

Accumulation (Bias) in meta-analysis

Judith ter Schure

CWI, Machine Learning group

A solid green vertical bar.

Viewpoint

 Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou

Lancet 2009; 374: 86-89

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Series



Research: increasing value
How to increase value
priorities are set

Research: increasing value, reducing waste 5

Reducing waste from incomplete or unusable reports of biomedical research

Paul Glasziou, Douglas G Altman, Patrick Bossuyt, Isabelle Boutron, Mike Clarke, Steven Julious, Susan Michie, David Maher, Elizabeth Wager

Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gülmezoglu, David W Howells, John P A Ioannidis, Sandy Oliver

Lancet 2014; 383: 156-65



Ensuring Value in Research (EViR)

Funders' Collaboration and Development Forum

Guiding Principles

Justifiable research priorities

Principle 1: Health-related research agendas and priorities should be set with the meaningful involvement of those who will use and be affected by health-related research.

Robust research design, conduct and analysis

Principle 2: Research should only be funded if set in the context of one or more existing systematic reviews of what is already known or an otherwise robust demonstration of a research gap.

Principle 3: Funders should take into account advances in research methodology and fund new research only if adequate steps have been taken to reduce bias.

COVID-evidence Database

This is a snapshot of the beta-version of the COVID-evidence BASIC database showing some of the key elements of COVID-evidence.

Last Update: 14 April 2020 14:00 CET

CSV Export Excel Export		Search							Columns
inter...	intervention na... ↑	cour	sta...	randomiz...	ar	blin	population condi...	primary outcome measure	
drug	Ganovo+ritonavir+/-	China	complet	non-randomized	1	none	COVID-19 pneumonia	Rate of composite adverse outcomes	↑
drug	hydroxychloroquine	France	complet	non-randomized	1	none	COVID 19 positive pat	viral clearance in nasopharyngeal swabs	
drug	Hydroxychloroquine	France	complet	non-randomized	2	none	Hospitalized patients	virological clearance at day-6 post-inclusion	
drug	lopinavir-ritonavir (	China	complet	randomized	2	none	COVID positive patien	time to clinical improvement	

.....

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D

Statistical review of *A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19* by B. Cao et al

April 8, 2020

Simon Gates, PhD - Professor of Biostatistics and Clinical Trials, Cancer Research UK Clinical Trials Unit, University of Birmingham, UK

Richard Emsley, PhD - NIHR Research Professor & Professor of Medical Statistics and Trials Methodology, Department of Biostatistics and Health Informatics, King's College London, UK

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difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80).

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interv...	intervention name	n...	country	status	randomized	arm	blind...	population c
drug	Abidol hydrochloride 0.2g once,3	400	China	recruiting	randomized	4	single blind	COVID-19 p
drug	conventional standardized treatm	328	China	recruiting	randomized	2	none	mild novel c
drug	DDarunavir/cobicistat DRV/c (800	100	China	not yet recruiting	randomized	3	none	novel coron
drug	Drug: Lopinavir/ritonavir 400mg/1	70	Hong Kong	recruiting	randomized	2	none	COVID-19
drug	lopinavir–ritonavir (400 mg and 1	199	China	completed	randomized	2	none	COVID posi
drug	lopinavir/ritonavir 400mg/200mg	4,000	United States	recruiting	randomized	4	double blind	SARS-CoV-2
drug	Lopinavir/ritonavir; Hydroxychloro	150	Korea, Rep	recruiting	randomized	3	none	COVID-19
drug	Oseltamivir 300mg (or 4-6 mg/kg	80	Thailand	not yet recruiting	randomized	8	none	COVID-19
drug	Remdesivir (200 mg intravenous I	3,200	International	not yet recruiting	randomized	4	none	Coronavirus
drug	Xiyanping injection in combination	348		not yet recruiting	randomized	2	none	COVID-19 p
drug	Xiyanping injection, 10-20ml daily,	80		planned	randomized	3	none	COVID-19 p

$N \approx 5\,000$

Covid-19 patients

interv...	intervention name	n...	country	status	randomized	arm	blindi...	population c
drug	darunavir 800 mg / cobicistat 150	3,040	Spain	recruiting	randomized	2	none	COVID-19
drug	experimental group 1:Hydroxychl	300	China	recruiting	randomized	3	double blind	novel coron
drug	Experimental group:Chloroquine	80	China	recruiting	randomized	2	none	Severe Nov
drug	Hydrochloroquine 400 mg orally	2,000	United States	not yet recruiting	randomized	2	single blind	healthy indi
drug	Hydroxychloroquine	1,660	Canada	not yet recruiting	randomized	2	double blind	COVID-19
drug	Hydroxychloroquine 200mg per d	400		not yet recruiting	randomized	4	double blind	COVID-19; S
drug	Hydroxychloroquine 200mg tablet	3,000	International	recruiting	randomized	2	double blind	COVID conf
drug	hydroxychloroquine 400 mg by m	300	United States	recruiting	randomized	2	none	Confirmed
drug	hydroxychloroquine 400 mg daily	440	Spain	recruiting	randomized	2	double blind	Healthy Hea
drug	hydroxychloroquine 400 mg twice	400	United States	not yet recruiting	randomized	6	double blind	COVID-19
drug	hydroxychloroquine 400mg per d	30	China	recruiting	randomized	2	none	Pneumonia,
drug	Hydroxychloroquine 800mg Qd p	2,486		not yet recruiting	randomized	2	single blind	exposed to

