HELMHOLTZ Open Science

BIH Berlin Institute of Health @Charité

60TH ONLINE SEMINAR

Preregistration: The Panacea for Trustworthy and Useful Science?

Ulrich Dirnagl @dirnagl

WWW, September 21, 2021

Preregistration: The panacea for trustworthy and useful science?

(Helmholtz Open Science Online-Seminar 21.9.2021)

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(Pre)registration research studies

In pre-registration, researchers describe their hypotheses, methods, and analyses before a piece of research is conducted, in a way that can be externally verified. Registration prioritizes theory, analysis and methods over results.

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[Houston] We have a problem...

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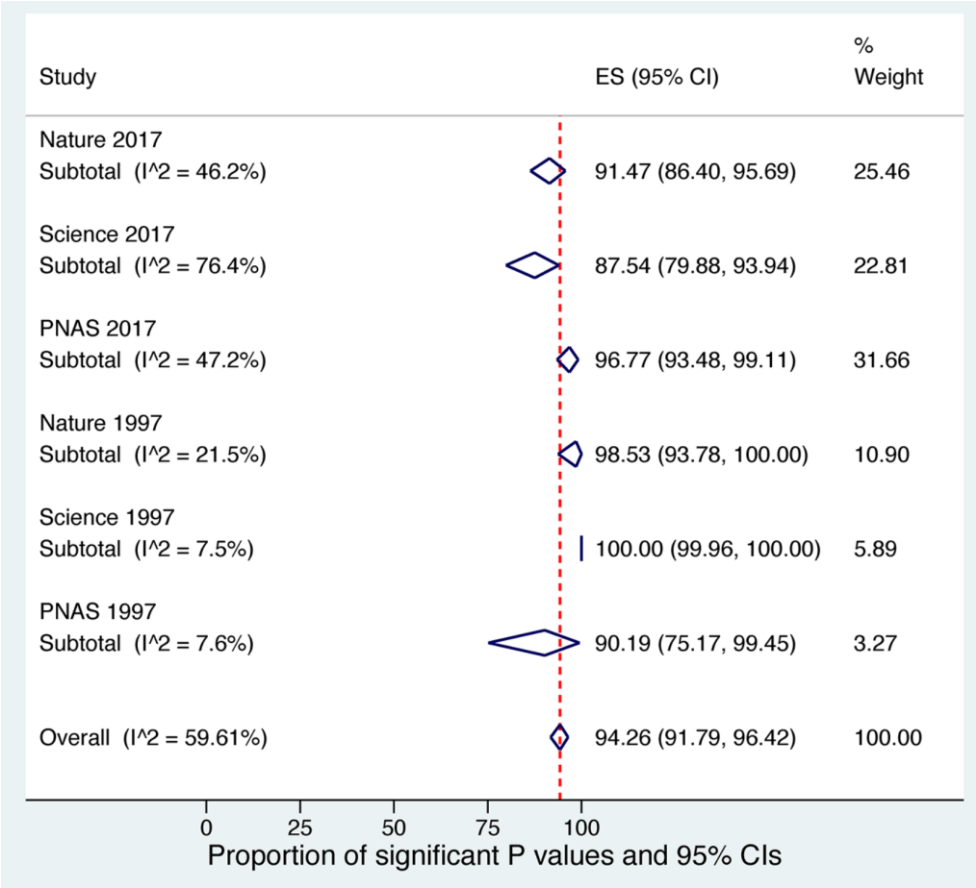
Inflation bias: *Almost every statistical test is significant (p≤0.05)*



Citation: Cristea IA, Ioannidis JPA (2018) *P* values in display items are ubiquitous and almost invariably significant: A survey of top science journals. PLoS ONE 13(5): e0197440. https://doi.org/10.1371/journal.pone.0197440

