GIMBE EVIDENCE FOR HEALTH

Aumentare il value delle risorse investite nella ricerca biomedica
La campagna Lancet-REWARD
Bologna, 9 novembre 2016

Raccomandazioni REWARD. Sessione II

Metodologia, regolamentazione e gestione della ricerca

DISCUSSANT

Gualberto Gussoni
Direttore scientifico Fondazione FADOI

Paolo Giorgi Rossi
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Aldo Maggioni
Direttore Centro Studi ANMCO

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Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Editor in Chief European Journal of Internal Medicine

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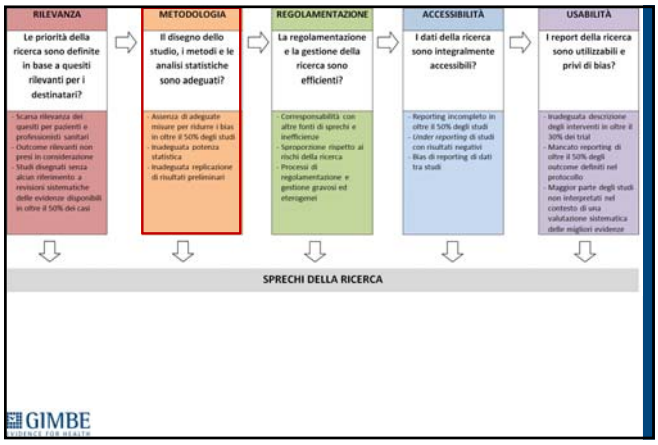

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Research: increasing value, reducing waste 2

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

Recommendations

1 Make publicly available the full protocols, analysis plans or sequence of analytical choices, and raw data for all designed and undertaken biomedical research
- Monitoring—proportion of reported studies with publicly available (ideally preregistered) protocol and analysis plans, and proportion with raw data and analytical algorithms publicly available within 6 months after publication of a study report

2 Maximise the effect-to-bias ratio in research through defensible design and conduct standards, a well trained methodological research workforce, continuing professional development, and involvement of non-conflicted stakeholders
- Monitoring—proportion of publications without conflicts of interest, as attested by declaration statements and then checked by reviewers; the proportion of publications with involvement of scientists who are methodologically well qualified is also important, but difficult to document

3 Reward (with funding, and academic or other recognition) reproducibility practices and reproducible research, and enable an efficient culture for replication of research
- Monitoring—proportion of research studies undergoing rigorous independent replication and reproducibility checks, and proportion replicated and reproduced

METODOLOGIA

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

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

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BMJ
LONDON, SATURDAY 29 JANUARY 1994

The scandal of poor medical research

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

DOUGLAS G ALTMAN

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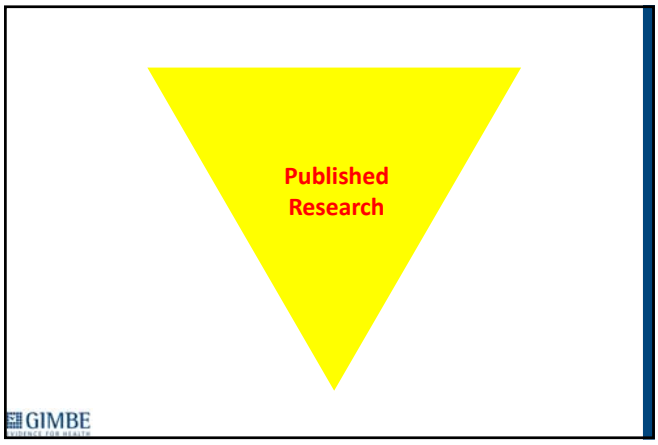

