GIMBE EVIDENCE FOR HEALTH

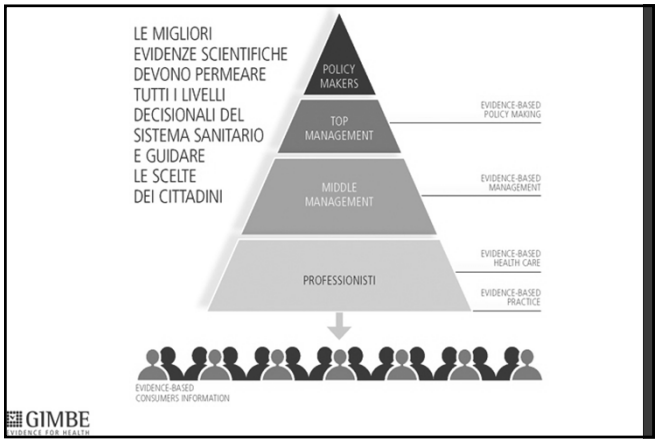
Sperimentazioni Cliniche
Nuove Sfide per i Comitati Etici
Bologna, 7 novembre 2014

Ridurre gli sprechi e aumentare il valore della ricerca biomedica Un mandato etico

Nino Cartabellotta
Fondazione GIMBE

Disclosure sui conflitti d'interesse

- La Fondazione GIMBE, di cui sono Presidente, eroga attività di formazione e consulenza sui temi trattati dalla mia relazione
- Nessun altro conflitto da dichiarare




BMJ 2014;348:g3725 doi: 10.1136/bmj.g3725 (Published 13 June 2014) Page 1 of 7

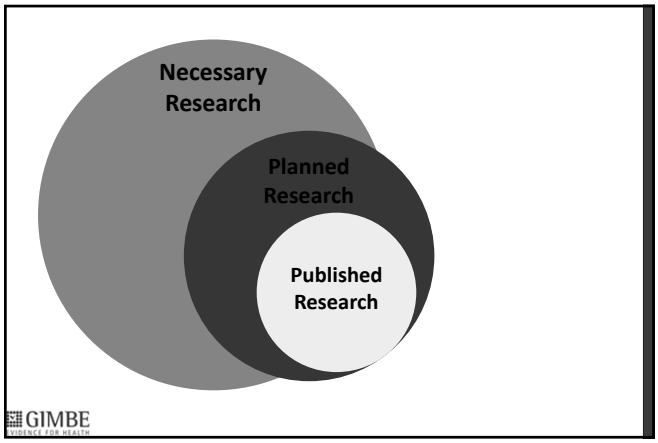
ANALYSIS

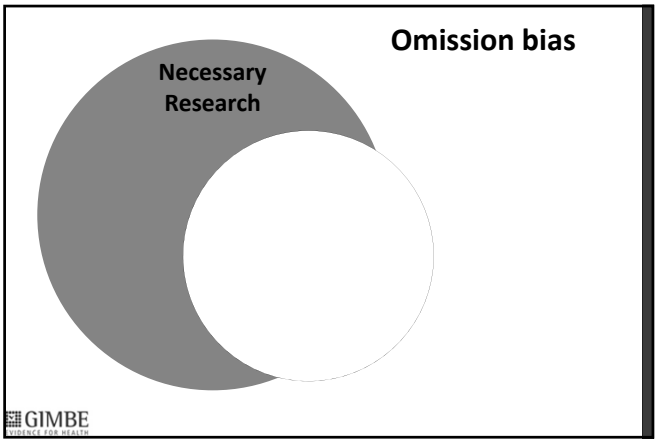
ESSAY

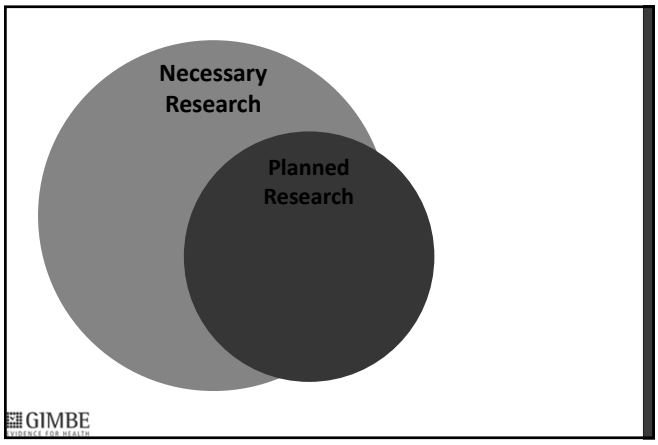
Evidence based medicine: a movement in crisis?

