Translational failure in preclinical research; how open science can help

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Disclosures

- **BMJ Open Science** (Editor-in-Chief)
  - I receive an honorarium for this role

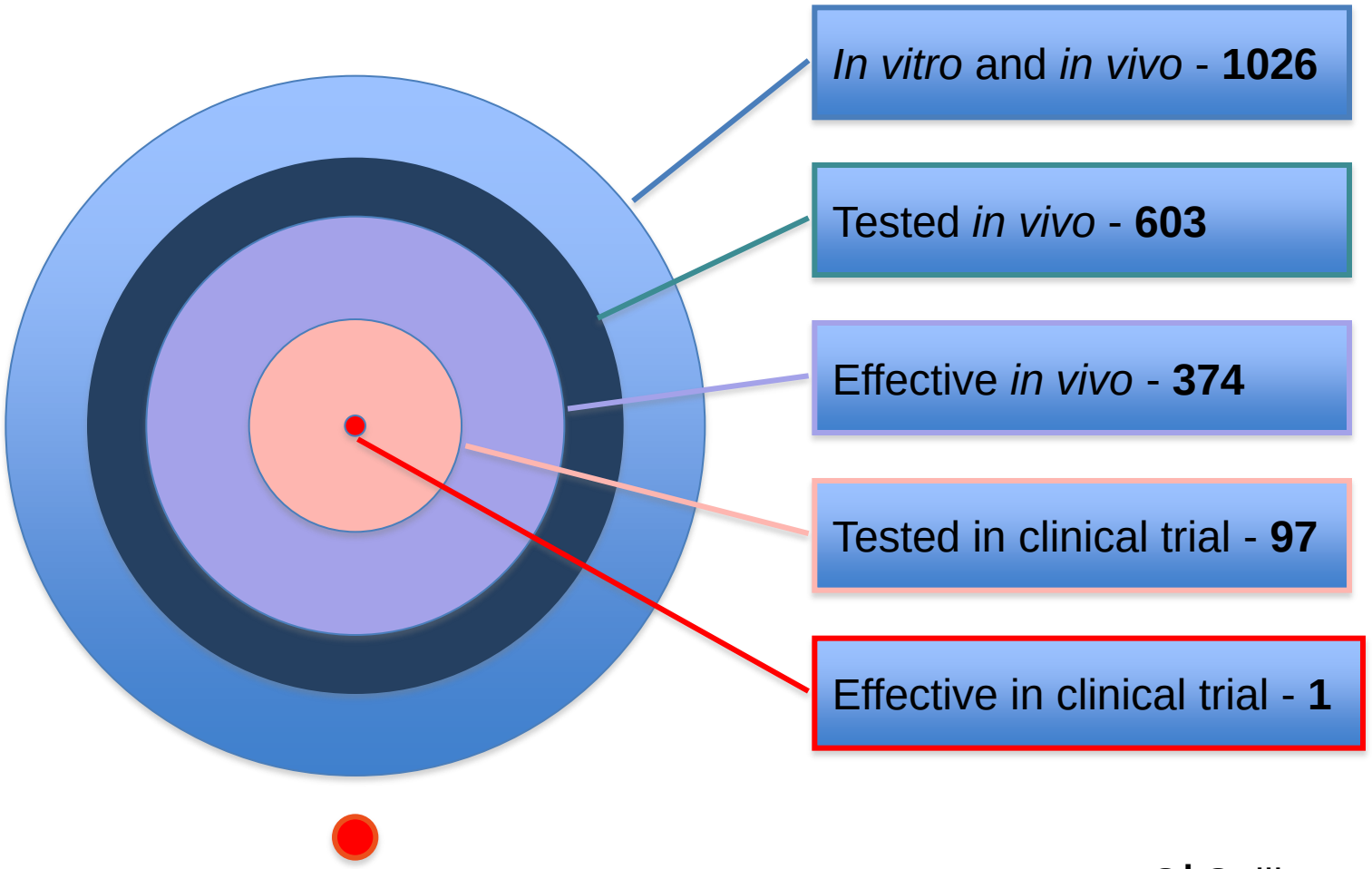
- I applied and have received (& will continue) grant funding for this research

My perspective

Theme

- Scale of the problem 
  - How the life cycle of a preclinical research study is not fit for purpose
- In an ideal world 
  - As a consumer of preclinical research what do I want
- Potential solutions 

What is translational failure?



