



# Introduction to the UK Reproducibility Network

## Why, What, Who and How

**Malcolm Macleod**

UKRN Steering Committee

Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies

Academic lead for Research Improvement and Research Integrity, University of Edinburgh



# Disclosures

- UK Commission for Human Medicines
- UK Reproducibility Network
- Independent Statistical Standing Committee, CHDI Foundation
- Project co-ordinator, EQIPD IMI



This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777364. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA



**New journal policies**  
**New publishing culture**  
 e.g. ReScience C & ReScience X  
<http://rescience.github.io>



**Publication bias & lack of data sharing**  
 ~92% positive & ~70% failure  
 Fanelli (2010); Wicherts et al. (2006)

**Publish experiment**

**Specify hypotheses**

**Lack of replication**  
 1 in 1000 papers  
 Makel et al. (2012)

**Registered Reports (2012)**  
 Partnerships between  
 Authors & Journals & Funders  
<http://cos.io/rr>

**Interpret data**

**HARKing**  
 ~50-90% prevalence  
 John et al. (2012); Kerr (1998)  
 (Hypotheses After Results are Known)

**Design study**

**Change policies & Incentives structures**  
 e.g. San Francisco Declaration on Research Assessment (DORA)  
<https://sfdora.org>

**P-hacking**  
 ~50-100% prevalence  
 John et al. (2012)

**Analyze data**

**Collect data**

**Low statistical power**  
 ~50% chance to detect medium effects  
 Cohen (1962); Sedlmeier & Gigerenzer (1989); Bezeau & Graves (2001)

**Better research practices**  
 e.g. Standards, Training, Peer-review

Munafò et al. (2017). A manifesto for reproducible science. Nature Human Behaviour, 1(1), 0021. <https://doi.org/10.1038/s41562-016-0021>

**UKRN: aiming to ensure the UK retains its place as a centre for world-leading research**



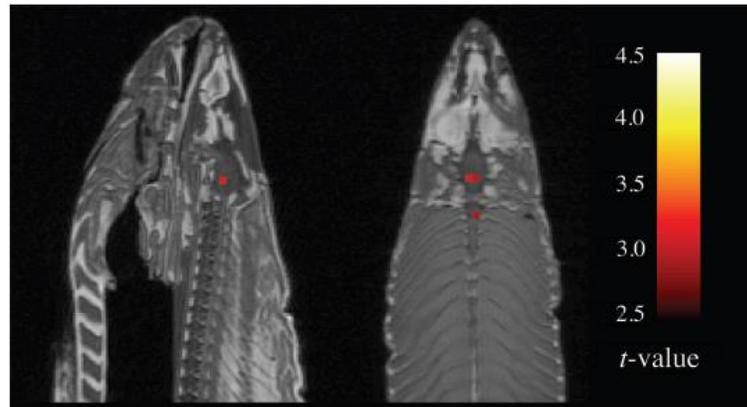
I am not in the office at the moment. Send any work to be translated.



## Neural Correlates of Interspecies Perspective Taking in the Post-Mortem Atlantic Salmon: An Argument For Proper Multiple Comparisons Correction

Craig M. Bennett<sup>1\*</sup>, Abigail A. Baird<sup>2</sup>, Michael B. Miller<sup>1</sup> and George L. Wolford<sup>3</sup>

One mature Atlantic Salmon (*Salmo salar*) participated in the fMRI study. The salmon measured approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning. It is not known if the salmon was male or female, but given the post-mortem state of the subject this was not thought to be a critical variable.



The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence, either socially inclusive or socially exclusive. The salmon was asked to determine which emotion the individual in the photo must have been experiencing.

Several active voxels were observed in a cluster located within the salmon's brain cavity (see Fig. 1). The size of this cluster was 81 mm<sup>3</sup> with a cluster-level significance of  $p = 0.001$ .

Either we have stumbled onto a rather amazing discovery in terms of post-mortem ichthyological cognition, or there is something a bit off with regard to our uncorrected statistical approach.



Winner of the 2012 Ignoble Prize for Neuroscience



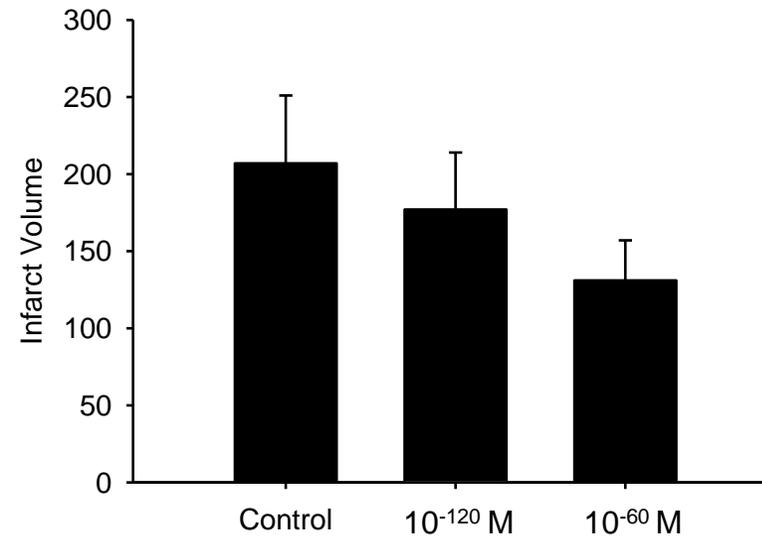
## Treatment of experimental stroke with low-dose glutamate and homeopathic *Arnica montana*\*

*W. Jonas*<sup>1</sup>, *Y. Lin*<sup>2</sup>, *A. Williams*<sup>2</sup>, *F. Tortella*<sup>2</sup>, *R. Tuma*<sup>3</sup>

<sup>1</sup> Uniformed Services University of the Health Sciences, Bethesda, Maryland

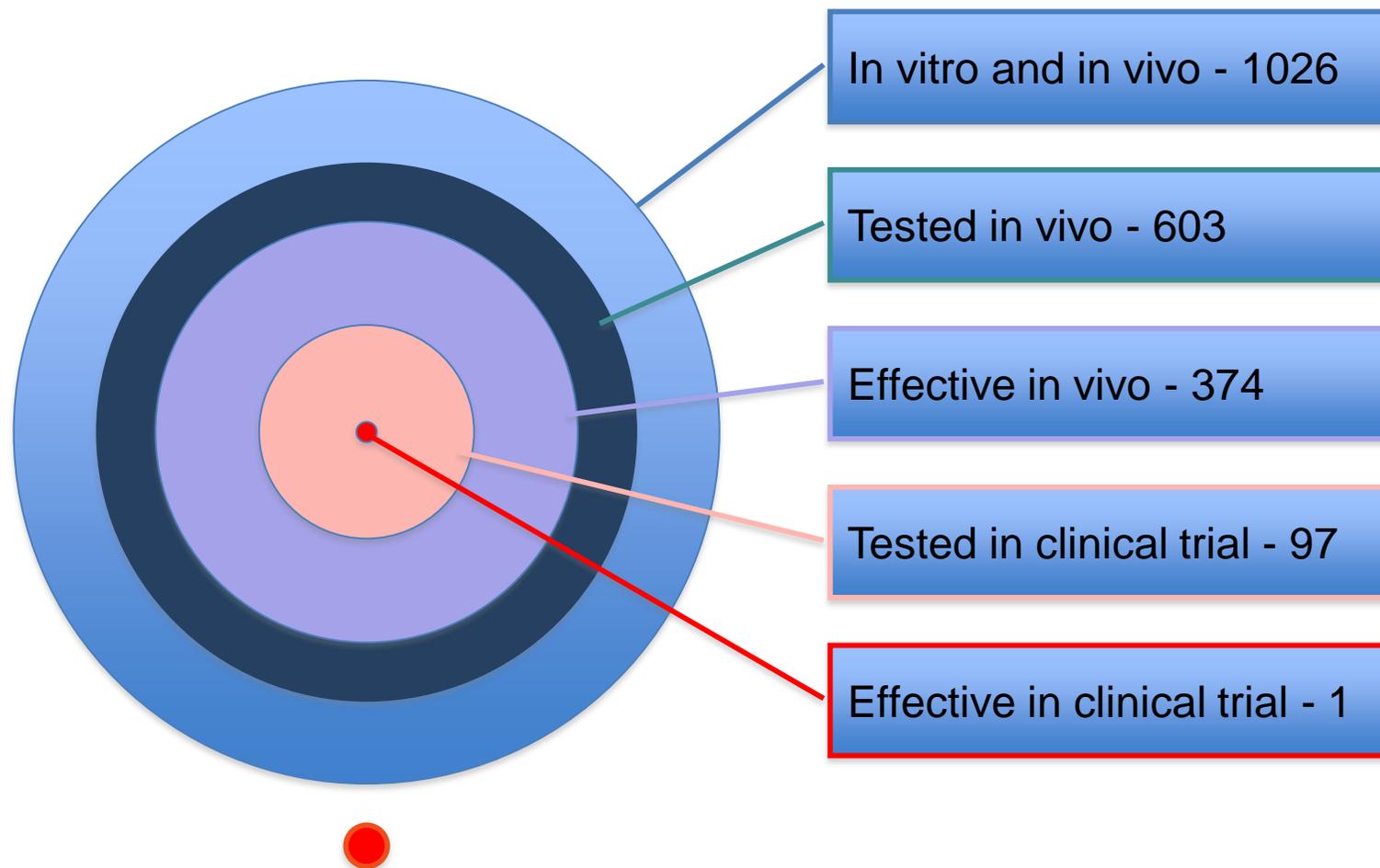
<sup>2</sup> Walter Reed Army Institute of Research, Washington, D.C.