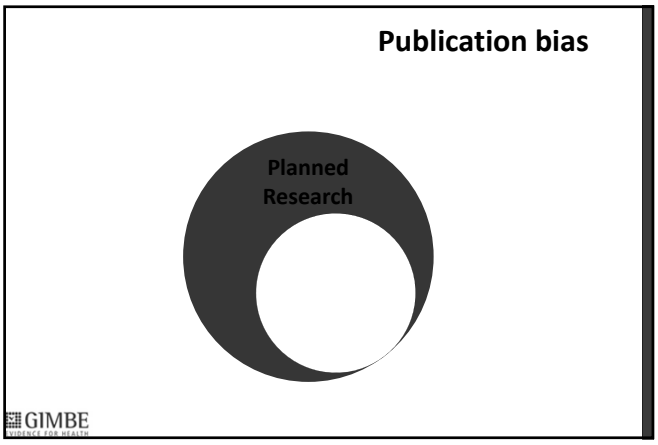
Trisha Greenhalgh and colleagues argue that, although evidence based medicine has had many benefits, it has also had some negative unintended consequences. They offer a preliminary agenda for the movement's renaissance, refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment

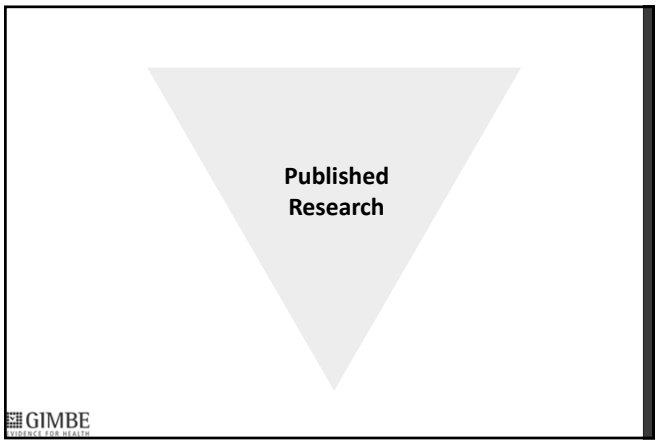
Trisha Greenhalgh *dean for research impact*[1], Jeremy Howick *senior research fellow*[2], Neal Maskrey *professor of evidence informed decision making*[3], for the Evidence Based Medicine Renaissance Group

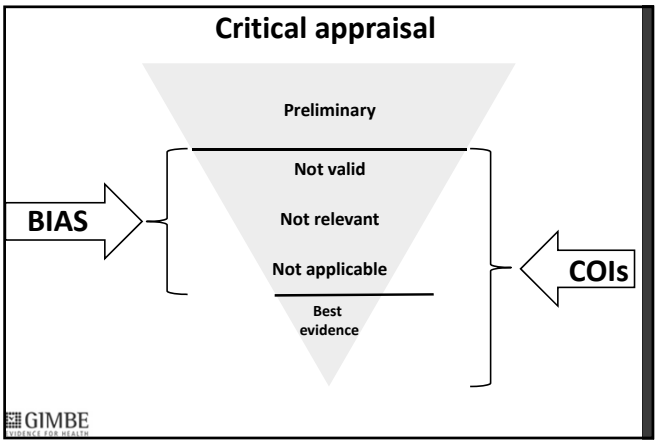


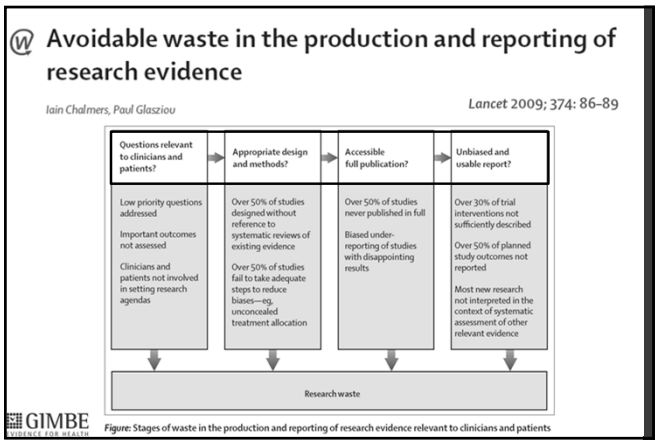



Necessary Research
Planned Research
GIMBE


Publication bias
Planned Research
GIMBE


Published Research
GIMBE


Critical appraisal
Preliminary
Not valid
Not relevant
Not applicable
Best evidence
BIAS
COIs
GIMBE


Avoidable waste in the production and reporting of research evidence
Iain Chalmers, Paul Glasziou
Lancet 2009; 374: 86–89
Questions relevant to clinicians and patients?
Appropriate design and methods?
Accessible full publication?
Unbiased and usable report?
Low priority questions addressed
Important outcomes not assessed
Clinicians and patients not involved in setting research agendas
Over 50% of studies designed without reference to systematic reviews of existing evidence
Over 50% of studies fail to take adequate steps to reduce biases—eg, unconcealed treatment allocation
Over 50% of studies never published in full
Biased under-reporting of studies with disappointing results
Over 30% of trial interventions not sufficiently described
Over 50% of planned study outcomes not reported
Most new research not interpreted in the context of systematic assessment of other relevant evidence
Research waste
Figure: Stages of waste in the production and reporting of research evidence relevant to clinicians and patients
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THE LANCET
"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."
Research: increasing value, reducing waste
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42 "wasters"

