



CaRe PhD Day May 16, 2018



Programme

Theme: Research integrity

10.00-10.05 Opening by prof. Onno van Schayck, Scientific Director CaRe

10.05-10.35 *Research integrity and publishing results*
Prof. Fiona Godlee, editor of BMJ

10.35-11.05 *Research integrity and reproducibility*
Prof. Lex Bouter, Professor of Methodology and Integrity, VU University Medical Center Amsterdam

11.05-12.30 Dilemma game scientific integrity

12.30 -13.15 *Lunch*



Programme

13.15 – 15.15 Presentations in small groups per research field of PhDs in the early stage of their trajectory

Check-in hotel from 14.00

15.15-15.45 *Coffee/tea break*

15.45-16.45 *Prevention research and governmental policy*
Paul Blokhuis, State Secretary for Health, Welfare and Sport

17.00-18.00 *PhD students can pick up their certificate at the registration desk*

17.00-18.00 *Drinks*

19.00 *Dinner*



We CaRe for you

The objectives of CaRe are to establish and guarantee a high quality PhD training programme for researchers, and to foster the development of new scientific knowledge in public health and care.



Netherlands School of Public
Health and Care Research



Research integrity and publishing results

Prof. Fiona Godlee
editor of BMJ

Research integrity and publishing results

Fiona Godlee
16th May 2018



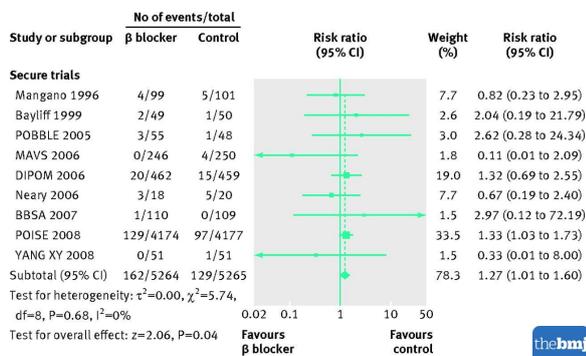
The principles of Evidence Based Medicine are sound...



The problem is that the evidence base is deeply flawed....

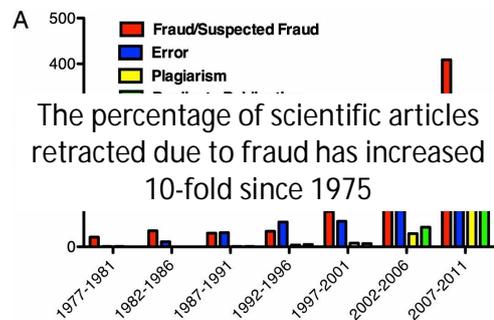


Mortality at 30 days in non-discredited randomised controlled trials of initiating perioperative β blockade



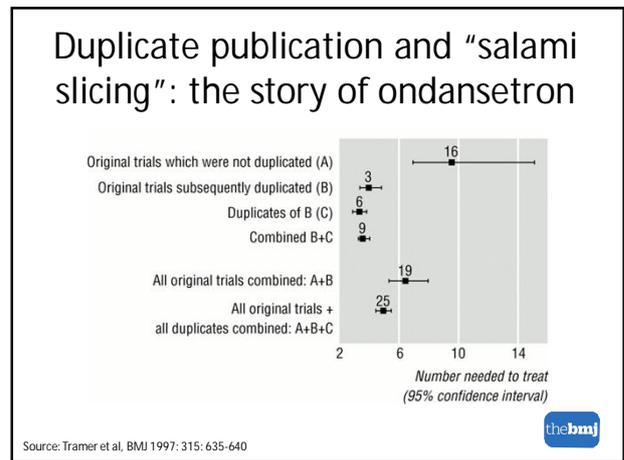
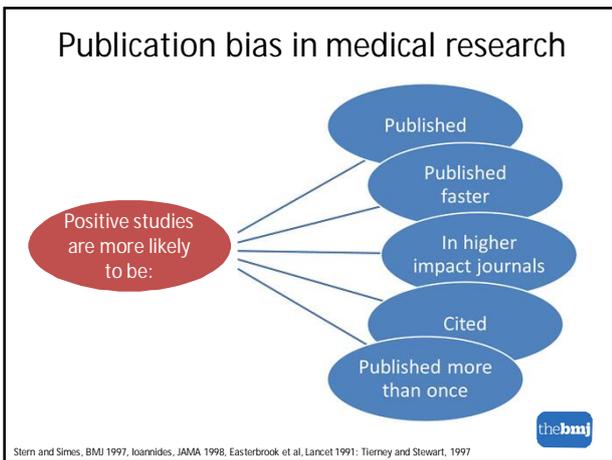
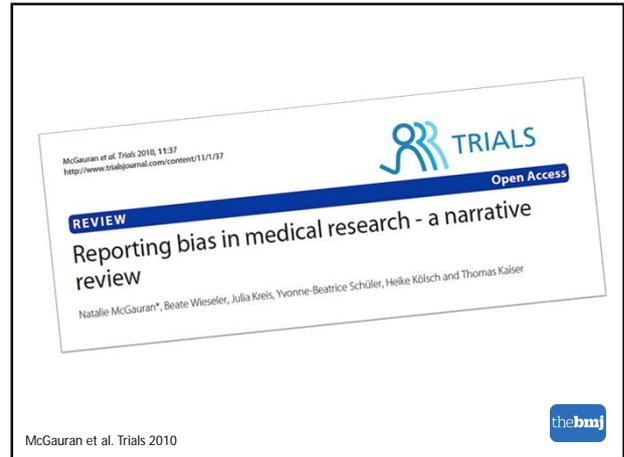
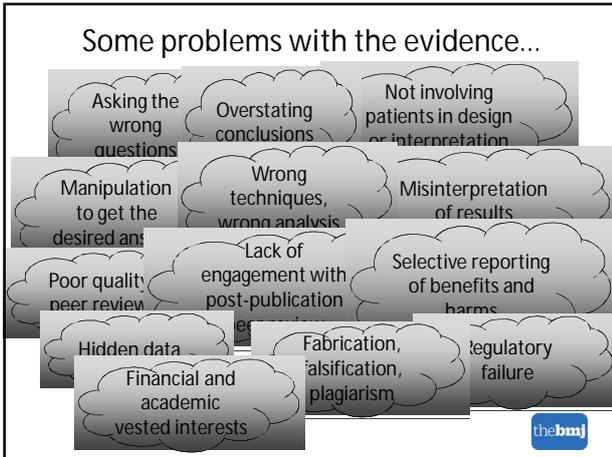
Graham D Cole, and Darrel P Francis, 2014 BMJ