<sup>3</sup> Temple University, Philadelphia, PA





# 1026 interventions in experimental stroke

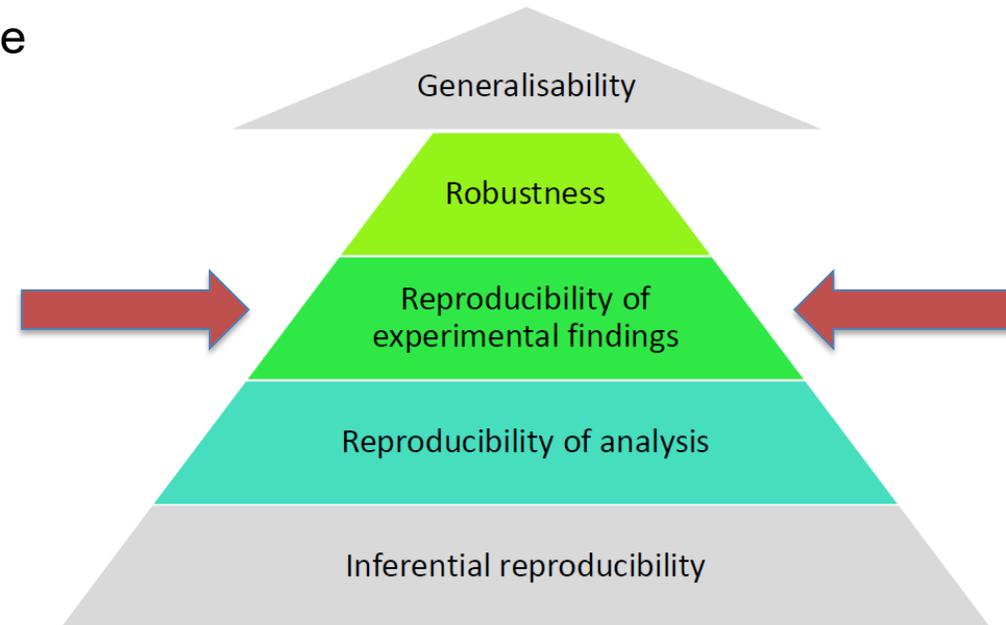


O' Collins et al, 2006

# Reproducibility and replication

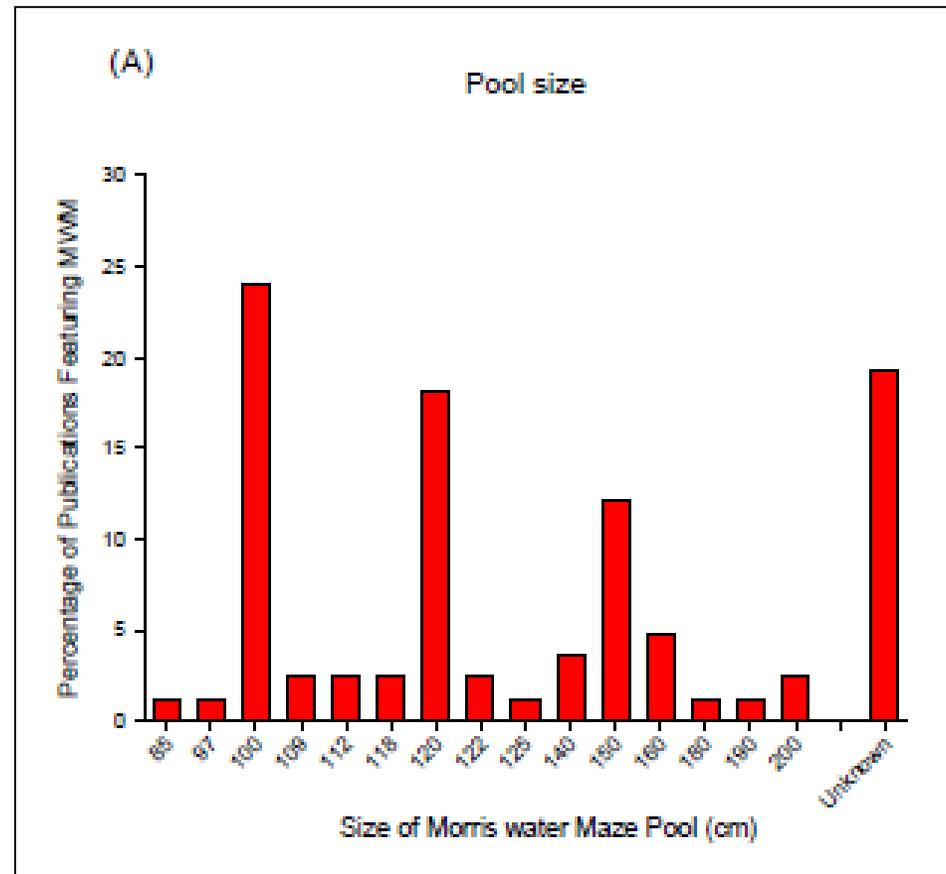
“Reproducibility” related to the re-analysis of existing data following the same analytical procedures.

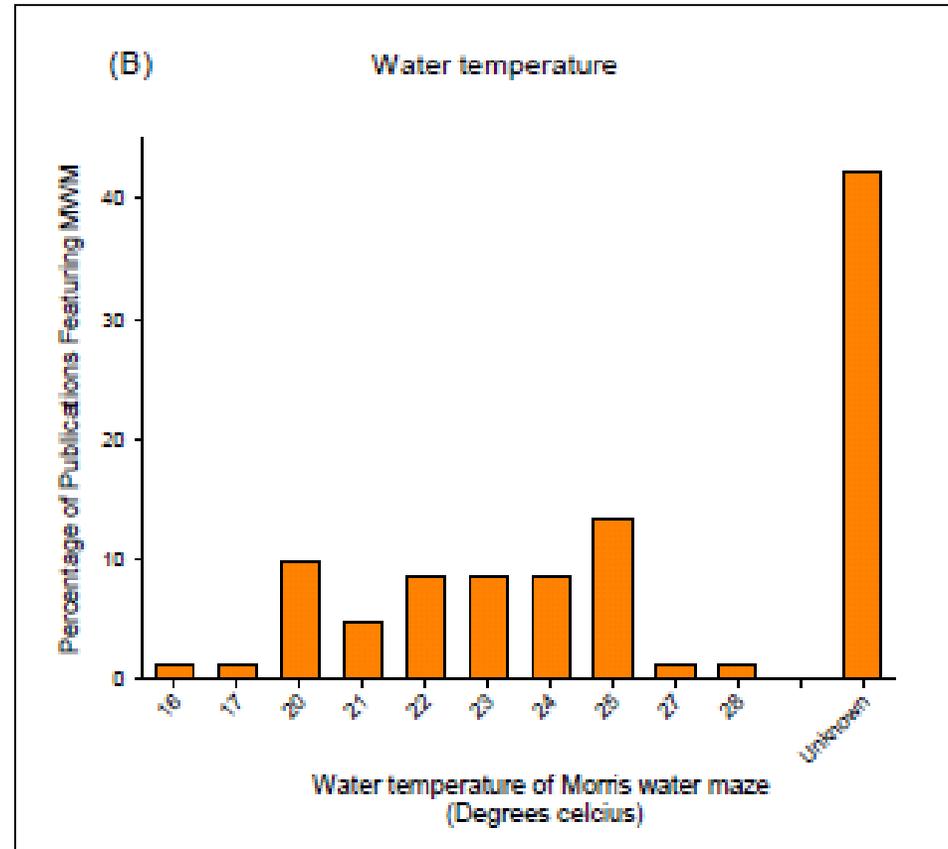
“Replication” was held to require the collection of new data, following the same methods.

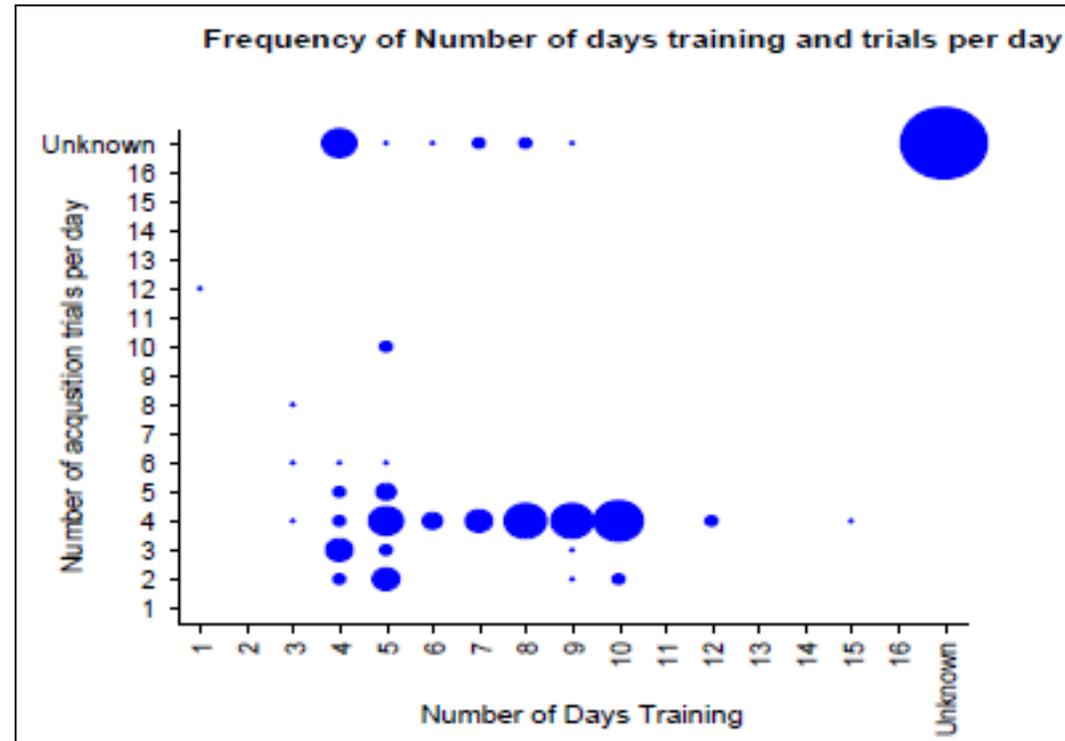




# Most studies are not described well enough to inform replication efforts









# Replication studies

1. **Retrospective** – Pharmaceutical companies sharing their historical experience when they have attempted replication

- Bayer 33% of 67
- Amgen 11% of 53

Selection bias (2 companies out of ?)

? Recall Bias



# Replication studies

2. **Prospective** - Academic led, great attention given to faithfulness to original study design, adequate statistical power, preregistration

– Psychology	36% of 97	$ES_R=49\%$
– Cancer biology	40% of 10	
– Economics	61% of 18	$ES_R=66\%$
– Social sciences	62% of 21	$ES_R=54\%$

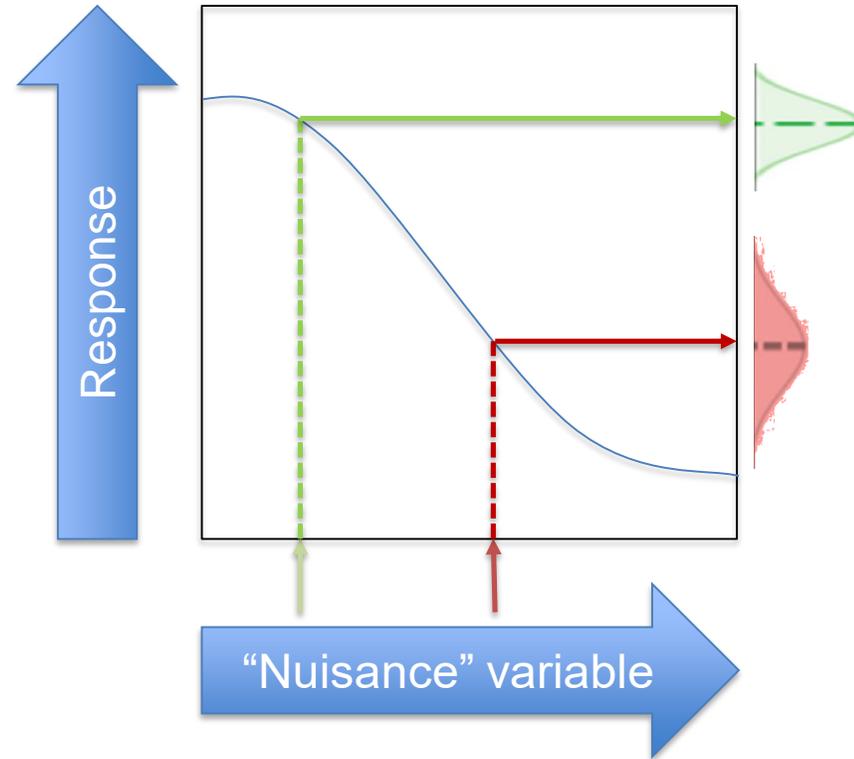
? Selection bias

how did they choose what to try to replicate?