A Metin Gülmezoglu, Andrew Vickers, An-Wen Chan, Ben Djulbegovic, David Moher, David W Howells, Davina Ghersi, Douglas G Altman, Elaine Beller, Elina Hemminki, Elizabeth Wager, Fujian Song, H Bart van der Worp, Harlan M Krumholz, Iain Chalmers, Ian Roberts, Isabelle Boutron, Janet Wisely, John P A Ioannidis, Jonathan Grant, Jonathan Kagan, Julian Savulescu, Kay Dickersin, Kenneth F Schulz, Malcolm R Macleod, Mark A Hlatky, Michael B Bracken, Mike Clarke, Muin J Khoury, Patrick Bossuyt, Paul Glasziou, Peter C Gøtzsche, Robert S Phillips, Robert Tibshirani, Rustam Al-Shahi Salman, Sander Greenland, Sandy Oliver, **Silvio Garattini**, Steven Julious, Susan Michie, Tom Jefferson, Ulrich Dirnagl

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Comment

Biomedical research: increasing value, reducing waste

Comment

How should medical science change?

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evidence

open access journal published by the GIMBE Foundation

Editoriale OPEN ACCESS

Gli sprechi della ricerca biomedica e la crisi dell'Evidence-based Medicine

Antonino Cartabellotta[1*]

Life sciences research in 2010

US$ 240.000.000.000

85% wasted

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Series Papers

How to increase value and reduce waste when research priorities are set
Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gülmezoglu, David W Howells, John P A Ioannidis, Sandy Oliver
Full Text | PDF

Increasing value and reducing waste in research design, conduct, and analysis
John P A Ioannidis, Sander Greenland, Mark A Hlatky, Muin J Khoury, Malcolm R Macleod, David Moher, Kenneth F Schulz, Robert Tibshirani
Full Text | PDF

Increasing value and reducing waste in biomedical research regulation and management
Rustam Al-Shahi Salman, Elaine Beller, Jonathan Kagan, Elina Hemminki, Robert S Phillips, Julian Savulescu, Malcolm Macleod, Janet Wisely, Iain Chalmers
Full Text | PDF

Increasing value and reducing waste: addressing inaccessible research
An-Wen Chan, Fujian Song, Andrew Vickers, Tom Jeff erson, Kay Dickersin, Peter C Gøtzsche, Harlan M Krumholz, Davina Ghersi,H Bart van der Worp
Full Text | PDF

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
Full Text | PDF

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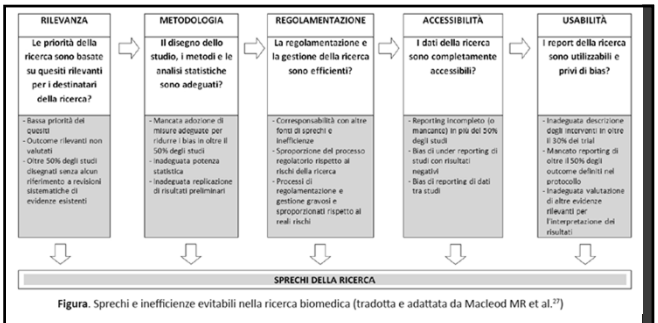

Figura. Sprechi e inefficienze evitabili nella ricerca biomedica (tradotta e adattata da Macleod MR et al.[27])

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Research: increasing value, reducing waste 1

How to increase value and reduce waste when research priorities are set

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

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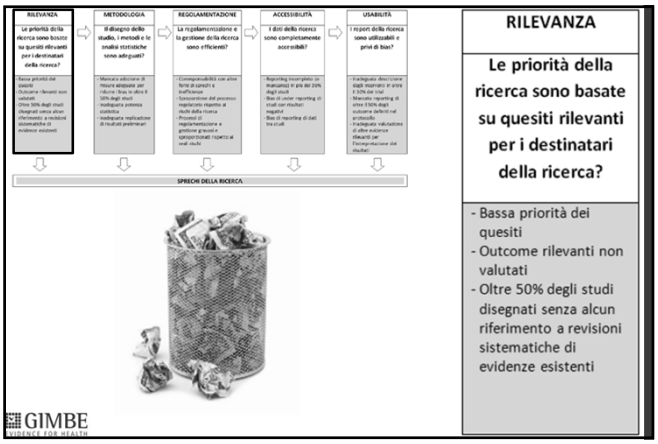