Research fraud



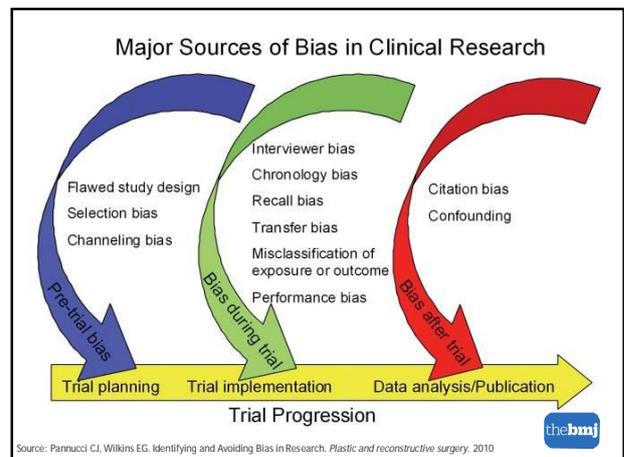
Fang et al, PNAS 2012





"What if the results should be thought about by researchers whose research techniques are not fully by through or are otherwise biased, the highest wrongly interpreted? Result people would results selectively agree that it is not selective, unprofessional, unjustified, unethical, and certainly unacceptable." We should be appalled."

thebmj



Essay

Why Most Published Research Findings Are False

John P.A. Ioannidis



JP Ioannidis, PLoS Medicine 2005



Methods used by pharmaceutical companies to get the results they want...

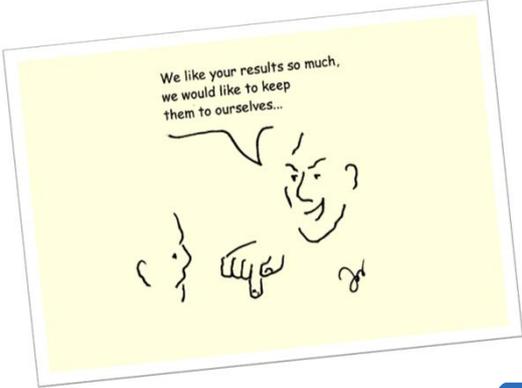
- Conduct a trial of a drug against a treatment known to be inferior.
- Trial a drug against too low/too high a dose of a competitor drug.
- Conduct trials that are too small to show differences from a competitor drug.
- Use multiple endpoints and select only favorable results.
- Use multi-centre trials and select only favorable results.
- Conduct subgroup analyses and select only favorable results.
- Manipulate results presentation (eg relative rather than absolute).

Smith R. Medical Journals are an extension of the marketing arm of pharmaceutical companies. PLoS Medicine 2005

CROs face a fundamental conflict of interest—if they do not please their commercial clients, they may be less likely to get more work from them



BMJ | 13 September 2008 | Volume 337

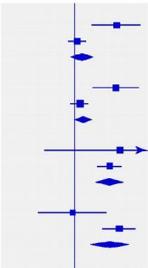
Source: Van der Meer, et al. Independent medical research? April 2007, Vol. 65, No. 4



