Avoidable Waste in Research: the problem and some solutions

Paul Glasziou, Bond University

www.crebp.net.au

equator network

Enhancing the QUAlity and Transparency Of health Research

Ottawa

Oxford
Paris

Gold Coast

REWARD

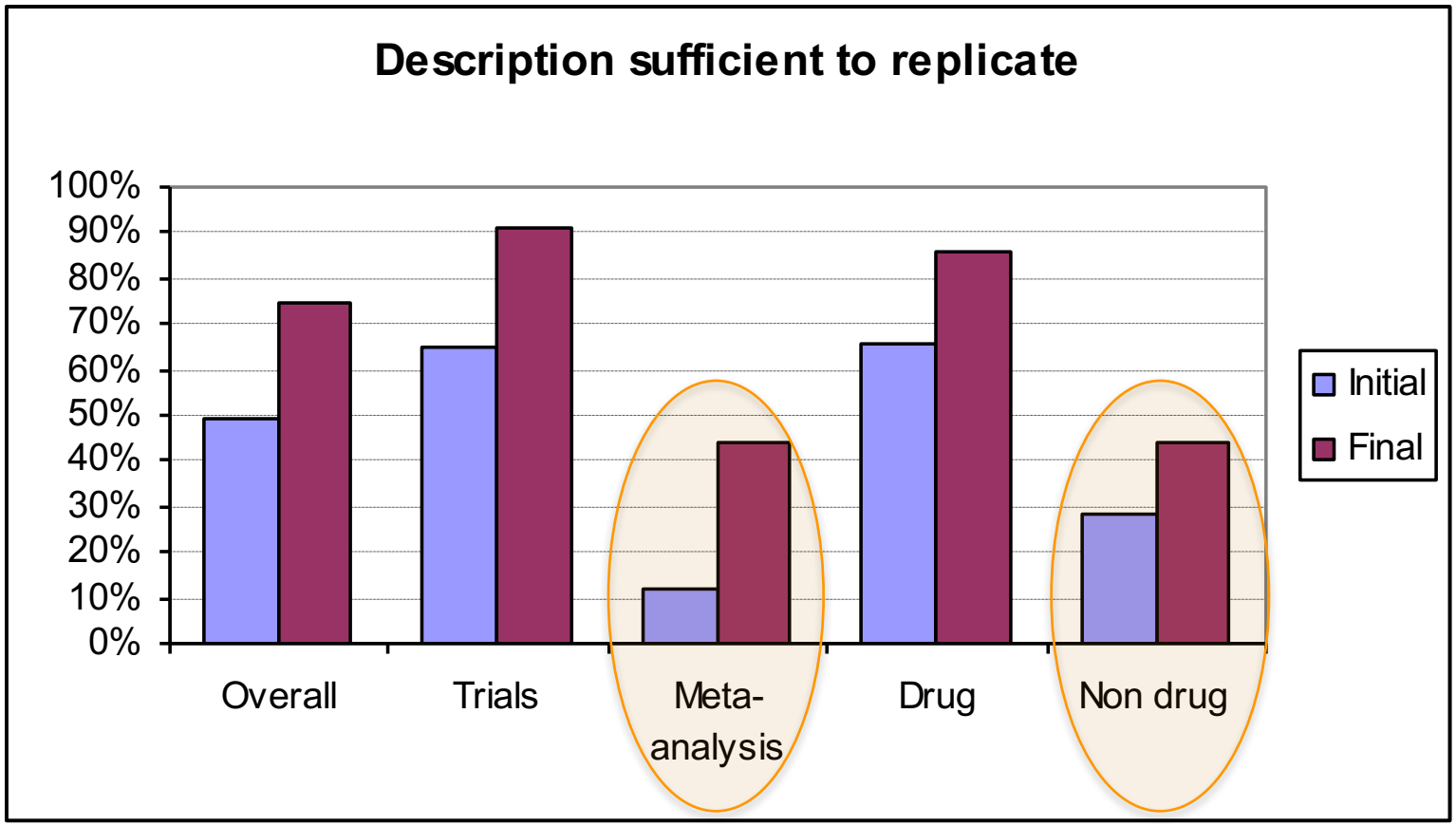
REduce research Waste And Reward Diligence

Life sciences research in 2010: US$ 240,000,000,000

85% wasted

Lancet 2013;382:1286-307 and *Lancet* 2009;374:86–9

Descriptions in 80 **successful** treatment studies selected for EBM journal were often inadequate



Glasziou, Heneghan, Meats BMJ, 2008

Waste in research

Questions relevant to clinicians & patients?