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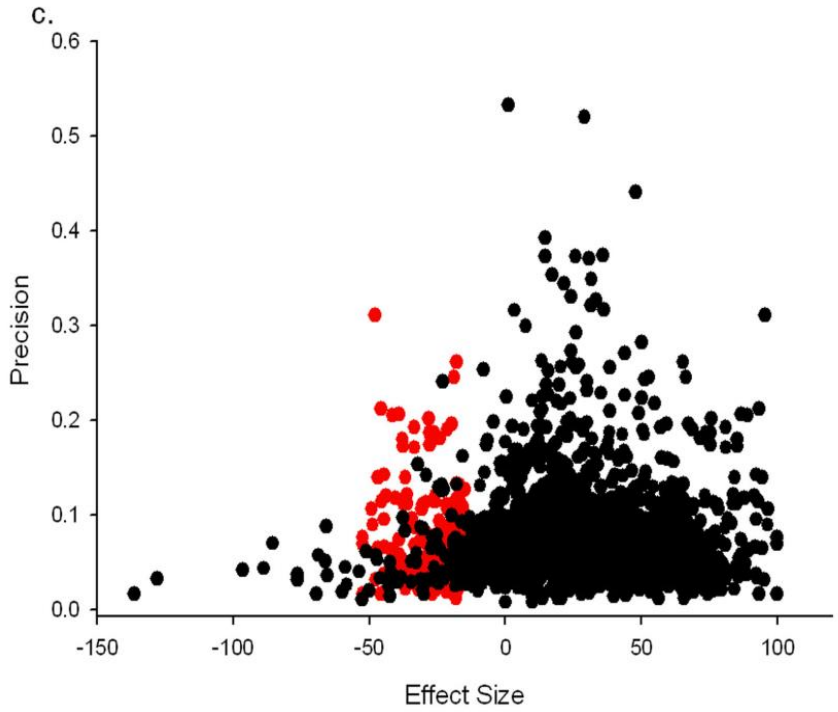
Problem: Publication bias

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]*



"Only ten publications (2%) [of 525] reported no significant effects on infarct volume and only six (1.2%) did not report at least one significant finding."

PLoS Biol. 2010; 8 e1000344

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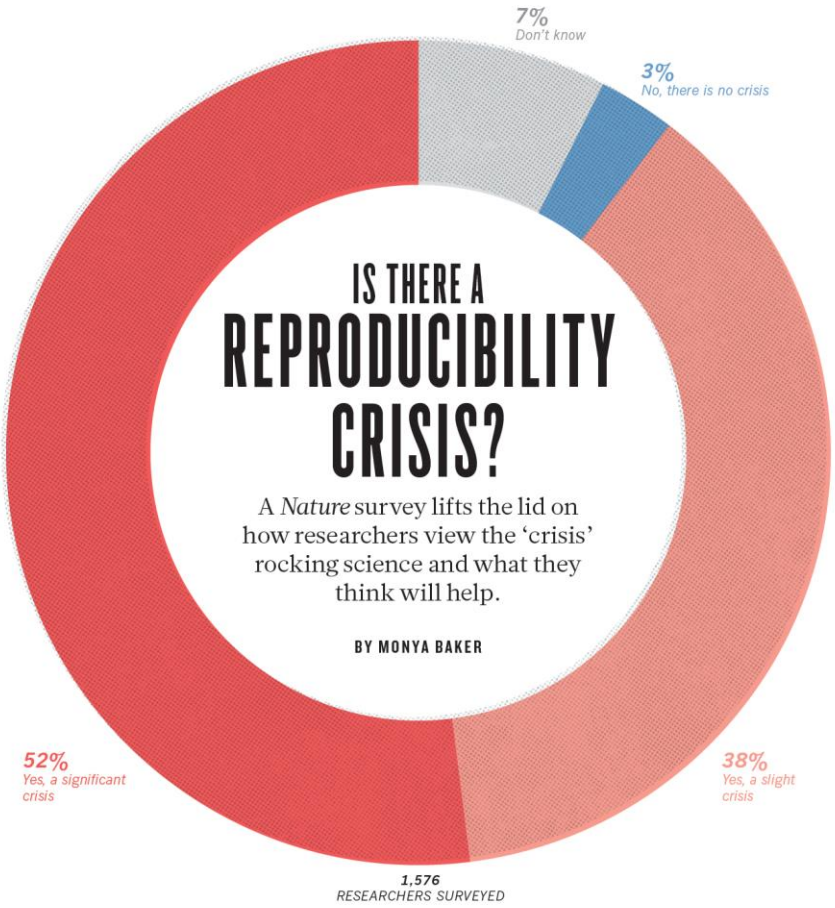
90 % of researchers surveyed by Nature think they are experiencing a ‚reproducibility crisis‘



THE CAUSE

The survey asked scientists what led to problems in reproducibility. More than 60% of respondents said that each of two factors — pressure to publish and selective reporting — always or often contributed. More than half pointed to insufficient replication in the lab, poor oversight or low statistical power.

WHAT CAN BE DONE?

Respondents were asked to rate 11 different approaches to improving reproducibility in science, and all got ringing endorsements. Nearly 90% — more than 1,000 people — ticked "More robust experimental design" "better statistics" and "better mentorship".

