

La campagna Lancet-REWARD:
ridurre gli sprechi e premiare
il rigore scientifico

Iain Chalmers
Coordinator, James Lind Initiative

GIMBE Convention Nazionale
Bologna, 9 novembre 2016

Some highlights over the past 40 years of
my association with Italian colleagues



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Milan, Italy, May 2-4, 1977

Final Program

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Clinical Pharmacology and Drug Epidemiology

1

**Epidemiological
Evaluation
of
Drugs**

F. Colombo
S. Shapiro
D. Slone
G. Tognoni
Editors

Elsevier/North-Holland

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI
NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p=0\cdot0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0-3, 3-6, 6-9, and 9-12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

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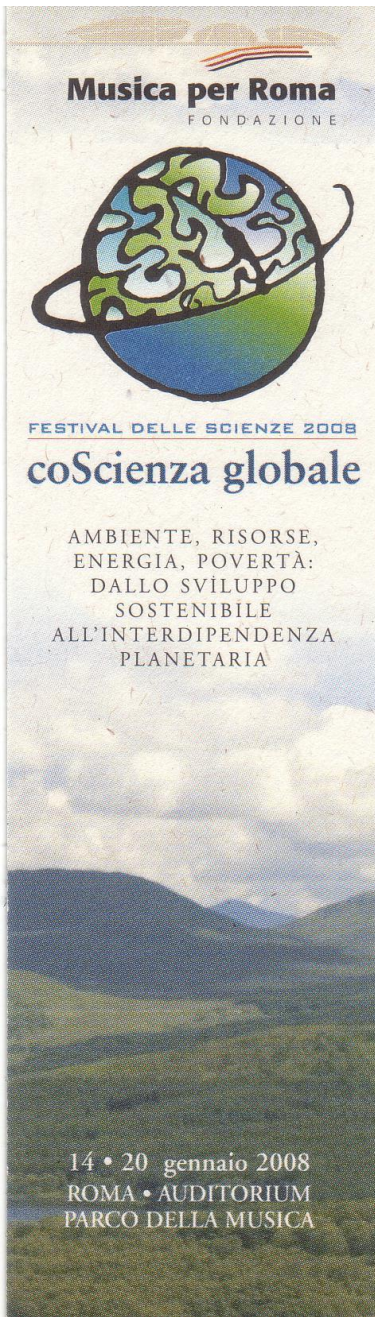
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IL FUTURO DELLA MEDICINA

Iain Chalmers, Silvio Garattini
Introduce Gianna Milano

**'How can the research community
serve the information needs of
patients, clinicians and the public
more effectively?'**

Iain Chalmers

James Lind Initiative, Oxford, UK

Silvio Garattini

Istituto Mario Negri, Milano, Italy

Rome International Science Festival
20 January 2008

Patients and the public deserve big changes in evaluation of drugs

Silvio Garattini and **Iain Chalmers** argue that ending the secrecy surrounding drug trials would benefit all parties [BMJ](#) | 4 APRIL 2009 | VOLUME 338

The monopoly that the drugs industry has in evaluating its own products, and the secrecy surrounding this process, leads to biased evidence that is currently only rarely questioned by independent studies.²¹

Italian law requires all drug companies operating in Italy to pay 5% of their promotional expenses to the agency to support independent clinical research

Agenzia Italiana del Farmaco

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Ben Goldacre

Bestselling author of *Bad Science*

How drug companies
mislead doctors and
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DONALD W. LIGHT AND ANTONIO F. MATURO

G  D
PHARMA

THE PUBLIC-HEALTH MODEL OF THE
MARIO NEGRI INSTITUTE

La campagna Lancet-REWARD: ridurre gli sprechi e premiare il rigore scientifico

Evolution of concern about waste in research

1994



Editorials



“

A core principle of all our applied statistical and methodological research is that it has the potential to benefit patients.

- Doug Altman
Director of CSM and UK EQUATOR Centre

The scandal of poor medical research

BMJ 1994; 308 doi: <http://dx.doi.org/10.1136/bmj.308.6924.283> (Published 29 January 1994)

What should we think about researchers who use the wrong techniques, use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common.

This is surely a scandal.

We need less research, better research, and research done for the right reasons.

Recent evolution of concern about waste in research

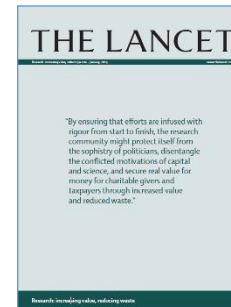
2009

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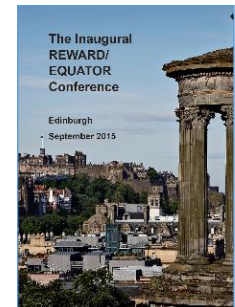
2014

42



2015

236



The BMJ

Paul Glasziou and Iain Chalmers: Is 85% of health research really “wasted”?

14 Jan, 16 | by BMJ



Our estimate that 85% of all health research is being avoidably “wasted” [Chalmers & Glasziou, 2009] commonly elicits disbelief. Our own first reaction was similar. “that can’t be right?” Not only did 85% sound too much, but given that \$200 billion per year is spent globally on health and medical research, it implied an annual waste of \$170 billion. That amount ranks somewhere between the GDPs of Kuwait and Hungary. It seems a problem worthy of serious analysis and attention.

"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

Lancet Adding Value, Reducing Waste 2014

www.researchwaste.net

NIHR Adding Value in Research Framework



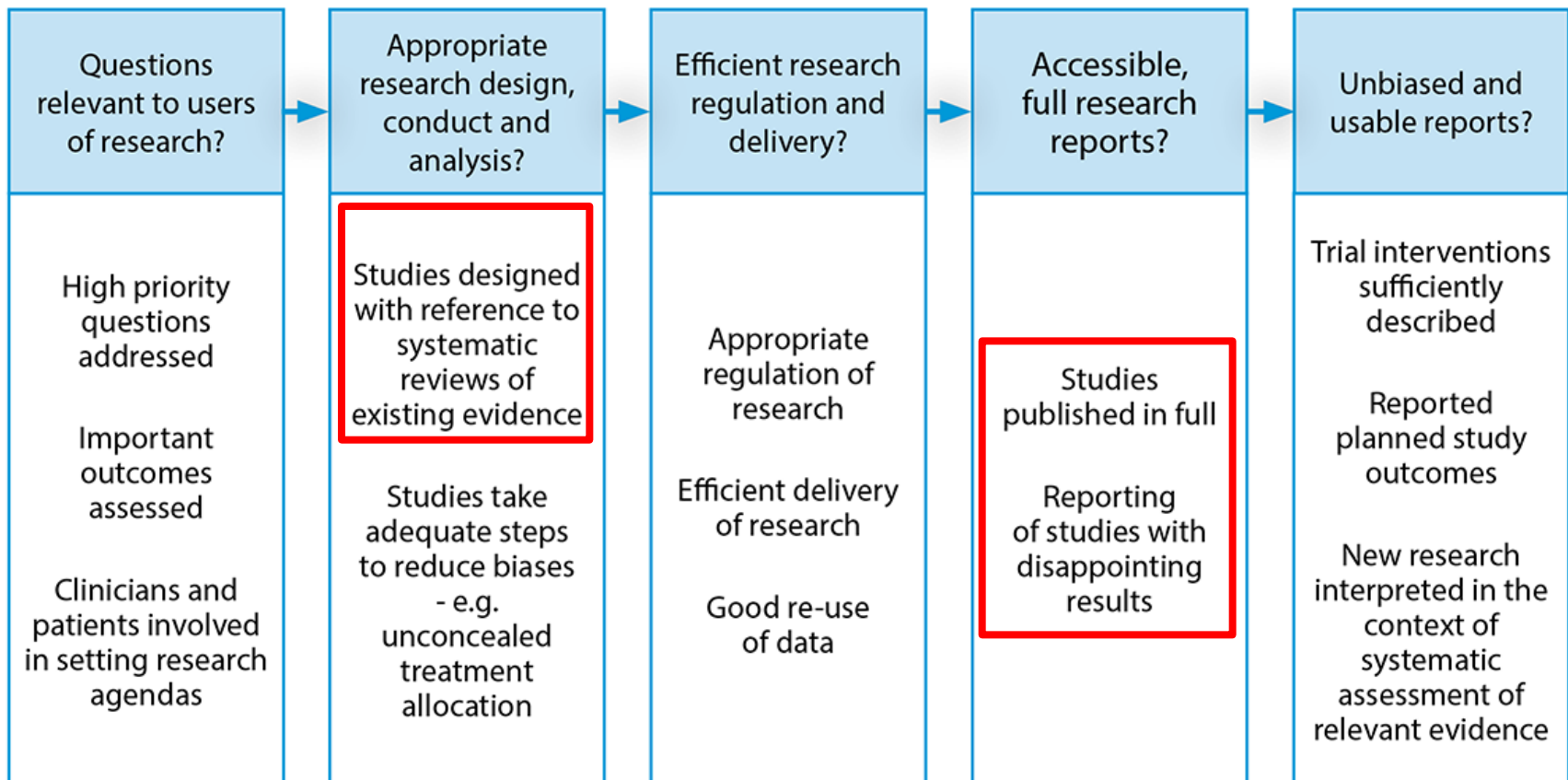
"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