O'Collins et al, 2006

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

Translational failure

Improving the translational hit of experimental treatments in multiple sclerosis

Multiple Sclerosis
0(00) 1–12

DOI: 10.1177/1352458510379612
msj.sagepub.com

Hanna M. Ve
Charles ffren
Siddharthan

PAIN® 154 (2013) 917–926

IASP

PAIN®

ORIGINAL ARTICLE

Animal mo

Gillian L. Curri
Hanna M. Vest

Treatment of Intracerebral Hemorrhage in Animal Models: Meta-Analysis

Review

Cell PRESS

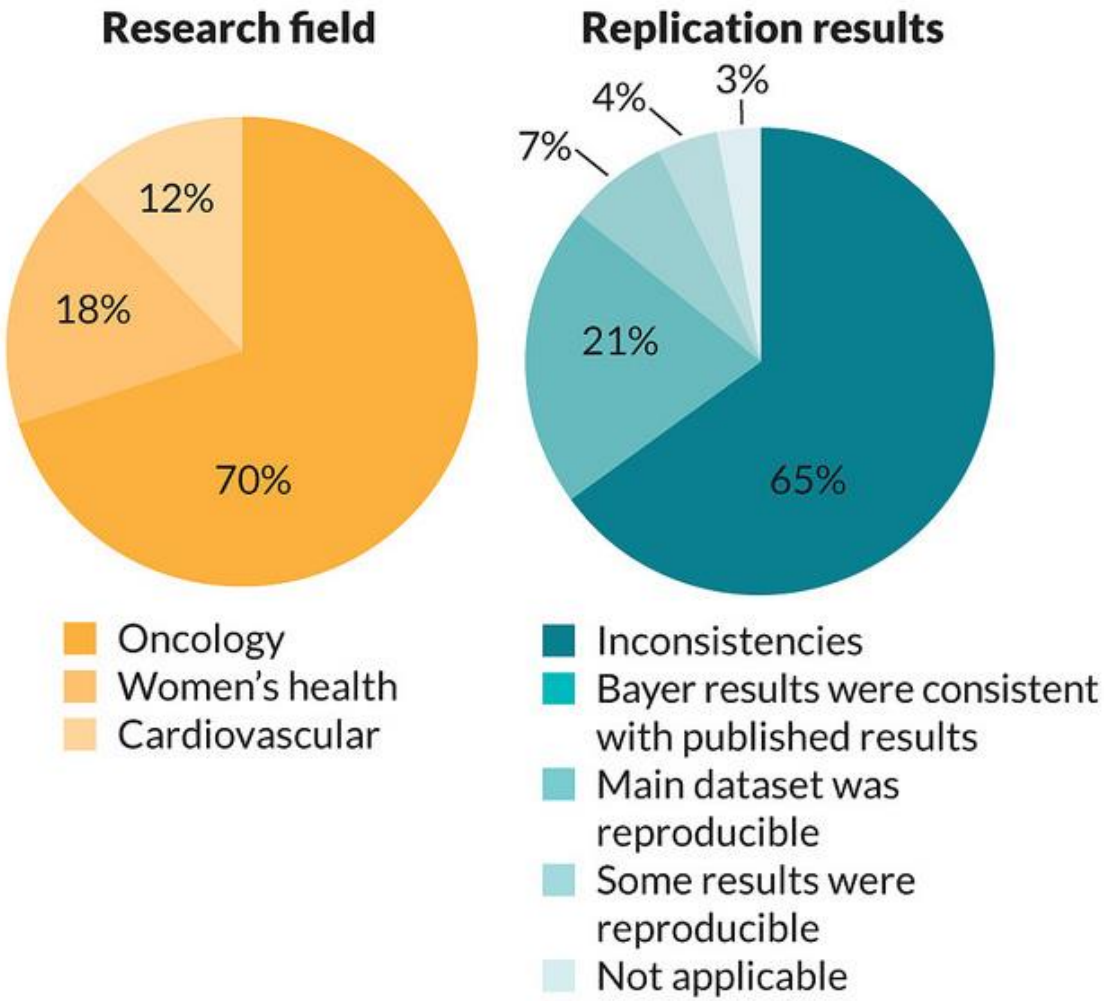
'Too much good news' – are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease?

Kathleen R. Zahs[1,2,4] and Karen H. Ashe[1,2,3,5]

[1] N. Bud Grossman Center for Memory Research and Care
[2] Department of Neurology
[3] Department of Neuroscience
[4] Department of Integrative Biology and Physiology, University of Minnesota Medical School, Minneapolis, MN 55455, USA
[5] Geriatric Research Education Clinical Center, Minneapolis VA Medical Center, Minneapolis, MN 55417, USA

What happens when pharma tries to replicate academic findings?

- Bayer, Berlin
- 67 in-house projects over 4 years



Prinz *et al*, Nature Reviews Drug Discovery, 2011

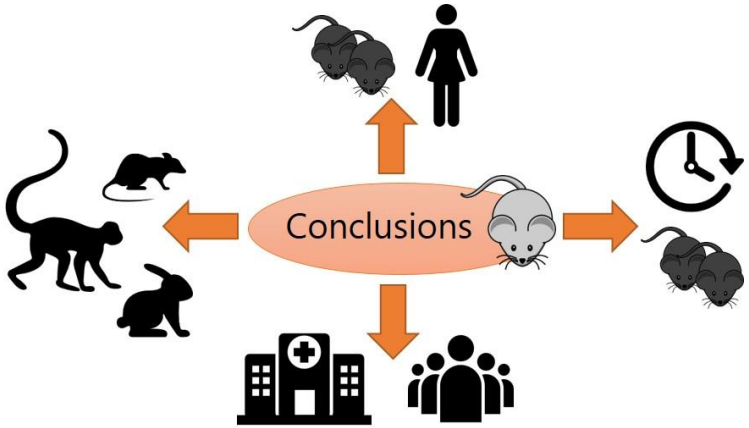
Rate of publication

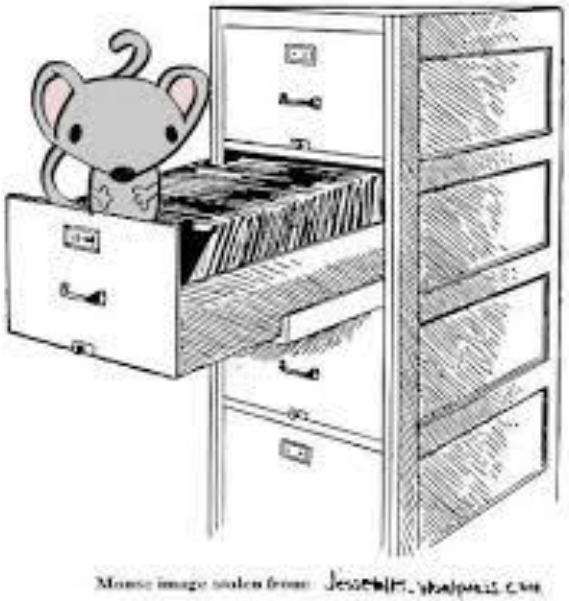
- There are more papers published in a day than most people could read in a month
- In 2013, 4700 new publications were added to PubMed every working day