Low priority questions

Unbiased and usable report?

Over 30% of trial

Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou

www.thelancet.com **Published online June 15, 2009**

agendas

not interpreted in the

Questions relevant to clinicians and patients?	→	Appropriate design and methods?	→	Accessible full publication?	→	Unbiased and usable report?

85% Research waste = over $100 Billion / year

Lancet Adding Value, Reducing Waste 2014
www.researchwaste.net

Five stages of waste in research

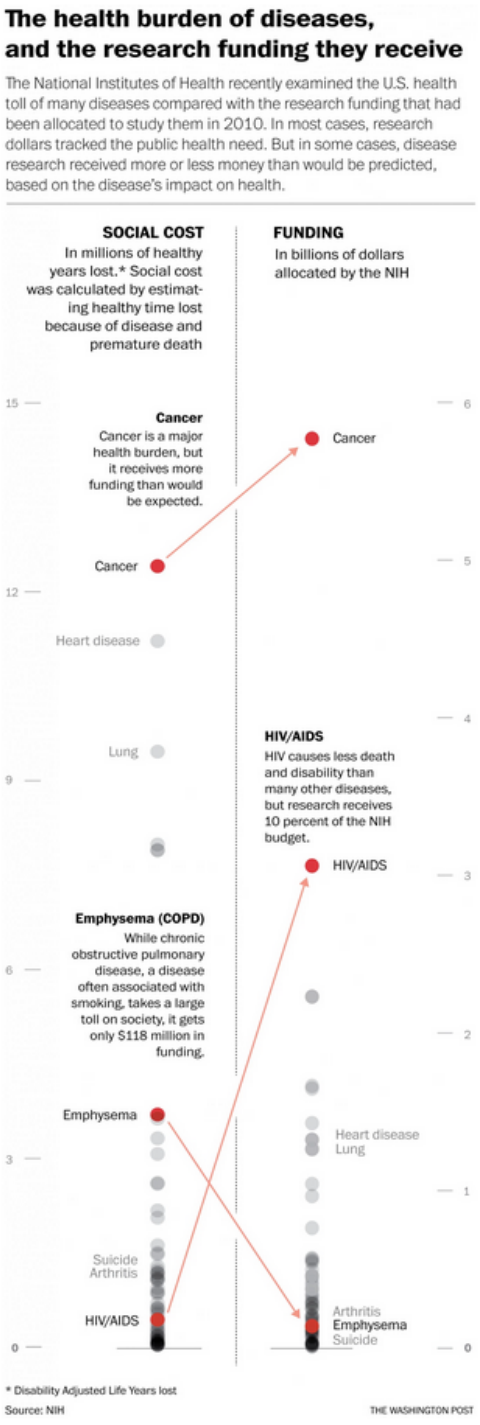
Questions relevant to users of research?	Appropriate research design, conduct and analysis?	Efficient research regulation and delivery?	Accessible, full research reports?	Unbiased and usable reports?
High priority questions addressed	Studies designed with reference to systematic reviews of existing evidence	Appropriate regulation of research	Studies published in full	Trial interventions sufficiently described
Important outcomes assessed	Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation	Efficient delivery of research	Reporting of studies with disappointing results	Reported planned study outcomes
Clinicians and patients involved in setting research agendas		Good re-use of data		New research interpreted in the context of systematic assessment of relevant evidence

Adding Value in Research framework

Mismatch of burden & research funding

- Research funding often poorly aligned with disease burden
- Research questions poorly aligned with patient & clinicians priorities

- www.nimh.nih.gov/funding/funding-strategy-for-research-grants/the-anatomy-of-nimh-funding.shtml



The unnecessary death of Ellen Roche

During PubMed searches,
"hexamethonium inhalation lung injury" gave 0 hits,
"hexamethonium inhalation" gave 42 hits (none referring to pulmonary toxicity),
"hexamethonium lung" yielded 3 useful articles,
"hexamethonium lung toxicity" gave 4 hits, but 0 useful articles,
"hexamethonium lung hypersensitivity" gave 16 hits with 3 useful articles, and
"hexamethonium lung fibrosis" gave 3 hits and 2 useful articles;
(4) the Micromedex data base had lung toxicity as the first adverse effect of hexamethonium.

