ebhc CONFERENCE 2023

THE ECOSYSTEM OF EVIDENCE

Lessons learned in the pandemic era and future challenges

10th International Conference for EBHC Teachers and Developers
10th Conference of the International Society for EBHC
Taormina, 25th - 28th October 2023

#EBHC2023

GIMBE EVIDENCE FOR HEALTH

Evidence-based translational medicine: connecting basic and clinical research

Prof Emily Sena
University of Edinburgh

Disclosures

- **PCI Registered Reports** (co-founder/managing board)

- CZI Open Science Advisory Board (receive honorarium)
- I applied (& will continue to) and have received grant funding for this research

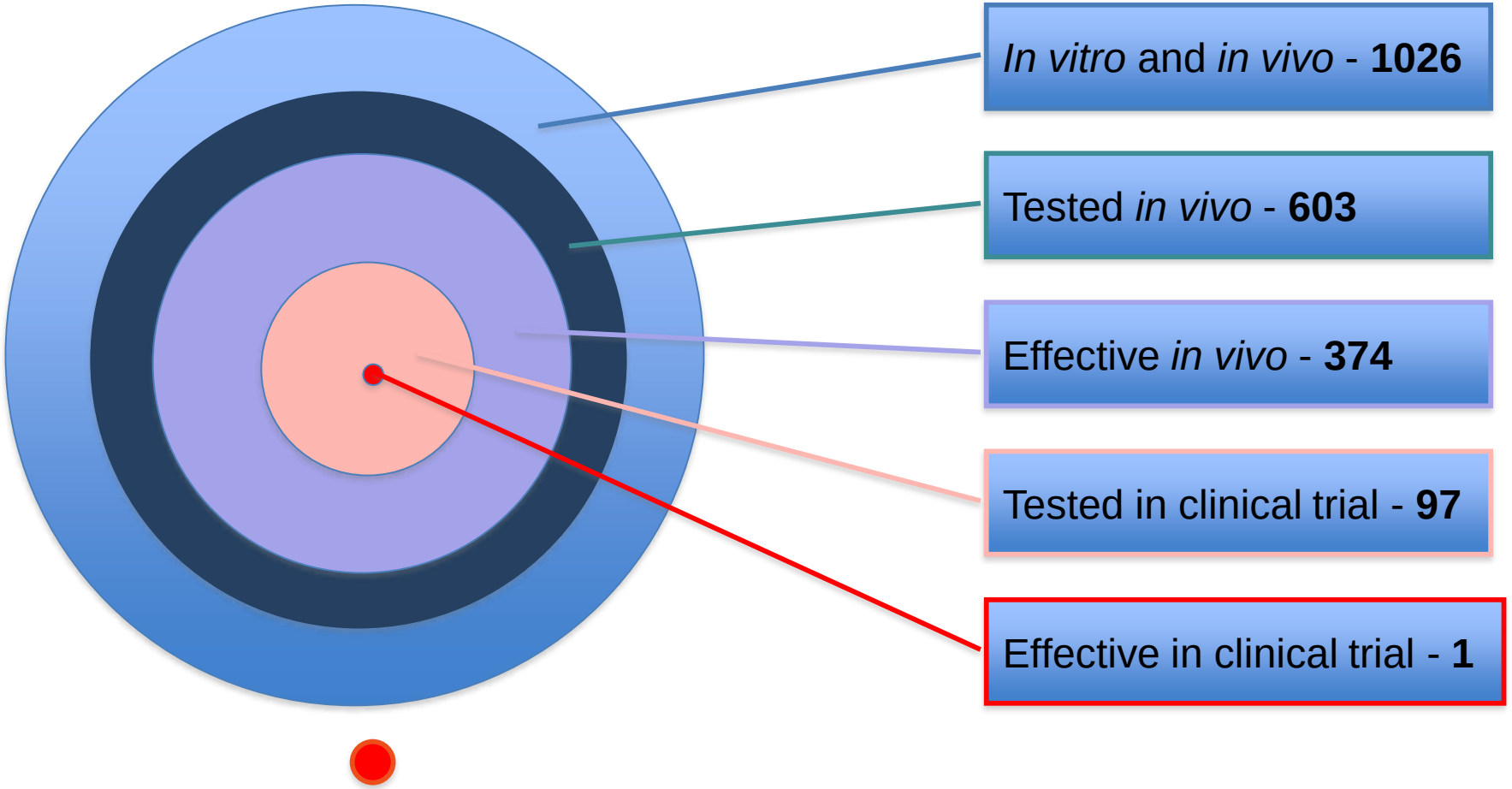
My perspective

The challenge of finding a path

Hypotheses

- In the life sciences there are perverse incentives (publication, funding, promotion) to produce positive results with little attention paid to their validity
- In the use of animal disease models, pressure to reduce the number of animals (cost, time, ethics, feasibility) results in studies either being underpowered or of unknown power
- These factors combine to compromise the utility of animal models and contribute to translational failure

What is translational failure?