N ≈ 20 000

N ≈ 95 000

Covid-19 patients

Covid-19 health care workers

[Subsidies](#)[Onderzoek & resultaten](#)[Actueel](#)[Home](#) > [Actueel](#) > [Nieuws](#) > [Eerste gehonoreerde onderzoeksprojecten subsidieregeling COVID-19](#)**Nieuws**

Eerste gehonoreerde onderzoeksprojecten subsidieregeling COVID-19

Subsidies

Onderzoek & resultaten

Actueel

[Home](#) > [Actueel](#) > [Nieuws](#) > [Eerste gehonoreerde onderzoeksprojecten subsidiere...](#)

Nieuws

Eerste gehonoreerde onderzoeksprojecten COVID-19

Gehonoreerde projecten

De projecten die een incidentele subsidie ontvangen, hebben de volgende onderwerpen:

- Onderzoek naar onder andere het verloop van de ziekte, langetermijnprognose, kruisreactiviteit, her-infectie, en het verloop van immuunrespons over de tijd in relatie tot prognose. Hiertoe wordt een cohort gevolgd van personen die hersteld zijn van COVID-19 (RECoVERED studie);
- Onderzoek naar dragerschap, ziektelast en transmissie van en naar kinderen (CoKids studie);
- Onderzoek op het gebied van ziekenhuisepidemiologie ter ondersteuning van infectiepreventiemaatregelen (COCON studie);
- Een farmacotherapeutische trial met anakinra bij COVID-19-patiënten op de intensive care (ANACOR-IC);
- Het in kaart brengen van virusevolutie, verspreiding en transmissie via sequencing om verspreidingsroutes te voorspellen;
- Sociaalwetenschappelijk onderzoek naar de impact van sociale isolatie op kwetsbare populaties en welke steun kwetsbare groepen hierbij nodig hebben;
- Trial van [chloroquine en hydroxychloroquine](#)-behandeling in patiënten die opgenomen zijn met matige tot ernstige COVID-19 (ARCHAIC studie);
- Medicijnontwikkeling: studies naar veiligheid en werkzaamheid van antilichamen tegen het coronavirus.