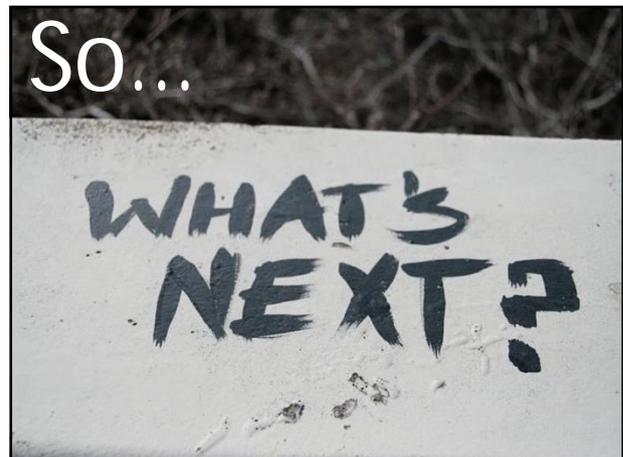
BMJ

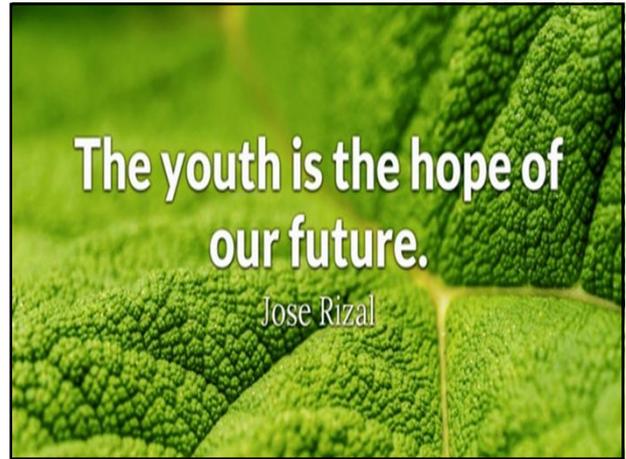
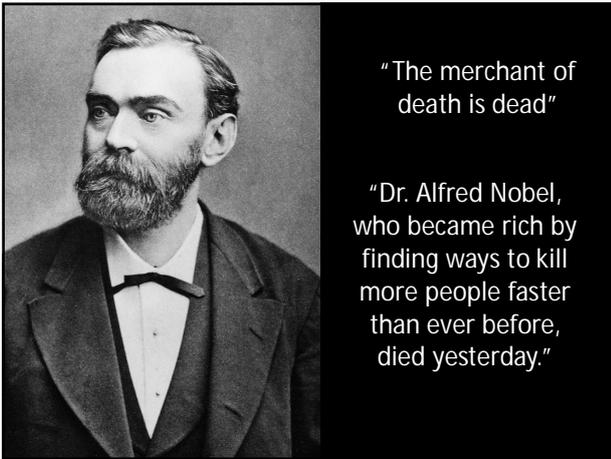
RESEARCH

	Reboxetine (n/N)	Placebo or selective serotonin reuptake inhibitor (n/N)	Odds ratio (95% CI)
Reboxetine v placebo			
Remission			
Published (1)	60/126	34/128	
Unpublished (6)	395/938	379/930	
Total (7)	455/1064	413/1058	
Response			
Published (1)	70/126	43/128	
Unpublished (6)	469/938	439/930	
Total (7)	539/1064	482/1058	
Patients with adverse events			
Published (2)	108/154	91/156	
Unpublished (6)	839/979	713/959	
Total (8)	947/1133	804/1115	
Withdrawal owing to adverse events			
Published (2)	15/154	16/156	
Unpublished (6)	122/979	48/959	
Total (8)	137/1133	64/1115	

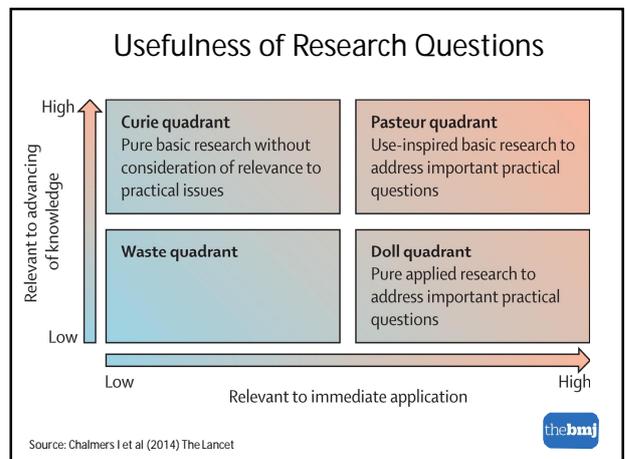
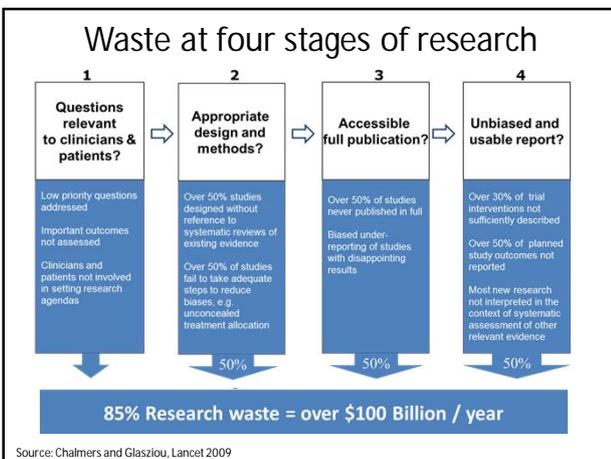


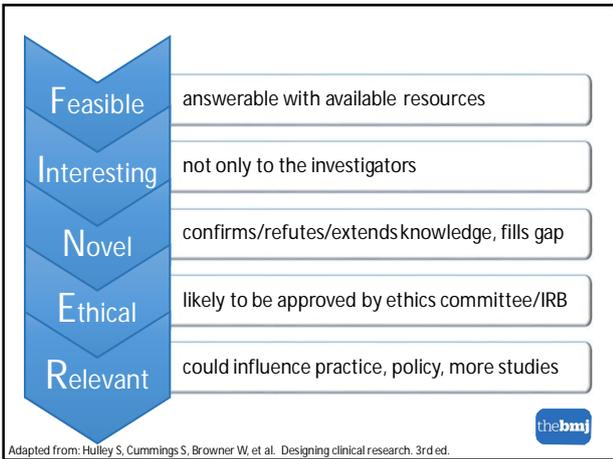
©2010 by British Medical Journal Publishing Group