Domain	Number
In vivo and in vitro	610
In vivo	350
Pharmacology	76
Neurosciences	52

- If you did nothing else but read neuroscience papers all year you would get through 30% of the total

Potential sources of bias in animal studies

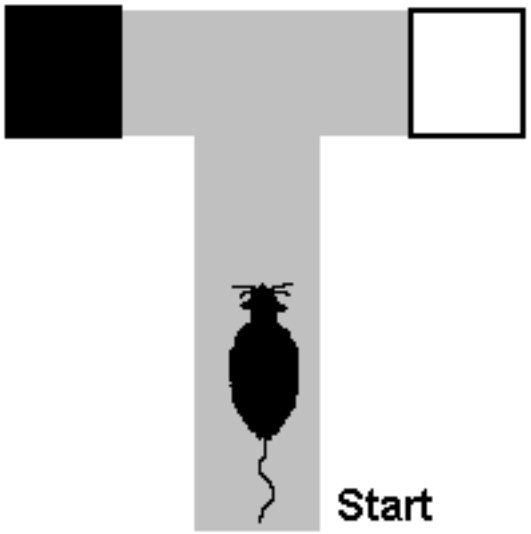




Is the File-Drawer Infested With Mice?

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"

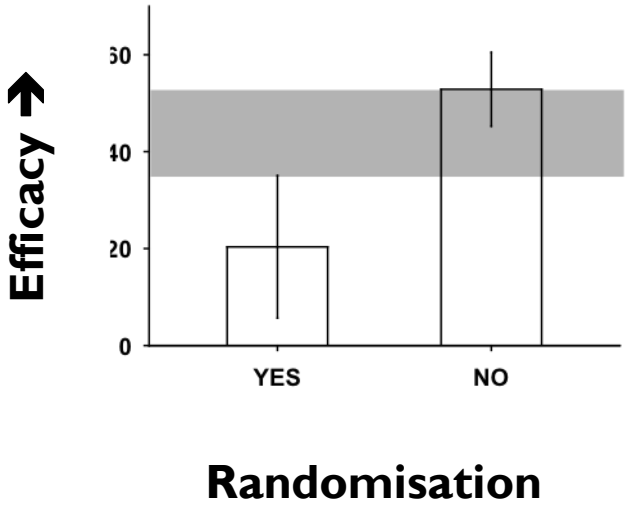


Group	Day 1	Day 2	Day 3	Day 4	Day 5
"Maze bright"	1.33	1.60	2.60	2.83	3.26
"Maze dull"	0.72	1.10	2.23	1.83	1.83
Δ	+0.60	+0.50	+0.37	+1.00	+1.43

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

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

Mouse image stolen from: Jessebliss.shutterfly.com

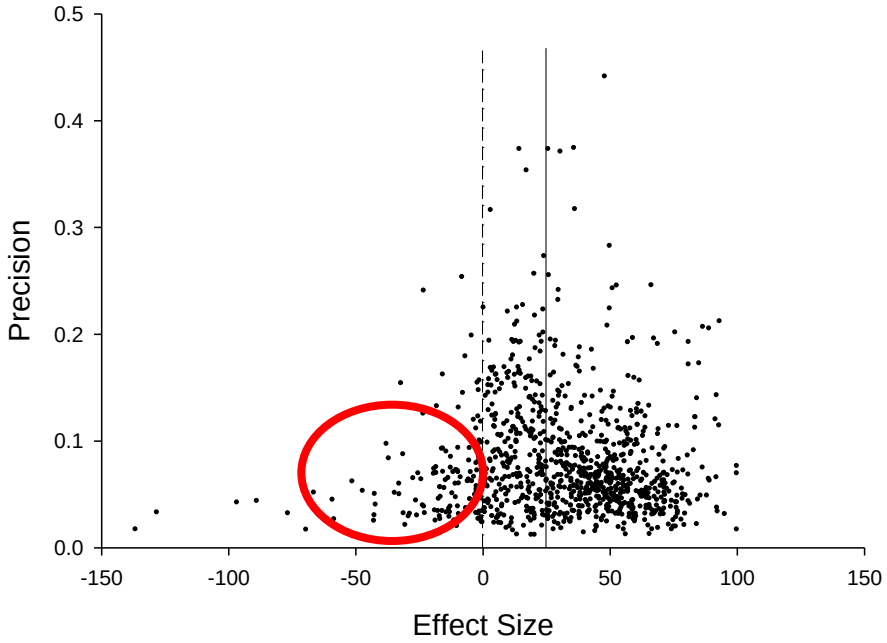
Is the File-Drawer Infested With Mice?