O'Collins et al, 2006

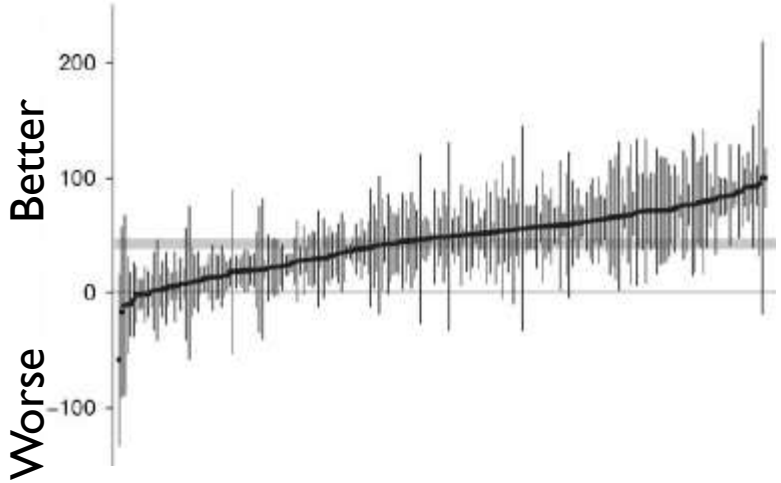
Why do we do meta-analysis of animal studies?

- Preclinical studies are often performed with the purpose of improving human health
- Used in preclinical research to:
  - assess the quality and range of evidence
  - identify gaps in the field
  - assess for publication bias
  - try to explain discrepancies between preclinical and clinical trial results
  - inform clinical trial design
- Fundamental differences:
  - Many small (10s) animal studies
  - Fewer large (100s/1000s) clinical trials

Animal data in stroke

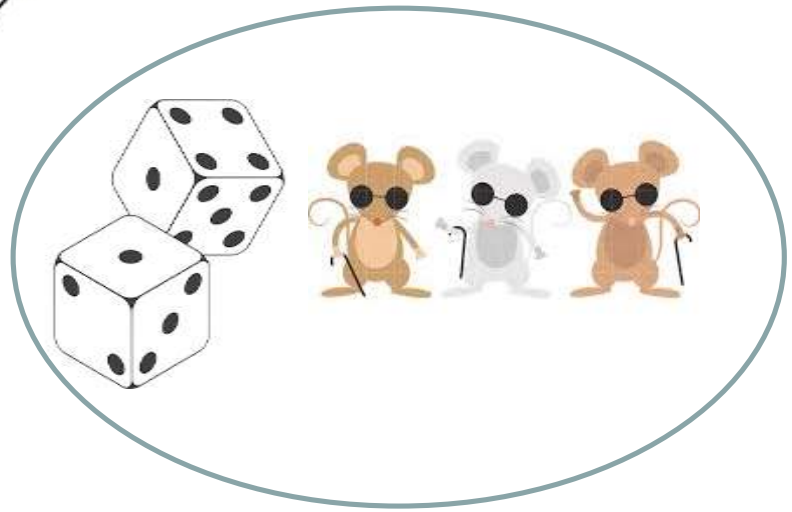
- There are huge amounts of often confusing data
- Systematic review can help to make sense of it
- If you select extreme bits of the evidence you can “prove” either harm or substantial benefit
- Investigating the sources behind this variation may be helpful in translation

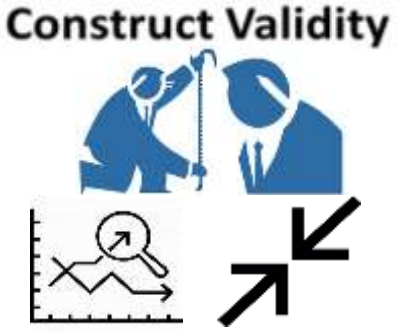
Hypothermia: a systematic search identified 222 experiments in 3353 animals