Accumulation Bias

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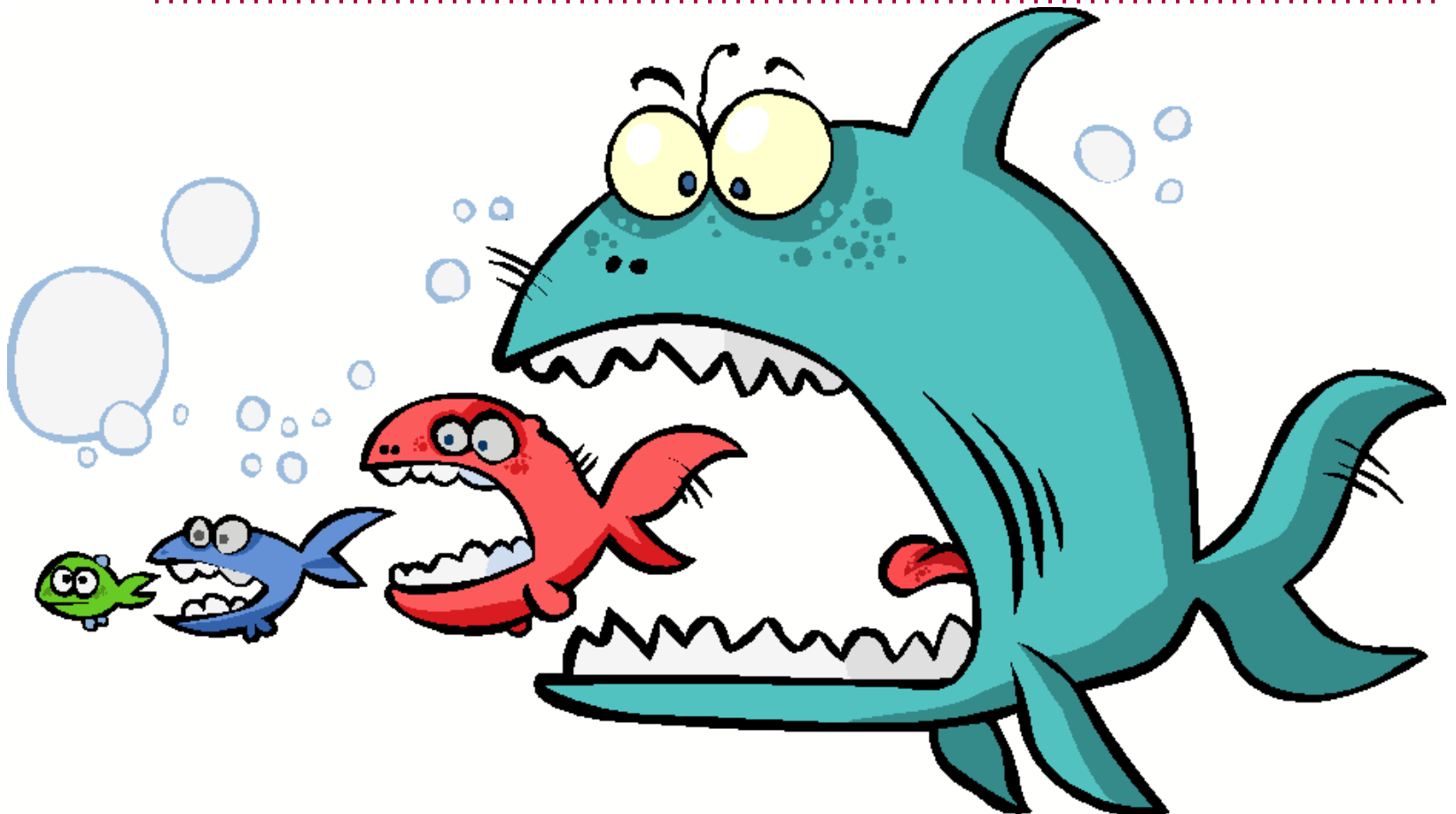
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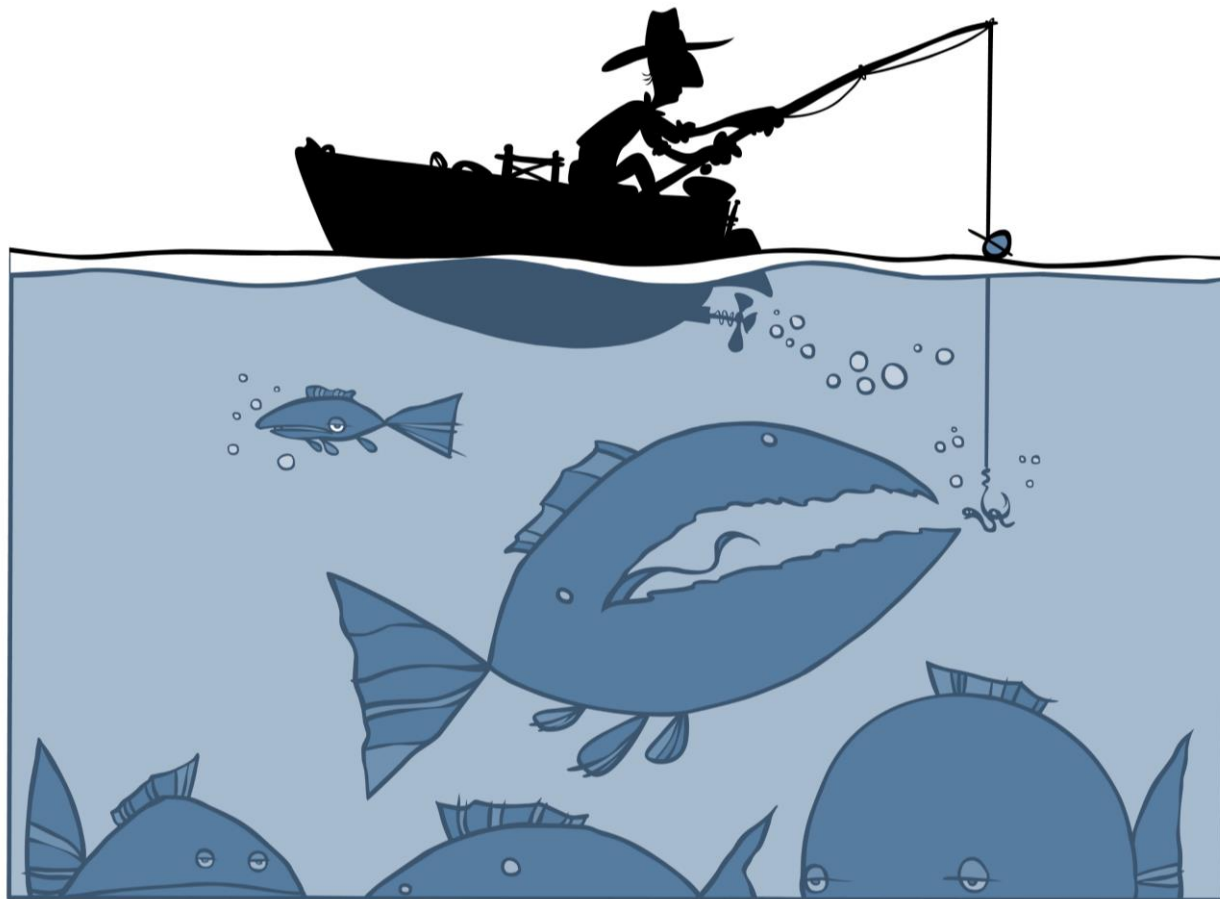
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Size is dependent on intermediate results