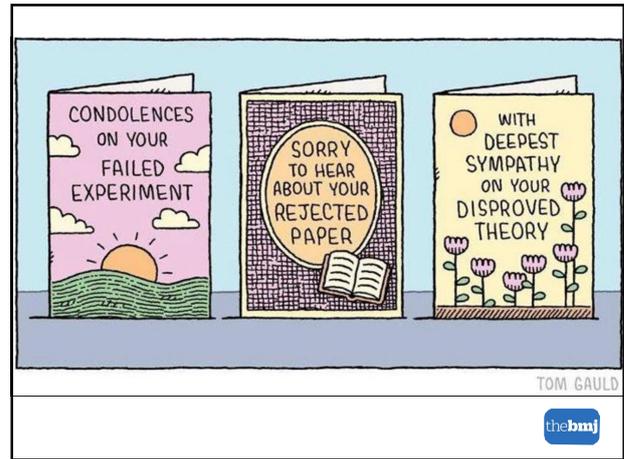
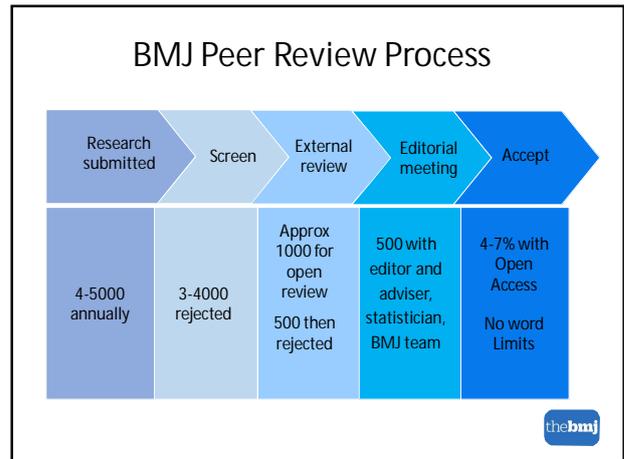
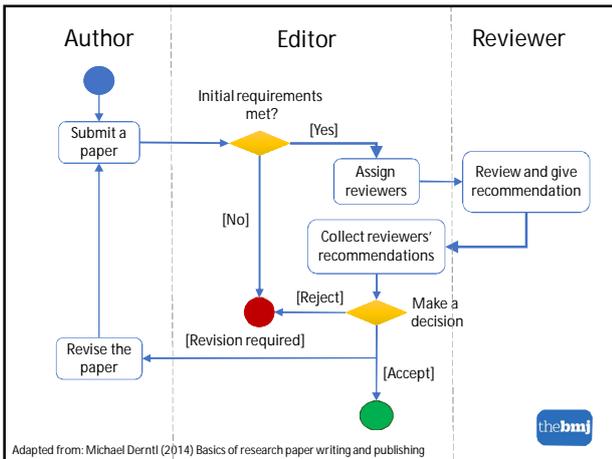





1. Put your effort into answering the right questions
2. Design your study well
3. Engage with the peer review process
4. Handle rejection well
5. Value your integrity above all things
6. Practise critical thinking







Rejection of rejection letter

[insert university emblem here]
 Dear Professor [insert name of editor],
 [Re: MS 2015_XXXX Insert title of ground-breaking study here]

Thank you for your rejection of the above manuscript.

Unfortunately we are not able to accept it at this time. As you are probably aware we receive many rejections each year and are simply not able to accept them all. In fact, with increasing pressure on citation rates and fiercely competitive funding structures we typically accept fewer than 30% of the rejections we receive. Please don't take this as a reflection of your work. The standard of some of the rejections we receive is very high.

In terms of the specific factors influencing our decision the failure by Assessor 1 to realise the brilliance of the study was certainly one of them. Simply stating "this study is neither novel nor interesting and does not extend knowledge in this area" is not reason enough. This, coupled with the use of Latin quotes by Assessor 2, rendered an acceptance of your rejection extremely unlikely.

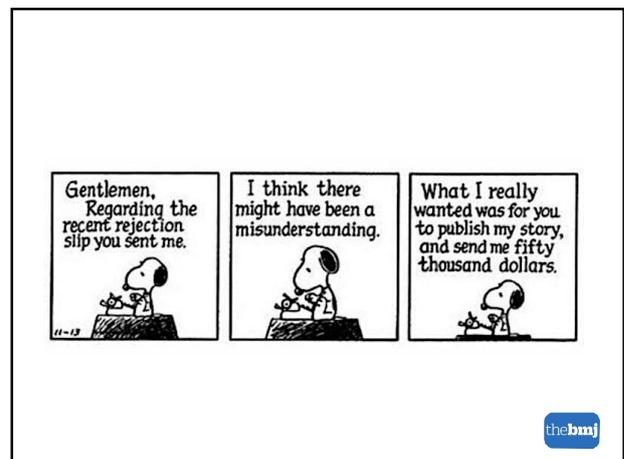
We do wish you and your editorial team every success with your rejections in the future and hope they find safe harbour elsewhere. To this end, may we suggest you send one to [insert name of rival research group] for consideration. They accept rejections from some very influential journals.

Please understand that our decision regarding your rejection is final. We have uploaded the final manuscript in its original form, along with the signed copyright transfer form.