# Both studies may be correct

## Reaction norms (Voelkl 2016)



# Lifespan in worms

Source of variation	Developmental Rate	Fertility
Genetic	83.1%	63.3%
Between labs	8.3%	7.9%
Within labs	3.8%	5.6%
Individual	4.8%	23.3%

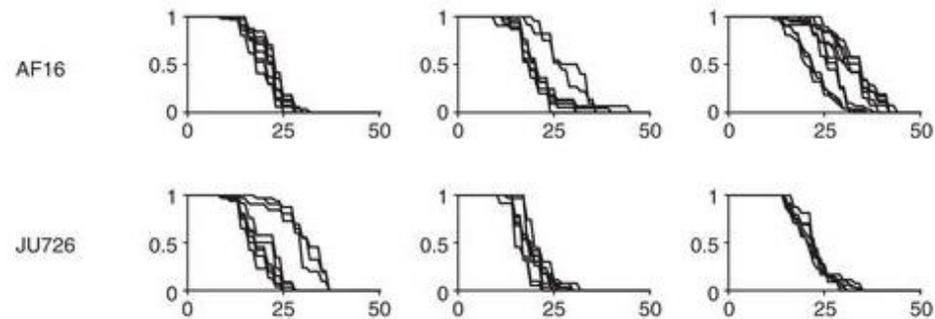
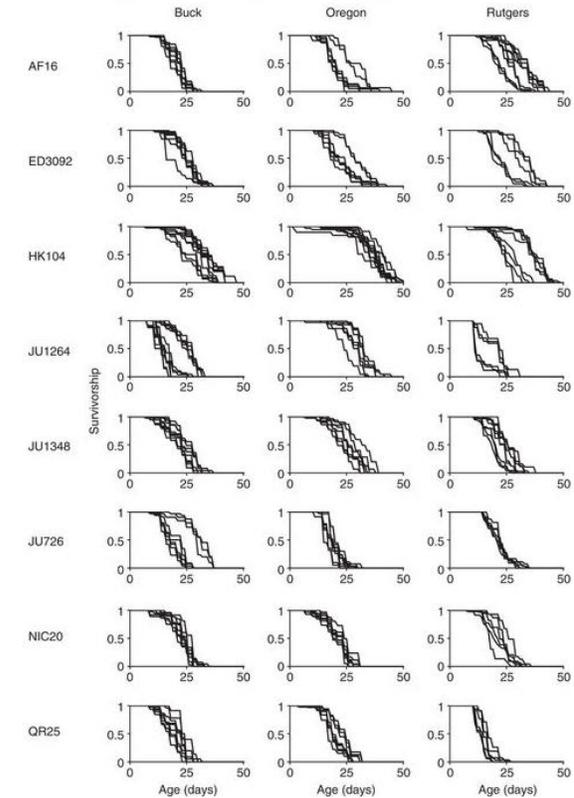


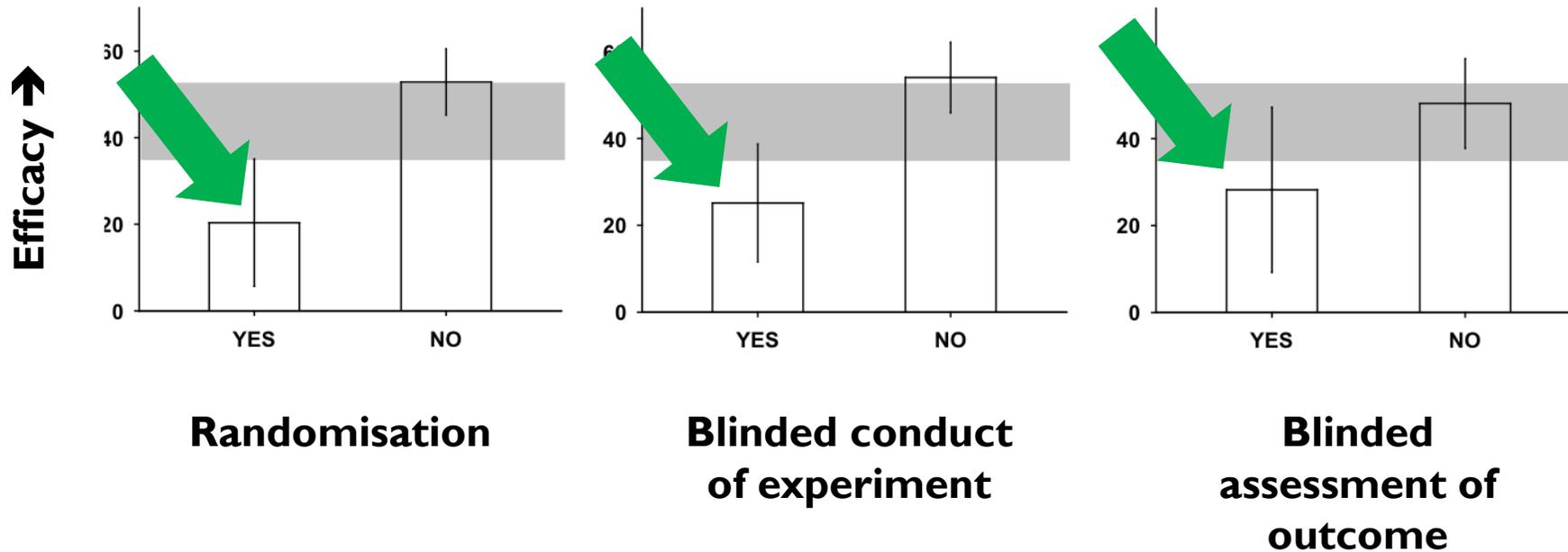
Figure 3: Variation in longevity within labs for each replicate plate for eight natural isolates of *C. briggsae*.



Lucanic et al Nature Comms 2017

# Risk of bias in animal studies

- Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)

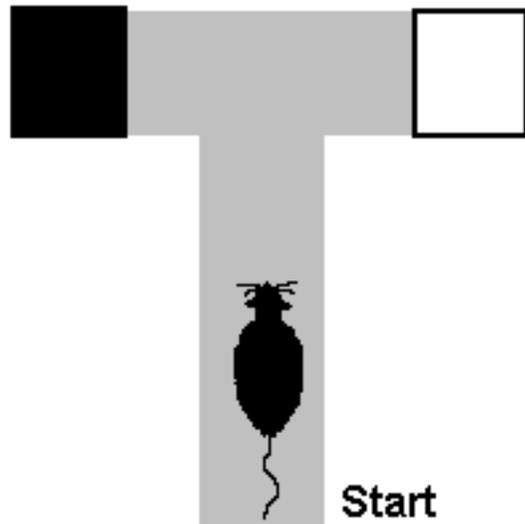


Macleod et al, 2008



# 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
$\Delta$	+0.60	+0.50	+0.37	+1.00	+1.43

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



# The scale of the problem

RAE 1173



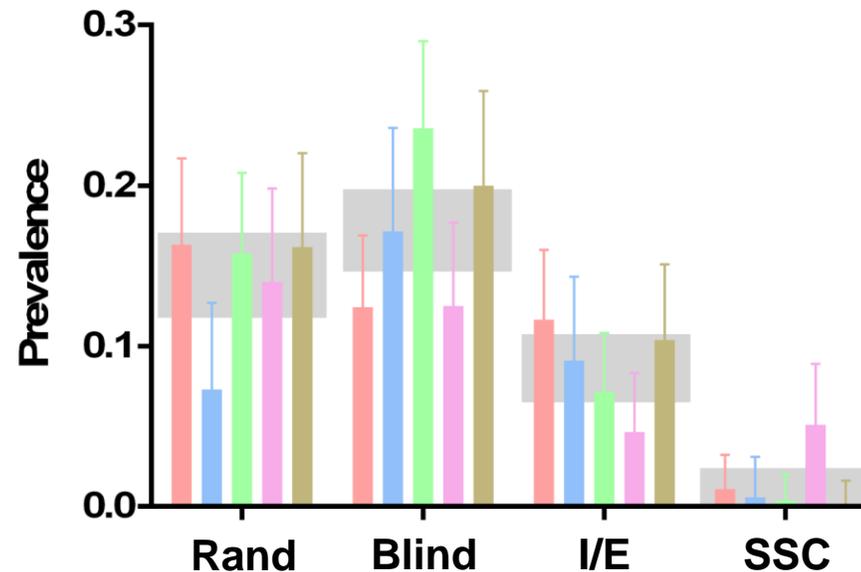
rae2008

Research Assessment Exercise

“an outstanding contribution to the internationally excellent position of the UK in biomedical science and clinical/translational research.”

“impressed by the strength within the basic neurosciences that were returned ...particular in the areas of behavioural, cellular and molecular neuroscience”

1173 publications using non human animals, published in 2009 or 2010, from 5 leading UK universities





# Research Improvement at Journals

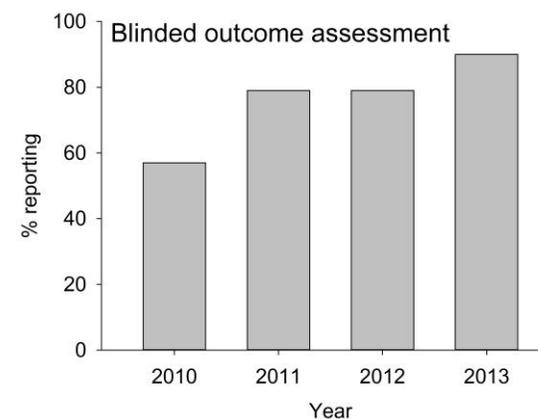
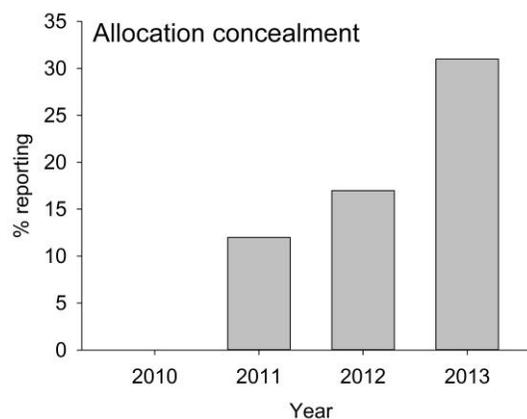
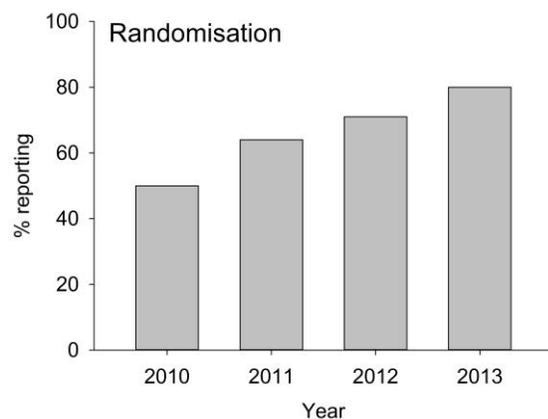