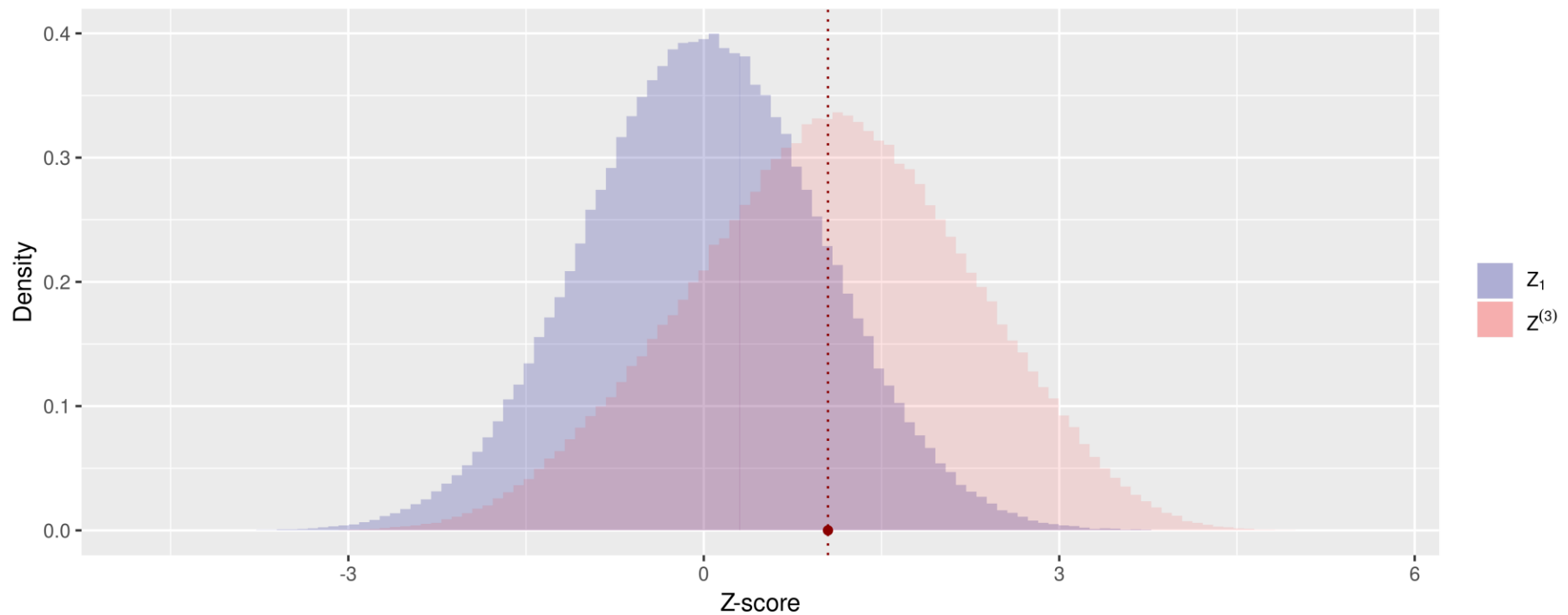


Timing is dependent on intermediate results

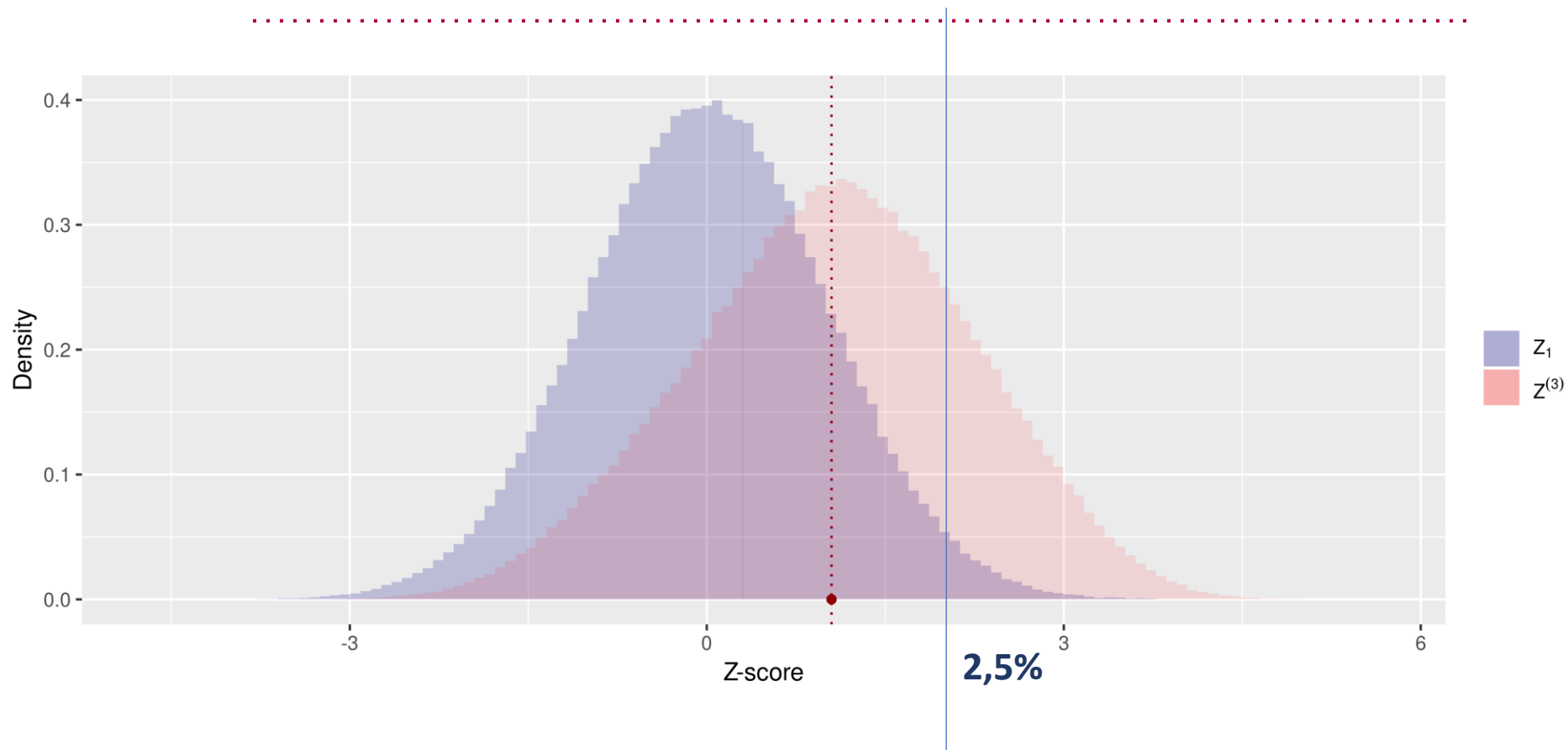


Accumulation Bias

Accumulation Bias



Inflated error rates



BMC Medical Research Methodology



Research article

Open Access

The **fading** of reported effectiveness. A meta-analysis of randomised controlled trials

Bernhard T Gehr¹, Christel Weiss² and Franz Porzsolt^{*3}

fading

Correspondence

How systematic reviews cause research waste

fading

Systematic reviews of small trials increase waste by advertising to the scientific community **inflated**, often significant treatment effects that become smaller or absent when large, high-quality trials are done. Effect estimates from systematic reviews often inform sample size calculations.⁴ However, because most reviews provide **exaggerated estimates** of treatment effects due to inclusion

We declare no competing interests.

**Ian Roberts, Katharine Ker*
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Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

fading

inflated,

exaggerated estimates

Perspective

**Why do Phase III Trials of Promising Heart Failure Drugs
Often Fail? The Contribution of 'Regression to the Truth'**

HENRY KRUM, MBBS, PhD, FRACP, ANDREW TONKIN, MD, FRACP

Victoria, Australia

fading

inflated,

exaggerated estimates

Regression to the Truth

fading

inflated,

exaggerated estimates



ELSEVIER

Journal of Clinical Epidemiology 58 (2005) 543–549

**Journal of
Clinical
Epidemiology**

REVIEW ARTICLES

Early extreme contradictory estimates may appear in published research: The Proteus phenomenon in molecular genetics research and randomized trials

John P.A. Ioannidis^{a,b,c,*}, Thomas A. Trikalinos^{a,b}

fading

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Systematic reviews and research waste

We share Ian Roberts' and Katharine Ker's frustration with the poor quality of much research (Oct 17,

their suggestion scientifically flawed, it is also unrealistic. Funders and regulators cannot be expected to support and endorse large studies without some reassurance from the results of smaller existing studies that the substantial investment needed is justified. We hope that, instead of promoting their

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Early extreme contradictory estimates