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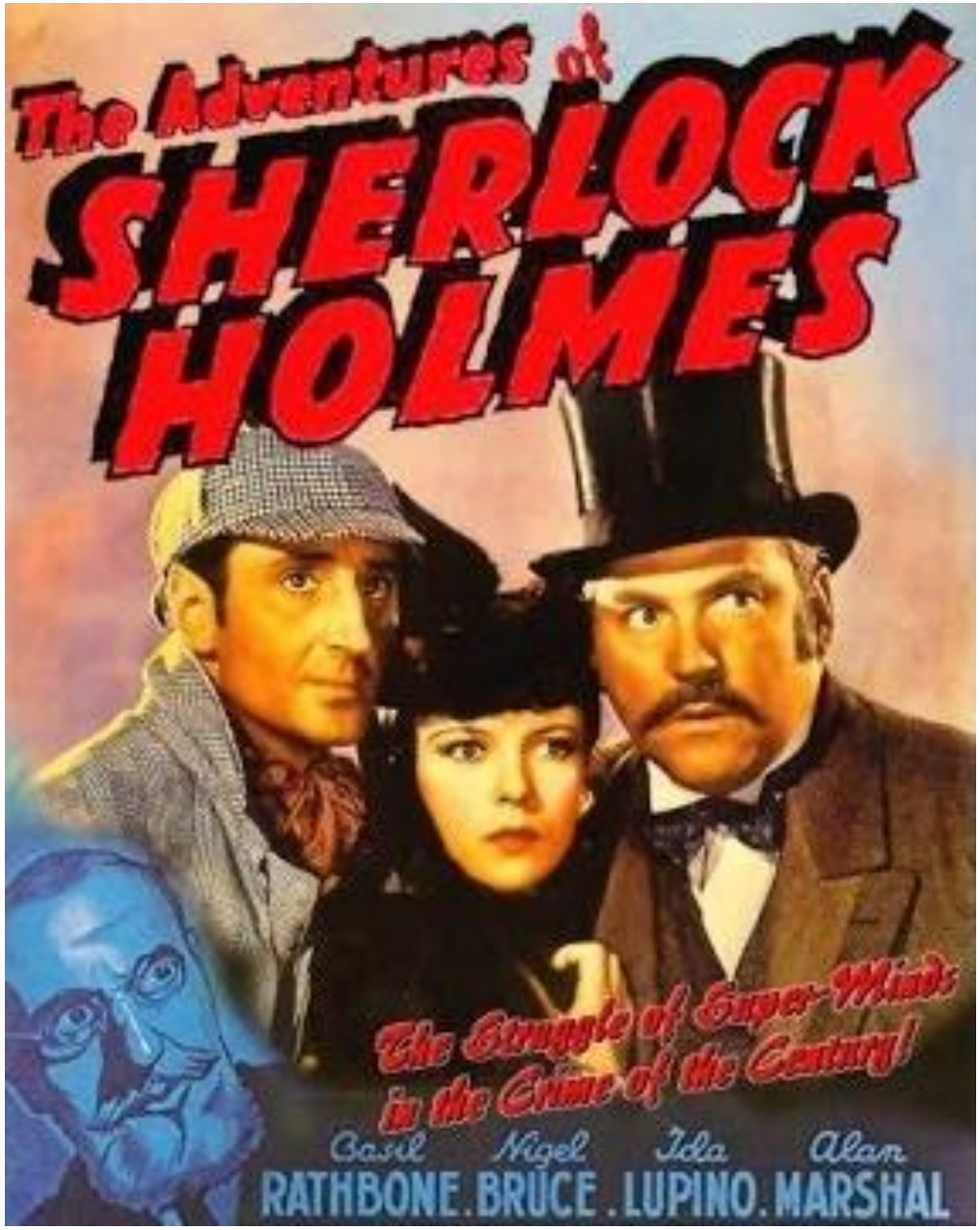

Inflation bias: p-Hacking

Researchers try out several statistical analyses and/or data eligibility specifications and then selectively report those that produce significant results.

E.g. by

- recording many response variables and deciding which to re-port post analysis
- conducting analyses midway through experiments to decide whether to continue collecting data
- deciding whether to include or drop outliers postanalyses
- ex-cluding, combining, or splitting treatment groups postanalysis
- including or excluding covariates postanalysis
- stopping data exploration if an analysis yields a significant p-value
- Perfoming multiple statistical tests without prespecification and reporting only the significant one(s)

"**If you torture the data long enough, it will confess to anything** "
Darrell Huff *How to Lie With Statistics* (1954).

