META-RESEARCH: A Bird's Eye View of OA

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Disclosure Information

Money paid to the Parker Institute: Abbott/AbbVie, Amgen, HealthCare Pharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Cambridge Weight Plan, Eli Lilly, Genzyme, GSK, Hospira, Ipsen, Laboratoires Expanscience, LEO Pharma, MSD, Mundipharma/Norpharma, Novartis, Pfizer, Roche, Rottapharm|Madaus, Sobi, and Wyeth;

RC reports being involved in health-care initiatives and research that could benefit from wide uptake of meta- research (including Cochrane Collaboration, OMERACT, IDEOM, GRADE Working Group).

AND

My presentation does not include discussion of off-label or investigational use.

Cochrane

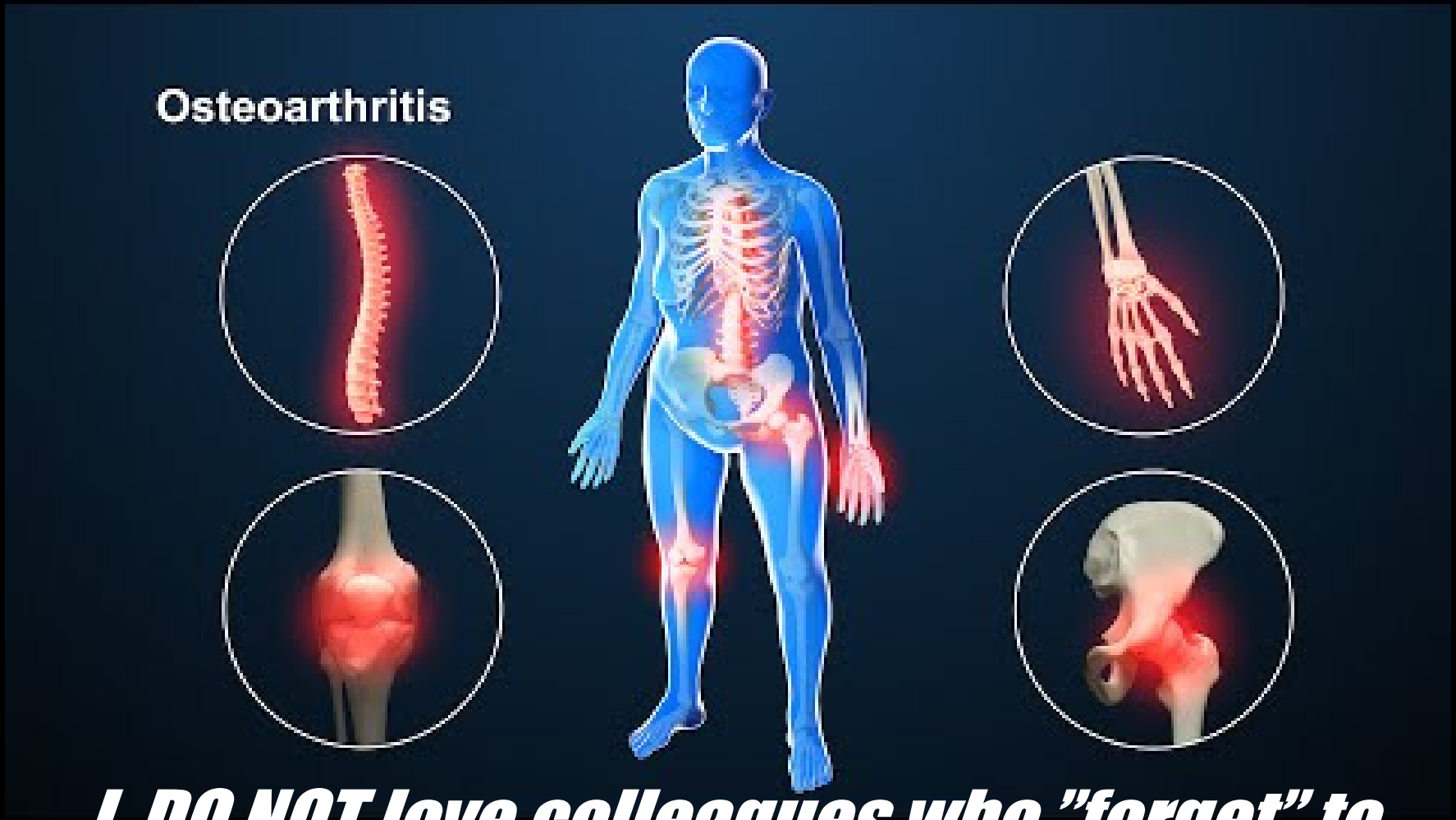
Trusted evidence.
Informed decisions.
Better health.