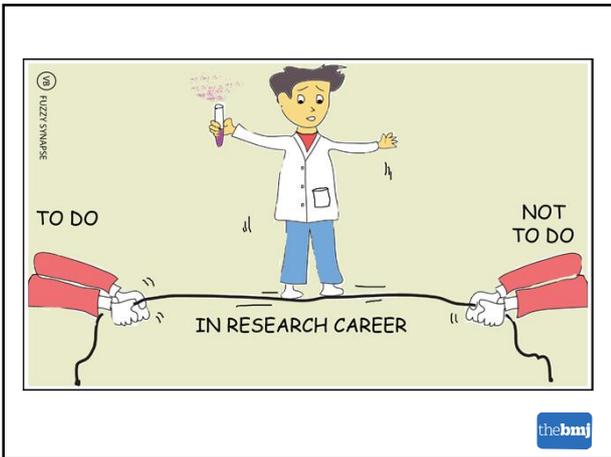
We look forward to receiving the proofs and to working with you in the future.

Yours sincerely
 Dr [insert name here]
 [insert research group acronym here]
 [insert university here]
 [insert country here—that is, Australia/New Zealand/small European Country/Canada]

Chapman C, Slade T. Rejection of rejection: a novel approach to overcoming barriers to publication *BMJ* 2015; 351 :h6326

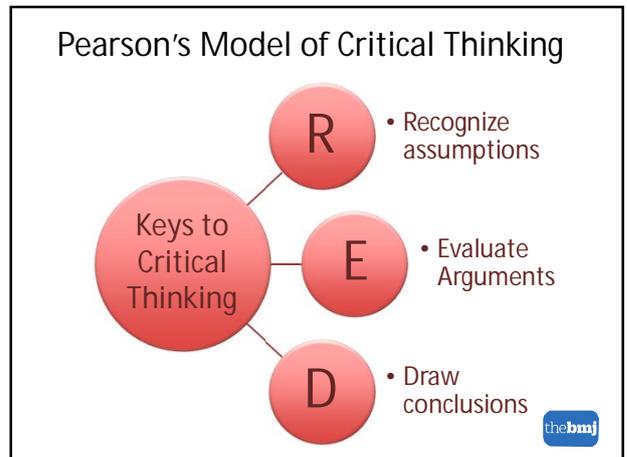


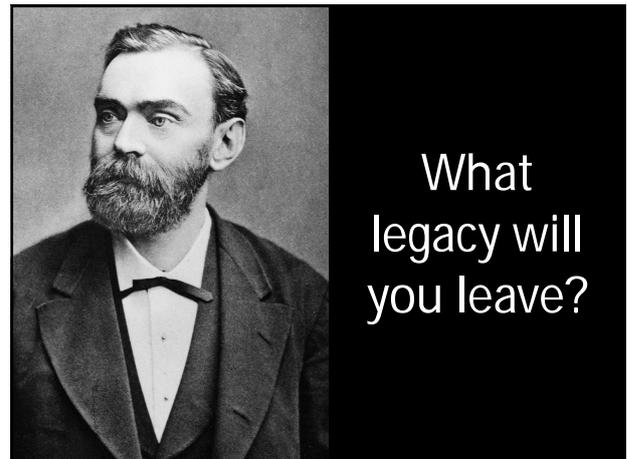
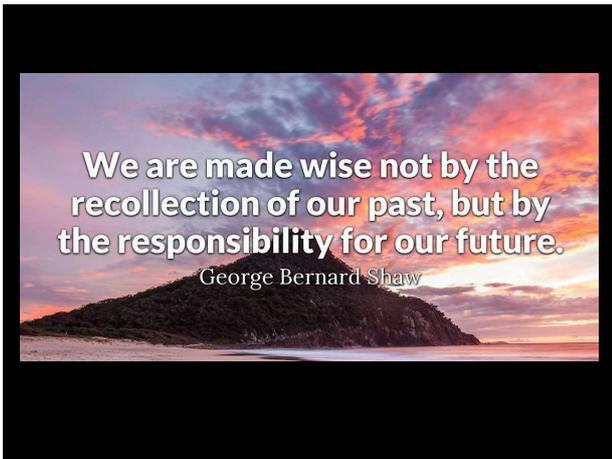
5. Value your integrity above all things



Integrity is doing the right thing, even when no one is watching.

6. Practise critical thinking






Research integrity and reproducibility

Prof. Lex Bouter
Professor of Methodology and Integrity
VU University MedicalCenter Amsterdam




Research Integrity and Reproducibility

Lex Bouter

Conclusion

- Scientists struggle with dilemmas
- Preference for positive findings leads to selective reporting and low reproducibility
- More transparency will partly solve the issues
- All stakeholders have a role to play

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Spectrum of research practices

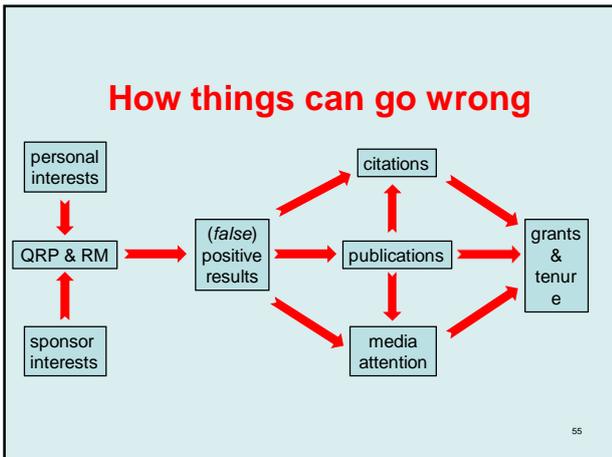
How it should be done:
Relevant, Valid, Reproducible, Efficient