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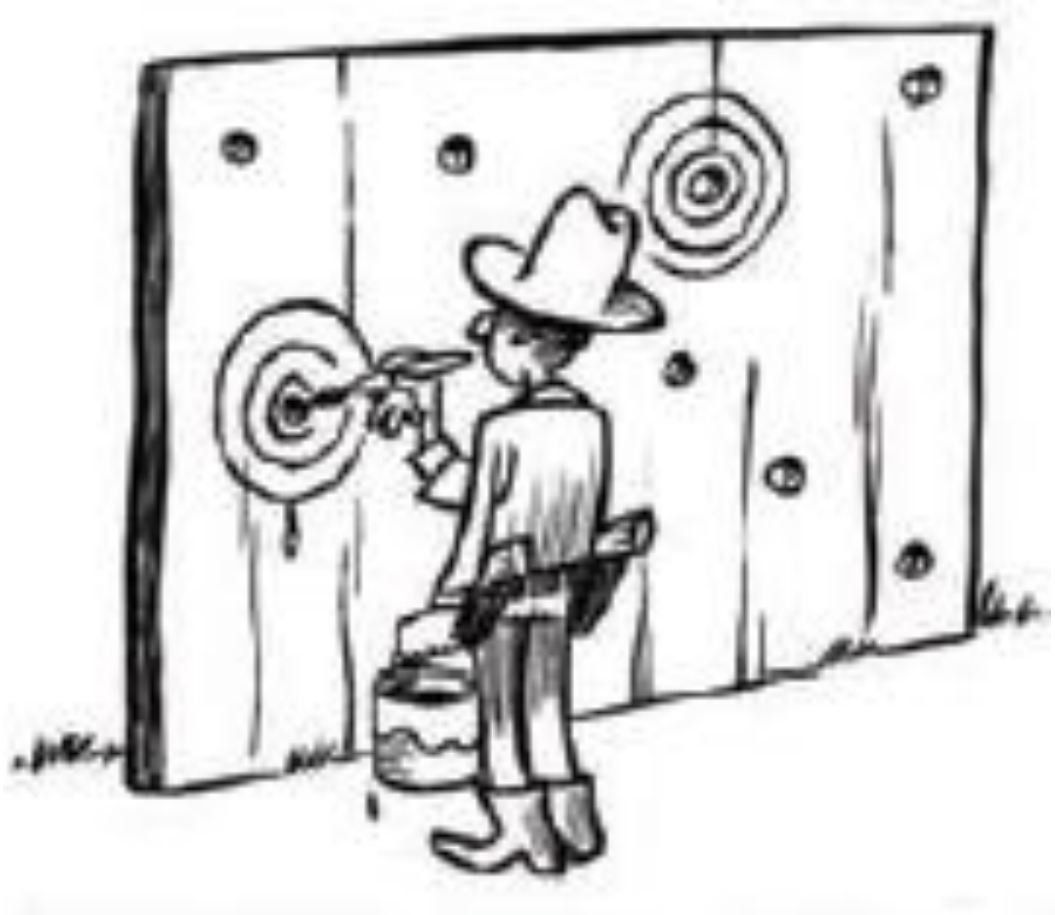
Inflation bias: *Hypothesizing after the results are known (HARKING)*



An Agenda for Purely Confirmatory Research

Eric-Jan Wagenmakers, Ruud Wetzels, Denny Borsboom, Han L. J. van der Maas, and Rogier A. Kievit
University of Amsterdam, The Netherlands

Perspectives on Psychological Science
7(6) 632–638

DOI: 10.1177/1745691612463078

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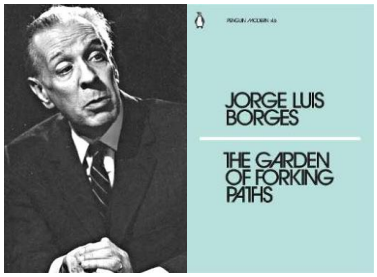
A hiking trip through the garden of forking paths…

… i.e. an exploratory biomedical research project



Andrew Gelman† and Eric Loken‡

http://www.stat.columbia.edu/~gelman/research/unpublished/p_hacking.pdf

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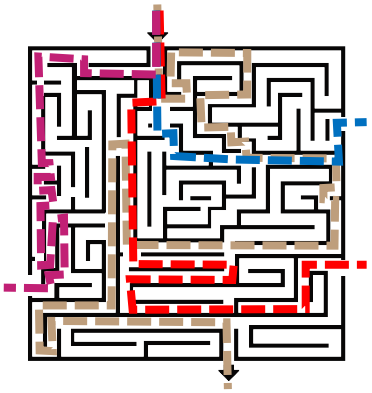

false pos

alt KO

alt paper

alt lit

False negative

alt antibody

alt strain

alt paper

alt interpretation

false pos

alt paper

alt pilot

confounder

alt paper

cell culture

alt primer

alt lit

alt paper

alt paper

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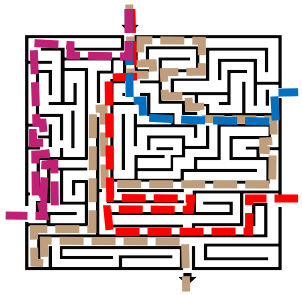
Undisclosed flexiblity in data collection and analysis – researcher's degree of freedom