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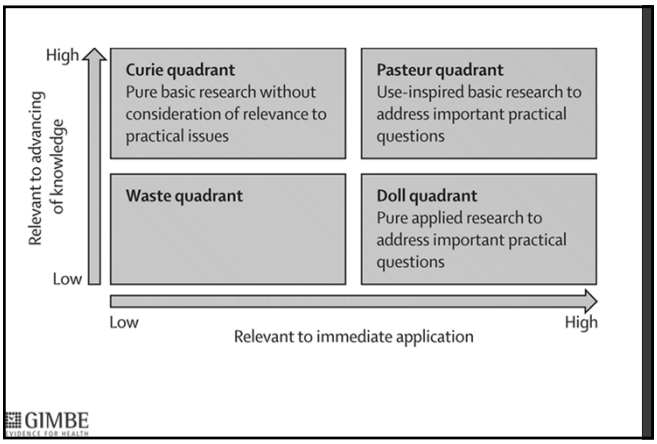

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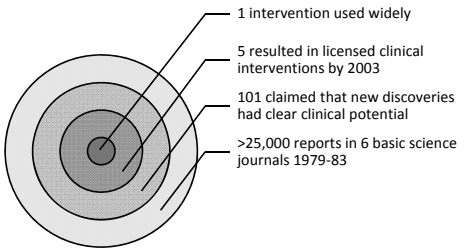
SPECIAL ARTICLES

Translation of Highly Promising Basic Science Research into Clinical Applications

Despina G. Contopoulos-Ioannidis, MD, Evangelia E. Ntzani, MD, John P. A. Ioannidis, MD

PURPOSE: To evaluate the predictors of and time taken for the translation of highly promising basic research into clinical experimentation and use.
METHODS: We identified 101 articles, published between 1979 and 1983 in six major basic science journals, which clearly stated that the technology studied had novel therapeutic or preventive promises. Each case was evaluated for whether the promising finding resulted in relevant randomized controlled trials and clinical use. Main outcomes included the time to published trials, time to published trials with favorable results ("positive" trials), and licensed clinical use.
RESULTS: By October 2002, 27 of the promising technologies had resulted in at least one published randomized trial, 19 of which had led to the publication of at least one positive randomized trial. Five basic science findings are currently licensed for clinical use, but only one has been used extensively for the licensed indications. Promising technologies that did not lead to a published human study within 10 to 12 years were unlikely to be tested in humans subsequently. Some form of industry involvement in the basic science publication was the strongest predictor of clinical experimentation, accelerating the process by about eightfold (95% confidence interval: 3 to 19) when an author had industry affiliations.
CONCLUSION: Even the most promising findings of basic research take a long time to translate into clinical experimentation, and adoption in clinical practice is rare. **Am J Med. 2003; 114:477–484.** ©2003 by Excerpta Medica Inc.

L'inefficienza della ricerca di base



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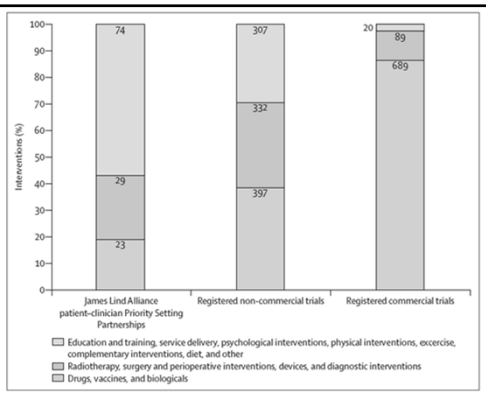
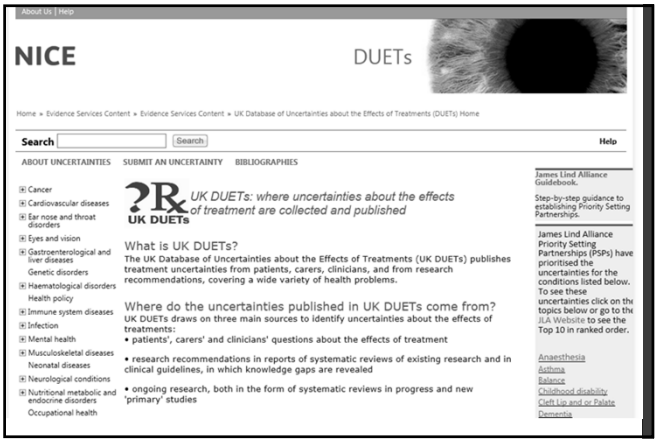


Figure 2: Interventions mentioned in research priorities identified by James Lind Alliance patient–clinician Priority Setting Partnerships[20] and in registered trials, 2003–12



Limitato riferimento a revisioni sistematiche

	May, 2009 (n=29)	May, 2012 (n=35)
Claims that clinical trial is the first to address the question	5	5
Contains an updated systematic review that was used to inform trial design	1	1
Previous systematic review* discussed that was not used in trial design	10	13
Contains references to other randomised trials	4	10
Does not contain references to other randomised trials or claim to be the first trial	9	6

Analysis of reports published in *The Lancet, New England Journal of Medicine, British Medical Journal, Journal of the American Medical Association,* and *Annals of Internal Medicine*.[14] *Systematic review in the topic area of the trial cited.