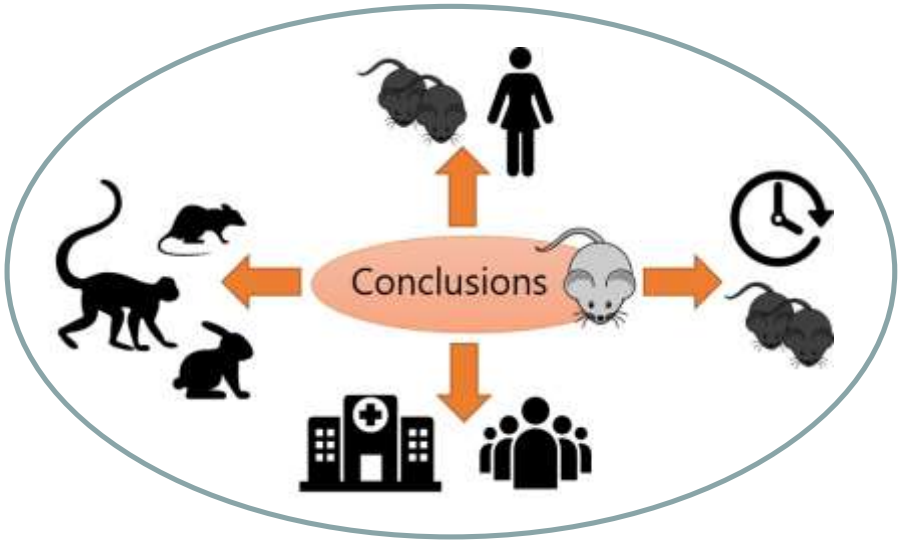


Van der Worp *et al Brain* 2007

Some potential sources of bias

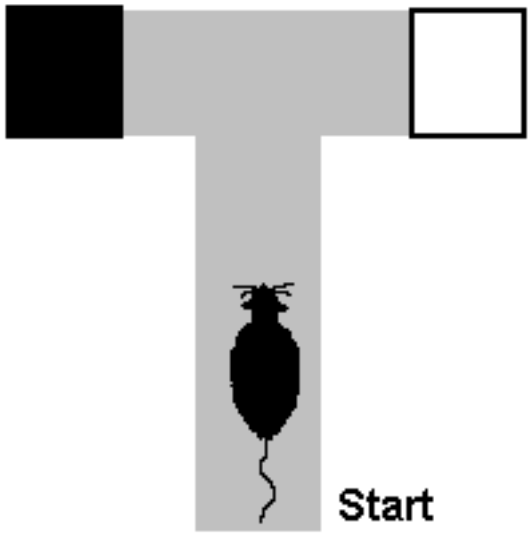






You can usually find what you're looking for …

- 12 graduate psychology students
- 5 day experiment: rats in T maze with dark arm alternating at random, and the dark arm always reinforced
- 2 groups – "Maze Bright" and "Maze dull"