Cochrane Musculoskeletal establishes Satellite Gro

The University of Southern Denmark, working in close collaboration with the Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, has established a new Cochrane Musculoskeletal satellite which will gather, evaluate, and distribute reviews on the effects of intervention and preventions strategies for people with musculoskeletal diseases, especially osteoarthritis.

Under the direction of Hans Lund, Associate Professor at University of Southern Denmark and Professor at Bergen University College (HiB), a Nordic satellite of Cochrane Musculoskeletal Group has been founded. The satellite office for Coc Musculoskeletal will be closely related to the Research Unit for Musculoskeletal

”*Our patients*” DO <u>NOT</u> love having OA.....



I DO <u>NOT</u> love colleagues who ”forget” to publish their research findings....

Special Communication

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Research should be based on a thorough knowledge of the scientific background,

- a careful assessment of risks and benefits,
- have a reasonable likelihood of benefit to the population studied and
- be conducted by suitably trained investigators using approved protocols, subject to independent ethical review and oversight by a properly convened committee.
- The protocol should address the ethical issues and indicate that it is in compliance with the Declaration.
- Studies should be discontinued if the available information indicates that the original considerations are no longer satisfied.
- Information regarding the study should be publicly available.

Statistical Logic: Inductive Inference

A scientific theory need to be falsifiable……
- ie, we try to reject a Null-Hypothesis (*Ho*)

OMERACT-OARSI Response: $\pi_{\text{Intervention}} = \pi_{\text{Placebo}}$

KOOS-Pain Average: $\mu_{\text{Intervention}} = \mu_{\text{Placebo}}$

Correlation: $\rho_{X,Y} = 0$

Meta-Analysis

(your study will be part of one!)

- A meta-analysis combines the results of several studies that address a set of related research hypotheses

- Enables a generalization to the population of studies

- Higher statistical power to detect an effect than in any single study

- "*Easier*" to read 1 overall paper instead of all the individual papers

Systematic review and/or Meta-analysis

- Systematic Review:
  - The application of scientific strategies that limit bias to the systematic assessment, critical appraisal and synthesis of all relevant studies on a specific topic

- Meta-Analysis:
  - Statistical method(s) to combine (means and standard errors) and summarize the results of several studies; not necessarily systematic – "simple" estimation across

"A good meta-analysis can only be based on a thorough systematic review!"

Meta-Analysis of Trials: Effect Sizes

The choice vary with the type of data at hand.....

OMERACT-OARSI Response: $\pi_{\text{Intervention}} = \pi_{\text{Placebo}}$

KOOS-Pain Average: $\mu_{\text{Intervention}} = \mu_{\text{Placebo}}$

Correlation: $\rho_{X,Y} = 0$

Ost
the

Peter Jüni[*] MD

A novel OMERACT-COSMIN-COMET-GRADE.... effort

Consensus on the Need for a Hierarchical List of Patient-reported Pain Outcomes for Metaanalyses of Knee Osteoarthritis Trials: An OMERACT Objective

Robin Christensen, Lara J. Maxwell, Peter Jüni, David Tovey, Paula R. Williamson, Maarten Boers, Niti Goel, Rachelle Buchbinder, Lyn March, Caroline B. Terwee, Jasvinder A. Singh, and Peter Tugwell

Met
Em

How to select an outcome measure from trials (Without Bias)

Meta-Analysis:

an example ("single PICO")

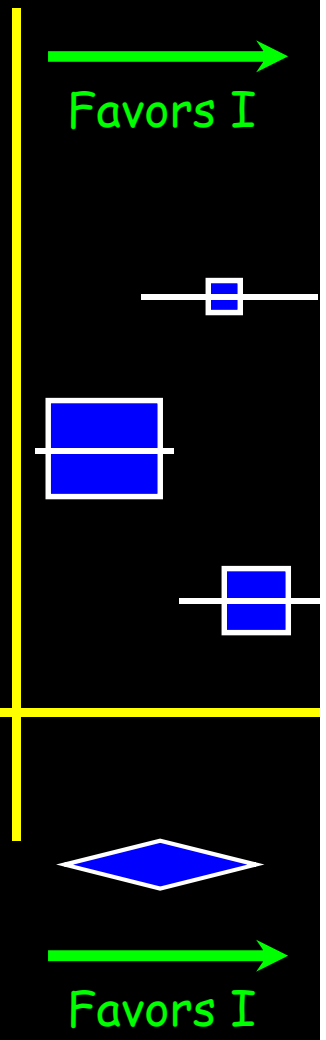
- Study #1: $I_1 - C_1 = ES_1$
- Study #2: $I_2 - C_2 = ES_2$
- Study #3: $I_3 - C_3 = ES_3$