## Comments, Opinions, and Reviews

### 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



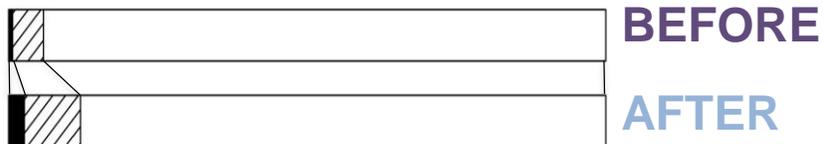
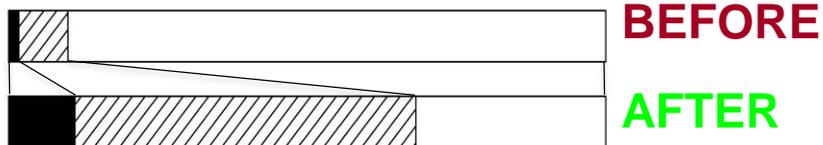
Minnerup et al, 2016



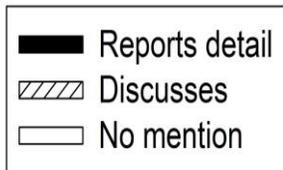
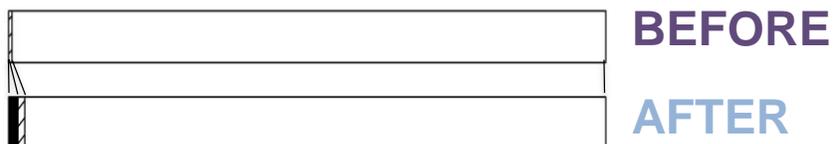
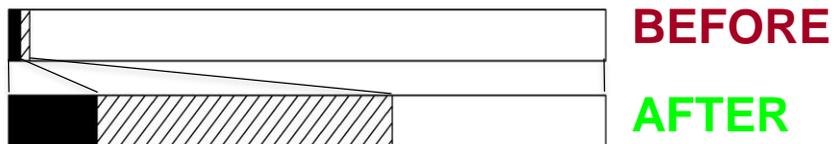
# Impact of NPG checklist



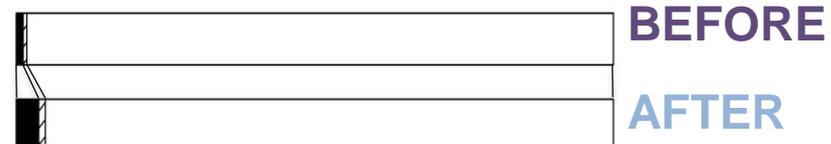
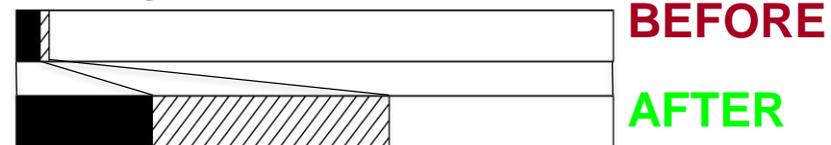
## Randomisation



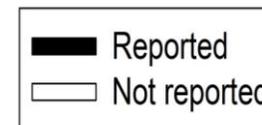
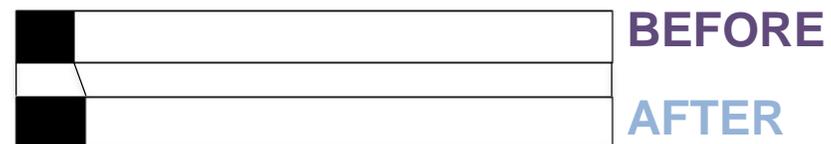
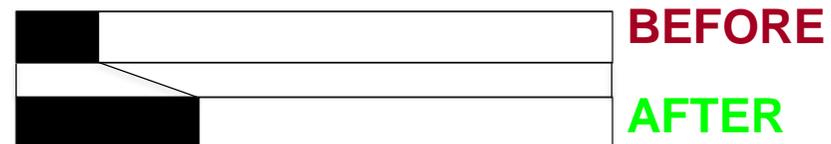
## Sample size calculation



## Blinding



## Reporting exclusions



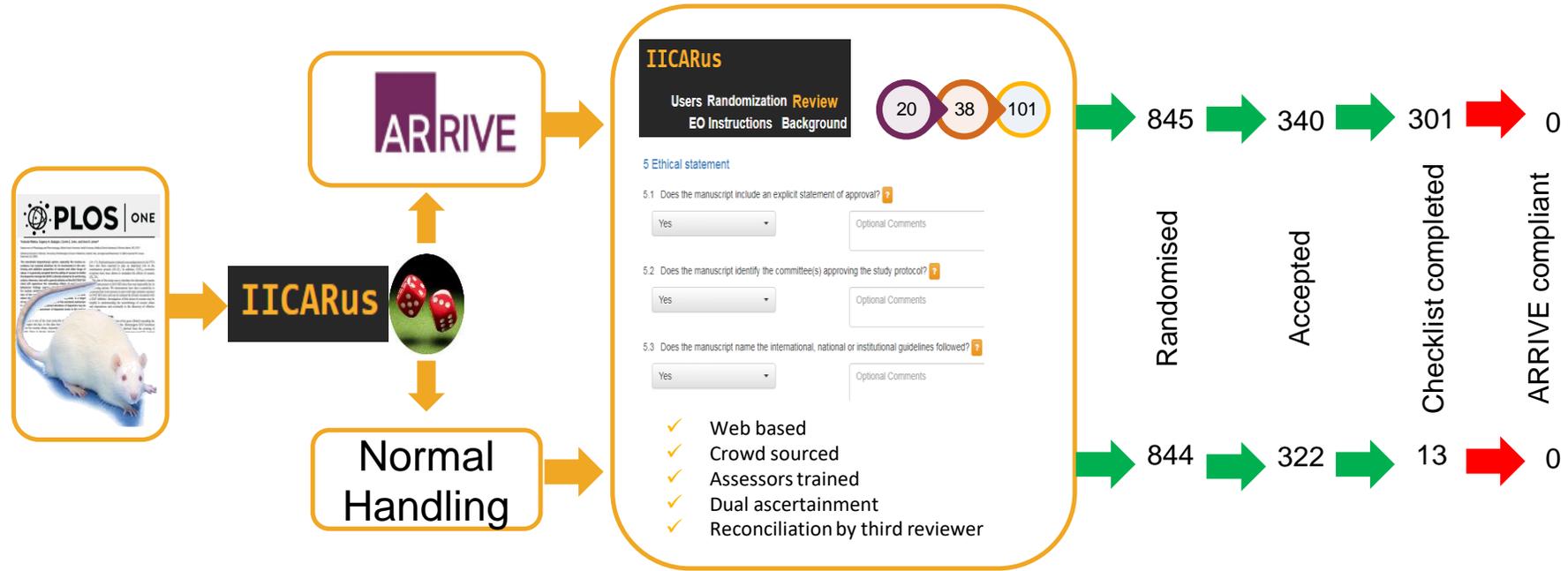


# Change in performance

Item	95% CI for compliance				95% CI for change in compliance	
	NPG before	NPG after	Non-NPG before	Non-NPG after	NPG	Non-NPG
In vivo: full Landis	–	11.7 to 22.2	0.0 to 4.2	0.0 to 3.7	11.1 to 21.6	–1.6 to 1.5
In vitro: full Landis	–	1.5 to 7.1	–	0 to 4.2	0.7 to 5.9	–0.6 to 1.8
In vivo: randomisation	6.3 to 15.5	60.9 to 74.8	3.0 to 11.5	7.2 to 17.7	49.1 to 65.7	–1.3 to 12.3
In vivo: blinding	3.1 to 9.8	55.3 to 69.2	0.6 to 5.6	3.3 to 10.4	48.7 to 64.0	–0.2 to 8.6
In vivo: exclusions reported	9.7 to 19.3	24.5 to 37.6	6.1 to 15.3	10.1 to 20.0	8.6 to 24.8	–2.3 to 11.3
In vivo: sample size calculation	1.7 to 7.3	57.1 to 70.9	0.0 to 4.4	1.8 to 7.7	52.7 to 67.6	–0.3 to 7.0
In vitro: randomisation	–	12.9 to 24.4	0.1 to 5.5	–	12.3 to 24.3	–4.4 to 1.8
In vitro: blinding	2.2 to 9.2	17.2 to 29.6	0.7 to 6.9	2.0 to 8.5	11.2 to 25.5	–2.8 to 6.4
In vitro: exclusions reported	4.8 to 13.6	11.3 to 22.0	2.5 to 10.6	4.6 to 12.9	0.1 to 14.6	–3.6 to 8.2
In vitro: sample size calculation	2.2 to 9.2	27.8 to 41.8	–	2.0 to 8.5	22.0 to 37.6	0.6 to 8.4



# RCT of an Intervention to Improve Compliance with the ARRIVE guidelines (IICARus; PI Sena)



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



# IICARus and NPQIP



- Telling scientists what they must do does not work (who knew?)
- Agreement between assessors often not much better than chance
  - Assessors are stupid?
  - Guideline items are poorly expressed?
  - Concepts are poorly understood?
- There is no magic bullet, improvement requires hard graft



AT THE  
NATIONAL  
ACADEMIES

## The MDAR (Materials Design Analysis Reporting) Framework for transparent reporting in the life sciences

Malcolm Macleod<sup>a,1</sup>, Andrew M. Collings<sup>b</sup>, Chris Graf<sup>c</sup>, Veronique Kiermer<sup>d</sup>, David Mellor<sup>a,1</sup>, Sowmya Swaminathan<sup>e</sup>, Deborah Sweet<sup>g</sup>, and Valda Vinson<sup>h</sup>



## PLOS BIOLOGY

PERSPECTIVE

### The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research

Nathalie Percie du Sert<sup>1\*</sup>, Viki Hurst<sup>1</sup>, Amrita Ahluwalia<sup>2,3</sup>, Sabina Alam<sup>4</sup>, Marc T. Avey<sup>5</sup>, Monya Baker<sup>6</sup>, William J. Browne<sup>7</sup>, Alejandra Clark<sup>8</sup>, Innes C. Cuthill<sup>9</sup>, Ulrich Dirnagl<sup>10</sup>, Michael Emerson<sup>11</sup>, Paul Garner<sup>12</sup>, Stephen T. Holgate<sup>13</sup>, David W. Howells<sup>14</sup>, Natasha A. Karp<sup>15</sup>, Stanley E. Lazic<sup>16</sup>, Katie Lidster<sup>1</sup>, Catriona J. MacCallum<sup>17</sup>, Malcolm Macleod<sup>18</sup>, Esther J. Pearl<sup>1</sup>, Ole H. Petersen<sup>19</sup>, Frances Rawle<sup>20</sup>, Penny Reynolds<sup>21</sup>, Kieron Rooney<sup>22</sup>, Emily S. Sena<sup>18</sup>, Shai D. Silberberg<sup>23</sup>, Thomas Steckler<sup>24</sup>, Hanno Würbel<sup>25</sup>



# An example from Health Economics



*Econometrica*, Vol. 72, No. 1 (January, 2004), 159–217

## WORMS: IDENTIFYING IMPACTS ON EDUCATION AND HEALTH IN THE PRESENCE OF TREATMENT EXTERNALITIES

BY EDWARD MIGUEL AND MICHAEL KREMER<sup>1</sup>

Intestinal helminths—including hookworm, roundworm, whipworm, and schistosomiasis—infect more than one-quarter of the world’s population. Studies in which medical treatment is randomized at the individual level potentially doubly underestimate the benefits of treatment, missing externality benefits to the comparison group from reduced disease transmission, and therefore also underestimating benefits for the treatment group. We evaluate a Kenyan project in which school-based mass treatment with deworming drugs was randomly phased into schools, rather than to individuals, allowing estimation of overall program effects. The program reduced school absenteeism in treatment schools by one-quarter, and was far cheaper than alternative ways of boosting school participation. Deworming substantially improved health and school participation among untreated children in both treatment schools and neighboring schools, and these externalities are large enough to justify fully subsidizing treatment. Yet we do not find evidence that deworming improved academic test scores.