Table 2: **Analysis of Introduction sections of reports of controlled trials published in five medical journals in May, 2009, and May, 2012**

SPECIAL COMMUNICATION

What Makes Clinical Research Ethical?

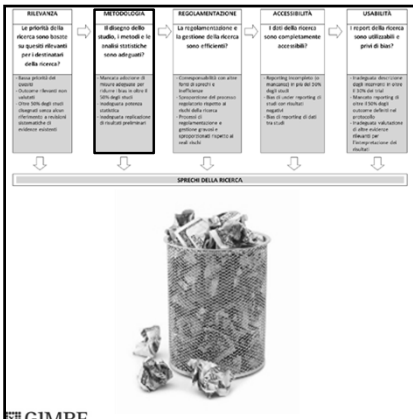
Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

JAMA. 2000;283:2701-2711

Research: increasing value, reducing waste 2

Increasing value and reducing waste in research design, conduct, and analysis

John P A Ioannidis, Sander Greenland, Mark A Hlatky, Muin J Khoury, Malcolm R Macleod, David Moher, Kenneth F Schulz, Robert Tibshirani



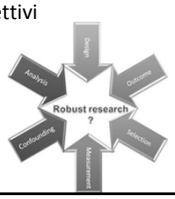
METODOLOGIA

Il disegno dello studio, i metodi e le analisi statistiche sono adeguati?

- Mancata adozione di misure adeguate per ridurre i bias in oltre il 50% degli studi
- Inadeguata potenza statistica
- Inadeguata replicazione di risultati preliminari

Methodological issues

- La maggior parte degli effetti terapeutici sono modesti
- E' difficile distinguere gli effetti modesti dai bias
- Nei trial randomizzati effetti del trattamento influenzati da:
  - modalità di generazione della sequenza di assegnazione
  - occultamento della lista di randomizzazione
  - blinding, in particolare se outcome soggettivi
- La ricerca è distorta da numerosi bias



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ELSEVIER

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 63 (2010) 1205–1215

ORIGINAL ARTICLES

Science mapping analysis characterizes 235 biases in biomedical research

David Chavalarias[a,b], John P.A. Ioannidis[c,d,*]

[a]Centre de Recherche en Epistémologie Appliquée, École Polytechnique - CNRS, 32 Bd Victor, 75015 Paris, France
[b]Institut des Systèmes Complexes de Paris Ile-de-France, 57–59 rue Lhomond, 75005, Paris, France
[c]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine and Biomedical Research Institute, Foundation for Research and Technology-Hellas, Ioannina 45110, Greece
[d]Tufts Clinical and Translational Science Institute and Institute for Clinical Research and Health Policy Studies, Tufts Medical Center and Department of Medicine, Tufts University School of Medicine, Boston, MA 02111, USA

Accepted 22 December 2009

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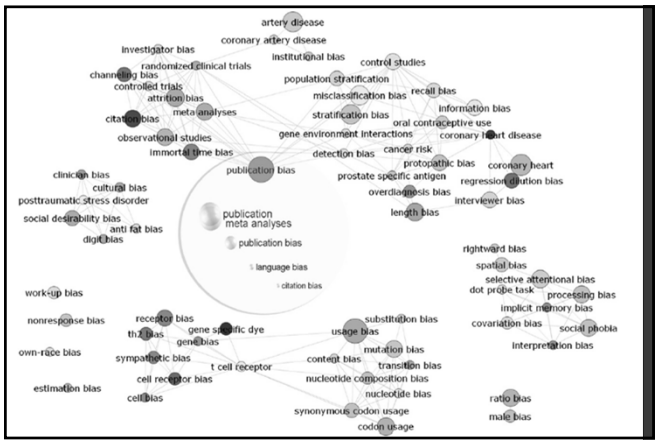

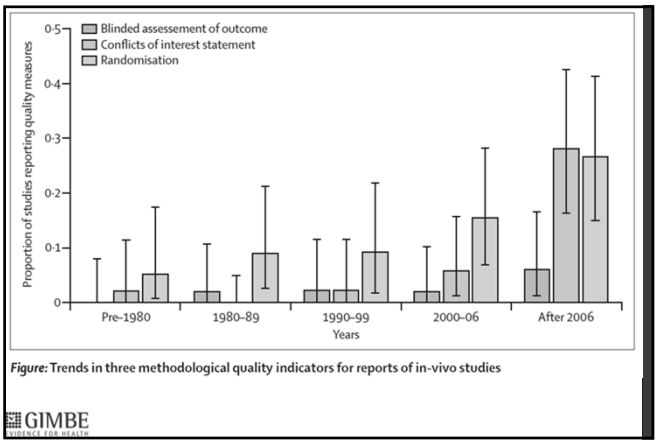

Figure: **Trends in three methodological quality indicators for reports of in-vivo studies**