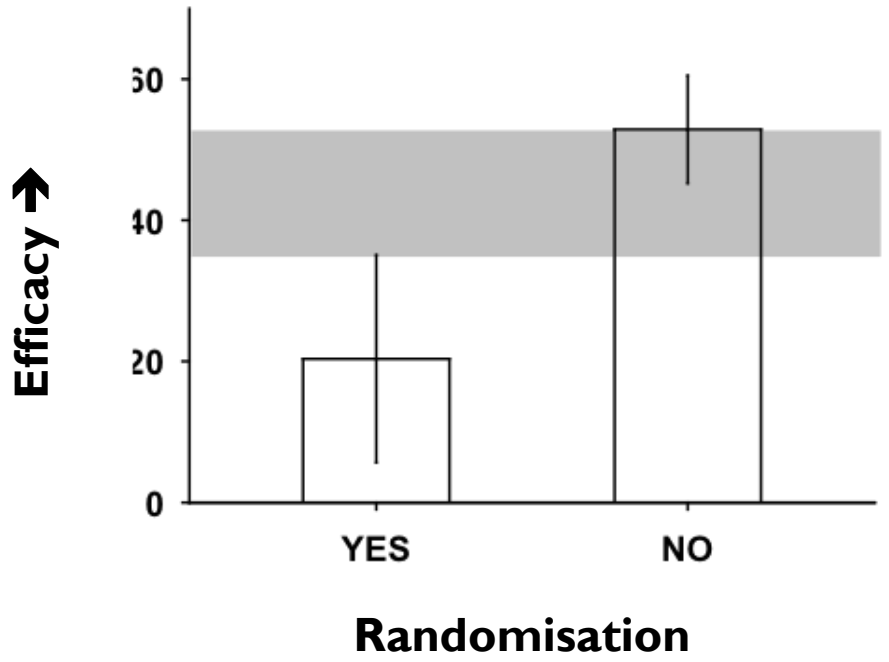


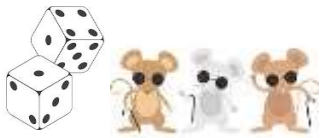
Group	Day 1	Day 2	Day 3	Day 4	Day 5
"Maze bright"	1.33	1.60	2.60	2.83	3.26
"Maze dull"	0.72	1.10	2.23	1.83	1.83
Δ	+0.60	+0.50	+0.37	+1.00	+1.43

Rosenthal and Fode (1963), Behav Sci 8, 183-9

Bias is prevalent and important

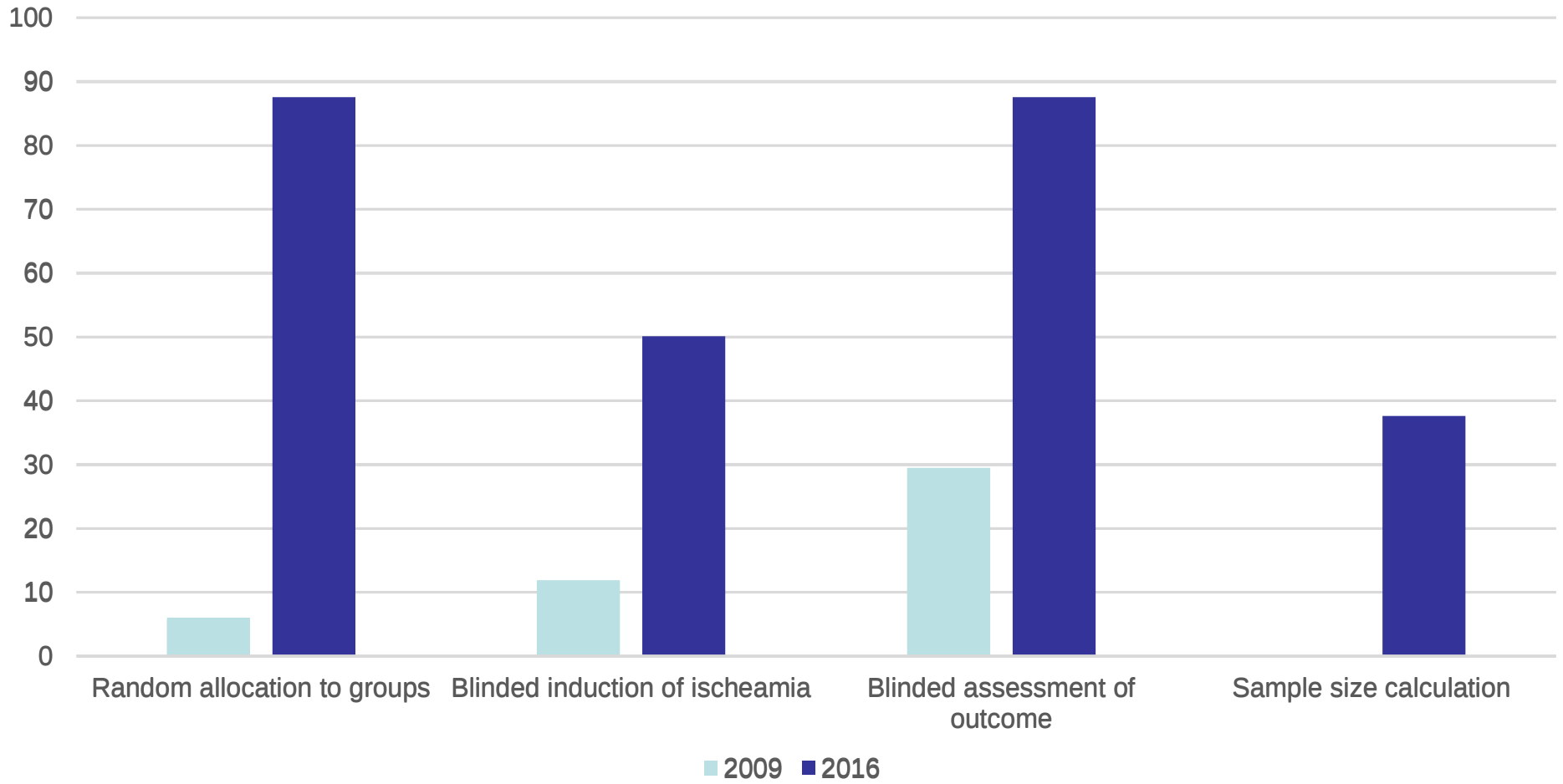
	Randomisation	Blinded Outcome Assessment
Stroke	36%	29%
MND	31%	20%
AD	15%	25%
PD	12%	15%
EAE	8%	15%
Glioma	14%	0%