- Meta-Analysis: $\Sigma\, ES_i \quad \Rightarrow$ Average $ES_{1\text{-}3}$

Meta-Analysis:

an example ("single PICO")

- Study #1: $I_1 - C_1 = ES_1$
- Study #2: $I_2 - C_2 = ES_2$
- Study #3: $I_3 - C_3 = ES_3$



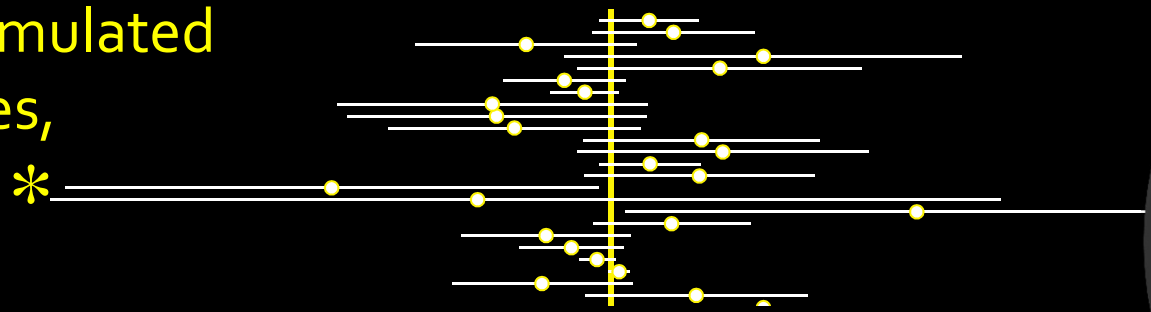
- Meta-Analysis: $\Sigma\, ES_i \quad \Rightarrow$ Average $ES_{1\text{-}3}$

Meta-Analysis of Trials:

What's likely gonna happen when you introduce - and test - a novel (promising) intervention in OA ?

We should be able to "live with" a null effect……

From 100 simulated studies,



The question is:

"What will happen if we only get access to "significant" findings"?

= Evidence-based medicine gets useless!

Is it difficult to win on the Roulette?

No it is not! ;

But it is difficult to get money out of it


You shouldn't be too impressed if a colleague tell you it's possible to "win" (*without knowing how much they've gambled for*)
Impressed?
You shouldn't trust a *p*-value without knowing where it came from

Since March 2016 - leading "statistical authorities" have banned the use of *p*-values

ASA News

AMERICAN STATISTICAL ASSOCIATION
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AMERICAN STATISTICAL ASSOCIATION RELEASES STATEMENT ON STATISTICAL SIGNIFICANCE AND *P*-VALUES

Provides Principles to Improve the Conduct and Interpretation of Quantitative Science