Lancet Adding Value, Reducing Waste 2014

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NIHR Adding Value in Research Framework

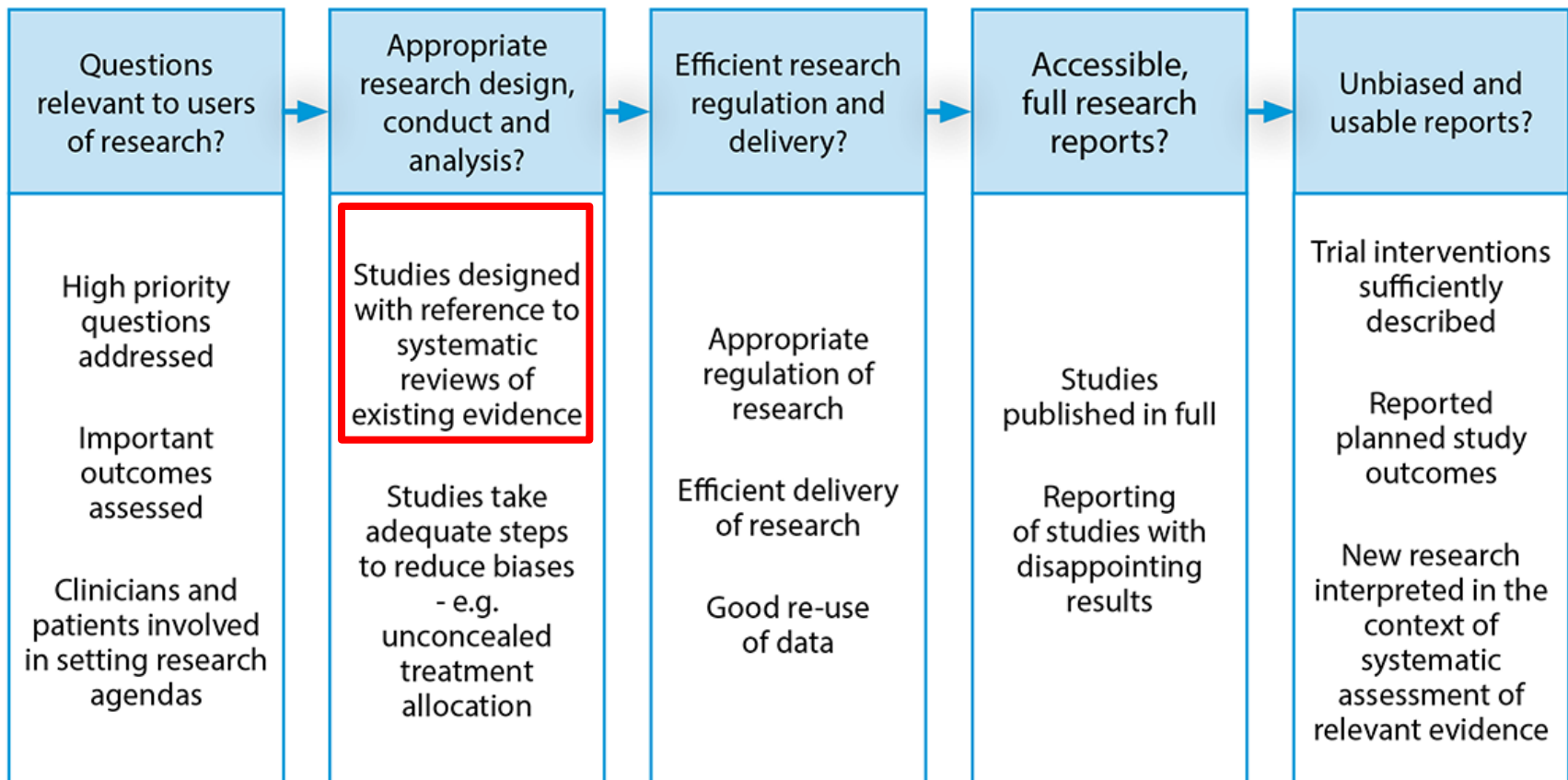


"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

Lancet Adding Value, Reducing Waste 2014

www.researchwaste.net

NIHR Adding Value in Research Framework



1. Waste resulting from funding and endorsing unnecessary or badly designed research

Need to realign patient-oriented and commercial and academic research



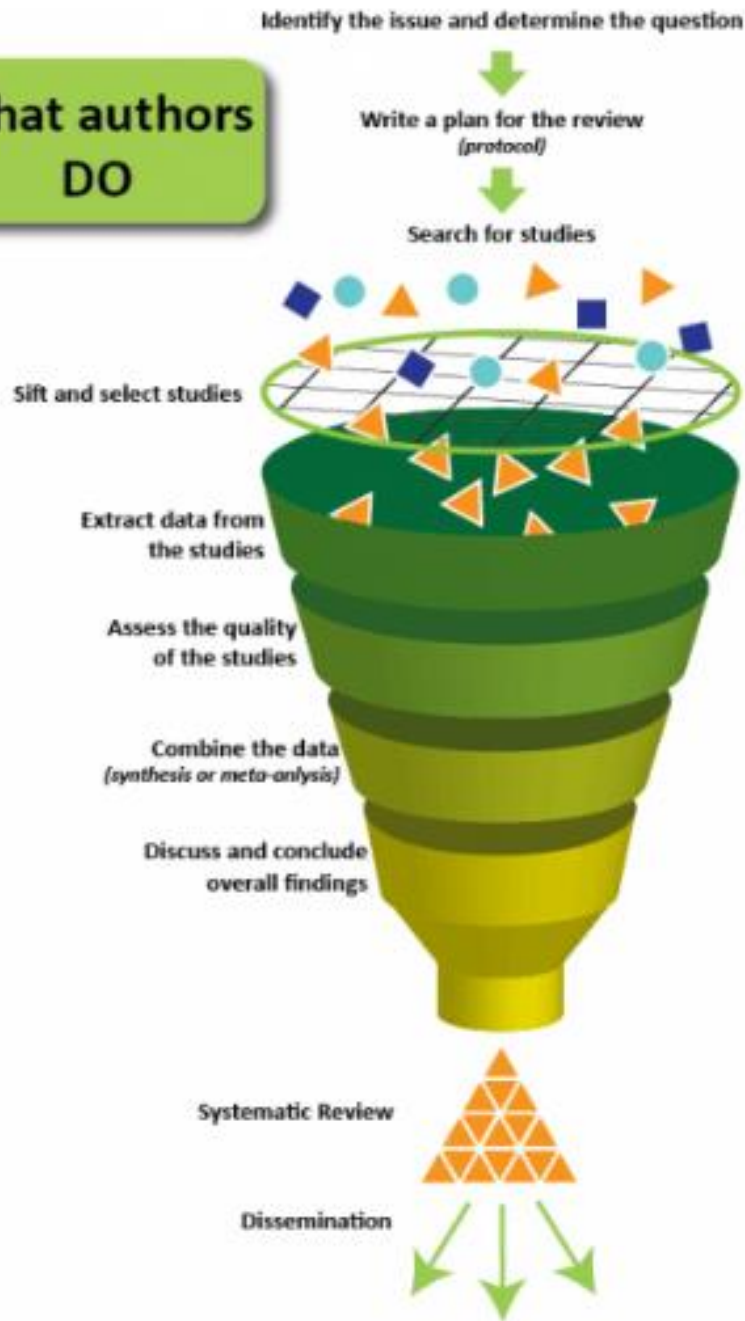
Alessandro Liberati

www.thelancet.com Vol 378 November 19, 2011

I have had the opportunity to consider from more than one perspective the mismatch between what clinical researchers do and what patients need. I am a researcher; I have responsibility for allocating funding for research; and I have had multiple myeloma for the past decade. A few years ago I stated publicly that several uncertainties I faced at the beginning of my disease were avoidable.³

An essential component of any new governance strategy would be to bring together all the stakeholders, starting from an analysis of existing and ongoing research, produced independently of vested interests.