+

Given the small samples and sensible but unexplored experimental approaches, other data patterns could easily occur by chance, which would naturally lead to different data analyses and inferences supporting alternative research hypotheses

=

'What we are saying is that the evidence in these research papers is not as strong as stated' (Gelman and Loken)

http://www.stat.columbia.edu/~gelman/research/unpublished/p_hacking.pdf

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WONDERFUL!
WONDERFUL!
WONDERFUL!
HOW COULD IT BE ANYTHING ELSE!
LIBERTY FILMS INC.
Presents
Frank
CAPRA'S
"IT'S A WONDERFUL LIFE"
Starring
James
STEWART
and Donna
REED
Produced and Directed by
FRANK CAPRA
LIONEL BARRYMORE · THOMAS MITCHELL
HENRY TRAVERS · BEULAH BONDI · WARD BOND
FRANK FAYLEN · GLORIA GRAHAME

Preregistration of study protocols

- Limits unwarranted and/or undisclosed researcher‘s degrees of freedom‘
- Prevents ‚outcome switching‘
- Prevents HARKING
- Provides scooping protection
- Reduces publication bias
- Distinguishes between exploratory/discovery and knowldege claiming / confirmatory research
- …

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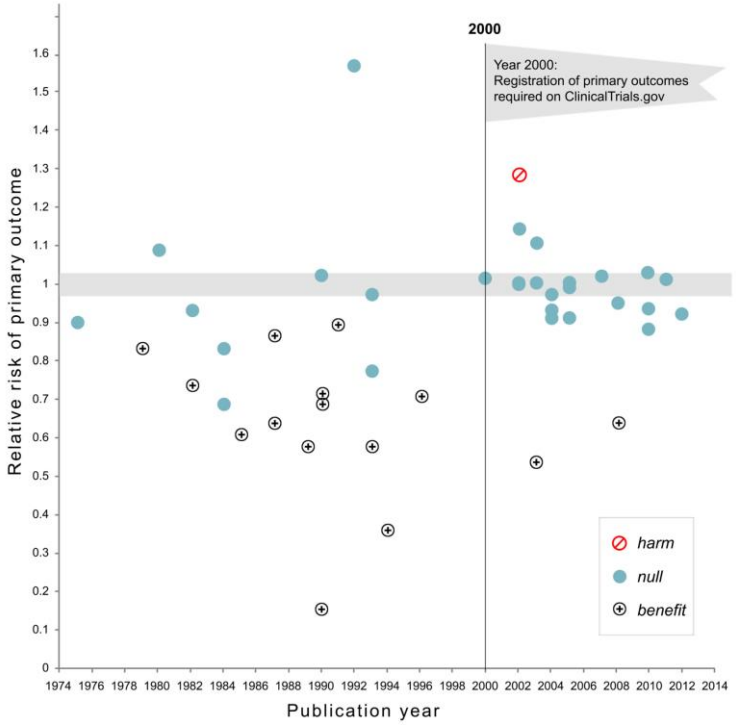
Preregistration of (interventional) clinical trials

Since the launch of the clinicaltrials.gov registry in 2000, which forced researchers to preregister their methods and outcome measures, the percentage of large heart-disease clinical trials reporting significant positive results plummeted from 57% to a mere 8%.



RESEARCH ARTICLE

Likelihood of Null Effects of Large NHLBI Clinical Trials Has Increased over Time

Robert M. Kaplan[1]*, Veronica L. Irvin[2]