Sloppy science: **34%**
Ignorance, honest error or dubious integrity

Scientific fraud: **2%**
Fabrication, Falsification, Plagiarism



3



Degrees of Freedom in Planning, Running, Analyzing, and Reporting Psychological Studies: A Checklist to Avoid *p*-Hacking

Jelle M. Wicherts¹, Coosje L. S. Veldkamp, Hilde E. M. Augusteijn, Marjan Bakker, Robbie C. M. van Aert and Marcel A. L. M. van Assen

34 Researcher Degrees of Freedom that can be used to get Positive Results

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What is good for the validity and reliability of science is not always good for your professional career

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The natural selection of bad science

Paul E. Smaldino¹ and Richard McElreath²

Poor research design and data analysis encourage false-positive findings. Such poor methods persist despite perennial calls for improvement, suggesting that they result from something more than just misunderstanding. The persistence of poor methods results partly from incentives that favour them, leading to the natural selection of bad science. This dynamic requires no conscious strategizing—no deliberate cheating nor loafing—

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Non-publication → **publication bias**
 Selective reporting → **reporting bias**

- Both favour preferred ('positive') findings
- Leading to a distorted picture in the published body of evidence

→ **Flawed Systematic Reviews**
 → **Low Replication Rates**

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Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

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Only 6 of 53 preclinical landmark cancer studies could be confirmed by replication

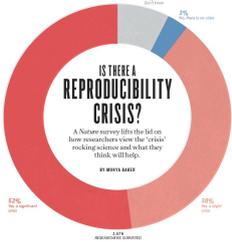
When negative studies are rarely published, published positive studies are likely to be chance findings

Non-confirmed studies

- sometimes inspire many new studies → **waste of resources!**
- sometimes lead to clinical trials → **unethical situation!**

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Replicability of studies is only 10-40 %

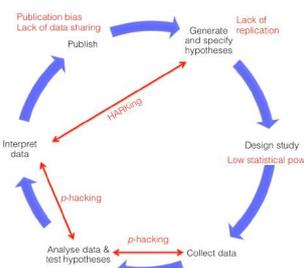
FOOLING OURSELVES

HUMANS ARE REMARKABLY GOOD AT SELF-DECEPTION, BUT GROWING CONCERN ABOUT REPRODUCIBILITY IS MOVING MANY RESEARCHERS TO SEEK WAYS TO FIGHT THEIR OWN WORST INSTINCTS.

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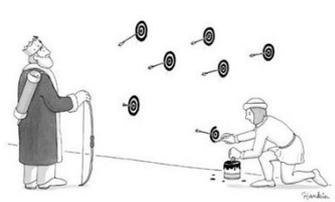
Important causes of 'replicability crisis'

- Selective reporting
- Low power
- P-hacking
- HARKing

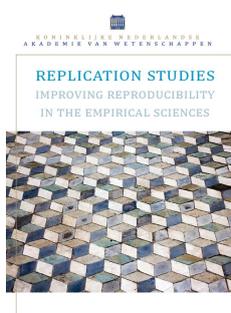


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Hypothesizing After the Results are Known (HARKing)



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REPLICATION STUDIES
IMPROVING REPRODUCIBILITY
IN THE EMPIRICAL SCIENCES

ADVISORY REPORT

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Every baby knows the **scientific method!**



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"Only when certain events recur in accordance with rules or regularities, as in the case of **repeatable** experiments, can our observations be tested—in principle—by anyone.... Only by such **repetition** can we convince ourselves **that we are not dealing with a mere isolated 'coincidence,'** but with events which, on account of their regularity and **reproducibility**, are in principle inter-subjectively testable."

Karl Popper. The Logic of Scientific Discovery. London: Hutchison. 1959, P. 45

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A manifesto for reproducible science

Marcus R. Munafó^{1,2*}, Brian A. Nosek^{2,4}, Dorothy V. M. Bishop⁵, Katherine S. Button⁶, Christopher D. Chambers⁷, Nathalie Perce du Sert⁸, Uri Simonsohn⁹, Eric-Jan Wagenmakers¹⁰, Jennifer J. Ware¹¹ and John P. A. Ioannidis^{12,13,14}

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Table 1 | A manifesto for reproducible science.

Theme	Proposal	Examples of initiatives/potential solutions (extent of current adoption)	Stakeholder(s)
Methods	Protecting against cognitive biases	All of the initiatives listed below (* to ****)	J, F
	Improving methodological training	Blinding (**) Rigorous training in statistics and research methods for future researchers (*) Rigorous continuing education in statistics and methods for researchers (*)	L, F
	Independent methodological support	Involvement of methodologists in research (**) Independent oversight (*)	F
	Collaboration and team science	Multi-site studies/distributed data collection (*) Team-science consortia (*)	L, F
Reporting and dissemination	Promoting study pre-registration	Registered Reports (*) Open Science Framework (*)	J, F
	Improving the quality of reporting	Use of reporting checklists (**) Protocol checklists (*)	J
	Protecting against conflicts of interest	Disclosure of conflicts of interest (***) Exclusion/containment of financial and non-financial conflicts of interest (*)	J

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Table 1 | A manifesto for reproducible science.