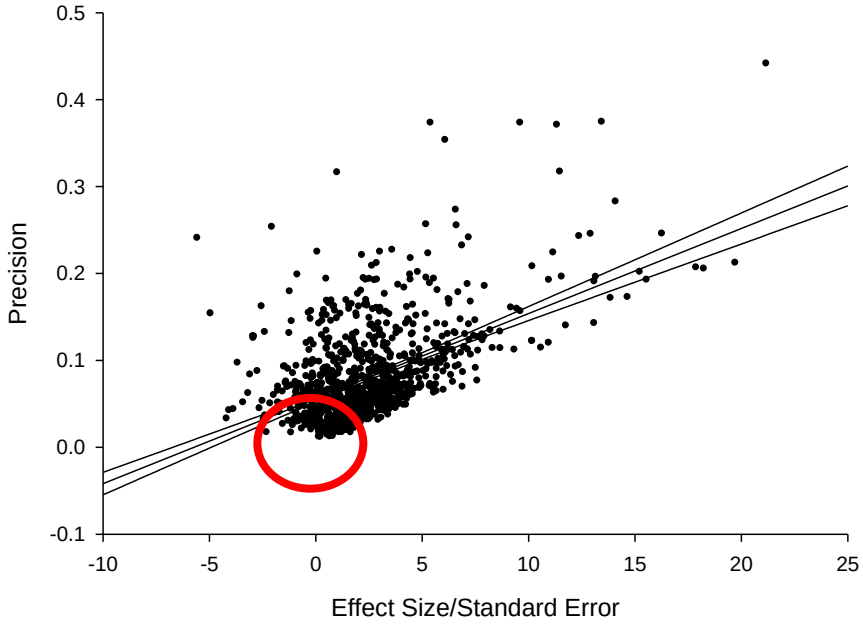
OPEN ACCESS Freely available online

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]*





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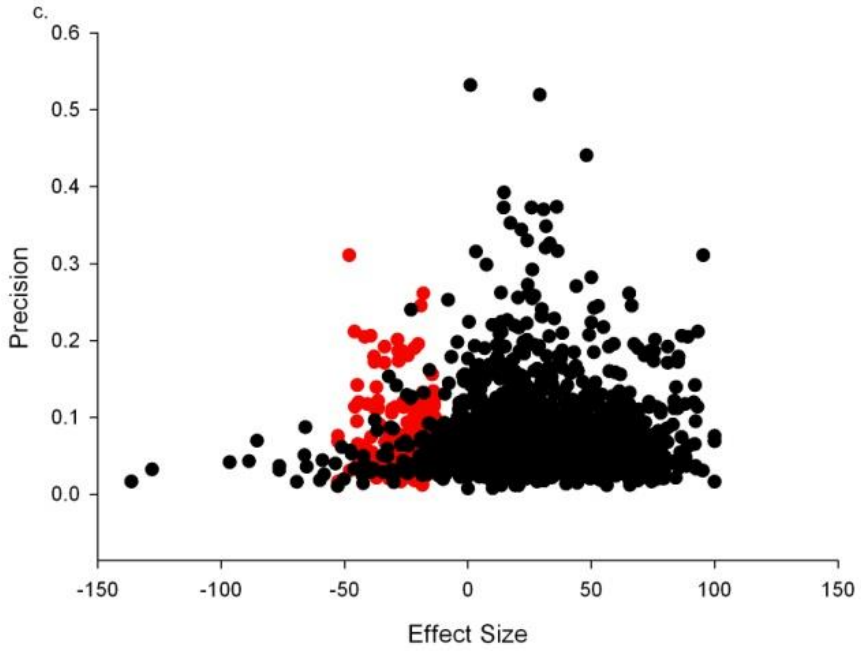


Overall efficacy was reduced from;
32% (95% CI 30 to 34%) to **26%** (95% CI 24 to 28%)

Publication bias in experimental stroke

- Trim and Fill suggested **16%** of experiments remain unpublished
- Best estimate of magnitude of problem
  - Overstatement of efficacy **31%**
- Only **2%** publications reported no significant treatment effects

Publication bias

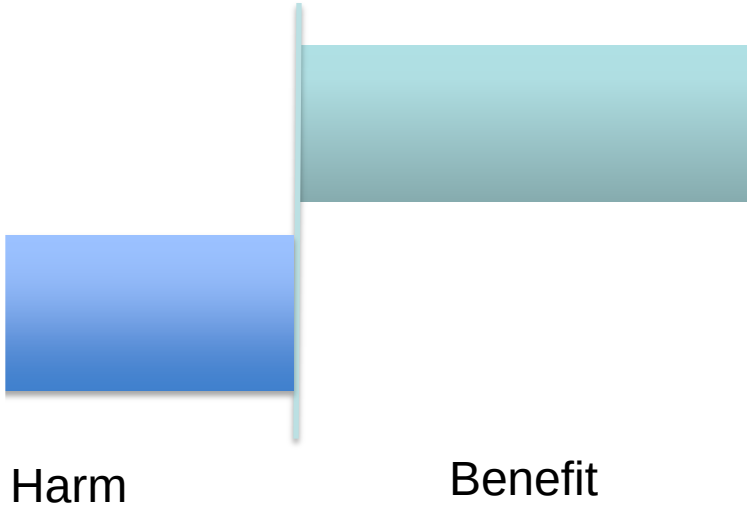
20%

- 32%

	n expts	Estimated unpublished	Reported efficacy	Corrected efficacy
Stroke – infarct volume	1359	214	31.3%	27.5%
EAE - neurobehaviour	1892	505	33.1%	15.0%
EAE – inflammation	818	14	38.2%	37.5%
EAE – demyelination	290	74	45.1%	30.5%
EAE – axon loss	170	46	54.8%	41.7%
AD – Water Maze	80	15	0.688 sd	0.498 sd
AD – plaque burden	632	154	0.999 sd	0.610 sd

Different patterns of publication bias in different fields

	outcome	observed	corrected	
Disease models	improvement	40%	30%	Less improvement
Toxicology model	harm	0.32	0.56	More harm



Ideally……

- Preclinical research will benefit from open science tools that facilitates:
  - Clarity of how studies were performed
  - Collaborative studies
  - Confirmation that studies report what they set our to do
  - Access to data that can be used and compared efficiently

How were the data generated?