PLOS ONE | DOI:10.1371/journal.pone.0132382

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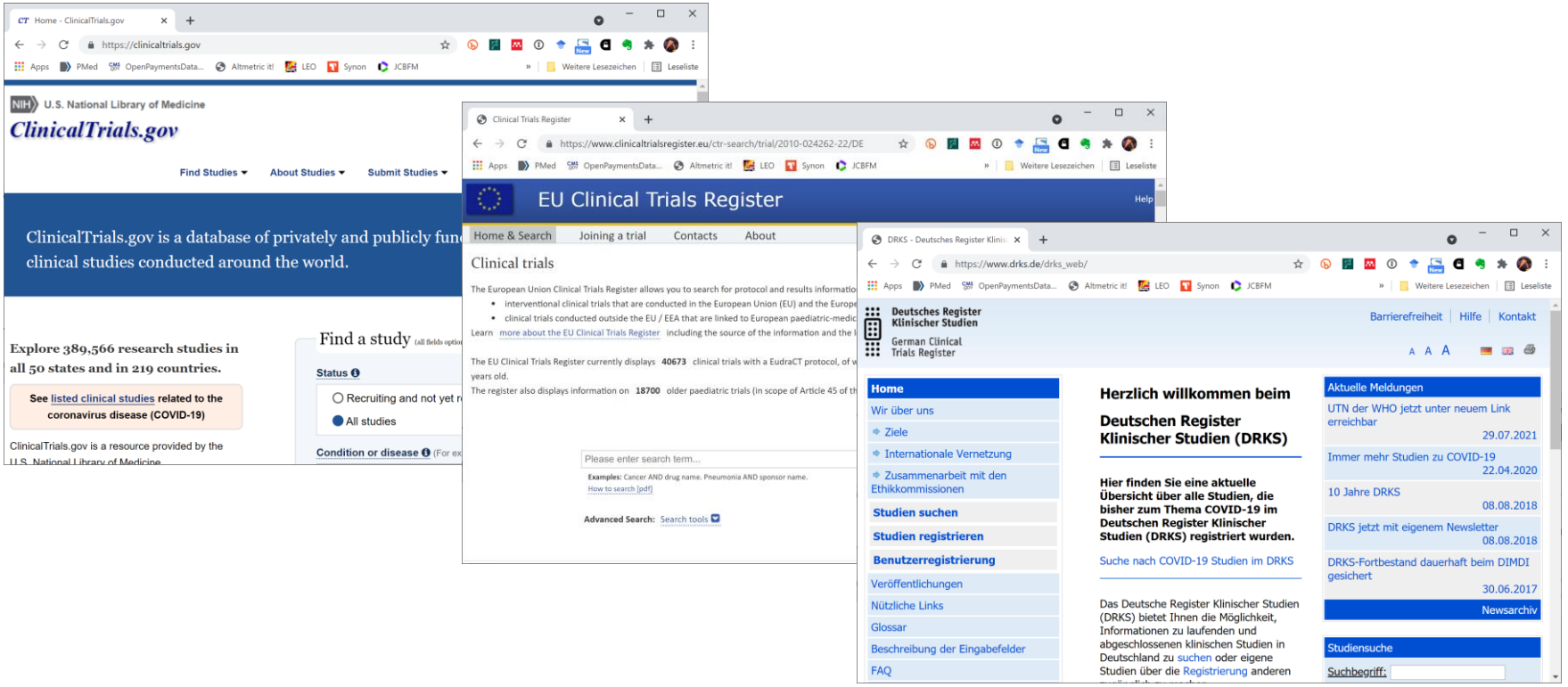
Clinical trial registers



Clinical trials need to be registered to be published in major journals (Consort)
Summary results need to be deposited within 12 month after study completion (WHO, EU)

https://clinicaltrials.gov/
https://www.clinicaltrialsregister.eu/
https://www.drks.de/

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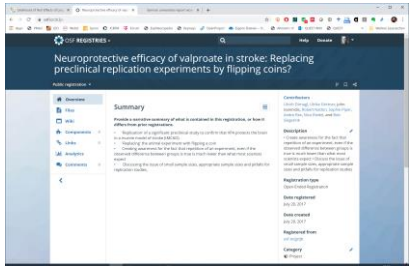
(Pre) Registration of non-clinical studies

All purpose registries
(**not** reviewed)

https://osf.io/

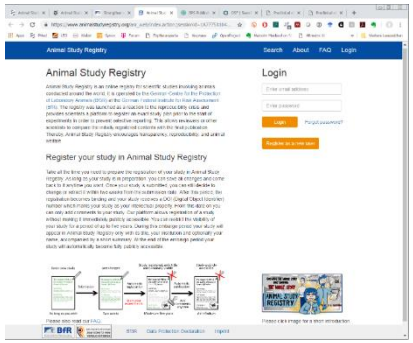
https://aspredicted.org/



Animal study registries (ASR)
(**not** reviewed)

German Centre for the Protection of Laboratory Animals
https://www.animalstudyregistry.org

Preclinicaltrials.eu https://preclinicaltrials.eu/



Timestamp servers / Blockchain
(**not** reviewed)

e.g. https://github.com/decred/dcrtimegui

Registered reports (Elife, PlosBiol, F1000Res etc.) (***reviewed!***)

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Registered reports

https://www.cos.io/rr

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Preregistration: Main stream?

https://www.theguardian.com/science/blog/2013/jun/05/trust-in-science-study-pre-registration

Preregistration: Science in chains?

Loss of exploration, creativity, flexibility which are the fundament of science.

Pre-registration would put science in chains

The pre-registration of study designs must be resisted, says Sophie Scott

'After all, even Newton sometimes employed dubious methodologies. His celebrated physical laws were supported by data, but history tends to overlook his equally enthusiastic pursuit of alchemy, which swam in a sea of null results. '

https://www.timeshighereducation.com/comment/opinion/pre-registration-would-put-science-in-chains/2005954.article

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Preregistration: Performative but not effective?

nature

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WORLD VIEW | 06 July 2021

Beware performative reproducibility

Well-meant changes to improve science could become empty gestures unless underlying values change.