Theme	Proposal	Examples of initiatives/potential solutions (extent of current adoption)	Stakeholder(s)
Reproducibility	Encouraging transparency and open science	Open data, materials, software and so on (* to **) Pre-registration (**** for clinical trials, * for other studies)	J, F, R
Evaluation	Diversifying peer review	Preprints (* in biomedical/behavioural sciences, **** in physical sciences) Pre- and post-publication peer review, for example, Publons, PubMed Commons (*)	J
Incentives	Rewarding open and reproducible practices	Badges (*) Registered Reports (*) Transparency and Openness Promotion guidelines (*) Funding replication studies (*) Open science practices in hiring and promotion (*)	J, L, F

Estimated extent of current adoption: *, <5%; **, 5–30%; ***, 30–60%; ****, >60%. Abbreviations for key stakeholders: J, journals/publishers; F, funders; L, institutions; R, regulators.

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Transparency of

Always prospectively

Publicly – if possible

Study Protocol
Analysis Plan
Amendments
Data Sets → **Open Data**
Reports → **Open Access**

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The preregistration revolution

Brian A. Nosek^{a,b,1}, Charles R. Ebersole^b, Alexander C. DeHaven^a, and David T. Mellor^a

Progress in science relies in part on **generating hypotheses** with existing observations and **testing hypotheses** with new observations. This distinction between **postdiction** and **prediction** is appreciated conceptually but is not respected in practice. Mistaking generation of postdictions with testing of predictions reduces the credibility of research findings. However, ordinary biases in human reasoning, such as **hindsight bias**, make it hard to avoid this mistake. An effective solution is to define the research questions and analysis plan before observing the research outcomes—a process called pre-registration. **Preregistration distinguishes analyses and outcomes that result from predictions from those that result from postdictions.**

2600–2606 | PNAS | March 13, 2018 | vol. 115 | no. 11

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Preregistration

- Essential for **hypothesis testing** research (**PREDICTION**)
- Alias context of justification, confirmatory research
- Optional for **hypothesis-generating** research (**POSTDICTION**)
- Alias context of discovery, exploratory research

- p-values only interpretable for **PREDICTION** + preregistration
- POSTDICTION** p-values likely due to **HARKing** and **p-hacking**
- In other words: due to **hindsight bias** or **data-driven**

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Open Science Framework
A scholarly commons to control, track and reuse research cycles



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



DataVerseNL



figshare



MENDELEY



PRECLINICALTRIALS.EU
International register of preclinical trial protocols

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	LEVEL 0	LEVEL 3
Citation standards	Journal encourages citation of data, code, and materials—or says nothing.	Article is not published until appropriate citation for data and materials is provided that follows journal's author guidelines.
Data transparency	Journal encourages data sharing—or says nothing.	Data must be posted to a trusted repository and reported analyses will be reproduced independently before publication.
Analytic methods (code) transparency	Journal encourages code sharing—or says nothing.	Code must be posted to a trusted repository, and reported analyses will be reproduced independently before publication.
Research materials transparency	Journal encourages materials sharing—or says nothing.	Materials must be posted to a trusted repository, and reported analyses will be reproduced independently before publication.

Almost 5000 signatories!

Transparency and Openness Promotion (TOP) Guidelines
From publisher's domain: Make information and data of significance accessible

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Design and analysis transparency	Journal encourages design and analysis transparency or says nothing.	Journal requires and enforces adherence to design transparency standards for review and publication.
Preregistration of studies	Journal says nothing.	Journal requires preregistration of studies and provides link and badge in article to meeting requirements.
Preregistration of analysis plans	Journal says nothing.	Journal requires preregistration of studies with analysis plans and provides link and badge in article to meeting requirements.
Replication	Journal discourages submission of replication studies—or says nothing.	Journal uses Registered Reports as a submission option for replication studies with peer review before observing the study outcomes.

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REGISTERED REPORTS
PEER REVIEW BEFORE RESULTS ARE KNOWN TO ALIGN SCIENTIFIC VALUES AND PRACTICES

ELIMINATE BIAS & INCREASE RIGOR

WRITE UP RESULTS
Published without regard to outcome after peer reviewed quality checks are met.

EXPLORATORY OUTCOMES
Data-led discovery. Generates new hypotheses.

CONFIRMATORY OUTCOMES
Shows results that reach the highest standards of reproducibility.

Stage 1 ↑ Peer Review

Stage 2 ↑ Peer Review

Used by 105 journals

Including BMJ Open Science

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equator network

Reporting guidelines for main study types

Randomised trials	CONSORT	Extensions	Other
Observational studies	STROBE	Extensions	Other
Systematic reviews	PRISMA	Extensions	Other
Case reports	CARE	Extensions	Other
Qualitative research	SRRQ	COREQ	Other
Diagnostic / prognostic studies	STARD	TRIPOD	Other
Quality improvement studies	SQUIRE		Other
Economic evaluations	CHEERS		Other
Animal pre-clinical studies	ARRIVE		Other
Study protocols	SPIRIT	BRISMA-P	Other
Clinical practice guidelines	AGREE	RIGHT	Other