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Research: increasing value, reducing waste 3

Increasing value and reducing waste in biomedical research regulation and management

Rustam Al-Shahi Salman, Elaine Beller, Jonathan Kagan, Elina Hemminki, Robert S Phillips, Julian Savulescu, Malcolm Macleod, Janet Wisely, Iain Chalmers

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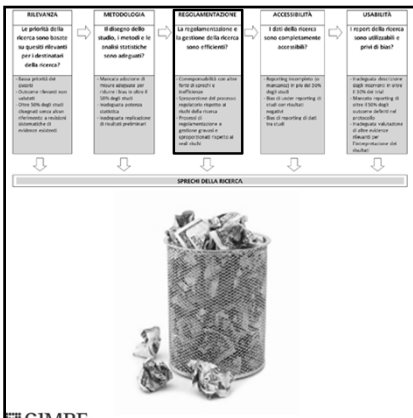

REGOLAMENTAZIONE

La regolamentazione e la gestione della ricerca sono efficienti?

- Corresponsabilità con altre fonti di sprechi e inefficienze
- Sproporzione del processo regolatorio rispetto ai rischi della ricerca
- Processi di regolamentazione e gestione gravosi e sproporzionati rispetto ai reali rischi

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Panel 1: An example from Sweden of the bureaucracy involved in applications for central research ethics committee approval

In 2010, a group of researchers in Sweden wanted to pool data from several cohort studies to identify risk factors for subarachnoid haemorrhage. They identified about 20 studies, and spent about 300 h contacting all investigators and getting signed data-sharing agreements and data security processes agreed. Sweden has a central research ethics committee to approve projects. The team recorded the time taken for each step of the approval process. About 200 h of office time was spent on the ethics approval and resubmission process alone. The research ethics committee wanted to see all information that the participants of all cohorts had been given about the purpose of the study. These documents had to be provided as 18 copies and submitted manually. It took the team 6 months to collect all the information sheets from the 20 different cohorts, several of which began recruitment in the 1960s and for which little knowledge about what information was given by whom to whom in the recruitment phase was poor. The research ethics committee eventually had the team advertise in national newspapers about the pooling project, listing all original cohorts so that all individuals who did not want the team to use their data for this project could withdraw their consent for the study. Not one participant withdrew. It took more than 3 years to reach the stage of pooling data from the cohorts, ready for analysis.

Figure 1: **Paperwork required for regulatory review of the research described in panel 1**

CURRENT OPINION

Int J Pharm Med 2007; 21 (6): 395-404
1364-9027/07/0006-0395/$44.95/0

Regulation of Therapeutic Research is Compromising the Interests of Patients[1]

Iain Chalmers
James Lind Library, James Lind Initiative, Oxford, UK

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Tre motivazioni principali

- Approvazione di protocolli di trial senza alcuna rilevanza clinica
- Approvazione di protocolli di trial con disegno inadeguato
- Incapacità di mettere in atto azioni concrete per ridurre il bias di pubblicazione

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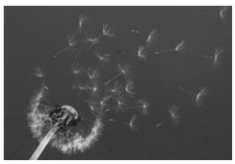
Seeding trials (trial di "disseminazione")

- Finti studi scientifici il cui vero obiettivo non è produrre nuove conoscenze, ma far familiarizzare i medici con l'uso di un farmaco in arrivo sul mercato
- Non sono etici ed espongono i partecipanti a inutili rischi
- N° elevato di centri sperimentali
- Pochi pazienti richiesti per ogni centro
- Compensi spropositati



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Annals of Internal Medicine

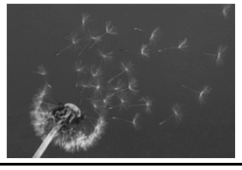
EDITORIAL

Seeding Trials: Just Say "No"

Harold C. Sox, MD
Editor

Drummond Rennie, MD
Deputy Editor, *JAMA*

Ann Intern Med. 2008;149:279-280.