Savulescu J. J Med Ethics 2002;28:3-4

Lancet Adding Value, Reducing Waste 2014
www.researchwaste.net

Five stages of waste in research

Questions relevant to users of research?	Appropriate research design, conduct and analysis?	Efficient research regulation and delivery?	Accessible, full research reports?	Unbiased and usable reports?
High priority questions addressed	Studies designed with reference to systematic reviews of existing evidence	Appropriate regulation of research	Studies published in full	Trial interventions sufficiently described
Important outcomes assessed	Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation	Efficient delivery of research	Reporting of studies with disappointing results	Reported planned study outcomes
Clinicians and patients involved in setting research agendas		Good re-use of data		New research interpreted in the context of systematic assessment of relevant evidence

Adding Value in Research framework

New research should build on previous research

Very Early Nimodipine Use in Stroke (VENUS)
A Randomized, Double-Blind, Placebo-Controlled Trial

J. Horn, MD; R.J. de Haan, PhD; M. Vermeulen, MD, PhD; M. Limburg, MD, PhD

Backgound and Purpose—The Very Early Nimodipine Use in Stroke (VENUS) trial was designed to test the hypothesis that early treatment with nimodipine has a positive effect on survival and functional outcome after stroke. This was suggested in a previous meta-analysis on the use of nimodipine in stroke. However, in a recent Cochrane review we were unable to reproduce these positive results. This led to the early termination of VENUS after an interim analysis.

Methods—In this randomized, double-blind, placebo-controlled trial, treatment was started by general practitioners or neurologists within 6 hours after stroke onset (oral nimodipine 30 mg QID or identical placebo, for 10 days). Main analyses included comparisons of the primary end point (poor outcome, defined as death or dependency after 3 months) and secondary end points (neurological status and blood pressure 24 hours after inclusion, mortality after 10 days, and adverse events) between treatment groups. Subgroup analyses (on final diagnosis and based on the per-protocol data set) were performed.

Results—At trial termination, after inclusion of 454 patients (225 nimodipine, 229 placebo), no effect of nimodipine was found. After 3 months of follow-up, 32% (n=71) of patients in the nimodipine group had a poor outcome compared with 27% (n=62) in the placebo group (relative risk, 1.2; 95% CI, 0.9 to 1.6). A treatment effect was not found for secondary outcomes and in the subgroup analyses.

Conclusions—The results of VENUS do not support the hypothesis of a beneficial effect of early nimodipine in stroke patients. **(*Stroke*. 2001;32:461-465.)**

Key Words: calcium channel blockers ■ cerebrovascular disorders ■ nimodipine ■ randomized controlled trials

New research should build on previous research

Nimodipine in Animal Model Experiments of Focal Cerebral Ischemia

A Systematic Review

J. Horn, MD; R.J. de Haan, PhD; M. Vermeulen, MD; P.G.M. Luiten, PhD; M. Limburg, MD

"20 studies were included. The methodological quality of the studies was poor."

"The results of this review did not show convincing evidence to substantiate the decision to perform trials with nimodipine in large numbers of patients."

Stroke 2001

Was enrolling 7,500 patients justified?

- VENUS trial -> 454 patients
- 28 human studies with 7,500 patients
- -> No clear effect

- 20 animal studies -> no clear effect

3 Research funders and regulators should demand that proposals for additional primary research are justified by systematic reviews showing what is already known, and increase funding for the required syntheses of existing evidence

- Monitoring—audit proposals for and reports of new primary research

REWARD
REduce research Waste And Reward Diligence

Research Paper

Multiple Sclerosis

Improving the translational hit of experimental treatments in multiple sclerosis

Multiple Sclerosis
0(00) 1–12

DOI: 10.1177/1352458510379612
msj.sagepub.com
SAGE

Hanna M. Vesterinen, Emily S. Sena, Charles ffrench-Constant, Anna Williams, Siddharthan Chandran and Malcolm R. Macleod

METHODS:
A systematic review of the literature describing experiments testing the effectiveness of interventions in animal models of multiple sclerosis was carried out.
RESULTS:
The use of a drug in a pre-clinical multiple sclerosis model was reported in 1152 publications, of which 1117 were experimental autoimmune encephalomyelitis (EAE). For 36 interventions analysed in greater detail, neurobehavioural score was improved by 39.6% …
CONCLUSIONS:
EAE has proven to be a valuable model in elucidating pathogenesis as well as identifying candidate therapies for multiple sclerosis … Our analysis provides an estimate of sample size required for different levels of power in future studies and suggests a number of interventions for which there are substantial animal data supporting efficacy.