Sena et al *TiNS* 2007

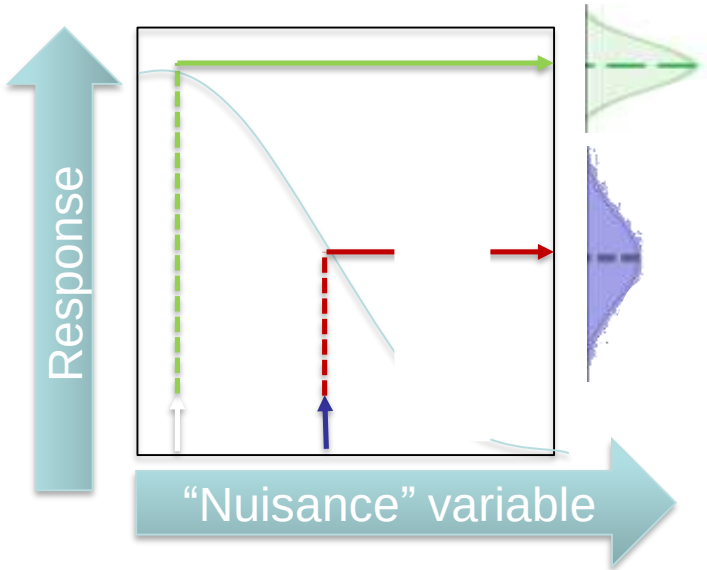
Things are improving

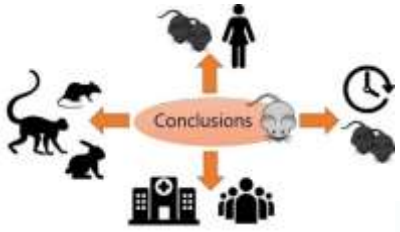


McCann SK, Cramond F, Macleod MR, Sena ES (2016). *Translational stroke research* **7**(5)**:** 395-406.

The standardisation fallacy

- Efforts to increase reproducibility by reducing variation by standardisation of:
  - lab environment
  - tests used
  - genetics of the animals
- Increases the risk of detecting effects with **low external validity** (or of missing effects with high external validity)