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Research: increasing value, reducing waste 4

Increasing value and reducing waste: addressing inaccessible research

An-Wen Chan, Fujian Song, Andrew Vickers, Tom Jefferson, Kay Dickersin, Peter C Gøtzsche, Harlan M Krumholz, Davina Ghersi, H Bart van der Worp

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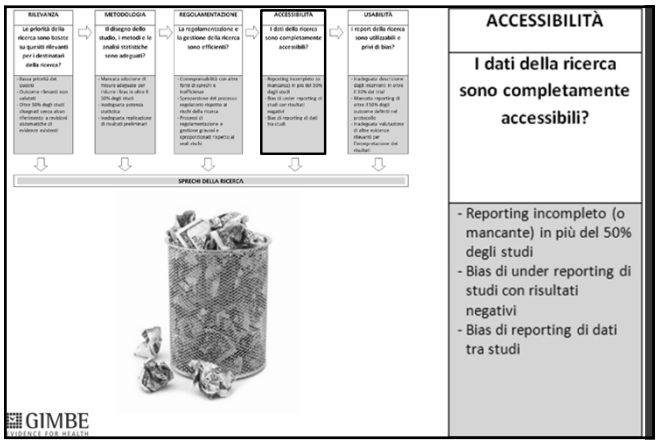

ACCESSIBILITÀ

I dati della ricerca sono completamente accessibili?

- Reporting incompleto (o mancante) in più del 50% degli studi
- Bias di under reporting di studi con risultati negativi
- Bias di reporting di dati tra studi

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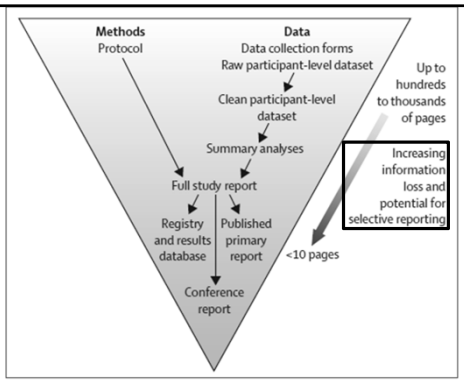

Figure 4: Key sources of information about study methods and results, with associated information loss and potential for selective reporting

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Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR.

Publication bias in clinical research

Lancet 1991;337:867-72

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OPEN ACCESS Freely available online PLoS MEDICINE

Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis

Joseph S. Ross[1,2]*, Gregory K. Mulvey[3], Elizabeth M. Hines[4], Steven E. Nissen[5], Harlan M. Krumholz[3,6,7]

1 Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, New York, United States of America, 2 HSR&D Research Enhancement Award Program and Geriatrics Research, Education, and Clinical Center, James J. Peters VA Medical Center, Bronx, New York, United States of America, 3 Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut, United States of America, 4 Amherst College, Amherst, Massachusetts, United States of America, 5 Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, United States of America, 6 Robert Wood Johnson Clinical Scholars Program and Section of Cardiolovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, United States of America, 7 Section of Health Policy and Administration, Yale University School of Epidemiology and Public Health, New Haven, Connecticut, United States of America

Published September 8, 2009

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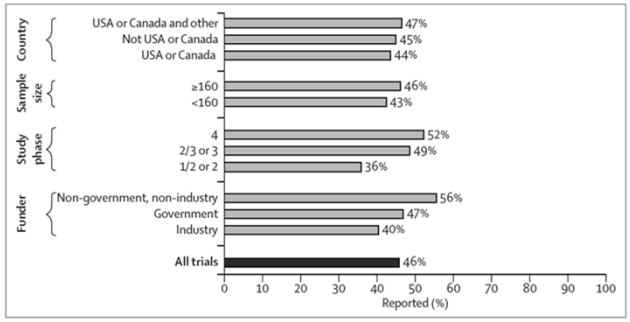

Figure 2: Reporting of completed trials, by study characteristic
Data taken from Ross and colleagues' analysis[11] of a random sample of 677 completed trials registered with ClinicalTrials.gov between 2000 and 2007.

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10 esempi clamorosi

- Oseltamivir
- Rosiglitazon
- Gabapentin
- TGN1412
- Paroxetine
- Lorcainide
- Rofecoxib
- Celecoxib
- Ezetimibe–simvastatin
- Vitamin A and albendazole

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Quali sprechi?

EU-funded health research from 1998-2006

- 6 billion of euros → 50% unpublished

Galsworthy MJ et al. Lancet 2012

Quali effetti su morbilità e mortalità?

- Rofecoxib 100.000 heart attacks in 1999-2004 (US)
- Lorcainide 50.000 deaths per year in 1980s (US)

Occultare i risultati dei trial clinici costa vite umane, spreca denaro e espone i pazienti a sofferenze e rischi evitabili: il caso della Lorcainide

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

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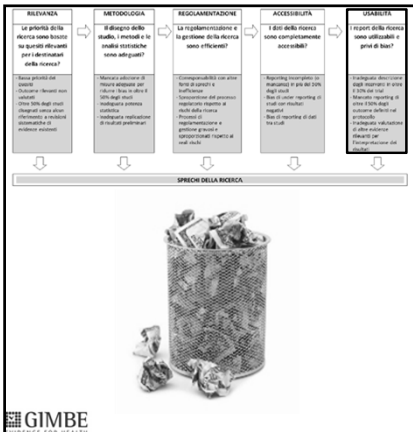

USABILITÀ

I report della ricerca sono utilizzabili e privi di bias?