OPEN ACCESS Freely available online

PLOS BIOLOGY

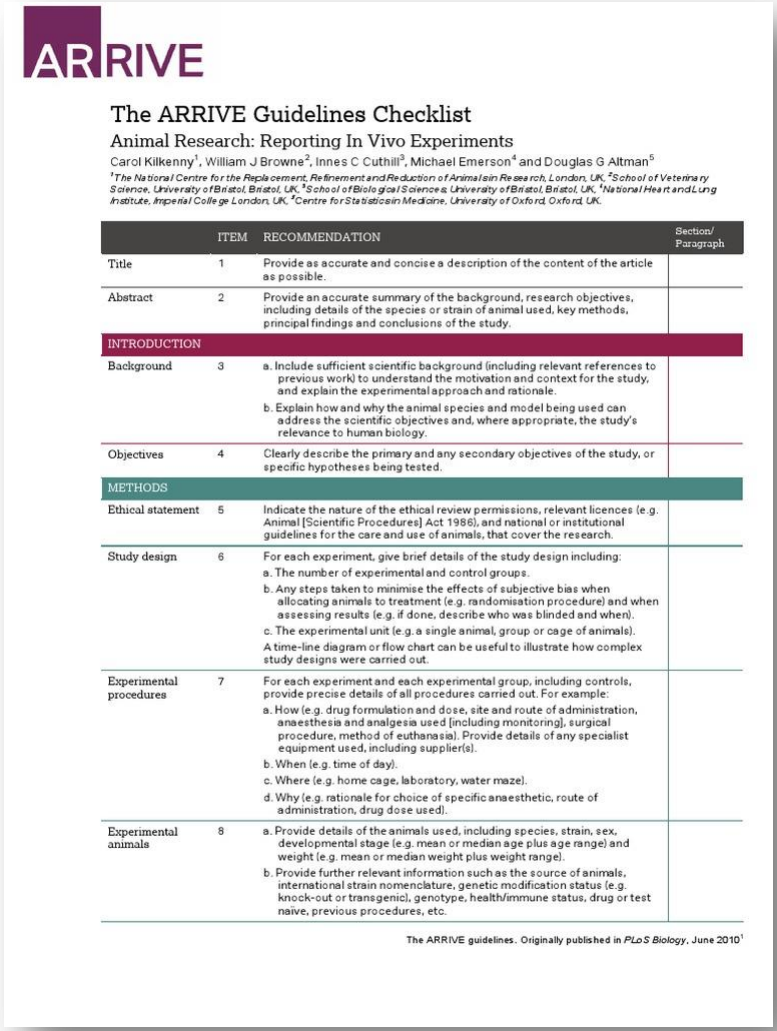
Perspective

Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research

Carol Kilkenny[1]*, William J. Browne[2], Innes C. Cuthill[3], Michael Emerson[4], Douglas G. Altman[5]

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

- Journals
- Funders
- Universities
- Learned societies



ARRIVE

The ARRIVE Guidelines Checklist

Animal Research: Reporting In Vivo Experiments

Carol Kilkenny[1], William J Browne[2], Innes C Cuthill[3], Michael Emerson[4] and Douglas G Altman[5]

[1]The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK, [2]School of Veterinary Science, University of Bristol, Bristol, UK, [3]School of Biological Sciences, University of Bristol, Bristol, UK, [4]National Heart and Lung Institute, Imperial College London, UK, [5]Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

	ITEM	RECOMMENDATION	Section/ Paragraph
Title	1	Provide as accurate and concise a description of the content of the article as possible.	
Abstract	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	
INTRODUCTION			
Background	3	a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.	
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.	
METHODS			
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.	
Study design	6	For each experiment, give brief details of the study design including: a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.	
Experimental procedures	7	For each experiment and each experimental group, including controls, provide precise details of all procedures carried out. For example: a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).	
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range). b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naive, previous procedures, etc.	

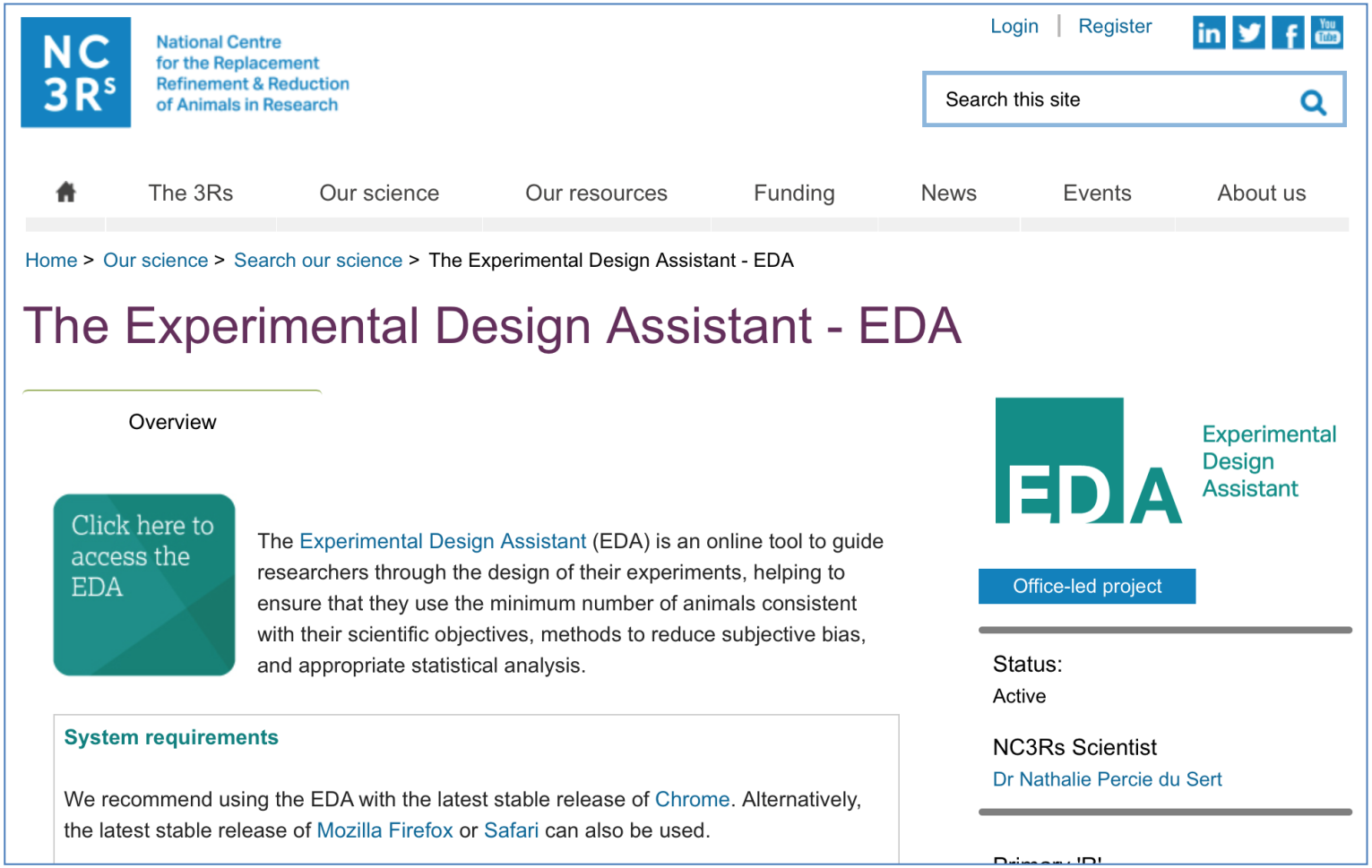
The ARRIVE guidelines. Originally published in *PLoS Biology*, June 2010[1]