Wurbel, H. (2000) Nat. Genet
Voekl (2016) PLOS Biolgy

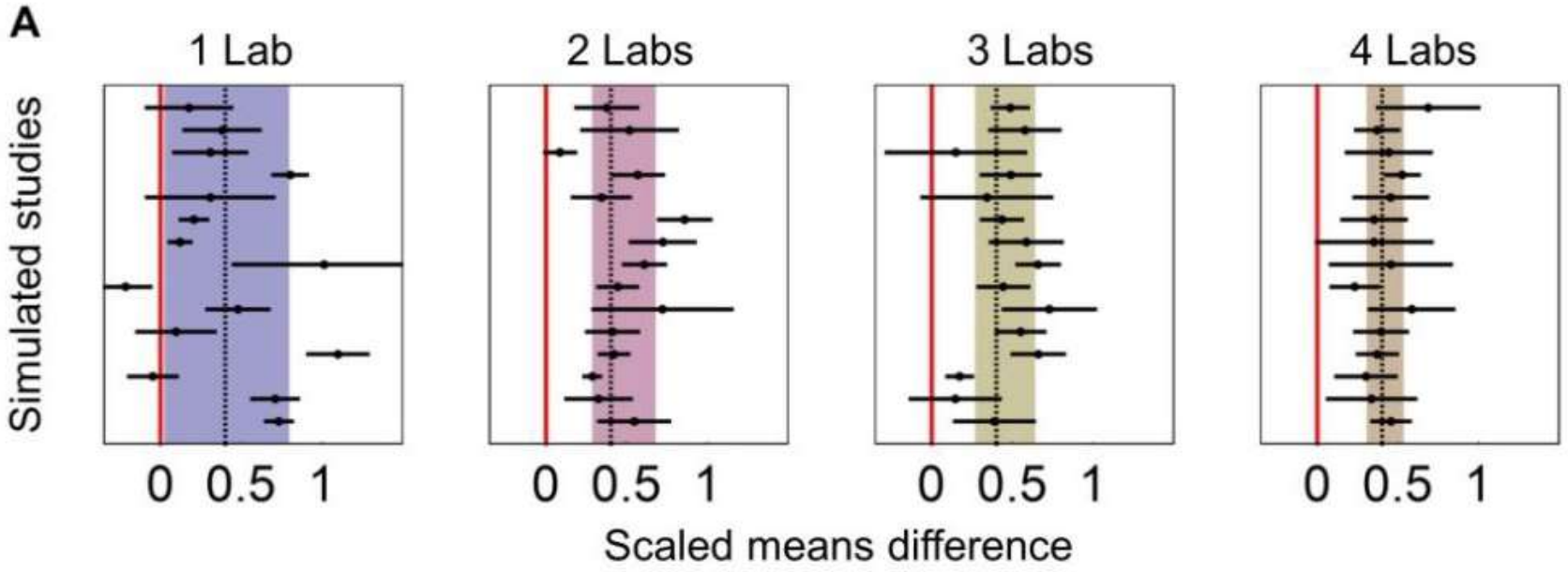
PLOS | BIOLOGY

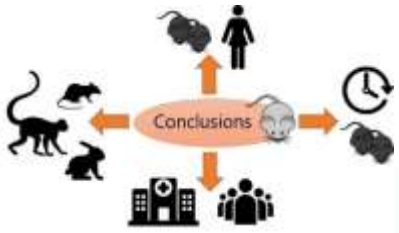
META-RESEARCH ARTICLE

Reproducibility of preclinical animal research improves with heterogeneity of study samples

Bernhard Voelkl[1], Lucile Vogt[1], Emily S. Sena[2], Hanno Würbel[1]*

1 Division of Animal Welfare, VPH Institute, Vetsuisse Faculty, University of Bern, Bern, Switzerland,
2 Centre for Clinical Brain Sciences, Chancellors Building, University of Edinburgh, Edinburgh, United Kingdom