Stuart Buck

https://www.nature.com/articles/d41586-021-01824-z

Goldacre *et al. Trials* (2019) 20:118
https://doi.org/10.1186/s13063-019-3173-2

Trials

RESEARCH Open Access

COMPare: a prospective cohort study correcting and monitoring 58 misreported trials in real time

Ben Goldacre[1*], Henry Drysdale[1], Aaron Dale[1], Ioan Milosevic[1], Eirion Slade[1], Philip Hartley[1], Cicely Marston[2], Anna Powell-Smith[1], Carl Heneghan[1] and Kamal R. Mahtani[1]

Abstract

Background: Discrepancies between pre-specified and reported outcomes are an important source of bias in trials. Despite legislation, guidelines and public commitments on correct reporting from journals, outcome misreporting continues to be prevalent. We aimed to document the extent of misreporting, establish whether it was possible to publish correction letters on all misreported trials as they were published, and monitor responses from editors and trialists to understand why outcome misreporting persists despite public commitments to address it.

Methods: We identified five high-impact journals endorsing Consolidated Standards of Reporting Trials (CONSORT) (*New England Journal of Medicine*, *The Lancet*, *Journal of the American Medical Association*, *British Medical Journal*, and *Annals of Internal Medicine*) and assessed all trials over a six-week period to identify every correctly and incorrectly reported outcome, comparing published reports against published protocols or registry entries, using CONSORT as the gold standard. A correction letter describing all discrepancies was submitted to the journal for all misreported trials, and detailed coding sheets were shared publicly. The proportion of letters published and delay to publication were assessed over 12 months of follow-up. Correspondence received from journals and authors was documented and themes were extracted.

Results: Sixty-seven trials were assessed in total. Outcome reporting was poor overall and there was wide variation between journals on pre-specified primary outcomes (mean 76% correctly reported, journal range 25–96%), secondary outcomes (mean 55%, range 31–72%), and number of undeclared additional outcomes per trial (mean 5.4, range 2.9–8.3). Fifty-eight trials had discrepancies requiring a correction letter (87%, journal range 67–100%). Twenty-three letters were published (40%) with extensive variation between journals (range 0–100%). Where letters were published, there were delays (median 99 days, range 0–257 days). Twenty-nine studies had a pre-trial protocol publicly available (43%, range 0–86%). Qualitative analysis demonstrated extensive misunderstandings among journal editors about correct outcome reporting and CONSORT. Some journals did not engage positively when provided correspondence that identified misreporting; we identified possible breaches of ethics and publishing guidelines.

(Continued on next page)

https://trialsjournal.biomedcentral.com/track/pdf/10.1186/s13063-019-3173-2.pdf

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Preregistration: Inference fallacies?

The illusion of transparency

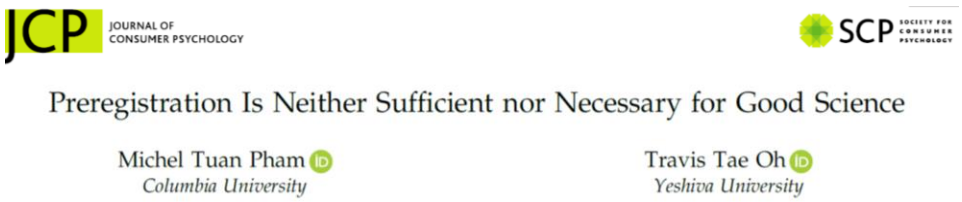
‚Under present systems of preregistration, there is still substantial room for selective reporting and researchers' degrees of freedom'

The illusion of robustness

‚The fact that a particular finding was anticipated under a preregistered protocol does not mean that one can reasonably expect to observe it again and again; it only means that one is likely to observe it under the specific conditions of the preregistered protocol.'

Reproducible but pointless science

'To elevate the quality of [...] science, it is not sufficient to encourage the preregistration of [...] studies as a means to enhance their reproducibility.'



https://myscp.onlinelibrary.wiley.com/doi/abs/10.1002/jcpy.1209

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Does preregistration interfere with claiming intellectual property?

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(Pre) Registration of ‚exploratory' research?

PLOS BIOLOGY

Citation: Dirnagl U (2020) Preregistration of exploratory research: Learning from the golden age of discovery. PLoS Biol 18(3): e3000690. https://doi.org/10.1371/journal.pbio.3000690

PERSPECTIVE

Preregistration of exploratory research: Learning from the golden age of discovery

Ulrich Dirnagl *

QUEST Center for Transforming Biomedical Research, Berlin Institute of Health, Berlin, Germany

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000690

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Exploration/Discovery vs. Confirmatiory (knowledge claiming) research

Exploration: Generates hypotheses and does not lead to a formal knowledge claim.