Open Methods

protocols.io

Resource Identification Initiative

Experimental Design Assistant

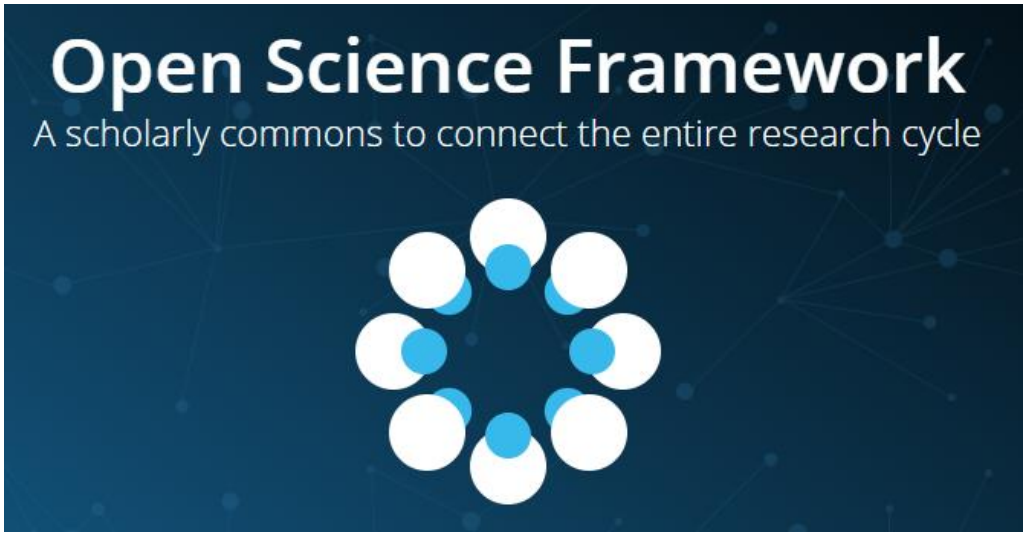


https://www.nc3rs.org.uk/experimental-design-assistant-eda

Study protocol registries

NIH U.S. National Library of Medicine
ClinicalTrials.gov

PRECLINICALTRIALS.EU
International register of preclinical trial protocols



Registered Reports

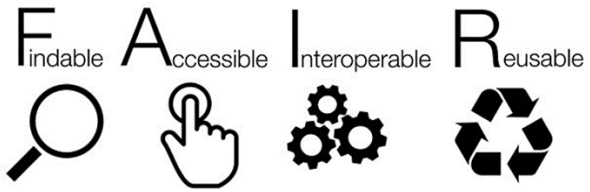
"Because the study is accepted in advance, the incentives for authors change from producing the most beautiful story to the most accurate one."

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?



Publish data

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.

BMJ Open Science

Data descriptor articles

BMJ Open Science will consider data descriptor articles of preclinical studies or studies relevant to preclinical research. These articles should describe scientific data to facilitate data-sharing and reuse; their focus is to enable others to reuse data rather than presenting new hypotheses, analyses or interpretations. Descriptor articles combine traditional narrative content with curated structured metadata. Data descriptor articles should include detailed descriptions of the methods used to collect the data and technical analyses to support the quality of data acquisition. Peer review evaluates the rigour with which experiments were conducted during data acquisition. Data must be stored in public and permanently available community-recognised repositories (e.g. Dryad, Figshare).

Who did what?

ORCID

CRediT

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

Obstacles to researchers…..