Lancet Adding Value, Reducing Waste 2014
www.researchwaste.net

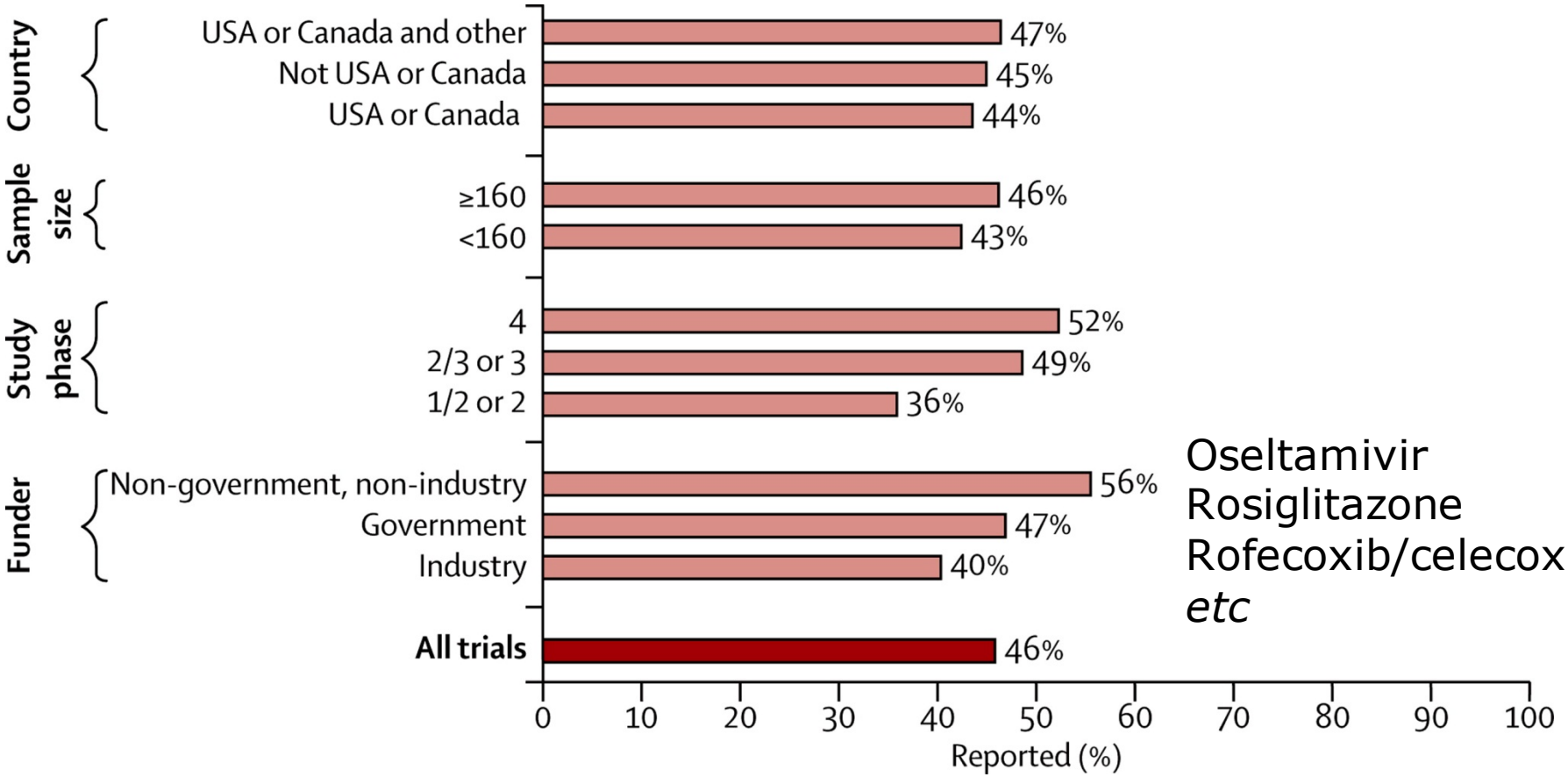
Five stages of waste in research

Questions relevant to users of research?	Appropriate research design, conduct and analysis?	Efficient research regulation and delivery?	Accessible, full research reports?	Unbiased and usable reports?
High priority questions addressed	Studies designed with reference to systematic reviews of existing evidence	Appropriate regulation of research	Studies published in full	Trial interventions sufficiently described
Important outcomes assessed	Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation	Efficient delivery of research	Reporting of studies with disappointing results	Reported planned study outcomes
Clinicians and patients involved in setting research agendas		Good re-use of data		New research interpreted in the context of systematic assessment of relevant evidence