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## Global development

This article is more than 6 years old

# New research debunks merits of global deworming programmes

### Re-analysis of existing studies finds that deworming schemes may not improve educational attainment as previously claimed

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About this content

**Sarah Boseley** Health editor

Thu 23 Jul 2015 00.19 BST



▲ Researchers now claim that an influential study in Kenya that suggested school attendance and results improved as a result of deworming programmes was misleading. Photograph: Sun Ruibo/Xinhua Press/Corbis

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*International Journal of Epidemiology*, 2015, 1572–1580  
doi: 10.1093/ije/dyv127  
Advance Access Publication Date: 22 July 2015  
Original article



*International Journal of Epidemiology*, 2015, 1581–1592  
doi: 10.1093/ije/dyv128  
Advance Access Publication Date: 22 July 2015  
Original article



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Deworming programmes, health and educational impacts

## **Re-analysis of health and educational impacts of a school-based deworming programme in western Kenya: a pure replication**

Alexander M Aiken,<sup>1\*</sup> Calum Davey,<sup>1</sup> James R Hargreaves<sup>1</sup> and Richard J Hayes<sup>2</sup>

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Deworming Programmes, Health and Educational Impacts

## **Re-analysis of health and educational impacts of a school-based deworming programme in western Kenya: a statistical replication of a cluster quasi-randomized stepped-wedge trial**

Calum Davey,<sup>1</sup> Alexander M Aiken,<sup>1\*</sup> Richard J Hayes<sup>2</sup> and James R Hargreaves<sup>1</sup>



Let us be clear: we have not reviewed the evidence base on the effects of school-based deworming and make no policy recommendations in this area. We did not set out to disprove the findings of the original study: our analysis and inference have been guided only by our experience in cluster-randomized trials. We have great admiration for the original authors, whom we have not set out to denigrate (unhelpful attempts to characterize these exchanges as ‘worm wars’, notwithstanding<sup>4</sup>). Readers would do well to consider how their own work would stand up to the level of scrutiny to which we have subjected M&K, who have been open with us throughout.



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# Replication Redux: The Reproducibility Crisis and the Case of Deworming

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Owen Ozier 

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## Replication Redux: The Reproducibility Crisis and the Case of Deworming

Owen Ozier 



- Original trial (starting in 1998) was cluster randomised at level of the school
- No trial registry or statistical analysis plan (ISRCTN began in 2000)
- Pure (verification) replication
  - Lots of data errors/ missingness
  - Coding error leading to under ascertainment of neighbouring schools 3-6km distant

	Original		Replication	
	Estimate	SE	Estimate	SE
Direct	5.4%	2.3%	5.8%	1.4%
0-3km	2.9%	1.4%	2.3%	1.3%
3-6km	-1%	1%	-4.0%	2.4%
Overall	7.5%	2.7%	3.9%	3.2%

*The World Bank Research Observer*, Volume 36, Issue 1, February 2021, Pages 101–130, <https://doi.org/10.1093/wbro/lkaa005>

**UKRN:** aiming to ensure the UK retains its place as a centre for world-leading research



## Replication Redux: The Reproducibility Crisis and the Case of Deworming

Owen Ozier 



- Original trial (starting in 1998) was cluster randomised at level of the school
- No trial registry or statistical analysis plan (ISRCTN began in 2000)
- Robustness reanalysis replication
  - Different statistical approach
  - Analytical choices
    1. Whether or not to control for additional covariates
    2. Restrict analysis to eligible pupils (girls > 13 did not receive) or take all pupils
    3. Timing – calendar year v when treatment actually given
    4. Weighting – by pupil number, or by attendance observation
    5. Year by year analysis or Full data set
- This gives 32 ( $2^5$ ) approaches to analysis
- All of [1] through [4] confirm original findings – but “in year stratified cluster summary analysis .. shows no clear evidence for improved school attendance ... when both years were combined, there was strong evidence of an effect on attendance”

*The World Bank Research Observer*, Volume 36, Issue 1, February 2021, Pages 101–130, <https://doi.org/10.1093/wbro/lkaa005>



# Lessons



- Replication studies are important
- If the study had been registered, we would have more confidence
- If the statistical analysis plan had been published, we would have more confidence
- If the data were shared earlier, they might have caught the errors earlier
- If the code were to be published, they might have found the error earlier



# UK Reproducibility Network (@UKRepro)

Co-founded 12/9/2018 by Chris Chambers, Marcus Munafò, Laura Fortunato & Malcom Macleod

Peer-led, academic consortium aiming to

- Understand factors that contribute to poor research reproducibility
- Provide training and disseminate best practice
- Support and test interventions to improve reproducibility
- Ensure coordination with stakeholders

- Open Research Working Groups at UK universities: <https://osf.io/vgt3x/>
- ReproducibiliTea
- Open Research and Reproducibility Short Course
- Hiring Policies Certification Scheme: <https://osf.io/qb7zm/>
- Laboratory Efficiency Assessment Framework (LEAF)
- Consortium-Based Student Projects
- Primers on Open Research Practices
- Accountable replication policies (with funders, institutions, publishers, policy makers)

UK Research and Innovation



Innovate UK



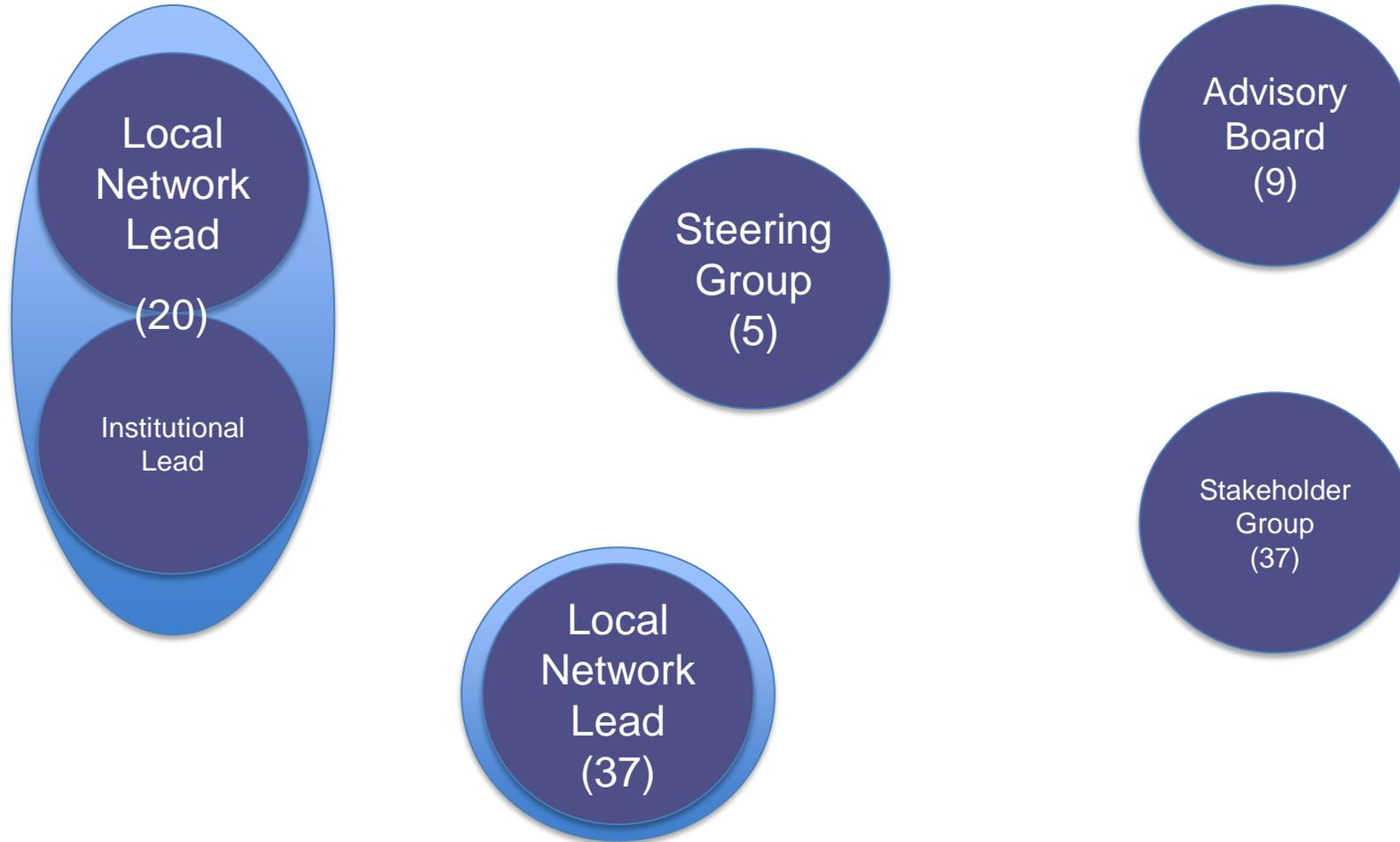
EMBL-EBI



UKRN: aiming to ensure the UK retains its place as a centre for world-leading research



# Organisation





### Terms of Reference

Our Terms of Reference outline how we work with individuals, institutions and external stakeholders.

[More](#)



### Code of Conduct

Our Code of Conduct outlines our expectations to provide a welcoming and supportive environment for all people.

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### Common Statements

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### Accountable Replication Policies

Journals' commitment to publish valid replications of their previously published studies.



### Editors4BetterResearch

Journal editors' public commitment to support open and reproducible research.



### Free Our Knowledge (FOK)

A platform for researchers to organise collective action in the pursuit of academic reform



### Registered Reports

Article format for study protocol peer review and pre-acceptance, regardless of eventual results.



### ReproducibiliTea

Early-career researcher community promoting open and reproducible research.



### RIOT Science Club

Providing training in Reproducible, Interpretable, Open and Transparent research.



### FORRT

Pedagogical support for open and reproducible research practices in higher education.



### Hiring Policies Certification Scheme

Academic employers' declaration to recruit based on record of open research practices.



### Laboratory Efficiency Assessment Framework (LEAF)

LEAF programme is a standard in environmentally sustainable laboratory practices.



### Universal Funders Policy

Policy to mandate open source records with published research as condition for funding.



### Octopus

Octopus is a new platform to replace journals and papers as the primary research record.



### Open Research Calendar

A community tool to gather all Open Research events in one place.



### Open Research Working Groups

Action-oriented teams reforming research for transparency, accessibility and reproducibility.



