Systemic Research Bias, Diagnosis and Treatment

Transforming the research machine from bench to bedside

Robin Young
RRY Publications, LLC

Lack of Clinical Study Reproducibility

crisis smoldering under the surface

FDA, National Institutes of Health, Leading Academic Institutions

- **Collins and Tabak, director and principal deputy director**, respectively, of the National Institutes of Health cited in their 2014 Nature paper a 2011 study by the Office of Research Integrity of the US Department of Health and Human Services that documented **12 cases of clinical study irreproducibility**.
- Collins, Tabak, NIH Plans to Enhance Reproducibility, Nature. 2014 Jan 30; 505(7485): 612-613

American Statistical Association Warnings

- On March 7, 2016 ASA, the world's oldest continuously operating professional science society, released its first statistical practice guidance document in history.
- The paper titled "American Statistical Association Releases Statement on Statistical Significance and *P*-Values", cautioned that scientific journal editors were becoming overly dependent on *p*-value as a gatekeeper for whether research is publishable.

Reproducibility: Science Journal Experiment

Science Journal's Reproducibility Test

Estimating the reproducibility of psychological science. *(2015)*
Science, 349 (6251). aac4716-aac4716. ISSN 0036-8075 DOI: 10.1126/science.aac4716 Nosek, Brian A., Aarts, Alexander A., Anderson, Christopher J., Anderson, Joanna E. and Kappes, Heather Barry,…

100 Replications of Studies which had been published in three psychology journals were duplicated to test reproducibility.

RESULTS

Replication effects were half the magnitude of original effects representing a substantial decline effect.

Ninety seven percent of original studies had significant results ($p < .05$). Thirty six percent of replications had significant results.

"In sum, a large portion of replications did not reproduce evidence supporting the original results despite using high powered designs and original materials when available. The open dataset provides a basis for hypothesis generation on the causes of irreproducibility."

Reproducibility: **John P.A. Ioannidis, MD, DSc,** Professor of Medicine, Health Research and Policy, and Statistics at Stanford University. He is also the founding Director Meta-Research Innovation Center at Stanford (METRICS)

Recent publications

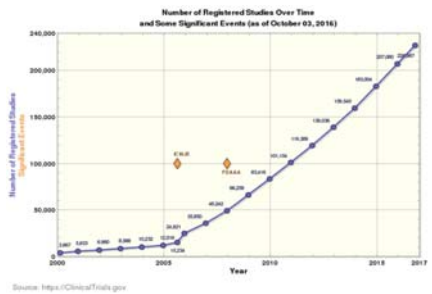
- ***Why Most Published Research Findings Are False***. PLoS Medicine, 2005. 4,254 citations
- ***Contradicted and initially stronger effects in highly cited clinical research***. JAMA, 2005. 926 citations

Recent quote

"When it comes to behavioral sciences, the United States studies are far more likely to find extreme results. Why is that? One might argue that maybe there's more pressure in the U.S. for an academic researcher more **to deliver an extreme finding in order to get it published in a major journal and get funding**." – John Ioannidis: "**Reproducible Research: True or False?" June 11, 2014 Lecture**

Types of Bias

1. Selection bias
2. Information bias
3. Confirmation bias
4. Publication bias
5. Outcome bias
6. P-Value < 0.05 bias and more.



By the Numbers

the explosion of scientific studies since 2004

By the numbers…

233, 365 Clinical Studies at Clinical Studies.gov in 2016

3,967 Clinical Studies at Clinical Studies.gov in 2000

0 Clinicians who think study quality has improved

By the numbers…

400,000 Number of clinical studies estimated for 2025

60% Percent of OUS clinical studies estimated for 2025

47% Percent of OUS clinical studies in 2016 (source: clinical studies.gov)

The Peer Review Bottle Neck

5,633 journals require peer review

63.4 million Hours devoted to peer review in 2015

18.9 million Hours devoted by top 5% of reviewers

Given the sheer volume of clinical research trying to squeeze into a comparatively fixed number of peer review journal openings, it should not be surprising that **attempts to circumvent the system have emerged**.

50,000 Peer Review papers tested, 50% made a math mistake

- Chris Hartgerink PhD and Michèle Nuijten
- Tilburg University's Meta-Research Center in the Netherlands
- Created **Statcheck** which automatically examined 50,000 published peer review articles for statistical accuracy – WITHOUT permission.
- They found that half of all papers in psychology journals contained a statistical error.
- **The publisher accused them of "harassment".**

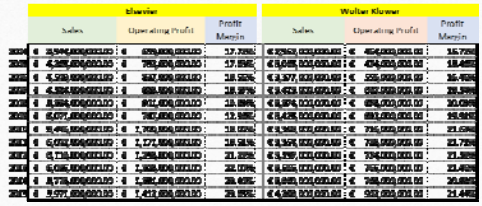
110 Published Studies Retracted due to Fake Peer Reviews

- From 2012 – 2014, *Nature* reports that journals have retracted over 110 papers due to faked peer reviews
- Elsevier, Taylor & Francis, Springer, SAGE and Wiley and BioMed Central have all been hit with fake reviews.
- Third-party agencies offer "services" to authors like language-editing and submission assistance which frequently involve fabricated reviewers. The authors may not even be aware.

More articles per journal. More hours per peer reviewer.

NOT higher research quality.

More articles per journal. More hours per peer reviewer. Higher publishing profit margins.



Today's Peer Review System is like THIS

3 issues undermine clinical study value…

- Reproducibility
- Scalability
- Bias

Who pays for declining research quality?

- Medical technology investors
- Pharma and med device companies
- FDA
- Scholars and scientific researchers
- Individual Physicians
- Patients

Medical Technology Investors

$16.0 Billion

Venture Capital in Healthcare in 2016

Pharma and Medical Device Companies

$70 billion annual R&D spending by U.S. pharma, biologic and medical device companies

The FDA

$525 billion sales annually

from FDA approved/cleared/licensed drugs, devices and biologics

Evidence of safety and/or efficacy

required for every one

The researchers **themselves**

Clinical research is one of the few methods at scholar's disposal to demonstrate academic talent. Failure to publish is, literally, to **perish** as an academician and scientist.

The Physician

$3.0 Trillion of Annual Billings
from
928.6 million patient / physician visits annually
4.3 billion prescriptions annually
232 million procedures / surgeries annually

How the current system works

Transfer of Title and Revenue

$83,000 / YR

$10 Billion / YR

Time to address the issue of clinical study quality

Transforming the passage of science from bench to bedside