Adding Value in Research framework

Half of research is not published

Associations with reporting



Oseltamivir
Rosiglitazone
Rofecoxib/celecoxib
etc

Lancet 2014;383:257–66

REWARD
REduce research Waste And Reward Diligence

Why don't researchers publish?

Original article

Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer

E. Lindholm, H. Brevinge and E. Haglind J. Kewenter (deceased)

Department of Surgery, Institute of Surgical Sciences, Göteborg University, Sahlgrenska University Hospital, Göteborg, Sweden
Correspondence to: Dr E. Haglind, Bruna Stråket 11B, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden (e-mail: eva.haglind@vgregion.se)

Methods

All 68 308 citizens in Göteborg born between 1918 and 1931, and aged 60–64 years, were recruited through the local population register for inclusion in the trial. To

British Journal of Surgery 2008; **95**: 1029–1036

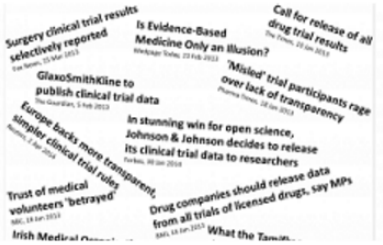
Follow-up

According to the trial protocol, the mortality analysis was planned for 31 December 2001. This resulted in a mean follow-up time of 15 years and 6 months (range 11 years

AllTrials

All Trials Registered | All Results Reported

Home | Find out more | Get involved | Supporters | News | **Sign the petition** | **Donate** | Q



Lancet Adding Value, Reducing Waste 2014
www.researchwaste.net

Five stages of waste in research

Questions relevant to users of research?	Appropriate research design, conduct and analysis?	Efficient research regulation and delivery?	Accessible, full research reports?	Unbiased and usable reports?
High priority questions addressed	Studies designed with reference to systematic reviews of existing evidence	Appropriate regulation of research	Studies published in full	Trial interventions sufficiently described
Important outcomes assessed	Studies take adequate steps to reduce biases - e.g. unconcealed treatment allocation	Efficient delivery of research	Reporting of studies with disappointing results	Reported planned study outcomes
Clinicians and patients involved in setting research agendas		Good re-use of data		New research interpreted in the context of systematic assessment of relevant evidence

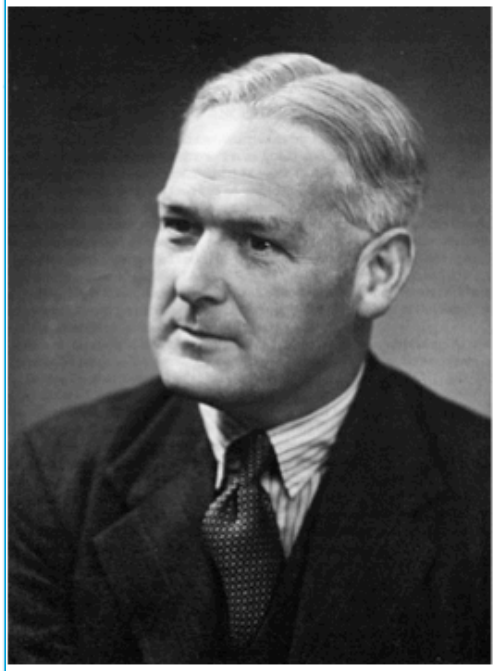
Adding Value in Research framework

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 Moher, Elizabeth Wager

Good Reporting of Clinical Trials



Austin Bradford Hill, 1965

Four questions to which readers want answers when reading reports of research.

1. Why did you start?
2. **What did you do?**
3. What answer did you get?
4. And what does it mean anyway?

Unbiased and usable reports?