N = 398

Enhancing the QUALity and Transparency Of health Research

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Conclusion

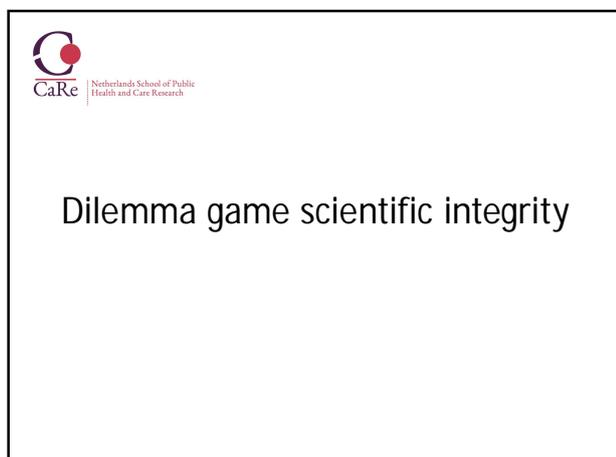
- Scientists struggle with dilemmas
- Preference for positive findings leads to selective reporting and low reproducibility
- More transparency will partly solve the issues
- All stakeholders have a role to play

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www.nrin.nl

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- Stand up
- Pick up your chair and move it to the wall

Ready? Let's play!

Rules

- Read the dilemma
- Read the options
- Choose an option
- Move to the section with the same colour, in time 🕒
- If asked elaborate on your choice
- Discuss with Prof Godlee and Prof Bouter



First dilemma



Spoilsport

I am using data from a widely used data source within my institute. While processing the data, I come across some systematic problems (missing values, outliers) that apparently nobody has ever bothered about before. Remedying the error accurately would take me half a year.

My supervisor suggests following "common practice", without specifying. Common practice is not to report the problem. Alternative sources are not readily available.

What do I do?



- I take extensive time to analyse the problems, even if that implies that my PhD will be delayed.
- I go to the head of the institute and ask for an investigation into past and current research based on the data set. The results might be problematic.
- I change the scope of my research project so that I no longer have to use the data.
- I contact researchers who published earlier on the database. If they agree with the supervisor I follow common practice.

Second dilemma



Re-routing

My paper has gone through two rounds of reviews with one particular journal and the reviewers are quite tough on me. But they do provide constructive comments and as they are not rejecting my paper, they probably do see some merit in my work.

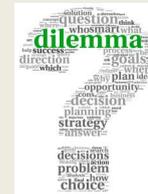
But now a call for a special issue has come in from for another journal, exactly in the area of my paper. My paper will have a very good chance of getting accepted for the special issue, and the process might be much faster than the tedious process with these other, tough reviewers.

What do I do?



- I also submit the paper to the special issue of the other journal. If it gets a quick first round review, I can decide then which of the two journals has the best chance and I will retract it from one of the two review processes.
- I also submit the paper to the special issue of the other journal. Chances are that the two manuscripts will develop in two different directions anyway with two different sets of reviewers.
- I retract the paper from the first journal and submit to the second, knowing that as a result of the two rounds of reviews, the paper has improved a lot and stands a good chance of getting accepted.
- I stick with the first journal until I get a final acceptance (or possibly a rejection).

Third dilemma



Writing for your audience

My PhD research is funded by a government organization. When discussing my conclusions with the organization, it becomes clear that my conclusions are much too nuanced to make any political statements.

The organization asks me to rewrite my conclusions so that they offer more clear-cut statements. Based on the data I think it is impossible to say things with such certainty.

When I discuss the matter with my supervisor he tells me that I need to learn to write for my audience and that I should be able to make bolder statements. I might need the government organization for financing future research.

What do I do?



- I rewrite my conclusions in the way the organization asks me to.
- I refrain from rewriting my conclusions.
- I decide to write an executive summary in which my conclusions are more certain and clear while keeping the nuanced conclusion in my dissertation.
- I ask an older researcher who is very strict on scientific guidelines to decide on the matter.

Fourth dilemma



Different estimates

I am a PhD student. I have just run a regression analysis and the results come out nicely.

To validate the results I decide to run two alternative estimation procedures.

However, it turns out that the results from the alternative tests are not significantly different from zero, although the point estimates are comparable to the first results.

What do I do?



- I only report the results of the first regression analysis.
- I report all results in order to show the robustness of my results.
- I do not report the results but mention in the paper that these strategies yield quantitatively similar conclusions.
- In my discussion I list a number of reasons why performing these additional analyses would be inappropriate.

Fifth dilemma



Free lunch?

I am starting my PhD project and as a first task I am asked to rewrite a paper by a former PhD colleague who has meanwhile left academia.

I notice the paper needs only small changes and the reviewers are very mild and friendly, so the paper may get accepted in the next round.

My professor suggests putting me as last author, to support my academic career, despite my limited contribution to the actual research process. He will himself be the first author.

The former PhD has agreed that others can use his work, but no specific agreements were made.

What do I do?



- I agree to the offer and get listed as last author.
- I suggest that I should be mentioned in a footnote, but not listed as author.
- I contact the former PhD and ask him whether he wants the publication in his name.
- I decline the revising job; I do not want to be involved.

Eight dilemma



Going for the top

At the very beginning of my PhD project, my supervisor tells me he really wants to publish in the absolute top journals.

I am afraid it will take more than five years to do so. As I am not planning on an academic career later, second tier journals will do.

What do I do?



- I agree with the goals of the supervisor and aim for top journals.
- I tell him I agree with his goals. In practice I will try to get my articles published in any relevant journal that will contribute to my PhD.
- I tell my supervisor of my limited ambitions, accepting the possibility that this jeopardizes my PhD track.
- I try to find another supervisor who is willing accept my more limited ambitions.

Enjoy your lunch!

“A Dilemma”