# RESEARCH IMPROVEMENT STRATEGIES

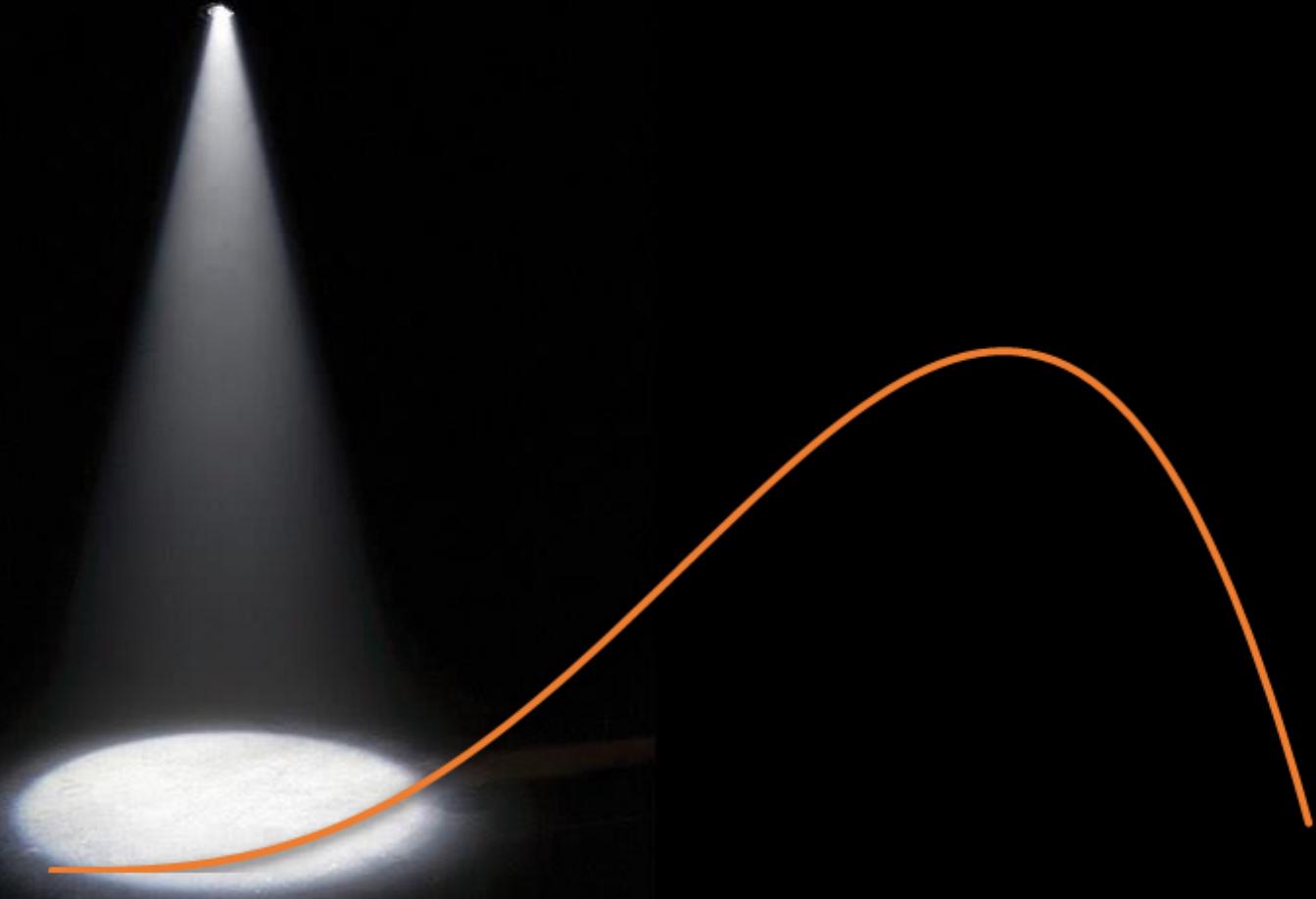
**UKRN:** aiming to ensure the UK retains its place as a centre for world-leading research

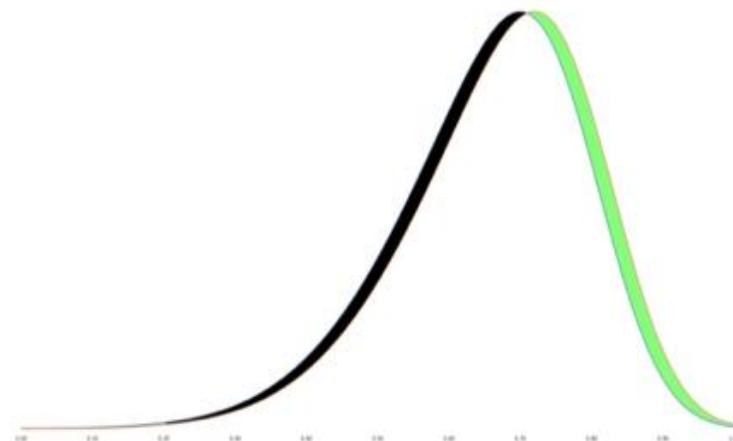
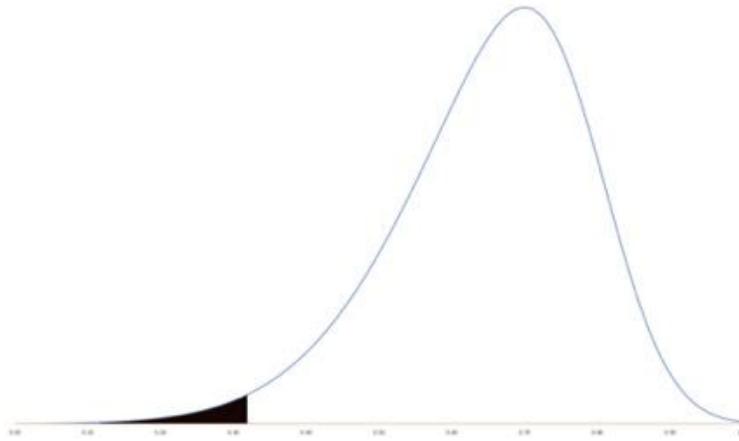
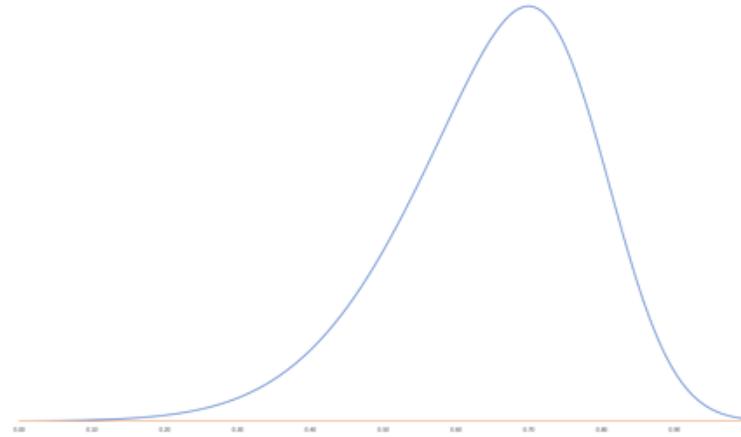