Hypothesis testing / Confirmatory / Knowledge claiming experiment: A clear, predefined hypothesis, including a clear predefined primary outcome measure to test the hypothesis and a predefined and appropriate statistical test. The proposed sample size should be stated, along with a justification based on the statistical power to detect a biologically important effect.

A given study can involve hypothesis-testing and exploratory parts, for instance by defining one primary endpoint (hypothesis-testing), with all other measured endpoints being exploratory

There is a one-way street between confirmatory and exploratory experiments: if you find interesting results which contradict your hypothesis, a confirmatory experiment can turn into an exploratory experiment. However, an exploratory experiment can never become confirmatory.

Exploration/ vs. confirmation

Exploration: Generates hypotheses and does not lead to a formal knowledge claim.

Hypothesis testing / Confirmatory / Knowledge claiming experiment: A clear, predefined hypothesis, including a clear predefined primary outcome measure to test the hypothesis and a predefined and appropriate statistical test. The proposed sample size should be stated, along with a justification based on the statistical power to detect a biologically important effect.

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There is a one-way street between confirmatory and exploratory experiments: if you find interesting results which contradict your hypothesis, a confirmatory experiment can turn into an exploratory experiment. However, an exploratory experiment can never become confirmatory.

Conclusions

Preregistration and Registered report **can (but not necessarily or automatically)**

- limit unwarranted/undislosed ‚researcher‘s degrees of freedom‘
- prevent ‚outcome switching‘
- prevent HARKING
- provide scooping protection
- reduce publication bias
- do not put ‚science in chains‘
- …

Open issues: RRs overburdening peer review? Preregistration of exploratory research? Inference fallacies?

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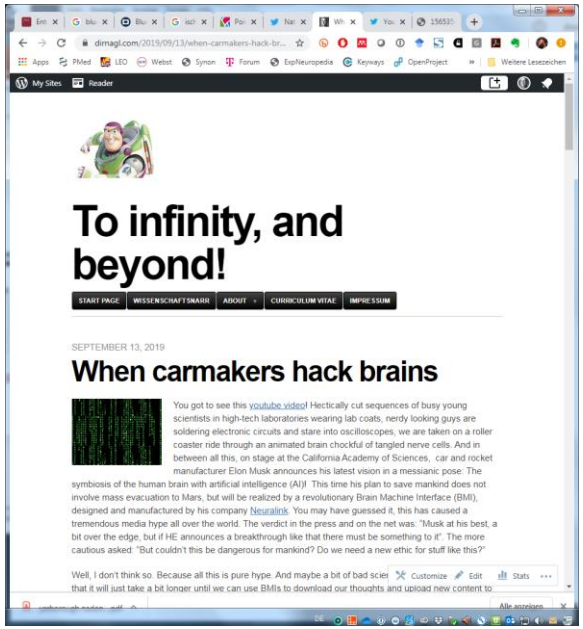
Laborjournal

SERIE

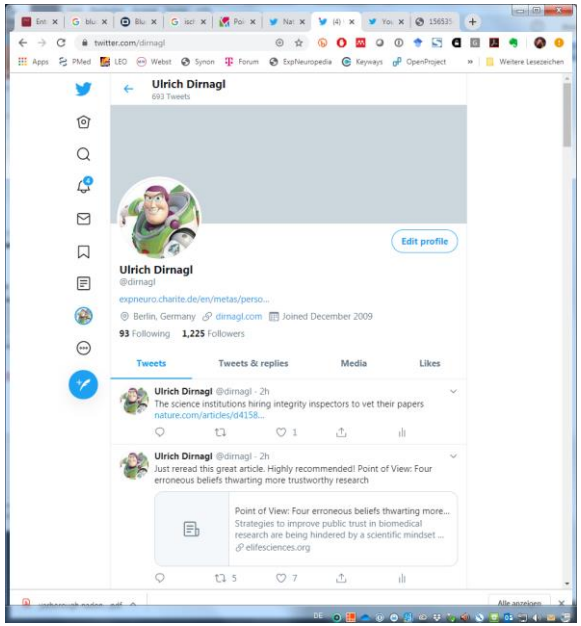
Einsichten eines Wissenschaftsnarren (24)

Warum trauen WIR dem Weltklimarat, die Klimaskeptiker aber nicht?

Monthly column
laborjournal.de



Blog
dirnagl.com



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- LinkedIn – Helmholtz Open Science Office

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