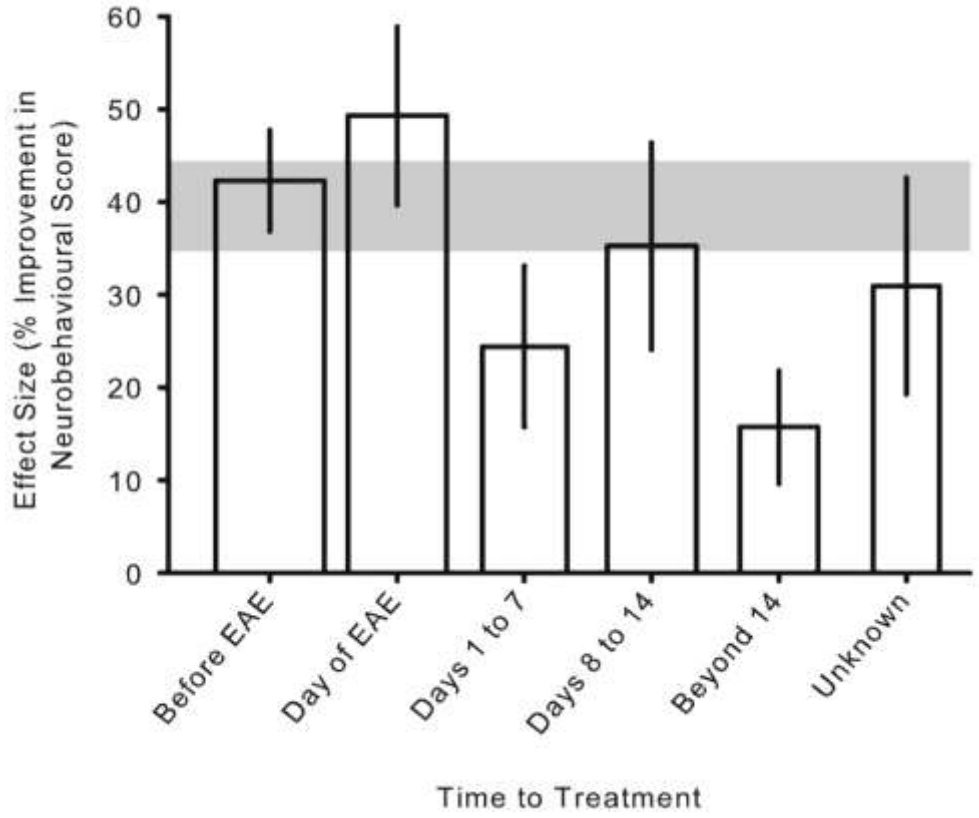




Time to Treatment in EAE

- Median: 0 days (IQR -11 to 4)
- 1% did not report time of administration

Before EAE	48%
Day of Induction	22%
After EAE	30%
Day of Symptom Onset	2%

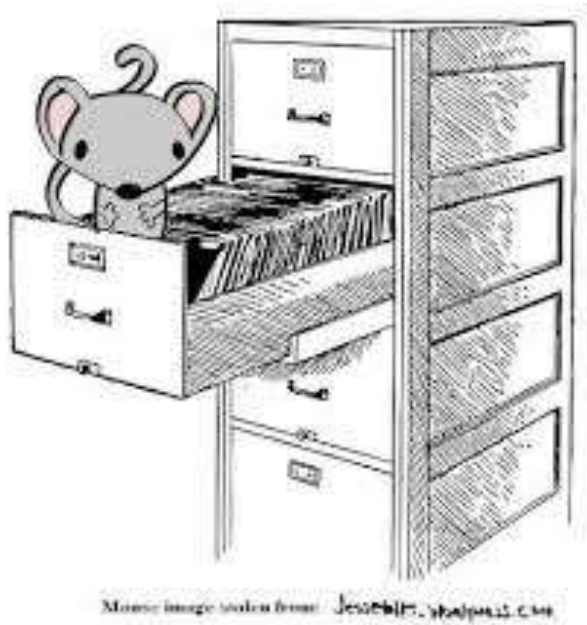


Vesterinen et al 2010 Multi Scler.

The umbrella of reporting bias

Not all outcomes and *a priori* analyses are reported

- Publication bias
  - Neutral and negative studies
  - Time lag/remain unpublished
  - Less likely to be identified
- p-hacking
  - Selective analysis
  - Selective outcome reporting



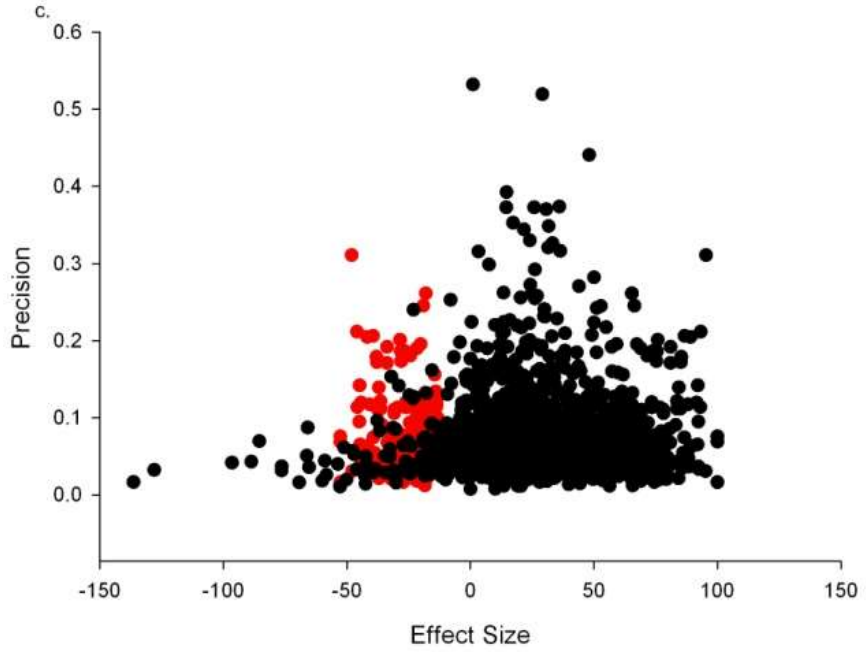
Is the File-Drawer Infested With Mice?

OPEN ACCESS Freely available online

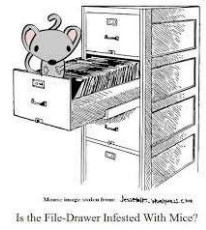
PLOS BIOLOGY

Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena[1,2,3], H. Bart van der Worp[4], Philip M. W. Bath[5], David W. Howells[2,3], Malcolm R. Macleod[1,6]*



- Overall efficacy was reduced from;
  - **32%** (95% CI 30 to 34%) to **26%** (95% CI 24 to 28%)
- 16% of experiments remain unpublished


Is the File-Drawer Infested With Mice?