# Researchers are different ...



Macleod and Mohan  
<https://doi.org/10.1093/ilar/ilz015>

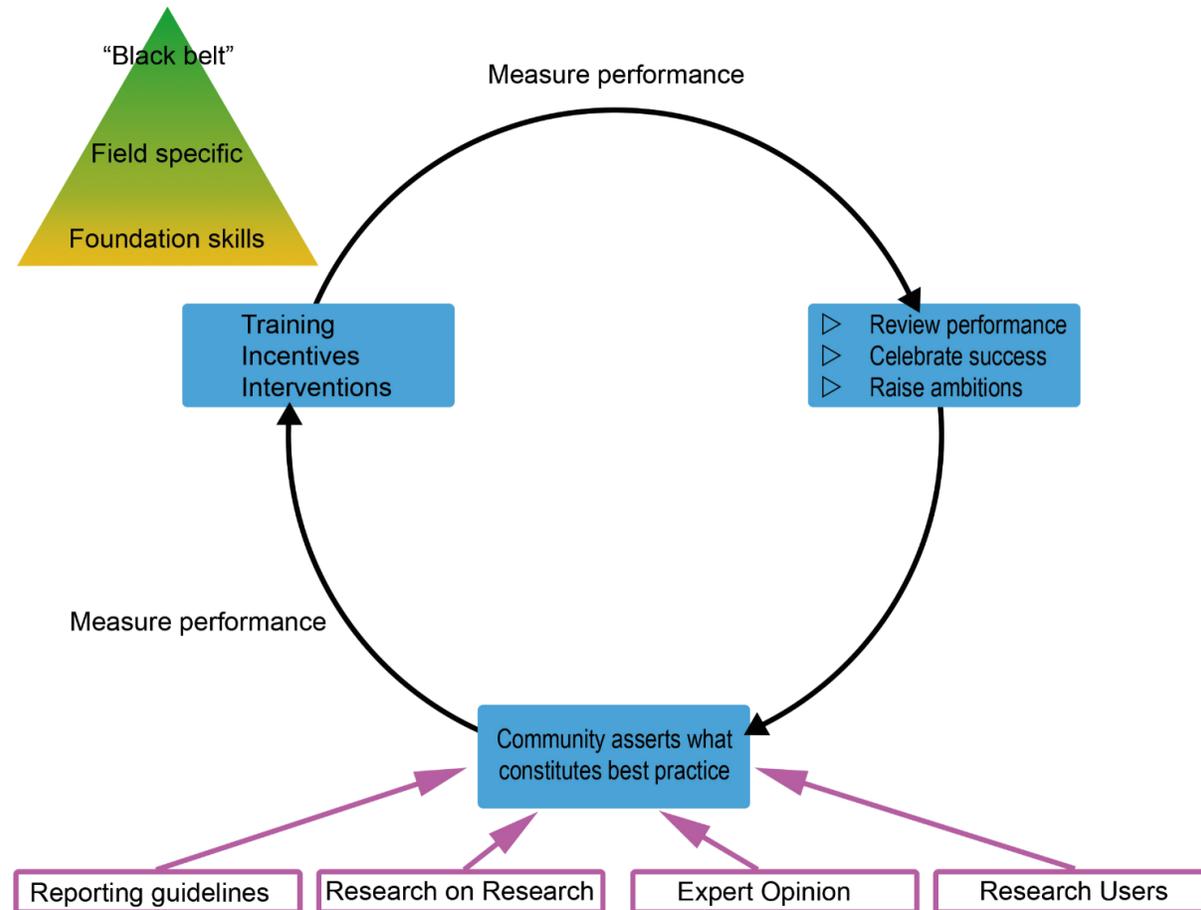




**UKRN:** aiming to ensure the UK retains its place as a centre for world-leading research



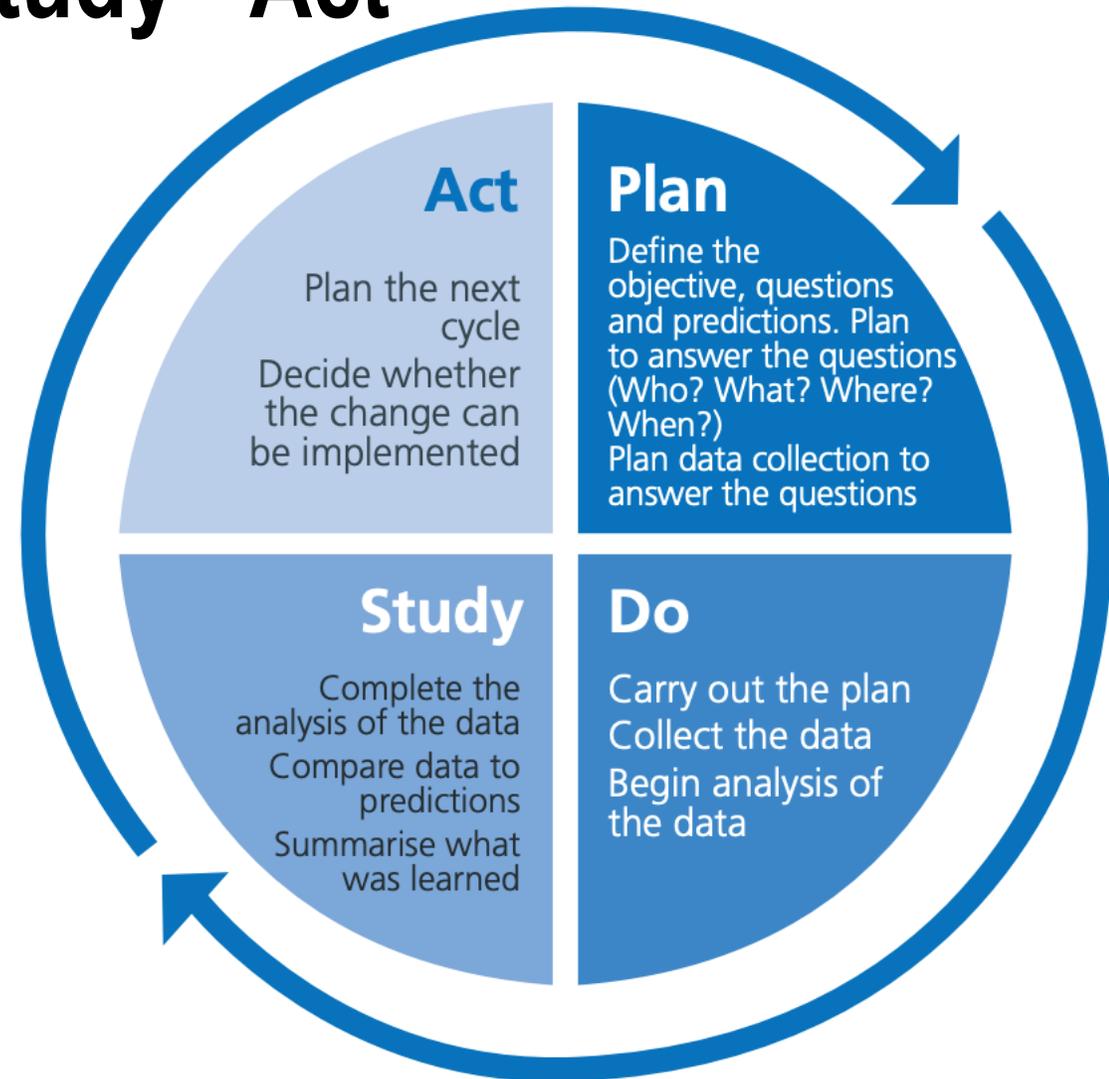
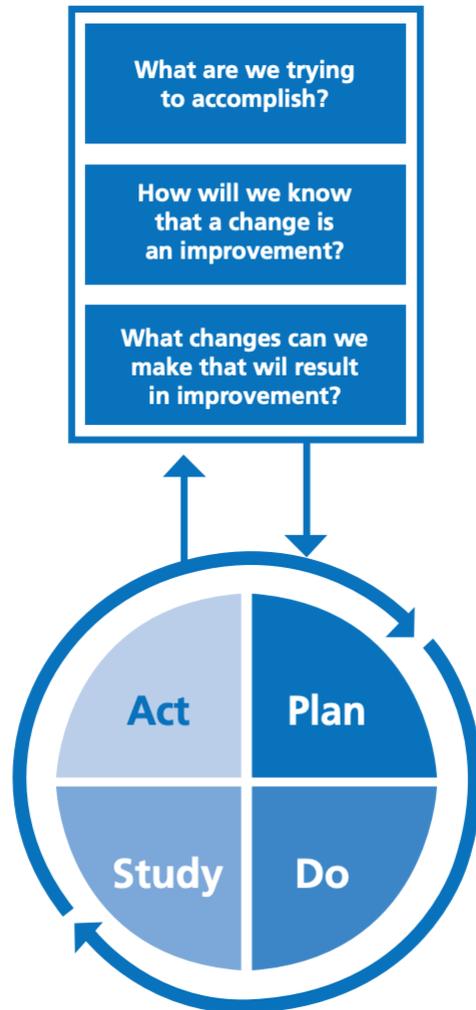
Research accountability	Research Improvement
Individual focused	Systems focused
Perfection myth	Fallibility recognized
Solo practitioners	Teamwork
(Local) peer review ignored	Local peer review valued
Shortcomings punished	Shortcomings seen as opportunities for learning



The UK Reproducibility Network Steering Group:  
Systematizing Effective Practice, Embedding It in Standard Practice  
Patterns <https://doi.org/10.1016/j.patter.2020.100151>

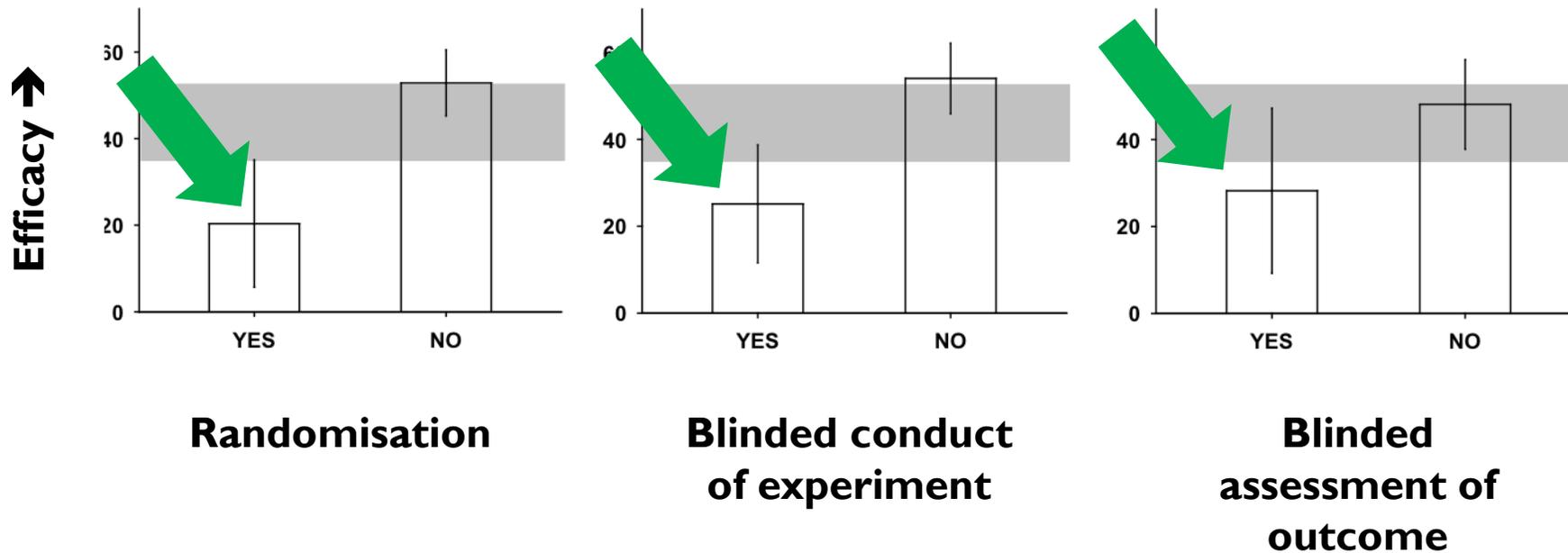


# Plan – Do – Study - Act



# Risk of bias in animal studies

- Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)



Macleod et al, 2008



# What to measure?



New Results THE PREPRINT SERVER FOR BIOLOGY

**Risk of Bias Assessment in Preclinical Literature using Natural Language Processing**

Qianying Wang, Jing Liao, Mirella Lapata,  Malcolm Macleod

doi: <https://doi.org/10.1101/2021.06.04.447092>

Qianying Wang  
John Climax UKRN /  
Chinese Scholarship  
Council PhD student



Table 4: Performance of the best NLP model and regular expression approach for each risk of bias item on the test set. A regular expression approach has not been developed for animal exclusions.

RoB item	Model/Approach	F1	Recall	Precision
Random allocation	RNN+Attn	<b>82.0</b>	86.8	79.5
	Regular expression	68.8	96.4	53.6
Blinded assessment of outcome	RNN+Attn	<b>81.6</b>	87.8	78.2
	Regular expression	68.3	59.8	79.6
Conflict of interests	CNN	<b>82.7</b>	80.6	86.2
	Regular expression	48.7	33.8	87.1
Compliance with animal welfare regulation	BERT-SE	<b>91.5</b>	91.4	92.0
	Regular expression	55.2	40.9	85.2
Animal exclusions	CNN	46.6	56.5	45.0
	Regular expression	--	--	--



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Protocol for an analysis of in vivo reporting standards by journal, institution and funder

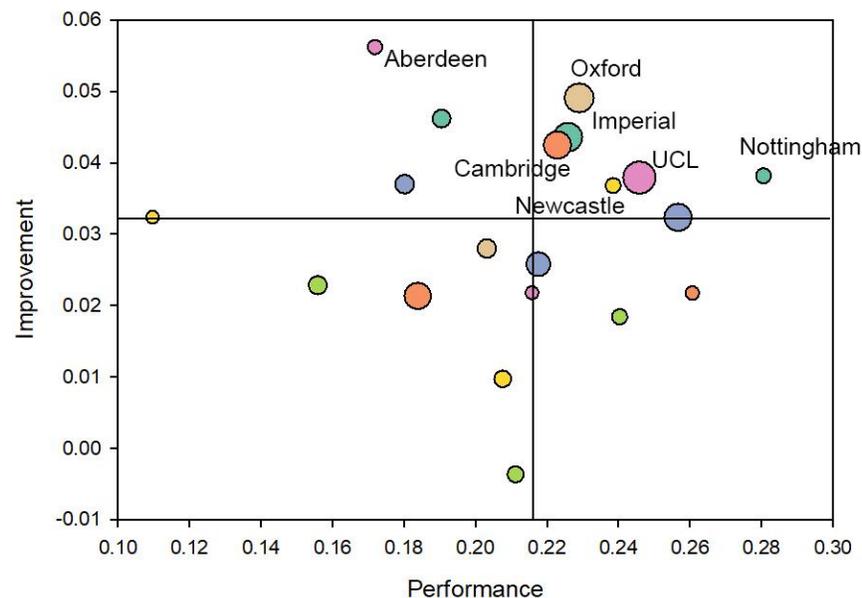
AUTHORS  
Qianying Wang, Kaitlyn Hair, Malcolm Macleod, Gillian Currie, Zsanett Bahor, Emily Sena, Jing Liao



# By UK institution, 2011-2018



Average reporting of randomisation and of blinding:  
 $(p(R)+p(B))/2$



	Blinding	Randomisation
1	UCL	Southampton
2	Edinburgh	Nottingham
3	Nottingham	Leicester
4	Sheffield	Newcastle
5	Oxford	Queen Mary London

	ΔBlinding	ΔRandomisation
1	Dundee	Southampton
2	Newcastle	Nottingham
3	Oxford	Leicester
4	Imperial College	Newcastle
5	Cardiff	Queen Mary London



This course will provide both **basic and enhanced research design training** based on the level to which you complete the course.