- Trial interventions sufficiently described
- Reported planned study outcomes
- New research interpreted in the context of systematic assessment of relevant evidence

Adding Value in Research framework

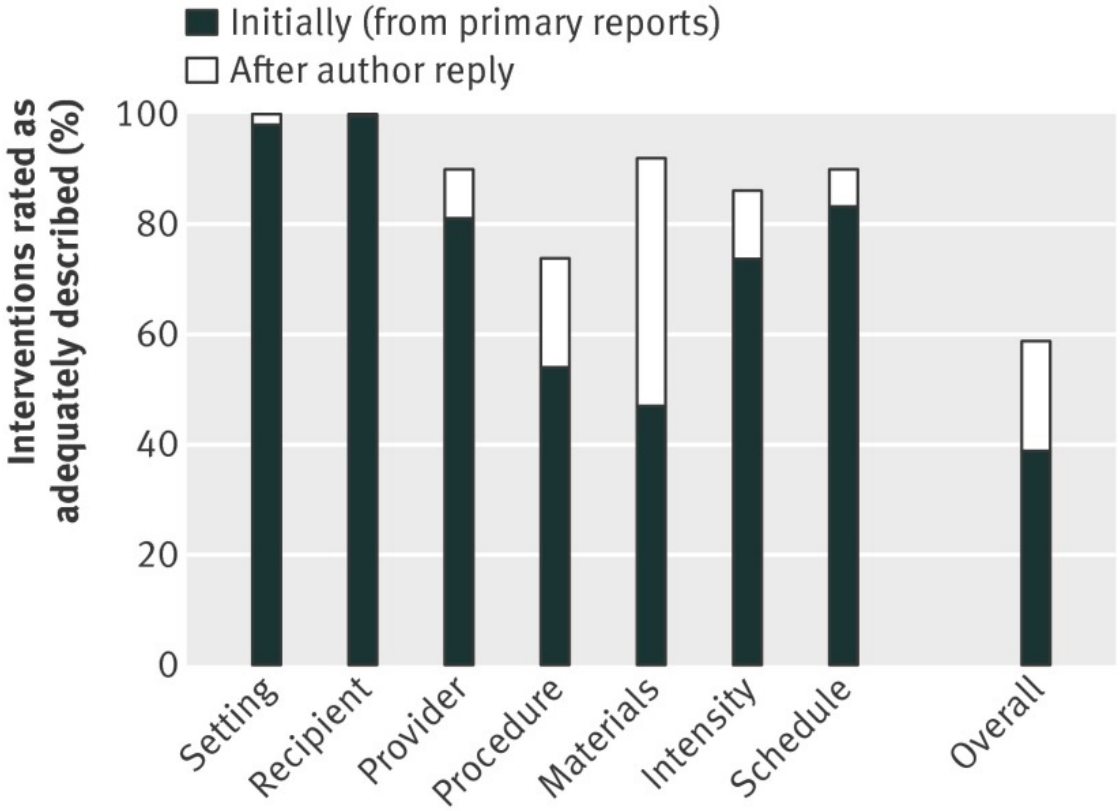
Reports of Randomized Trials are often missing essential methods

	Dec 2000 (N=519)	Dec 2006 (N=616)
Defined primary outcome(s)	**45%**	**53%**
Sample size calculation	**27%**	**45%**
Method of random sequence generation	**21%**	**34%**
Method of allocation concealment	**18%**	**25%**
Whether blinded	**40%**	**41%**

[Chan & Altman, *Lancet* 2005; Hopewell et al, *BMJ* 2010]

equator network

Poor reporting of non-pharmacological interventions in 6 major medical journals



Of 133 trials in 2010

59% adequate after contacting author

39% adequate in primary sources

Hoffmann, Erueti, Glasziou. Poor description of non-pharmacological interventions: A remediable barrier to evidence use in practice? BMJ 2013

REWARD
REduce research Waste And Reward Diligence

The TIDieR checklist (1-7)

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.		
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.		