The Proteus phenomenon

Regression to the Truth

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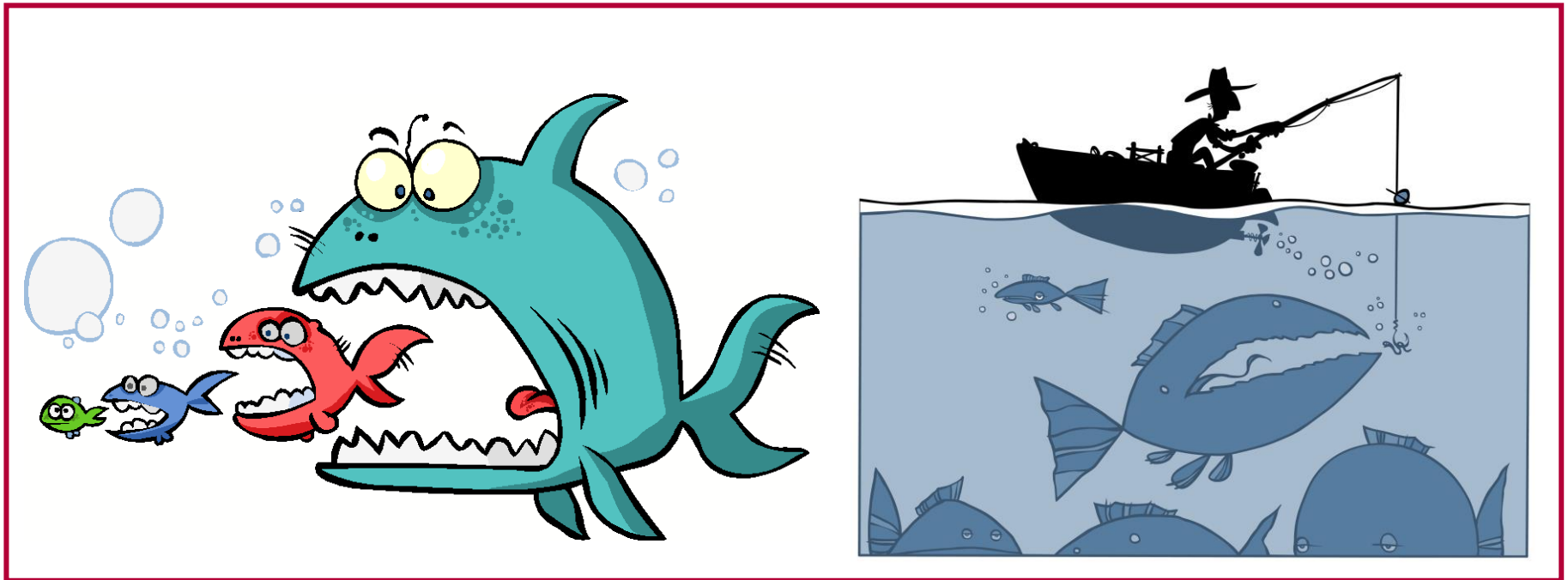
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Accumulation Bias framework

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Accumulation Bias framework

$$A(t)$$

Accumulation Bias Framework

$$A(t \mid z_1, \dots, z_t) := \mathbf{P}[\mathcal{A}^{(t)} \mid T \geq t, z_1, \dots, z_t] \\ \cdot S(t-1 \mid z_1, \dots, z_{t-1}),$$

Accumulation Bias Framework

$$A(t \mid z_1, \dots, z_t) := \mathbf{P}[\mathcal{A}^{(t)} \mid T \geq t, z_1, \dots, z_t] \\ \cdot S(t-1 \mid z_1, \dots, z_{t-1}),$$

where we define

$$S(t-1 \mid z_1, \dots, z_{t-1}) := \mathbf{P}[T \geq t \mid z_1, \dots, z_{t-1}].$$

Accumulation Bias Framework

$$A(t | z_1, \dots, z_t) := \mathbf{P}[\mathcal{A}^{(t)} \mid T \geq t, z_1, \dots, z_t] \\ \cdot S(t-1 | z_1, \dots, z_{t-1}),$$