- Emphasising rigour in grant award
- Emphasising rigour in appointment panels
- CPD opportunities for scientists

Efficacy of research improvement

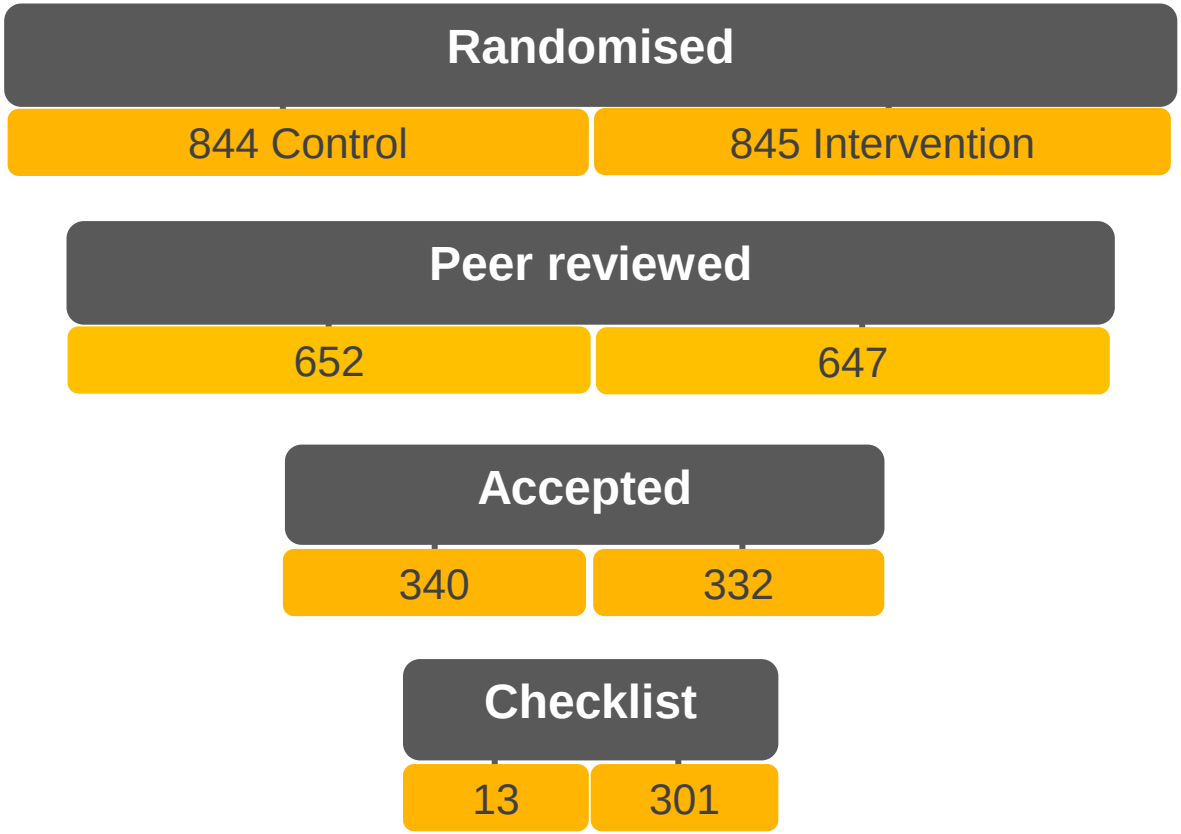
- **Research Improvement Activity:** Things done by stakeholders to increase the usefulness of research with which they are associated

- Important to assess whether interventions can be effectively delivered
- Important to assess whether interventions improve research quality and reduce waste

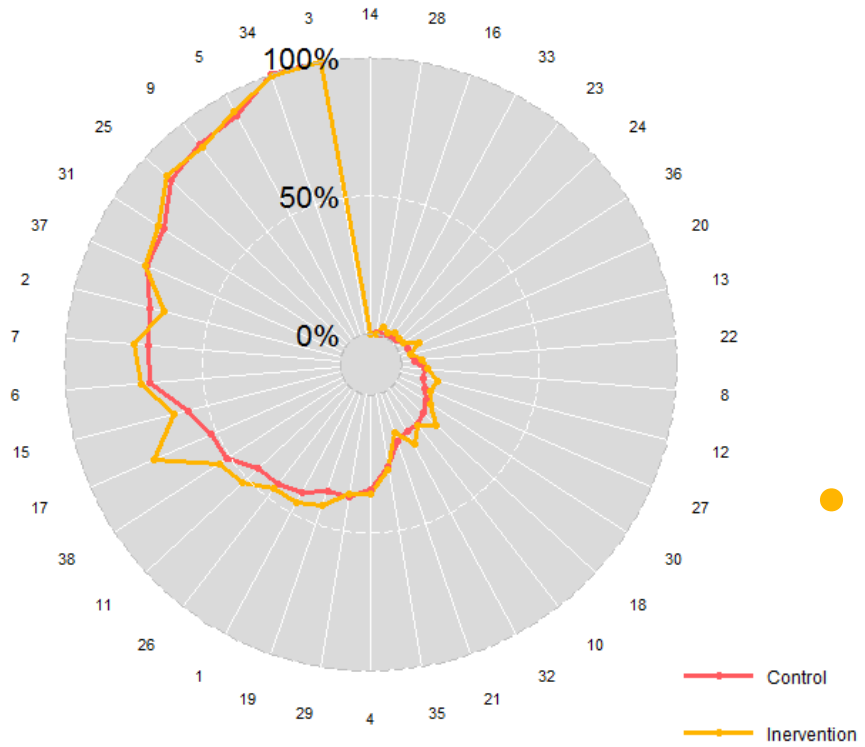
Impact of an Intervention to Improve Compliance With the ARRIVE Guidelines (IICARus)

Protocol: Open Science Framework (February 2017)
Data Analysis Plan: Open Science Framework (September 2017)
Funding: MRC, NC3Rs, BBSRC & Wellcome Trust
Ethics: BMJ Ethics Committee

