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
Established 1994

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.

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

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Evolution of concern about waste in research

The scandal of poor medical research

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
2

2014
42

2015
236

1. Waste resulting from funding and endorsing unnecessary or badly designed research
Reports of new research should begin and end with systematic reviews of what is already known.

Failure to do this has resulted in avoidable suffering and death.
Inappropriate continued use of placebo controls in clinical trials assessing the effects on death of antibiotic prophylaxis for colorectal surgery


"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; N. Vemmos, ND; P.G.M. Luijten, 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."

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

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."


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.

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.”

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


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


Five stages of waste in research

NETSCC’s Adding value in Research Framework

- Questions relevant to some outcomes
- Appropriate research design, conduct and analysis
- Efficient research reporting and dissemination
- Accessible, full research reports
- Utilised and visible reports

Studies designed with reference to systematic reviews of existing evidence

Studies take into account result and refute biases, e.g., unexplained treatment allocations

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail

Studies published in detail

Studies summarised in detail
Alessandro Liberati

**Avoidable waste in the production and reporting of research evidence**

*Lancet* 2009; 374: 86-89

Without accessible and usable reports, research cannot help patients and their clinicians. In a published personal view, 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 nowhere 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 to draw to look at? How far can we tolerate the butterfly behaviour of researchers, moving on to the next flower even before the previous one has been fully explained?”

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


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UK HTA program

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

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

Kerry Dean, Douglas G. Altman, Jula A. Arnaud, Bill Howard, Al-Wen Chao, Eugenia Conlon, Evelynne Desclee, Philippe J. Easterbrook, Elin Von Elm, Carrol Gamba, Orvaline Grobe, John P. A. Ioannidis, John Simes, Paolo R. Williamson

“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.”


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**Inadequate Dissemination of Phase I Trials: A Retrospective Cohort Study**

60% unpublished after 8 years

80% unpublished after 8 years

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**Failure to report Phase I trials**

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**TGN 1412: 13 March 2006**

*Side effects may include...*
Compendium of Unpublished Phase III Trials in Oncology: Characteristics and Impact on Clinical Practice

Vince C. Toek, Jan J. Tanwari, Christine Hossey, Jennifer Rase, and Masaki K. Engawanaka


**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.

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**Deadly Medicine**

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

Thomas J. Moore

1995

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**Disclosure of Clinical Trial Results When Product Development Is Abandoned**

Michael A. Rogawski and Howard J. Federoff

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 their new 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.

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.”

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

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% of its trials are missing results. See

Since Jan 2006, University of Rome La Sapienza completed 34 eligible trials and hasn’t published results for 19 trials. That means 56% 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% of its trials are missing results. See

Since Jan 2006, GlaxoSmithKline completed 105 eligible trials and hasn’t published results for 105 trials. That means 100% 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?

Step 1: Review systematically what is already known

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


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

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 in BioMed Central.

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

Lancet 2004;364:1321-28
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 to prevent thousands of iatrogenic deaths

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 trying 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.”

To contribute to reducing waste and increasing value in research, join

The Reward Alliance
www.rewardalliance.net

Attend and contribute to:

5th World Conference on Research Integrity
28-31 May 2017, Amsterdam, NL
www.wcri2017.org