**What authors
DO**



A Systematic Examination of the Citation of Prior Research in Reports of Randomized, Controlled Trials

Karen A. Robinson, PhD, and Steven N. Goodman, MD, MHS, PhD

Conclusion: In reports of RCTs published over 4 decades, fewer than 25% of preceding trials were cited, comprising fewer than 25% of the participants enrolled in all relevant prior trials. A median of 2 trials was cited, regardless of the number of prior trials that had been conducted. Research is needed to explore the explanations for and consequences of this phenomenon. Potential implications include ethically unjustifiable trials, wasted resources, incorrect conclusions, and unnecessary risks for trial participants.



Ann Intern Med. 2011;154:50-55.

Reports of new research should begin and end with systematic reviews of what is already known.

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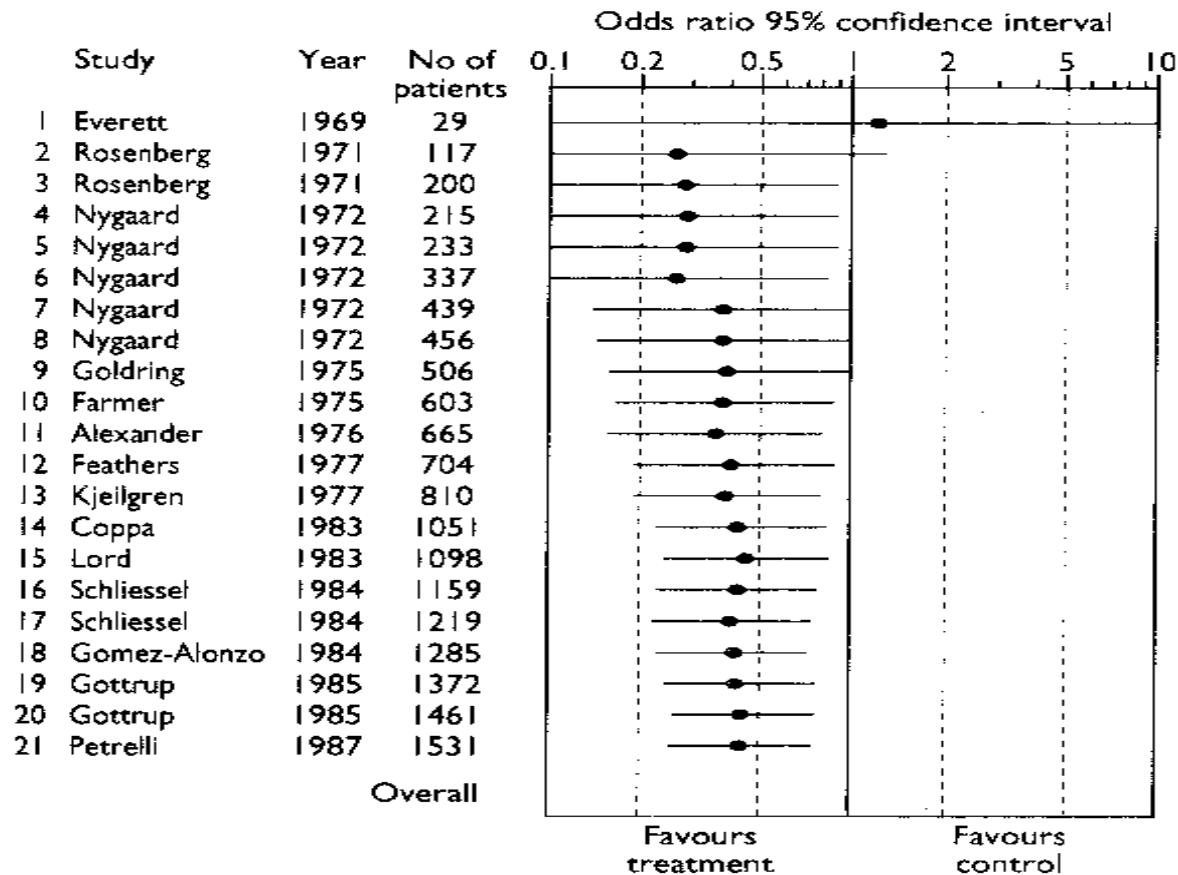
Failure to do this has resulted in avoidable suffering and death.

Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability

Julian Savulescu, Iain Chalmers, Jennifer Blunt

The results of recent empirical investigations in research synthesis imply that research ethics committees are behaving unethically by endorsing new research which is unnecessary and by acquiescing in biased under-reporting of research which they have approved.

Inappropriate continued use of placebo controls in clinical trials assessing the effects on death of antibiotic prophylaxis for colorectal surgery



Reprinted from the *BMJ*, 30 November 1996, Vol 313, p 1390-1393

**Are research ethics committees behaving unethically?
Some suggestions for improving performance and accountability**

Horn J, Limburg M. **Calcium antagonists for acute ischemic stroke.** *Cochrane Database of Systematic Reviews*, 2001.

“46 trials were identified of which 28 were included (7521 patients). **No effect of calcium antagonists** on poor outcome at the end of follow-up (OR 1.07, 95% CI 0.97/1.18), or on death at end of follow-up (OR 1.10, 95% CI 0.98/1.24) **was found.**”

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

Stroke 2001;32:2433-8

“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.”

Avoidable injuries in healthy volunteers in a Phase 1 drug evaluation



TGN 1412: 13 March 2006



Establishing risk of human experimentation with drugs: lessons from TGN1412

M J H Kenter, A F Cohen

Lancet 2006; 368: 1387-91

Discussion

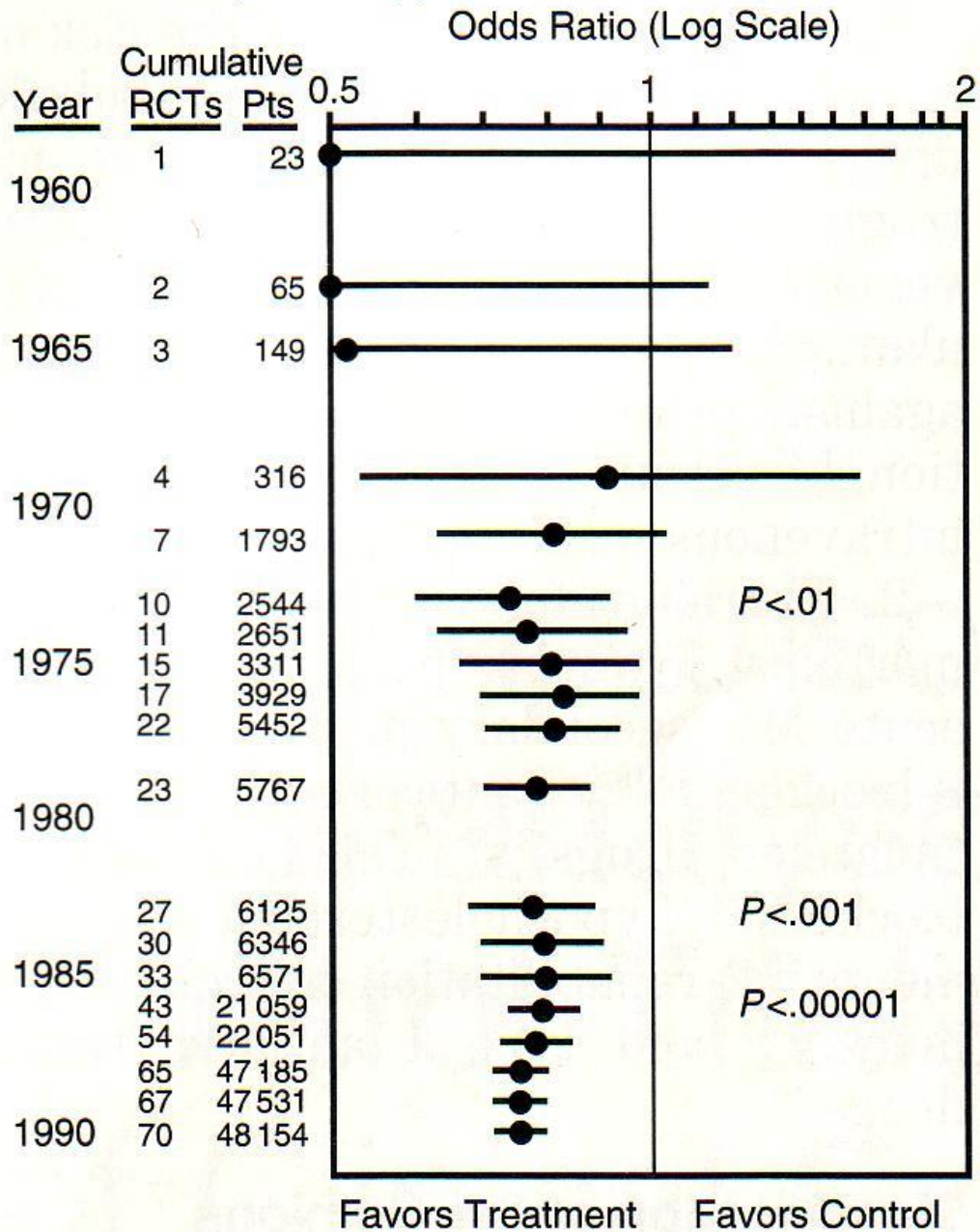
The above risk analysis, undertaken with data available in the research file and public domain before the TGN1412 trial started, shows that essential information was absent and the antibody was a high-risk compound unlikely to be suitable for administration to healthy people without additional preclinical experiments.