The problem…..

- The reproducibility, replicability, and reliability of biomedical research is under threat.
- If research results are non-replicable, then:
  - scientific progress is stalled
  - research cannot be translated into clinical applications
  - time and money are wasted
  - the public loses trust in scientific findings
  - capable and talented early career researchers are disillusioned and leave the field.

Ideally……

- Studies will benefit from strategies that facilitate:
  - Robust design
    - Internal validity/robustness
  - Collaborative studies
    - External validity
  - Clarity of how studies were performed
    - Robustness/replication
  - Confirmation that studies report what they set out to do
    - Reporting biases
  - Access to data that can be used and compared efficiently
    - Robustness/replication

Improvement strategies

- Design
  - EDA
  - Multi-centre studies
  - Statistical input
- Conduct

The Experimental Design Assistant - EDA

Overview | Publications

The Experimental Design Assistant (EDA) is a free online tool from the NC3Rs, designed to guide researchers through the design of their experiments, helping to ensure that they use the minimum number of animals consistent with their scientific objectives, methods to reduce subjective bias, and appropriate statistical analysis.

Click here to access the EDA

EDA

span

NIH

protocols.io

Improvement strategies

PRECLINICALTRIALS.EU

International register of preclinical trial protocols

About Animal Study Registry

Animal Study Registry is an online registry for scientific studies involving animals conducted around the world. It is operated by the German Centre for the Protection of Laboratory Animals (Bf3R) at the German Federal Institute for Risk Assessment (BfR). All registrations are voluntary and free of charge. We strongly believe that our Animal Study Registry will enhance the reproducibility of in vivo biomedical studies and improve the quality of biomedical research by:

Improvement strategies

- Reporting
  - Guidelines (ARRIVE, CONSORT etc)
  - Publication policies

- Publication
  - Support new models (data, registered reports)

SCIENTIFIC DATA

Scientific Data aims to **promote wider data sharing and reuse, as well as credit those that share their data** and is open to submissions from a wide range of areas in the natural, clinical and social sciences – including descriptions and analysis of big and small data, from major consortiums, single labs and individuals.

Peer Community In
Registered Reports
Free and transparent pre- and post-study recommendations across research fields

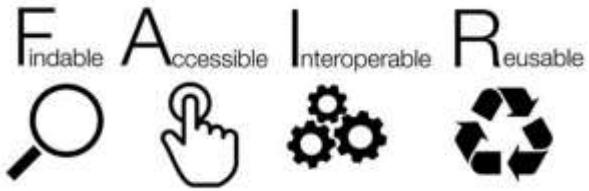
  - Encourage rapid publication anywhere, not vanity publishing in journals of the highest “impact”….preprints

Allow others to check your work

- Data should be available

figshare DRYAD MENDELEY DATA Put your research data online today zenodo

- Undocumented data dumps
  - No quality control
  - Often not linked to original study
  - How to re-analyse?



Who did what?

ORCID

CRediT

Contributor Role	
Conceptualization	Resources
Data Curation	Software
Formal Analysis	Supervision
Funding Acquisition	Validation
Investigation	Visualization
Methodology	Writing – Original Draft Preparation
Project Administration	Writing – Review & Editing

To bring evidence to translational medicine

- Primary research reports include
  - Information that allows the reliability of the findings to be assessed
  - Methodological details that describe how the study was done, and allow the methods to be reproduced
  - Research context and relevance that helps with the interpretation of the findings
  - Meta-data information that allows studies to be identified, and be used to their full potential in retrospective studies
  - Clarity on what the researchers set out to do

What we know

- *In vivo* studies which do not report simple measures to avoid bias give larger estimates of treatment effects
- Most do not report simple measures to reduce bias
- Reporting biases are important and prevalent
- Most *in vivo* research is underpowered (or of unknown power)
- All stakeholders have a role to play
- You can only find these things out by studying large numbers of studies
- Help is at hand but improvement strategies must be tested
- Any experimental design can be subverted; what's important is knowing how to recognise when this has happened

Thanks to.....

Stroke association

Wissenschaftskolleg zu Berlin
INSTITUTE FOR ADVANCED STUDY

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

wellcome

MRC Medical Research Council

ljaf laura and john arnold foundation