. by summarization or normalization) prior to analysis, is the method for doing this specified in the study protocol/SOP?	
Are rules for treating data as outliers in the analysis specified in the protocol/SOP	
Is the analysis specified in the study protocol /SOP? Is it fit for purpose?	

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)	**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: 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 they 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

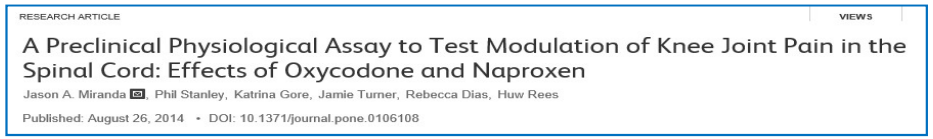
ACT Internal Pfizer Adoption

- Since 2013 the ACT has been created for many assays across many projects, but it is still work in progress
- It is promoted by statisticians within Pfizer, but it should be owned by the scientists creating assays
- With the aid of statisticians, project teams are starting to use the ACT to influence their decision making
- Goals are 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

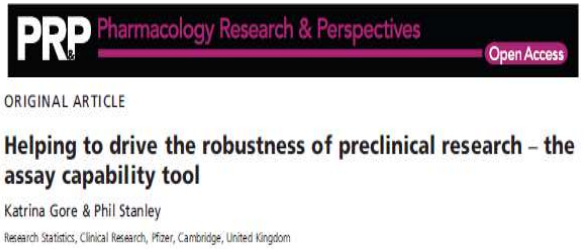
Published: August 26, 2014 • DOI: 10.1371/journal.pone.0106108

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



The Headlines Keep Coming …

ANNALS OF SCIENCE DECEMBER 13, 2010 ISSUE

THE TRUTH WEARS OFF

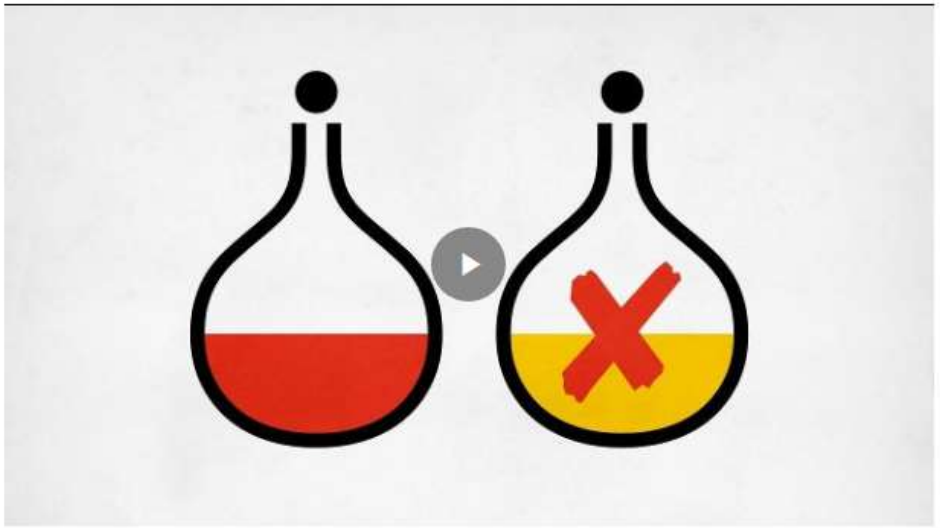
Is there something wrong with the scientific method?

By Jonah Lehrer

nature

SCIENTIFIC AMERICAN

Is There a Reproducibility Crisis in Science?