The human costs of failing to cumulate evidence from research scientifically

"Advice on some life-saving therapies has been delayed for more than a decade, while other treatments have been recommended long after controlled research has shown them to be harmful."

Antman et al. *JAMA* 1992;268:240-8.

A. Thrombolytic Therapy



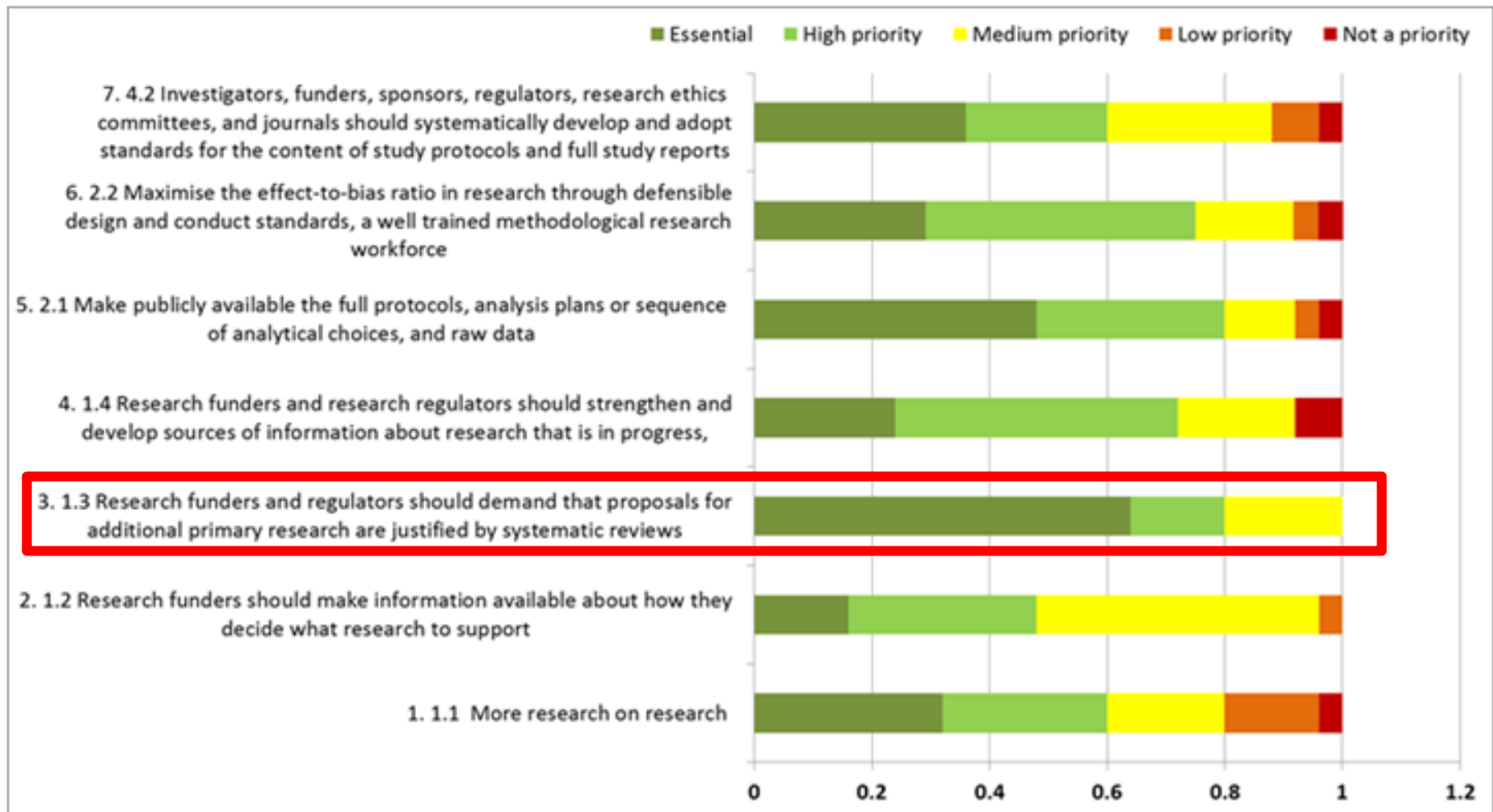
Textbook/Review Recommendations

	Routine	Specific	Rare/Never	Experimental	Not Mentioned
					21
					5
				1	10
				1	2
				2	8
					7
					8
		1			12
M		1		8	4
M		1		7	3
M		1		7	3
M	5	2		2	1
M	15	8			1
M	6	1			

Patients are suffering and dying because new research is done without reviewing systematically what is already known.

Embarking on research without reviewing systematically what is already known is **unethical, unscientific, and wasteful.**

Survey of priorities among recommendations made in *The Lancet* series on waste in research



Legend: Essential (dark green), High priority (light green), Medium priority (yellow), Low priority (orange), Not a priority (red)

Research funders and regulators can help to reduce avoidable suffering and death from this form of research misconduct.

- 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

The National Institute for Health Research advises researchers applying for support for **new primary research** as follows:



“Where a systematic review already exists that summarises the available evidence this should be referenced, as well as including reference to any relevant literature published subsequent to that systematic review. Where no such systematic review exists, it is expected that the applicants will undertake an appropriate review of the currently available and relevant evidence.

All applicants must also include reference to relevant ongoing studies.”

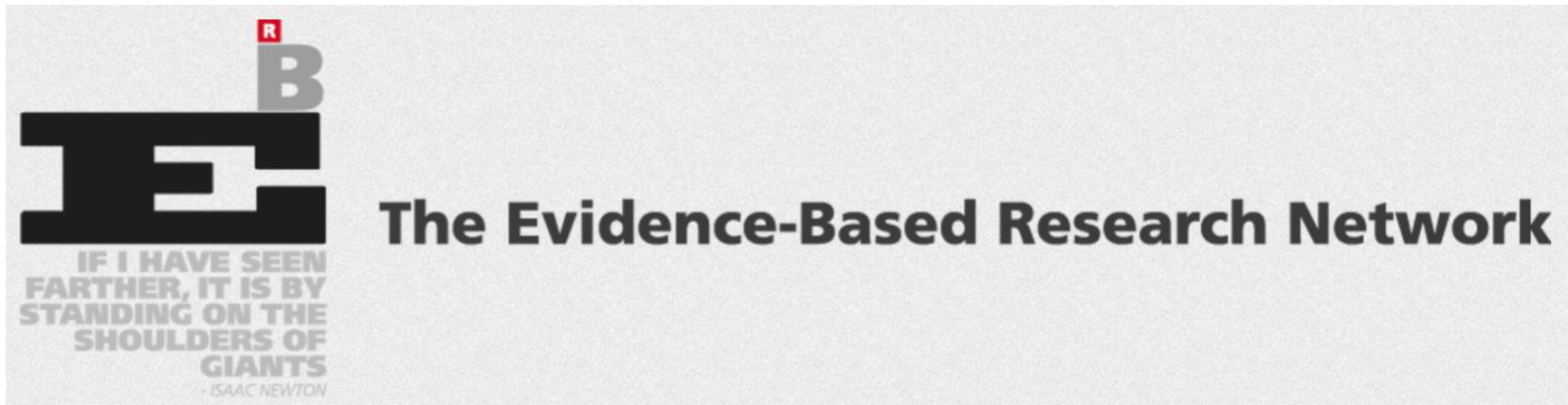
Some research regulators now require applicants for research approval to refer to systematic reviews of existing evidence



The **Health Research Authority in the UK** states:

“Any project should build on a review of current knowledge. Replication to check the validity of previous research is justified, but unnecessary duplication is unethical.”