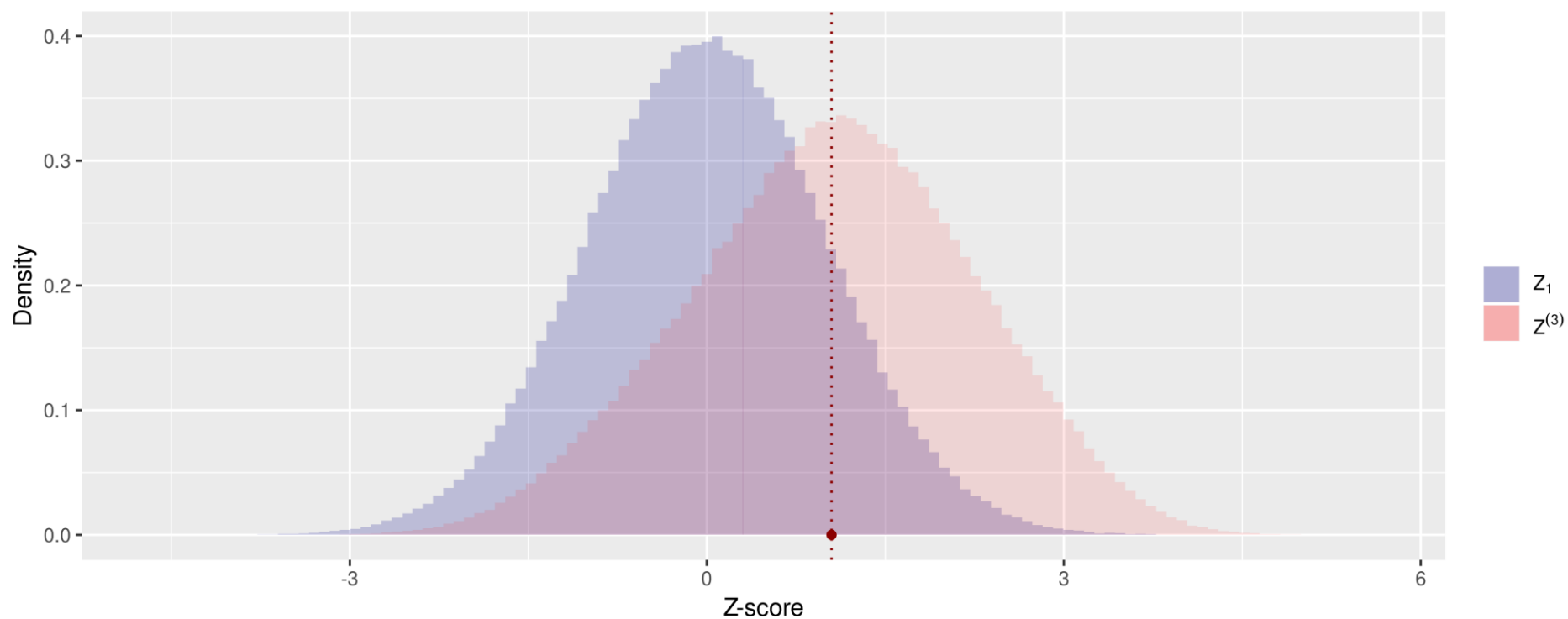
where we define

$$S(t-1 | z_1, \dots, z_{t-1}) := \mathbf{P}[T \geq t | z_1, \dots, z_{t-1}].$$

$$S(t-1 | z_1, \dots, z_{t-1}) = \prod_{i=0}^{t-1} (1 - \lambda(i | z_1, \dots, z_i)).$$

$$\lambda(t | z_1, \dots, z_t) := \mathbf{P}[T = t \mid T \geq t, z_1, \dots, z_t].$$

Accumulation Bias



$A(t)$

Early extreme contradictory estimates

The Proteus phenomenon

 $A(t)$

Regression to the Truth

fading

 $A(t)$

inflated,

 $A(t)$

exaggerated estimates

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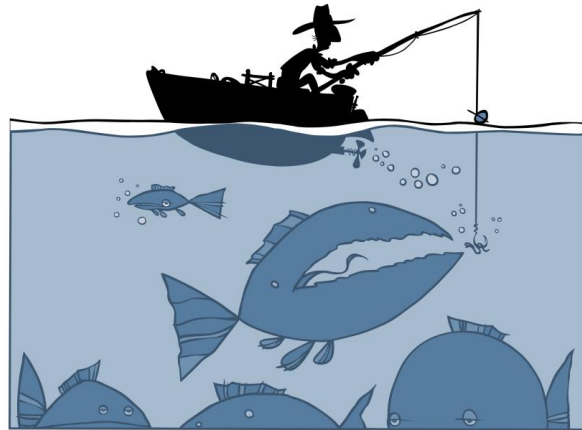
So, bias right?
How come we can
still do inference?

$$\mathbf{LR}_{10}^{(t)}$$

$$\mathbf{LR}_{10}^{(t)} = \frac{f_1(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)}$$

$$\begin{aligned}\mathbf{LR}_{10}^{(t)} &= \frac{f_1(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)}{f_0(z_1, \dots, z_t) \cdot A(t \mid z_1, \dots, z_t)} \\ &= \frac{f_1(z_1, \dots, z_t)}{f_0(z_1, \dots, z_t)} \\ &= \mathbf{LR}_{10}(z_1, \dots, z_t).\end{aligned}$$

- ter Schure J and Grünwald P. Accumulation Bias in meta-analysis: the need to consider *time* in error control
F1000Research 2019, **8**:962
(<https://doi.org/10.12688/f1000research.19375.1>)



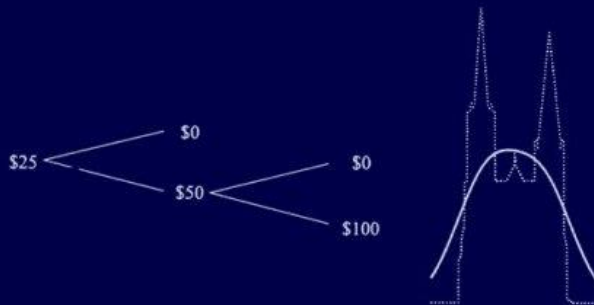
Accumulating Science needs Accumulating Tests



Probability and Finance

It's Only a Game!