The course consists of the following modules:

- **Welcome Module**
- **[1] Study Design & Data Analysis**
- **[2] Experimental Procedure**
- **[3] Pre-registration & Reporting**

Modules 1-3 consist of a **CORE** component and an **EXTENDED** component. To successfully complete the course, **CORE components are mandatory** and **EXTENDED components are optional**.

There will be quiz questions to **test your knowledge** throughout the course.

We will signpost **further reading** materials on most topics.

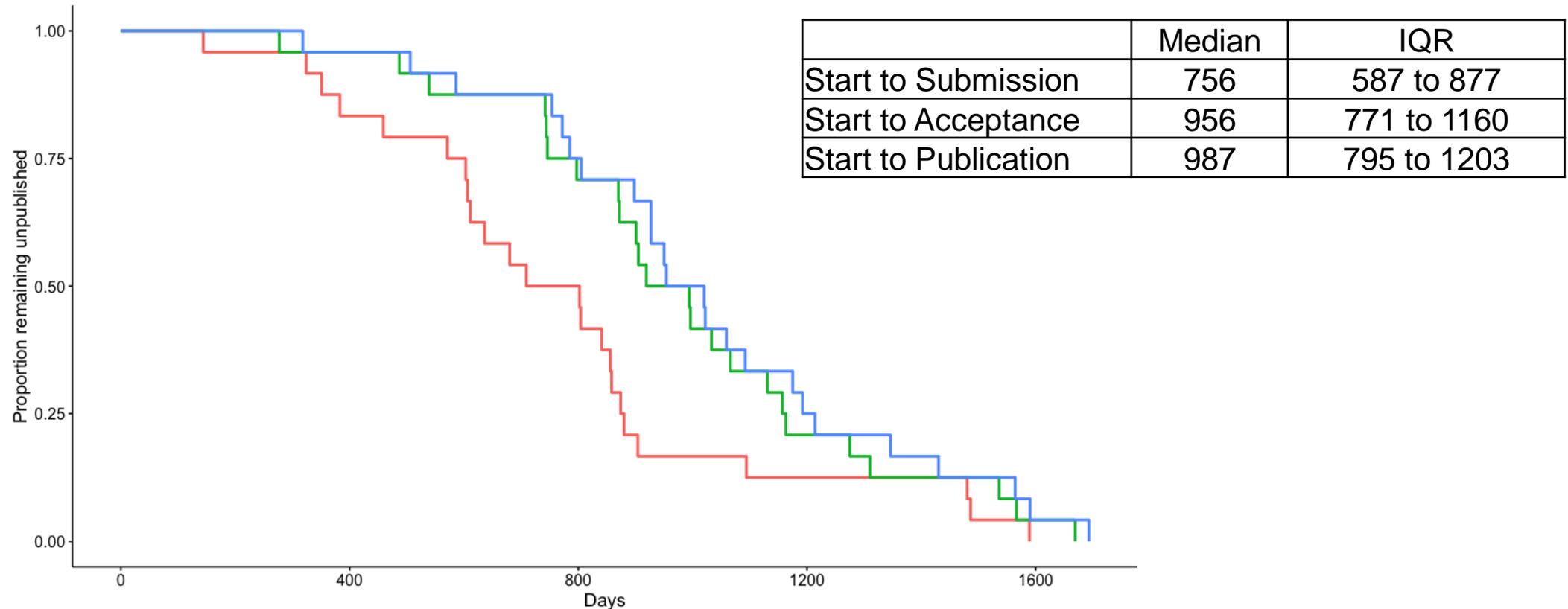
Curriculum derived from Vollert et al. [doi.org/ 10.1136/bmjos-2019-100046](https://doi.org/10.1136/bmjos-2019-100046)



# PREMISE: Delays to publication cause delay to benefit - and so reduce Harm-Benefit position

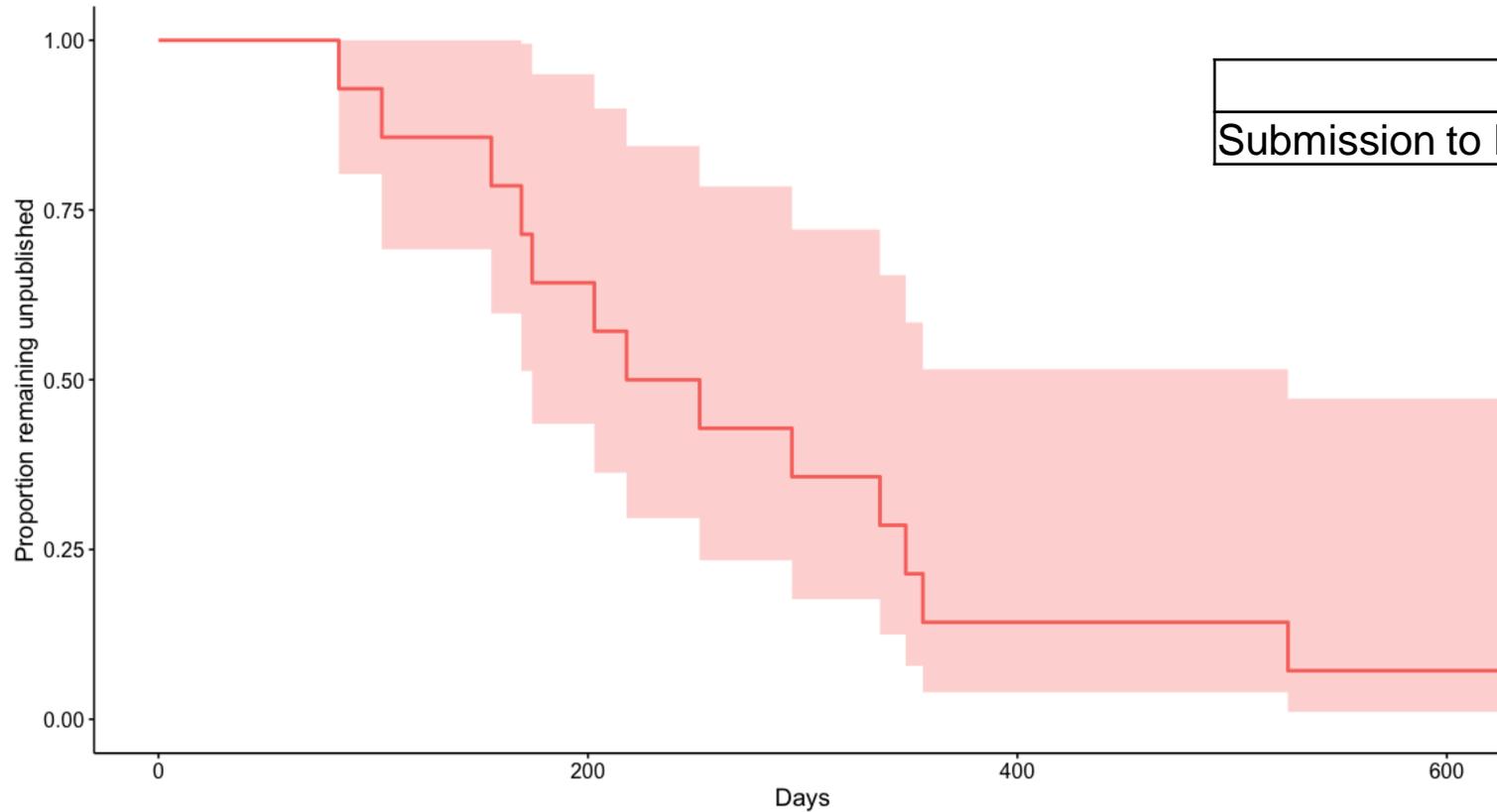


Sample: UoE Experiment Request Form submissions 2014





# Possible benefit in encouraging use of preprint servers



	Median	IQR
Submission to Publication	235	169 to 348

~25% of research cycle

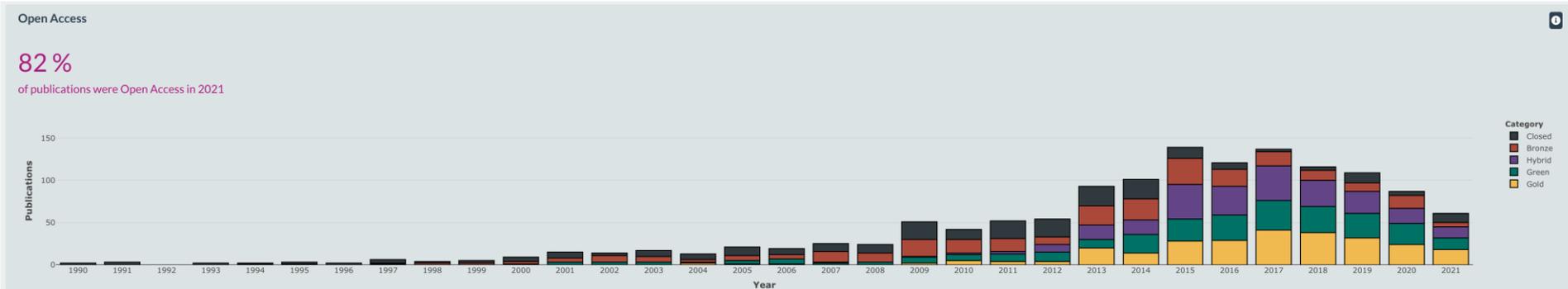


# PREMISE: Open Publication is more useful

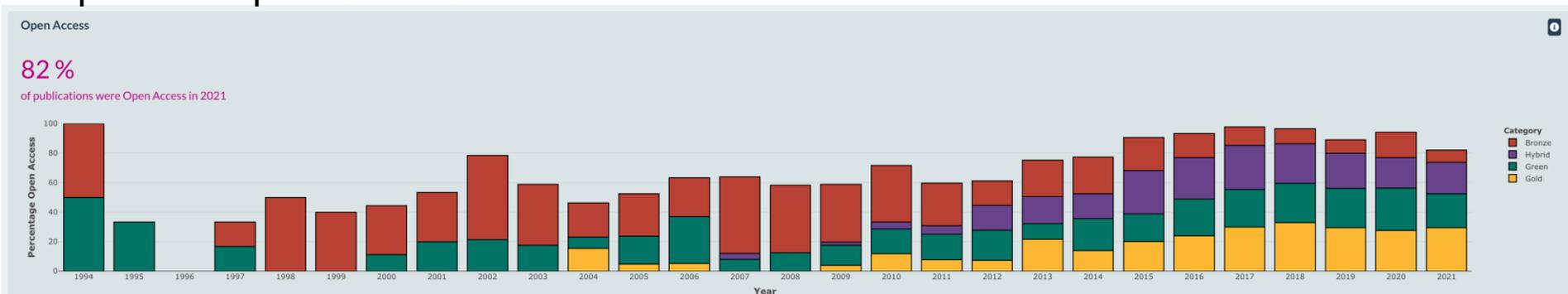
Centre for Clinical Brain Sciences Stroke Research Group  
1483 publications: Orcid API -> Unpaywall API  
Hat Tip: Nico Riedel, Charite



## Number of publications



## Proportion of publications





# Thank you!



- [Ukrn-admin@bristol.ac.uk](mailto:Ukrn-admin@bristol.ac.uk)
- malcolm.macleod@ed.ac.uk