Manuscripts

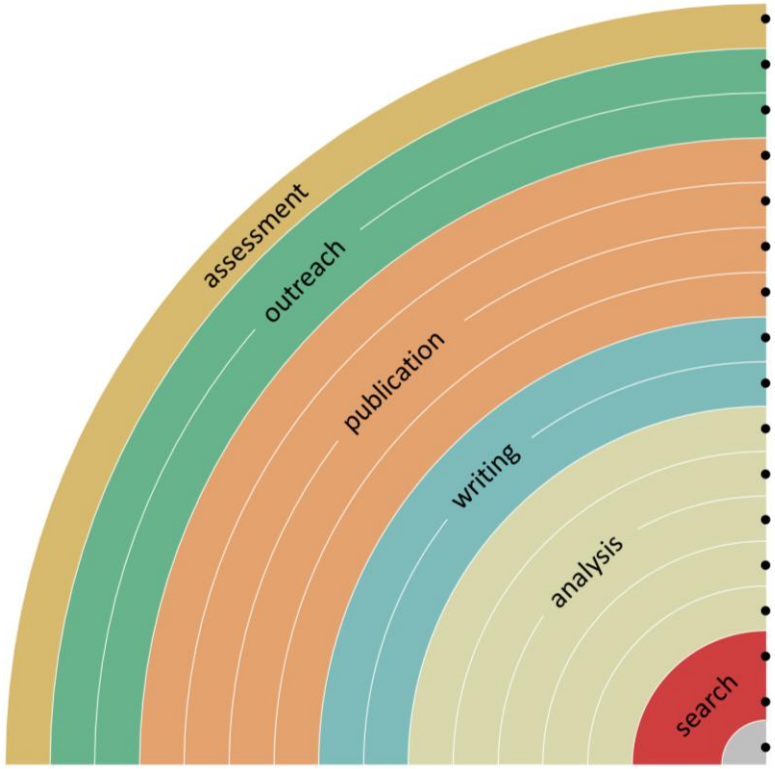


Primary outcome



- Control:
  - 100% compliance n=0 manuscripts
  - Median compliance 36.8% (29.7-42.1) of relevant items
- Intervention:
  - 100% Compliance n= 0
  - Median compliance 39.5% (31.6-44.7) of relevant items

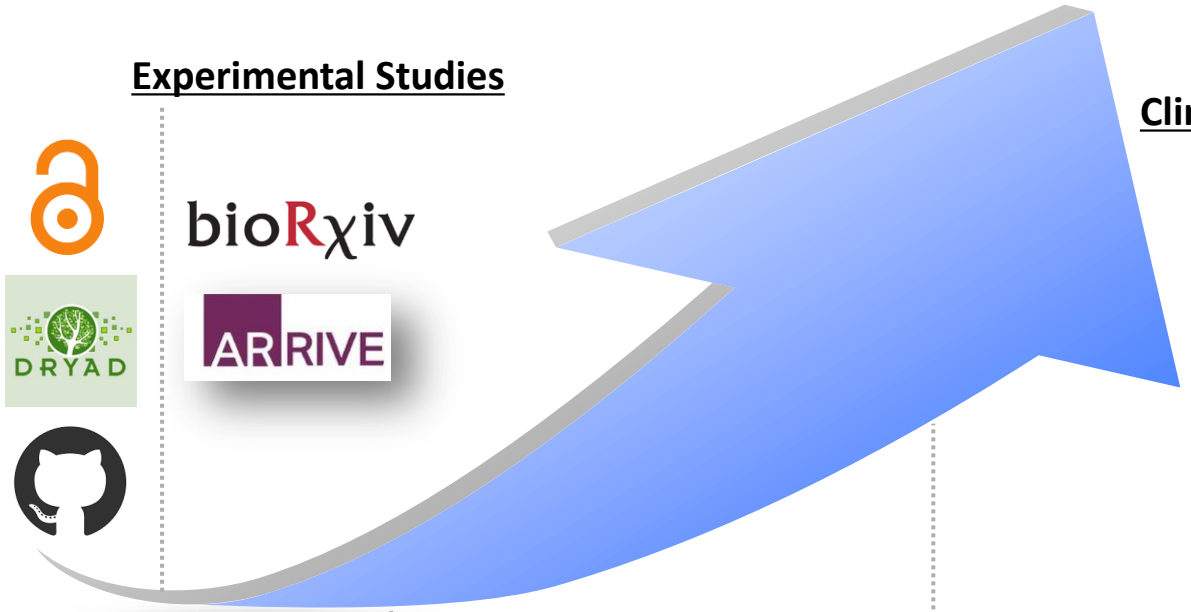
THE open workflow



- adding alternative evaluation, e.g. with altmetrics
- communicating through social media, e.g. Twitter
- sharing posters & presentations, e.g. at FigShare
- using open licenses, e.g. CC0 or CC-BY
- publishing open access, 'green' or 'gold'
- using open peer review, e.g. at journals or PubPeer
- sharing preprints, e.g. at OSF, arXiv or bioRxiv
- using actionable formats, e.g. with Jupyter or CoCalc
- open XML-drafting, e.g. at Overleaf or Authorea
- sharing protocols & workfl., e.g. at Protocols.io
- sharing notebooks, e.g. at OpenNotebookScience
- sharing code, e.g. at GitHub with GNU/MIT license
- sharing data, e.g. at Dryad, Zenodo or Dataverse
- pre-registering, e.g. at OSF or AsPredicted
- commenting openly, e.g. with Hypothes.is
- using shared reference libraries, e.g. with Zotero
- sharing (grant) proposals, e.g. at RIO

DOI: 10.5281/zenodo.1147025

How Open Science can help preclinical research



Key messages

- *In vivo* studies which do not report simple measures to avoid bias give larger estimates of treatment effects
- Most *in vivo* studies do not report simple measures to reduce bias
- Publication and selective outcome reporting biases are important and prevalent
- You can only find these things out by studying large numbers of studies
- Any experimental design can be subverted; what's important is knowing how to recognise when this has happened

Finally……

- Some (useful) tools exists
  - I'm confused
- Development/implementation needs resource
- Research is required to determine their efficacy
- Education will help, including training in critical appraisal
- Reward/incentives will likely drive change

Thanks to……

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®