Glenn Shafer
Vladimir Vovk



WILEY SERIES IN
PROBABILITY AND STATISTICS

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Glenn Shafer | Vladimir Vovk



Neyman Pearson *all-or-nothing* bet

$$\$_{NP} = 0 \quad \text{if } p\text{-value} > \alpha$$

$$\$_{NP} = \frac{1}{\alpha} \quad \text{if } p\text{-value} \leq \alpha$$

see

- Grünwald, De Heide & Koolen (2019)
- Shafer (2019)
and for the *all-or-nothing* strategy vs Kelly gambling, see:
- Tijms (2018)

Accumulating Science needs Likelihood Ratios



How to define a bet

Fair bet: $\mathbf{E}_0[s(Z_t)] = \$1.$

Reinvesting

$$s(Z_1) \cdot s(Z_2) \cdot s(Z_3)$$

How to define a bet: likelihood ratio!

Fair bet: $\mathbf{E}_0[s(Z_t)] = \$1.$

if we set $s(Z_t) = f_1(Z_t)/f_0(Z_t)$

$$\mathbf{E}_0\left[\frac{f_1(Z_t)}{f_0(Z_t)}\right] = \int_z f_0(z) \frac{f_1(z)}{f_0(z)} dz = \int_z f_1(z) dz = 1.$$

Reinvesting (i.i.d. studies!): $s(Z_1) \cdot s(Z_2) \cdot s(Z_3)$

How to turn the bet into a test

Universal bound / Robbins (1970) / Ville's inequality

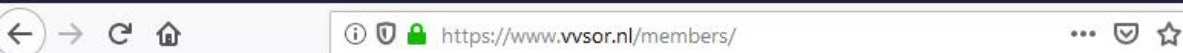
Likelihood ratios are martingales, therefore:

$$\mathbf{P}_0 \left[\exists t > 0 : \mathbf{LR}_{10}^{(t)}(Z_1, \dots, Z_t) \geq \frac{1}{\alpha} \right] \leq \alpha.$$

Safe Tests generalize Likelihood Ratios to common test scenarios

- T-test (one-sided, two-sided)
- Test of two proportions (contingency tables)
- LogRank test (survival / time-to-event analysis)
- Meta-Analysis under heterogeneity

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DE VVSOR REACTIE OP HET
CURRICULUM.NU VOORSTEL REKENEN &
WISKUNDE

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statistica neerlandica

Special Issue: Benchmarking, Temporal Disaggregation,
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Guest Editors: Baseline Chen, Tommaso Di Fonzo
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The screenshot shows the VVSOR website banner. At the top left is the VVSOR logo, which consists of a stylized blue and green starburst icon followed by the text 'VVSOR'. To the right of the logo is a navigation menu with the following items: 'HOME', 'ABOUT', 'PUBLICATIONS', 'MEMBERS', 'JOIN', and 'CONTACT'. Below the navigation menu is a large banner with a background image of a microscope lens. The banner contains the following text: 'SAMEN TILLEN WE DE KWALITEIT VAN NEDERLANDS COVID-19 ONDERZOEK NAAR EEN (NOG) HOGER PLAN' in small capital letters, followed by 'Covid-19 Protocol Review' in large, bold, white serif font. At the bottom of the banner, in a white box, is the text: 'Statistici slaan landelijk de (virtuele) handen ineen voor de kwaliteit van klinisch onderzoek naar covid-19' and 'Contact: covidprotocol@vvsor.nl'.

Vereniging voor Statistiek en Operations Research

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SAMEN TILLEN WE DE KWALITEIT VAN NEDERLANDS COVID-19 ONDERZOEK NAAR EEN (NOG) HOGER PLAN

Covid-19 Protocol Review

Statistici slaan landelijk de (virtuele) handen ineen voor de
kwaliteit van klinisch onderzoek naar covid-19

Contact: covidprotocol@vvsor.nl

Promote to send in a proposal for review!

Background reading (*more papers coming up*)

- ter Schure J and Grünwald P. Accumulation Bias in meta-analysis: the need to consider *time* in error control *F1000Research* 2019, **8**:96
- Grünwald, P., de Heide, R., & Koolen, W. (2019). Safe testing. *arXiv preprint arXiv:1906.07801*.
- Shafer, G. (2019). The language of betting as a strategy for statistical and scientific communication. *arXiv preprint arXiv:1903.06991*. (most current version: <http://probabilityandfinance.com/articles/54.pdf>)
- Package 'SafeStats' on CRAN and GitHub

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Thank you!

Contact me on: schure@cw.nl

penningmeester@vvsor.nl