Poor reporting in publications: range of 24% to 89% "missing"

Abstract
38%, 49%

Methods
40-89%, 33%
65%, 31%

Results
50%, 65%,
54%, 92%,
24%, 40%

Discussion
50%

Data
Almost all

Abstract

Trials: missing effect size and confidence interval (38%); no mention of adverse effects (49%)[72]

Methods

Trials: 40–89% inadequate treatment descriptions[11, 13]
fMRI studies: 33% missing number of trials and durations[3]
Survey questions: 65% missing survey or core questions[25]
Figures: 31% graphs ambiguous[45]

Results

Clinical trials: outcomes missing: 50% efficacy and 65% harm outcomes per trial incompletely reported[6]
Animal studies: number of animals and raw data missing[17] (54%, 92%); age and weight missing (24%)
Diagnostic studies: missing age and sex (40%)[15]

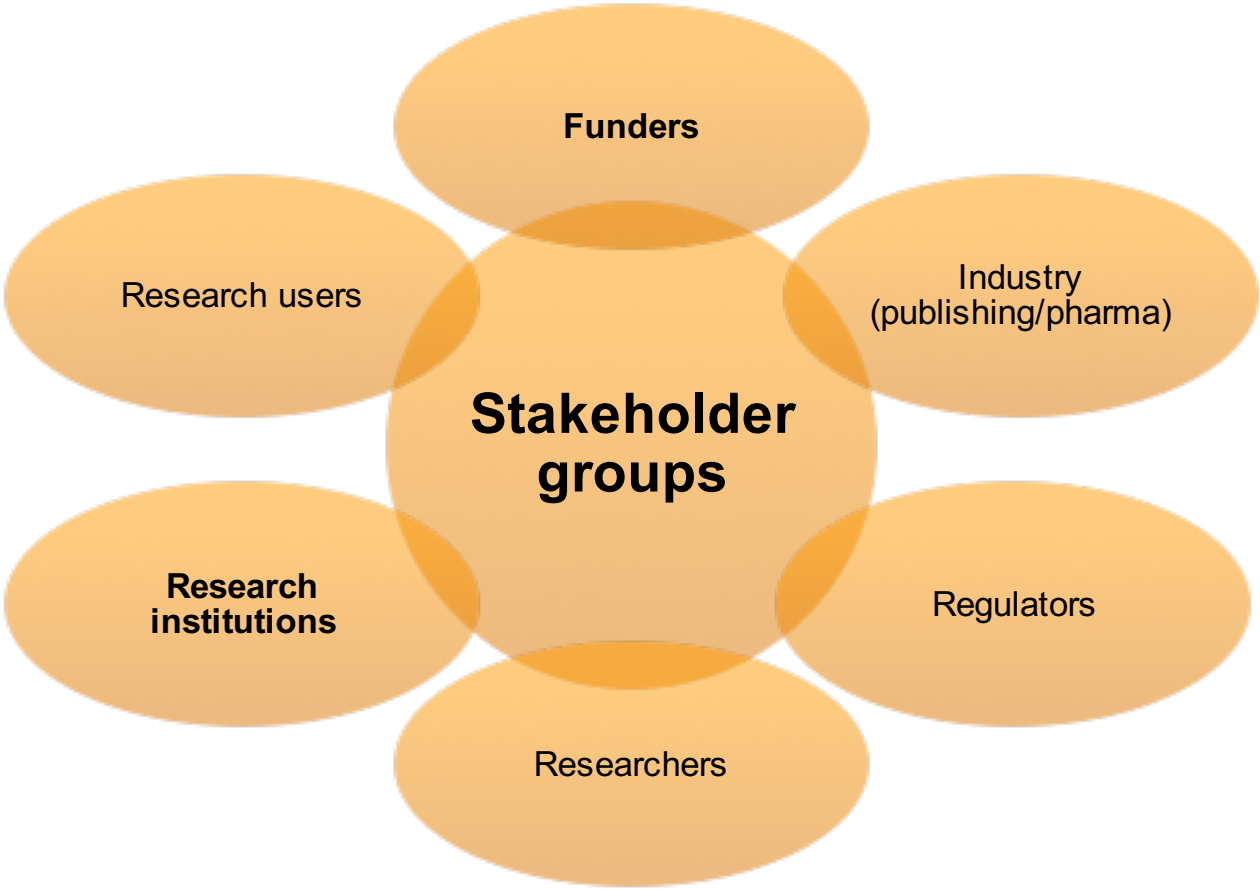
Discussion

Trials: no systematic attempt to set new results in context of previous trials (50%)[69]

Data

Trials: most data never made available; author-held data lost at about 7% per year

17 recommendations*, and how to monitor progress



* www.RewardAlliance.net

REWARD
REduce research Waste And Reward Diligence

Partner *The Lancet*'s REWARD campaign!

- Priorities
- Design, conduct, analysis
- Regulation and management
- Accessibility
- Complete and usable reporting
- Action and recommendations
- Statement

www.thelancet.com/campaigns/efficiency