**Evidence-Based Research:
new research should build
systematically on previous
research**



www.EBRNetwork.org

ANALYSIS

A manifesto to reduce research waste

To avoid waste of research, no new studies should be done without a systematic review of existing evidence, argue

Hans Lund and colleagues

Lund H, Brunnhuber K, Juhl, Robinson K, Leenars M, Dorch B, Jamtvedt G, Nortvedt M, Christensen R, Chalmers I. *BMJ* 2016;355:i5440 [29 October]

KEY MESSAGES

- Embarking on research without reviewing systematically what is already known, particularly when the research involves people or animals, is unethical, unscientific, and wasteful
- A systematic review of relevant evidence can establish whether the proposed research is truly needed
- Some research funders now require applicants to refer to a systematic review of existing research
- Research waste can also be reduced by efficient production, updating, and dissemination of systematic reviews

All health researchers should begin their training by preparing at least one systematic review

Kamal R Mahtani

Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG, UK

Corresponding author: Kamal R Mahtani. Email: kamal.mahtani@phc.ox.ac.uk

Because:

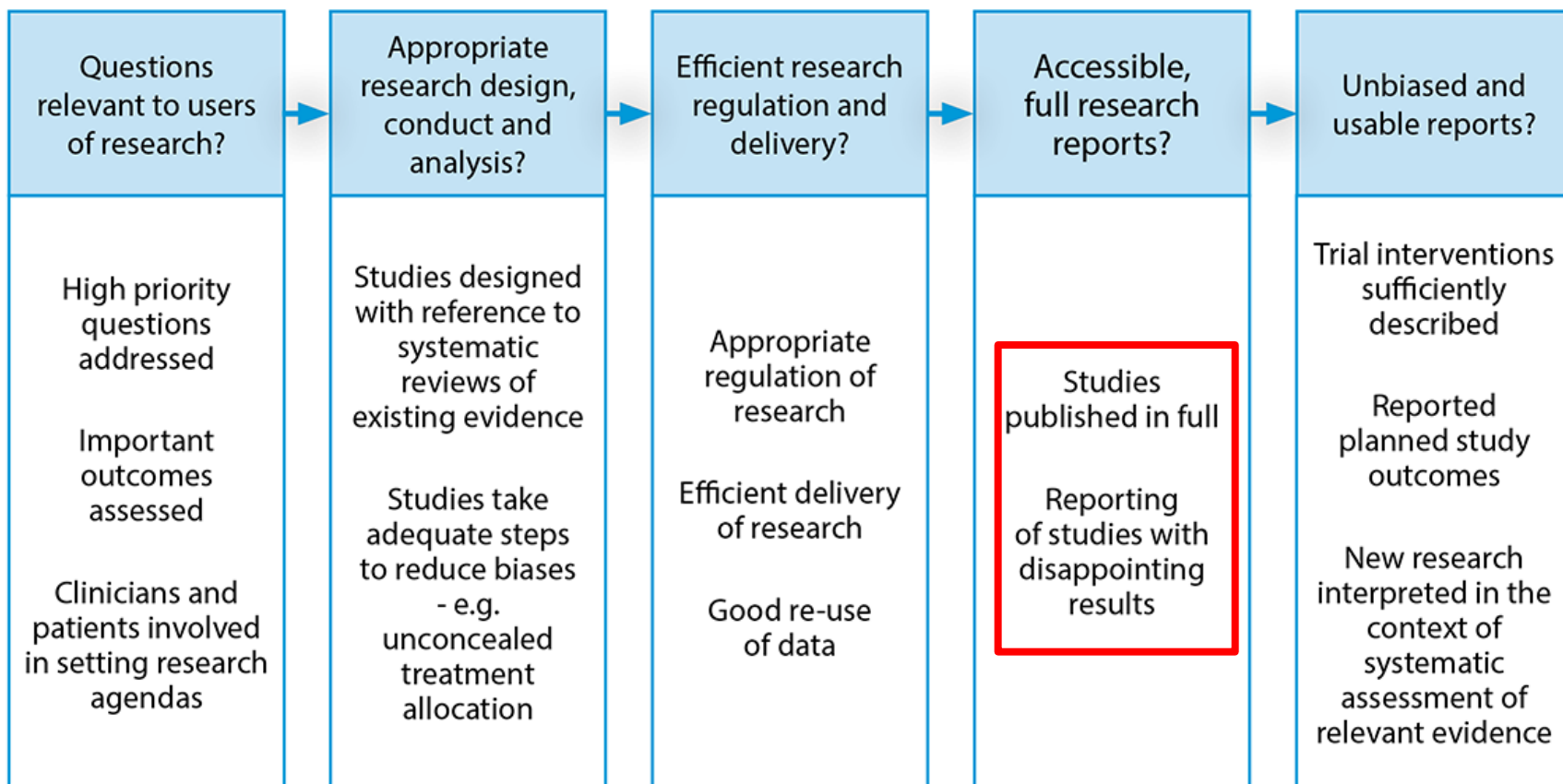
- Systematic reviews of research are needed in health care
- Systematic reviews of research are needed in health research
- Systematic reviews reduce research waste
- Clinical trials should begin and end with systematic reviews

2. Waste from acquiescing in biased under-reporting of research

"By ensuring that efforts are infused with rigour from start to finish, the research community might protect itself from the sophistry of politicians, disentangle the conflicted motivations of capital and science, and secure real value for money for charitable givers and taxpayers through increased value and reduced waste."

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

Five stages of waste in research NETSCC's Adding value in Research Framework



Avoidable waste in the production and reporting of research evidence

Iain Chalmers, Paul Glasziou

Lancet 2009; 374: 86–89



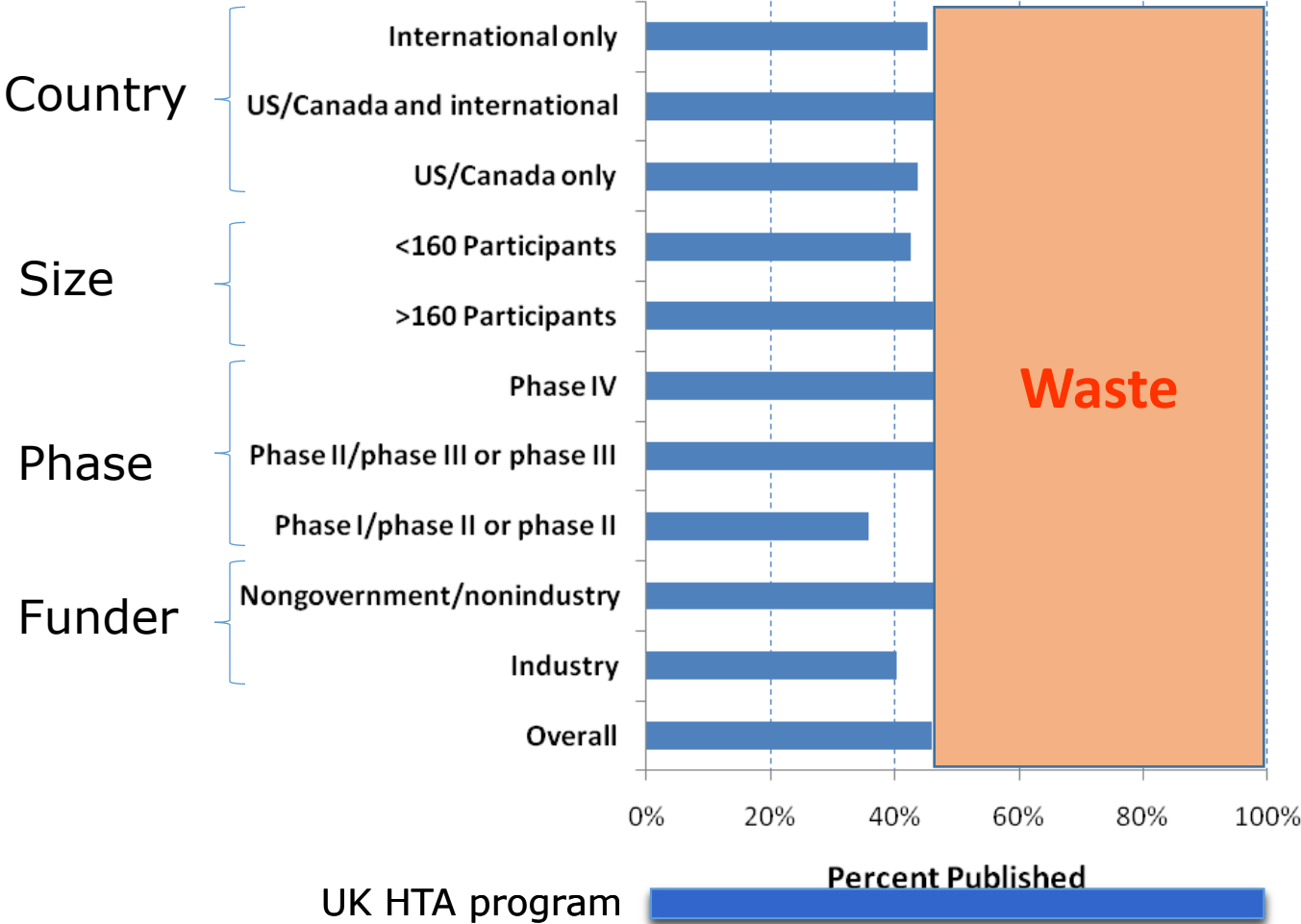
Alessandro Liberati

Without accessible and usable reports, research cannot help patients and their clinicians. In a published Personal View,¹ a medical researcher with myeloma reflected on the way that the results of four randomised trials relevant to his condition had still not been published, years after preliminary findings had been presented in meeting abstracts:

“Research results should be easily accessible to people who need to make decisions about their own health... Why was I forced to make my decision knowing that information was somewhere but not available? Was the delay because the results were less exciting than expected? Or because in the evolving field of myeloma research there are now new exciting hypotheses (or drugs) to look at? How far can we tolerate the butterfly behaviour of researchers, moving on to the next flower well before the previous one has been fully exploited?”

Proportion (%) of clinical trials registered by 1999 and published by 2007

(from Ross et al. PLoS Med 2009;6(9): e1000144).



(from Turner et al. BMJ Open 2013;3:e002521)

Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias

Kerry Dwan^{1*}, Douglas G. Altman², Juan A. Arnaiz³, Jill Bloom⁴, An-Wen Chan⁵, Eugenia Cronin⁶, Evelyne Decullier⁷, Philippa J. Easterbrook⁸, Erik Von Elm^{9,10}, Carrol Gamble¹, Davina Gherzi¹¹, John P. A. Ioannidis^{12,13}, John Simes¹⁴, Paula R. Williamson¹

“**Studies** that report positive or significant results are more likely to be published and **outcomes** that are statistically significant have higher odds of being fully reported.”

PLoS ONE, August 2008;3:e3081

Failure to report Phase I trials



TGN 1412: 13 March 2006



EXPERT SCIENTIFIC GROUP ON PHASE ONE CLINICAL TRIALS

Professor Terry Hamblin, Professor Martin Gore and Dr. Monica Preuss,
representing the Gene Therapy Advisory Committee (GTAC).

presented unpublished data regarding a study he had carried out in a single patient subject
in 1994 using a tri-specific anti-CD3/CD2/CD28 antibody.

The presentation covered two main areas, first dosing in man, healthy volunteers versus
patients and the first in man study of a tri-specific anti-CD3/CD2/CD28 antibody which
was performed in 1994. The effects of this antibody had parallels with the effects of
TGN1412.

Failure to report Phase III trials

Compendium of Unpublished Phase III Trials in Oncology: Characteristics and Impact on Clinical Practice

Vincent C. Tam, Ian F. Tannock, Christine Massey, Jennifer Rauw, and Monika K. Krzyzanowska

J Clin Oncol 2011;29:3133-3139.

Conclusion

A substantial number of cancer clinical trials with potential influence on clinical practice remain unpublished and many other trials are published after a substantial delay.

Non-publication of clinical trials breaks an implicit contract with participants, institutional review boards, and sponsors.

Deadly Medicine

Why tens of thousands of heart patients died in America's worst drug disaster

Thomas J. Moore

1995

At the peak of the use of anti-arrhythmic drugs in myocardial infarction in the late 1980s, Moore estimates that they were killing every year as many Americans as were killed during the whole of the Vietnam war.

The effect of lorcainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias

A.J. Cowley^a, A. Skene^b, K. Stainer^a and J.R. Hampton^a

^a*Cardiovascular Medicine, University Hospital, Nottingham, UK* and ^b*British Heart Foundation Cardiovascular Statistics Group, Nottingham University, Nottingham, UK*

When we carried out our study in 1980 we thought that the increased death rate that occurred in the lorcainide group was an effect of chance,

The development of Lorcainide was abandoned for commercial reasons, and this study was therefore never published; it is now a good example of ‘publication bias’. The results described here could have appeared before recruitment to the CAST Study began, and might have provided an early warning of trouble ahead.

Disclosure of Clinical Trial Results When Product Development Is Abandoned

Michael A. Rogawski^{1*} and Howard J. Federoff²

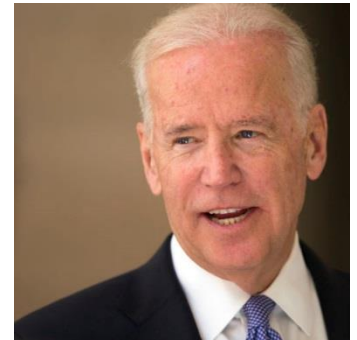
Currently, sponsors are not required to report the outcomes of clinical research on drugs or devices that do not lead to an approved product. Consequently, the public cannot benefit from scientific information derived from all failed or abandoned drugs and devices. Provisions in the U.S. Food and Drug Administration Amendments Act of 2007 provide an opportunity for the Department of Health and Human Services to rectify this situation. By reporting the results of clinical trials of abandoned products in a publicly accessible database and in the peer-reviewed journal literature, sponsors would satisfy a core ethical obligation of clinical research and enhance translational science.

Research funders and regulators can help to reduce avoidable suffering, death and waste from this form of research misconduct.

3 Funders, sponsors, regulators, research ethics committees, journals, and legislators should endorse and enforce study registration policies, wide availability of full study information, and sharing of participant-level data for all health research

- Monitoring—assessment of the proportion of stakeholder policies that endorse dissemination activities, and the proportion of studies that are registered and reported with available protocols, full study reports, and participant-level data

Biden threatens to fine researchers who fail to report clinical trial results



By [DAVID NATHER](#) [@DavidNather](#) and [CHARLES PILLER](#) [@cpiller](#) JUNE 29, 2016

WASHINGTON — At a national cancer summit Wednesday, Vice President [Joe Biden](#) threatened to cut funds to medical research institutions that don't report their clinical trial results in a timely manner.

“Under the law, it says you must report. If you don't report, the law says you shouldn't get funding,” Biden said, citing a [STAT investigation](#) that found widespread reporting lapses.

“I'm going to find out **if it's true**” that the research centers aren't reporting the results, Biden said — “and if it's true, I'm going to cut funding. That's a promise.”

Monitor publication of the research for which you are responsible

See, for example

Tompson AC, Petit-Zeman S, Goldacre B, Heneghan CJ (2016).

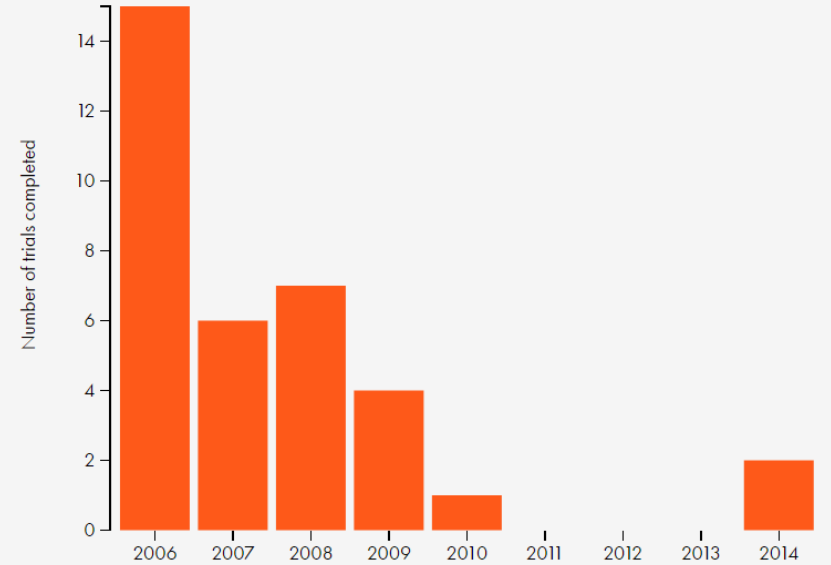
Getting our house in order: an audit of the registration and publication of clinical trials supported by the National Institute for Health Research Oxford Biomedical Research Centre and the Musculoskeletal Biomedical Research Unit

Conclusions It was feasible to conduct an internal audit of registration and publication in 2 major research institutions. Performance was similar to, or better than, comparable cohorts of trials sampled from registries. The major resource input required was manually seeking information: **if all registry entries were maintained, then almost the entire process of audit could be automated—and routinely updated—for all research centres and funders.**