- Inadeguata descrizione degli interventi in oltre il 30% dei trial
- Mancato reporting di oltre il 50% degli outcome definiti nel protocollo
- Inadeguata valutazione di altre evidenze rilevanti per l'interpretazione dei risultati

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ANALYSIS

What is missing from descriptions of treatment in trials and reviews?

Replicating non-pharmacological treatments in practice depends on how well they have been described in research studies, say **Paul Glasziou** and **colleagues**

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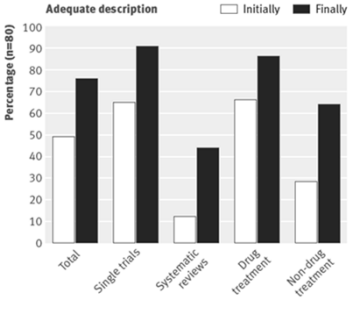

Fig 2 | Percentage of studies with sufficient description of treatment initially (based only on the published paper) and after supplementary information was obtained

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BMJ 2013;347:f3755 doi: 10.1136/bmj.f3755 (Published 10 September 2013)

RESEARCH

Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials

OPEN ACCESS

Tammy C Hoffmann *associate professor of clinical epidemiology*, Chrissy Erueti *assistant professor*, Paul P Glasziou *professor of evidence-based medicine*

Centre for Research in Evidence-Based Practice, Faculty of Health Sciences and Medicine, Bond University, Qld, Australia, 4229

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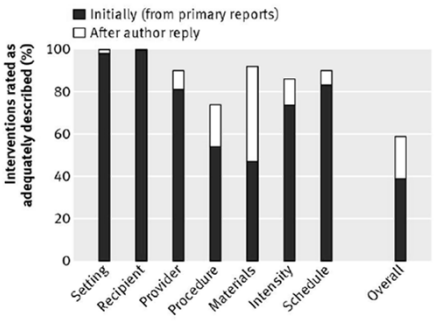

Fig 1 Percentage of interventions rated as adequately described, in primary report and after author reply, for each checklist item

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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%)[35]
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

***Figure 3*: Estimates of the prevalence of some reporting problems (see publication column, figure 1).**
fMRI=functional MRI.

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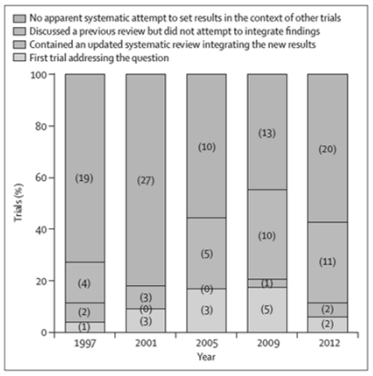

***Figure 2*: Percentage (and number) of trials that set their results in the context of a systematic review by 4 year intervals**
Data from references 69 and 70.

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Sperimentazioni Cliniche
Nuove Sfide per i Comitati Etici
Bologna, 7 novembre 2014

Ridurre gli sprechi e aumentare il valore della ricerca biomedica
Un mandato etico

Nino Cartabellotta
Fondazione GIMBE

CURRENT OPINION

Int J Pharm Med 2007; 21 (6): 395-404
1364-9027/07/0006-0395/$44.95/0

Regulation of Therapeutic Research is Compromising the Interests of Patients[1]

Iain Chalmers
James Lind Library, James Lind Initiative, Oxford, UK

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Tre motivazioni principali

- Approvazione di protocolli di trial senza alcuna rilevanza clinica
- Approvazione di protocolli di trial con disegno inadeguato
- Incapacità di mettere in atto azioni concrete per ridurre il bias di pubblicazione

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Necessarie azioni e reazioni

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Azioni

- Utilizzare checklist standardizzate e condivise a livello internazionale per valutare i protocolli delle sperimentazioni cliniche

SPIRIT

- Richiedere il numero di registrazione del trial per confermare in maniera definitiva l'approvazione delle sperimentazioni cliniche

+AllTrials

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Reazioni: attenti ai protocolli di trial…

- …che non fanno riferimento a revisioni sistematiche
- …con outcome surrogati, di rilevanza clinica non provata
- …in cui lo sponsor mantiene la proprietà dei dati
- …vs placebo in presenza di trattamenti efficaci
- …con disegno di non inferiorità
- …di disseminazione (*seeding trials*)

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Red flags: survey

Qual è il rischio che i protocolli di sperimentazioni cliniche con una o più *red flag* alimentino gli sprechi della ricerca, senza migliorare la salute di cittadini e pazienti?

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Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Published: August 30, 2005

1,152,733	1,413	13,400	10,526
VIEWS	CITATIONS	SAVES	SHARES

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PLOS | MEDICINE

Essay

How to Make More Published Research True

John P. A. Ioannidis[1,2,3,4]*

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Published October 21, 2014

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