The New York Times

SundayReview

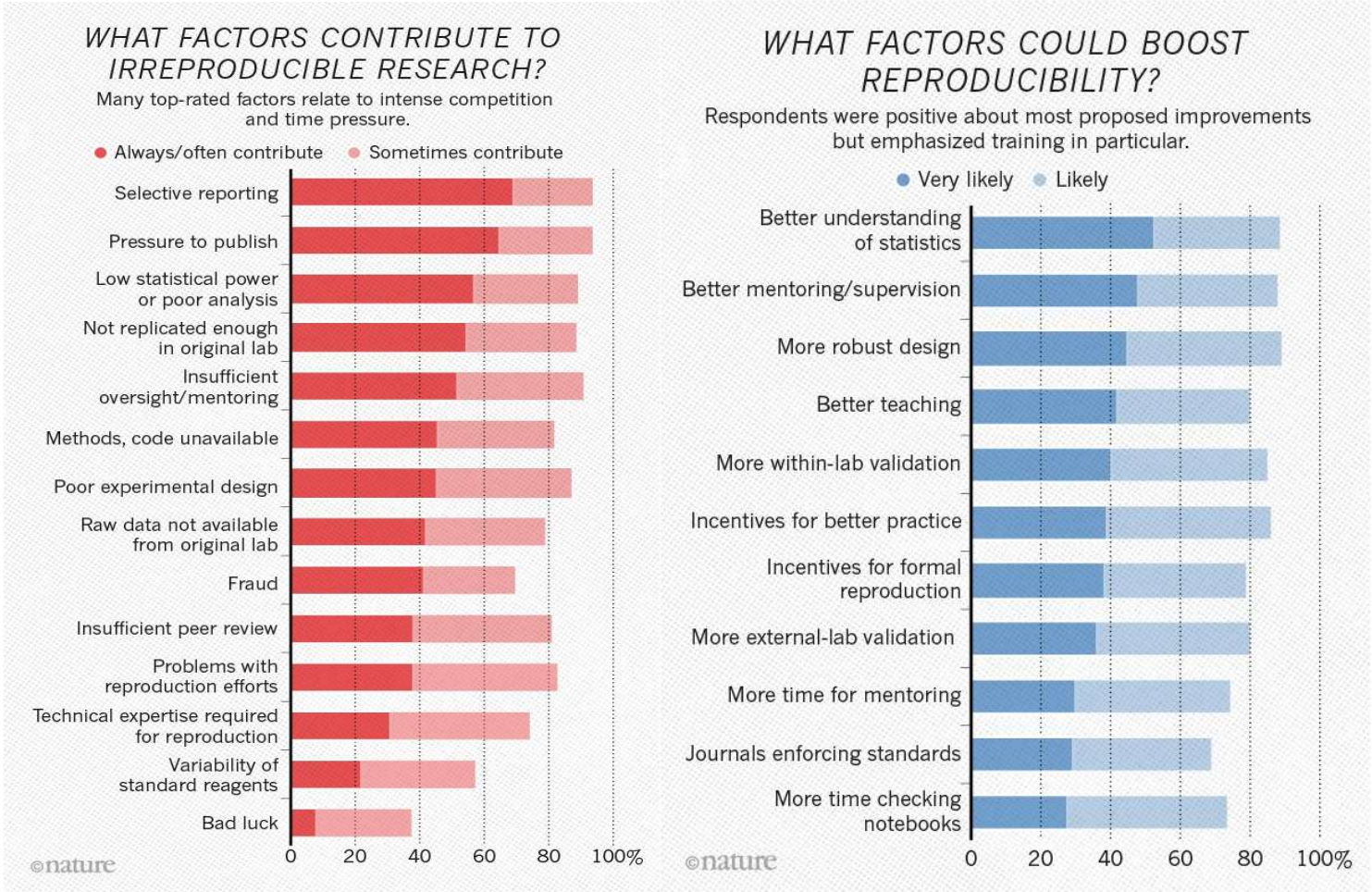
Why Do So Many Studies Fail to Replicate?

Gray Matter

By JAY VAN BAVEL MAY 27, 2016

Is There a Reproducibility Crisis?

- A recent Nature survey asked 1576 researchers about reproducibility



Is Anything Fundamentally Changing?

- Journals and funding bodies are requiring more transparency in reporting, increasing space for methods and focusing on statistics
- Statistical articles within key biomedical journals are increasing and statisticians are getting more involved in the review process
- Scientists are starting to agree on terminology
- Tools / checklists / good practice are being shared and issues highlighted
- The impact of guidelines such as ARRIVE are being assessed (**I**ntervention to **I**mprove **C**ompliance with **AR**RIVE g**u**idelin**e**s)
- IMI launched the Data Quality in preclinical R&D proposal
- NC3Rs Experimental Design Assistant has launched

Summary

- There are many challenges facing nonclinical statisticians
  - Tools such as the ACT enable greater visibility, extend the potential for impact and influence the quality of preclinical research
- Externally there are changes that give hope for a more robust and reproducible future for preclinical research
- A high proportion of the solutions highlight the importance of the basics of experimental design / statistical principles
  - Yet very few acknowledge the need for more statisticians …

Acknowledgements

- Initial ACT co-developers
  - Kat Gore, Phil Stanley & Phil Woodward
- Global ACT development & launch team
  - Ed Kadyszewski, Kat Gore, Maya Hanna, Max Kuhn, Phillip Yates, Yanwei Zhang, Yao Zhang
- The ACT pilot groups
  - The many scientists at Pfizer Neusentis!
- NCS2016
  - Prof. Malcolm Macleod, Ros Walley, Prof. Andy Grieve