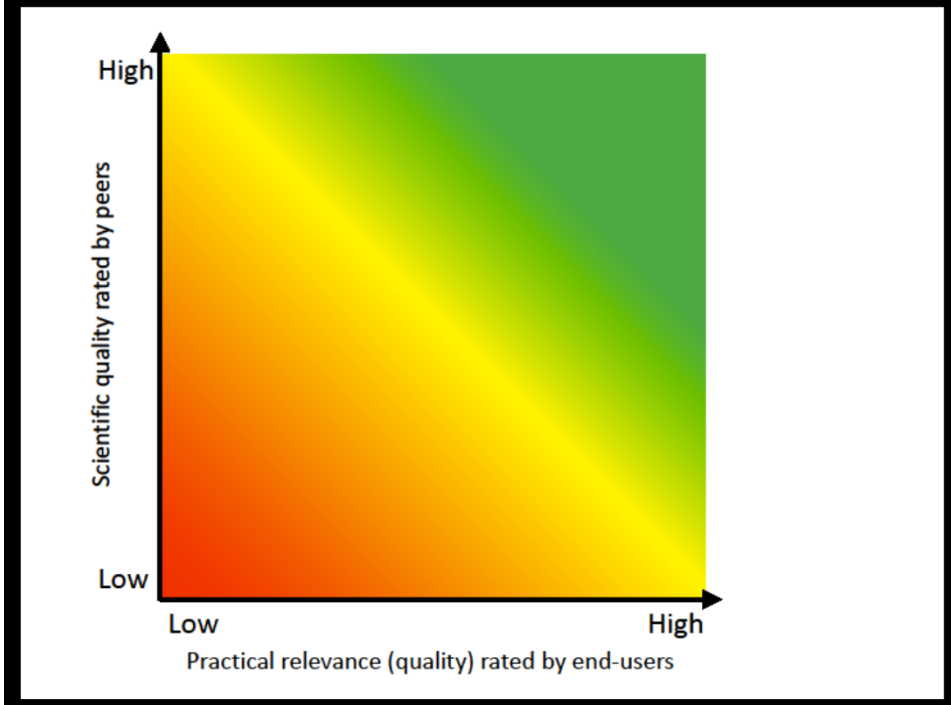
March 7, 2016

My POV:

In order for the OA-community to "*trust a significant finding*", a pre-specified protocol needs to be available to the public!

Before initiating a study:

(ask yourself)
Would the null-finding be exciting on its own?



Subsequently, ask yourself "what will be the impact" envisioning the null-hypothesis to be accepted?

Henriksen M & Ch

Some famous null-findings.....

Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up

thebmj

Nina Jullum Kise,[1] May Arna Risberg,[2,3,4] Silje Stensrud,[2] Jonas Ranstam,[5] Lars Engebretsen,[3,6,7] Ewa M Roos[8]

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Daniel O. C
James R. O
Michael H
Larry W. Mor
Jerry A. Molitor, M
Helen Shi,

ORIGINAL ARTICLE

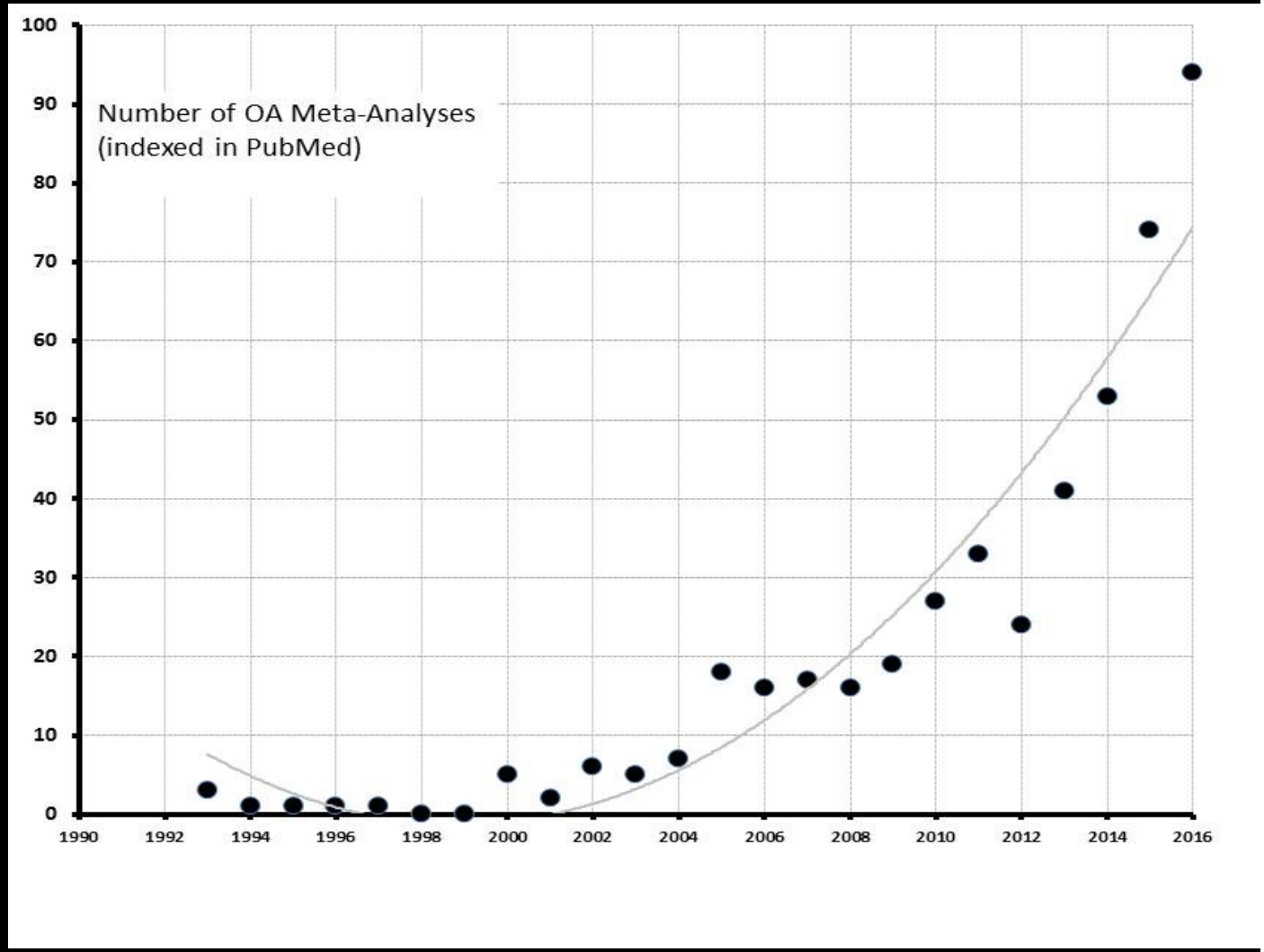
A Randomized Trial of Treatment for Acute Anterior Cruciate Ligament Tears