BMJOpen 2016;6:e009285 doi:10.1136/bmjopen-2015-009285

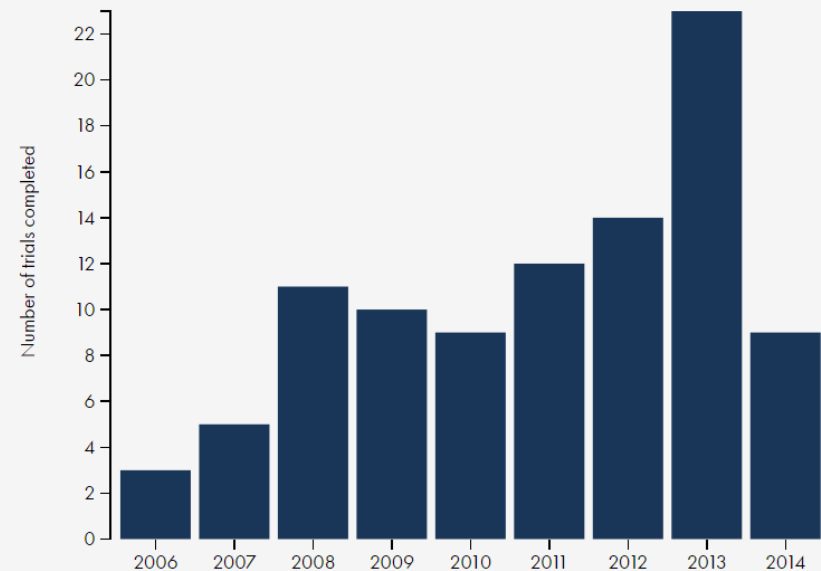
The trial sponsors **most guilty** of under-reporting

		↕	↕	↕	↕
	Name of sponsor		Trials missing results	Total eligible trials	Percent missing
1	Ranbaxy Laboratories Limited		35	35	100.0%
2	Nanjing Medical University		32	35	91.4%
3	Rambam Health Care Campus		27	30	90.0%
4	Isfahan University of Medical Sciences		44	49	89.8%
5	City of Hope Medical Center		39	44	88.6%
6	University Hospital, Caen		34	39	87.2%
7	National Institute on Drug Abuse (NIDA)		33	38	86.8%



The trial sponsors **least guilty** of under-reporting


		↕	↕	↕	↕
	Name of sponsor		Trials missing results	Total eligible trials	Percent missing
284	Johnson & Johnson Vision Care, Inc.		4	69	5.8%
285	Genentech, Inc.		4	70	5.7%
286	Allergan		9	166	5.4%
287	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.		3	58	5.2%
288	Eli Lilly and Company		15	292	5.1%
289	Bristol-Myers Squibb		5	115	4.3%
290	Colgate Palmolive		1	32	3.1%
291	Shire		0	96	0.0%



Under-reporting of registered clinical trials

By academia

Since Jan 2006, **University of Oxford** completed 50 eligible trials and **hasn't published results for 22 trials**. That means **44.0%** of its trials are missing results. See

Since Jan 2006, **University of Roma La Sapienza** completed 34 eligible trials and **hasn't published results for 19 trials**. That means **55.9%** of its trials are missing results. See [all its completed trials on ClinicalTrials.gov](#) .

By industry

Since Jan 2006, **Chiesi Farmaceutici S.p.A.** completed 39 eligible trials and **hasn't published results for 29 trials**. That means **74.4%** of its trials are missing results. See

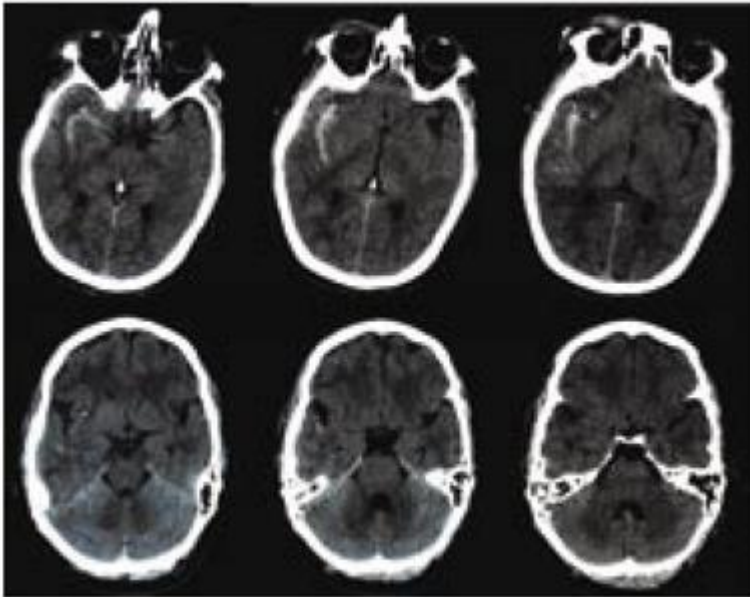
Since Jan 2006, **GlaxoSmithKline** completed 809 eligible trials and **hasn't published results for 183 trials**. That means **22.6%** of its trials are missing results.

Data analysis built by Anna Powell-Smith and Ben Goldacre at the [Evidence-Based Medicine Data Lab](#), University of Oxford.

**Patients are suffering and dying
because research results are not being
reported.**

Failure to report the results of research is
unethical, unscientific, and wasteful.

An example of what is needed: What are the effects of giving systemic steroids to people with acute traumatic brain injury?



Reports of clinical trials should begin and end with up-to-date systematic reviews of other relevant evidence: a status report

Mike Clarke¹ Sally Hopewell¹ Iain Chalmers²

J R Soc Med 2007;**100**:187-190

Step 1: Review systematically what is already known

Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials

Philip Alderson, Ian Roberts

Alderson P, Roberts I (1997). *BMJ* 314:1855-9;
and *Cochrane Database of Systematic Reviews*

The review revealed important uncertainty about whether systemic steroids did more good than harm.

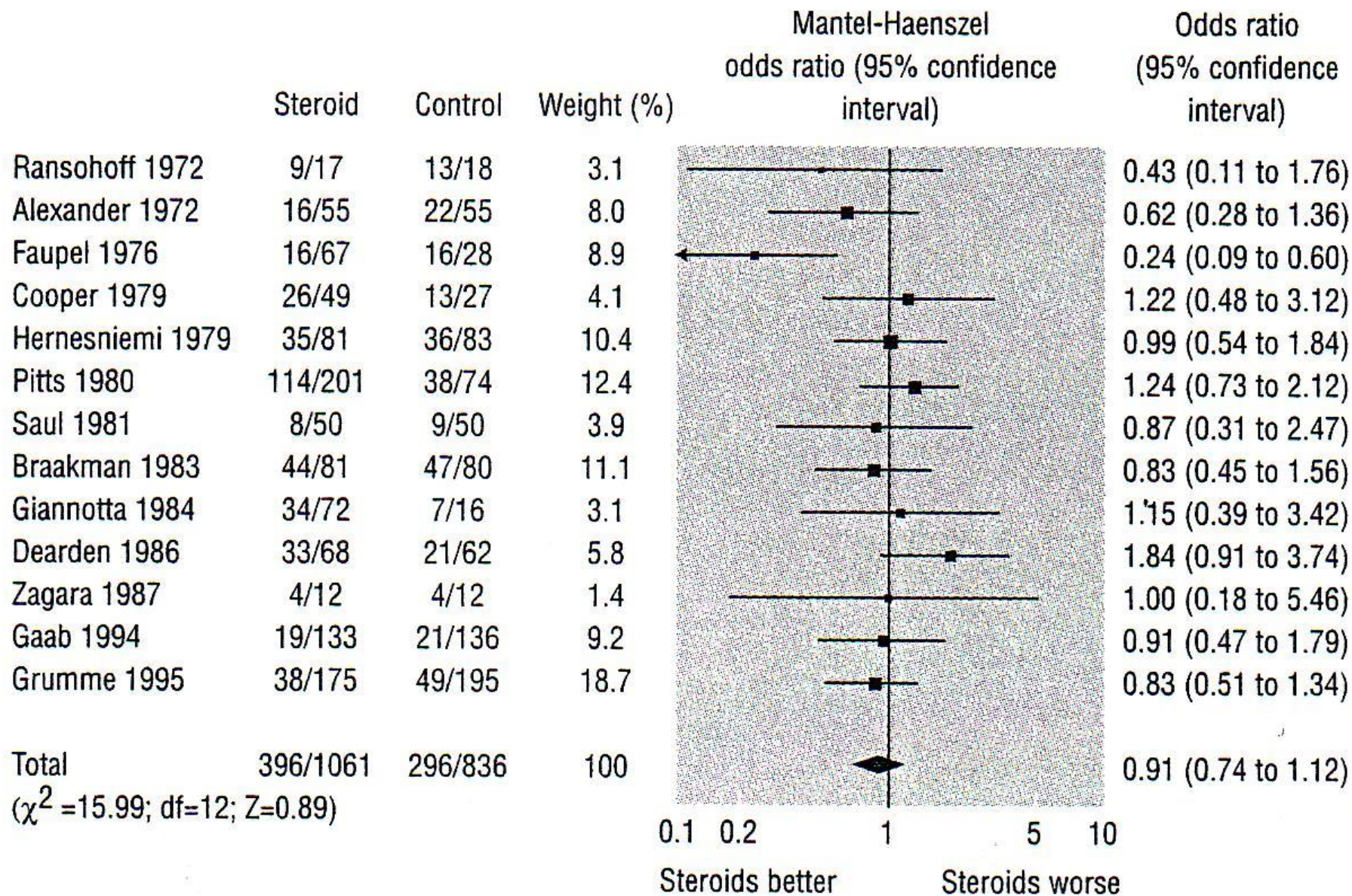


Fig 1 Summary odds ratio for death at end of study

Step 2: Address important uncertainties in well-designed additional research

Because the systematic review and a survey of clinical practice had revealed important uncertainty, **a large, publicly-funded, multicentre randomized trial was organised to address the uncertainty**

The trial was registered prospectively

The protocol for the trial was published

Step 3: Update the original systematic review in the report of the new evidence

Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial

*CRASH trial collaborators**

Lancet 2004;364:1321-28

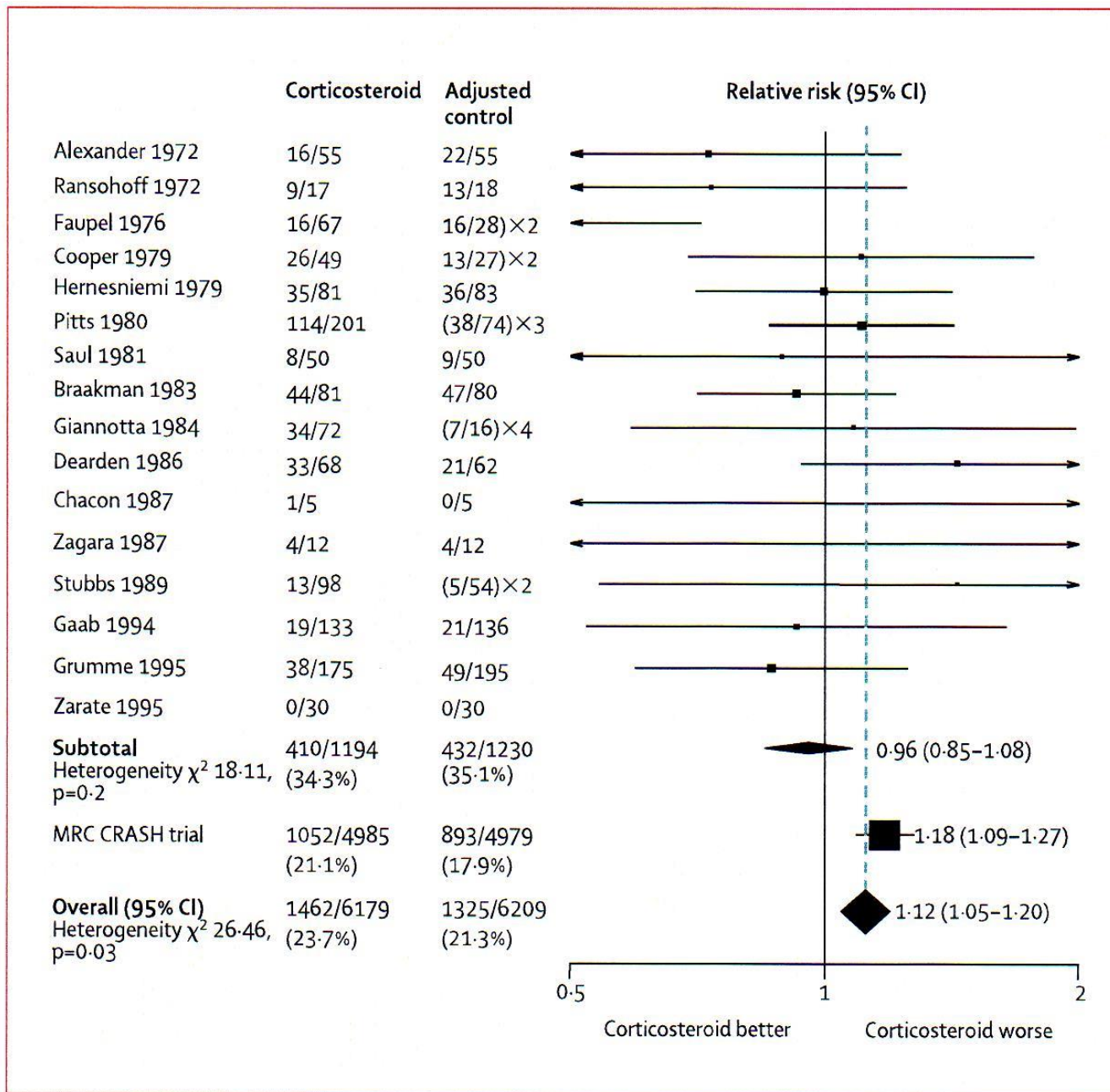
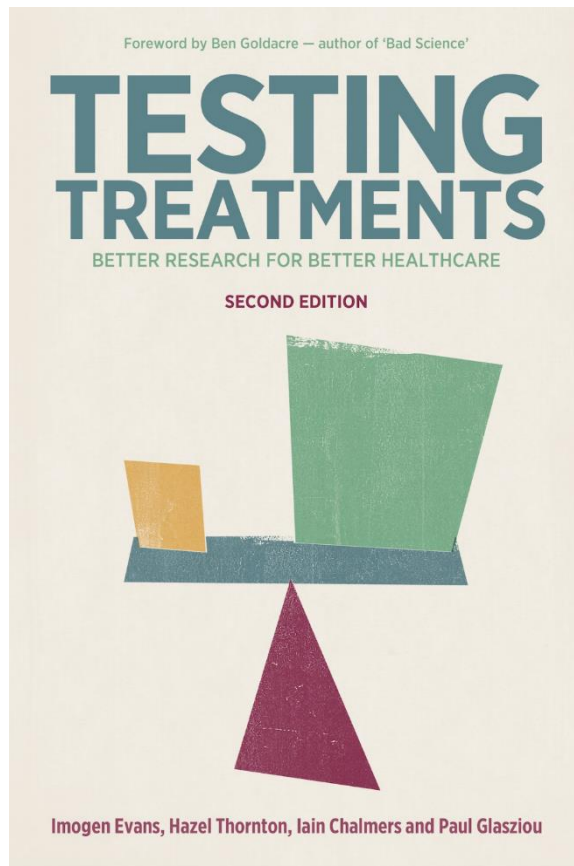


Figure 5: Updated meta-analysis of effect of corticosteroids on death after head injury

- **The report of the CRASH trial is exemplary because:**
- it refers to current uncertainty about the effects of a treatment, manifested in a **systematic review of all the existing evidence**, and in **variations in clinical practice**
- It notes that the **trial was registered and the protocol published** prospectively
- it sets the new results in the context of **an updated systematic review of all of the existing evidence**
- it provides readers with **all the evidence needed for action**

What should patients do when they are invited to support or participate in medical research?



www.testingtreatments.org

AN ACTION PLAN – THINGS YOU CAN DO

Promote research on the effects of treatments...

“Encourage and work with health professionals, researchers, research funders, and others who are try to promote research addressing inadequately answered questions about the effects of treatment which you regard as important.”

AN ACTION PLAN – THINGS YOU CAN DO

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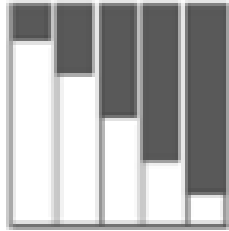
“Encourage and work with health professionals, researchers, research funders, and others who are try to promote research addressing inadequately answered questions about the effects of treatment which you regard as important.”

...but only if it meets scientific and ethical principles.

“Agree to participate in a clinical trial on condition that:

- (i) the study protocol has been registered and made publicly available
- (ii) the protocol refers to systematic reviews of existing evidence showing that the trial is justified
- (iii) you receive a written assurance that the full study results will be published.”

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