Richard B. Frobell, Ph.D., Ewa M. Roos, P.T., Ph.D., Harald P. Roos, M.D., Ph.D., Jonas Ranstam, Ph.D., and L. Stefan Lohmander, M.D., Ph.D.

META-RESEARCH:
Far too many meta-analyses?

Too many meta-analyses recent years (almost 100 in 2016)
- incl. redundancies

Meta-research can help us explore various limitations in current res. practice



META-RESEARCH: What it is…

PLOS | BIOLOGY
October 2, 2015

Meta-research: Evaluation and Improvement of Research Methods and Practices

John P. A. Ioannidis*, Daniele Fanelli, Debbie Drake Dunne, Steven N. Goodman

Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California, United States of America

…. an evolving scientific discipline that aims to evaluate and improve research practices.

…. includes thematic areas of methods, reporting, reproducibility, evaluation, and incentives (how to do, report, verify, correct, and reward science).

Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study

BMJ

Eveline Nüesch, research fellow,[1,2] Sven Trelle, associate director,[1,2] Stephan Reichenbach, senior research fellow,[1,3] Anne W S Rutjes, senior research fellow,[1,4] Beatrice Tschannen, research fellow,[1] Douglas G Altman, director and professor of statistics in medicine,[5] Matthias Egger, head of department and professor of epidemiology and public health,[1] Peter Jüni, head of division and professor of clinical epidemiology[1,2]

T P Meta-Epidemiologic Study

EVELINE NÜESCH,[1] STEPHAN REICHENBACH,[2] SVEN TRELLE,[1] ANNE W. S. RUTJES,[3] KATHARINA LIEWALD,[4] REBEKKA STERCHI,[4] DOUGLAS G. ALTMAN,[5] AND PETER JÜNI[1]

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 12, December 15, 2009, pp 1633–1641

BMJ

The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study

Eveline Nüesch, research fellow,[1,2] Sven Trelle, associate director,[1,2] Stephan Reichenbach, senior research fellow,[1,3] Anne W S Rutjes, senior research fellow,[1,4] Elizabeth Bürgi, research fellow,[5] Martin Scherer, professor of health services research,[6,7] Douglas G Altman, professor of statistics in medicine,[8] Peter Jüni, head of division[1,2]

RESEARCH on RESEARCH: Evidence-Based Research!

Towards evidence based research

To avoid waste of research, no new studies should be done without a systematic review of existing evidence, argue **Hans Lund and colleagues**

Hans Lund *professor*[1 2], Klara Brunnhuber *product manager*[3], Carsten Juhl *associate professor*[1 4], Karen Robinson *associate professor*[5], Marlies Leenaars *associate professor*[6], Bertil F Dorch *director*[7], Gro Jamtvedt *dean*[2 8], Monica W Nortvedt *dean*[2], Robin Christensen *professor*[9], Iain Chalmers *coordinator*[10]

thebmj

- In order to INCREASE value and REDUCE waste in OA research, we need to be proud of performing research on our methodologies.
- To avoid waste of research, no new studies should be done without a systematic review of existing evidence.

TAKE HOME MESSAGES:
Meta-Research in OA

- Encourage our colleagues to publish negative findings
- When designing new studies (incl basic science) – consider how you'll interpret a negative finding(?)
- A "significant *p*-value" shouldn't be used as a proxy for a good study outcome

- (Rather) A good "exciting protocol" = an exciting project !!!

- I would encourage more research on OA research…..

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