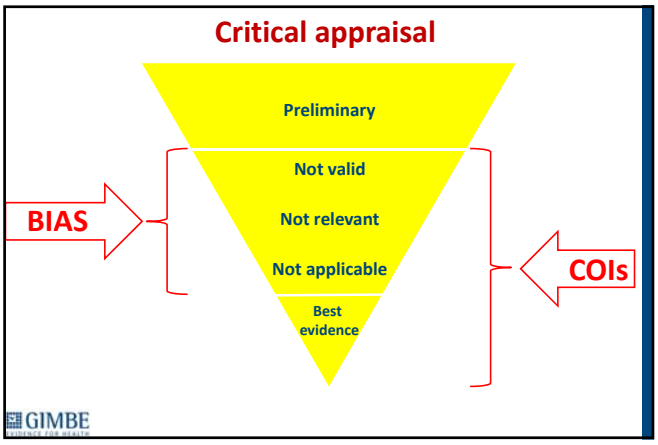

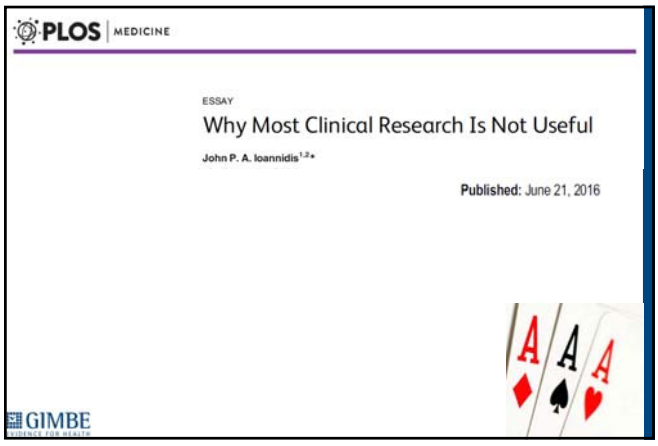

Methodological issues

- 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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The problems

- **Development of protocols and improvement of designs**
- **Effect-to-bias ratio**: la maggior parte degli effetti terapeutici sono modesti ed è difficile distinguerli dai bias
- **Reproducibility practices and reward systems**

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Tetzlaff et al. Systematic Reviews 2012, 1:43
http://www.systematicreviewsjournal.com/content/1/1/43

SYSTEMATIC REVIEWS

RESEARCH Open Access

Guidelines for randomized clinical trial protocol content: a systematic review

Jennifer M Tetzlaff[1*], An-Wen Chan[2], Jessica Kitchen[2], Margaret Sampson[3], Andrea C Tricco[4] and David Moher[1]

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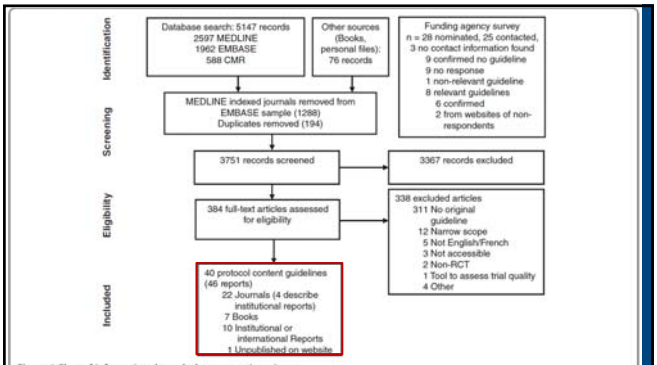

Figure 1 Flow of information through the systematic review.

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Linee guida protocolli trial clinici

- Notevole variabilità di obiettivi e raccomandazioni
- Metodologie di sviluppo spesso non descritte
- Raramente riportano:
  - adeguato coinvolgimento degli stakeholders
  - evidenze scientifiche a supporto delle raccomandazioni

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Research and Reporting Methods | Annals of Internal Medicine

SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

An-Wen Chan, MD, DPhil; Jennifer M. Tetzlaff, MSc; Douglas G. Altman, DSc; Andreas Laupacis, MD; Peter C. Gøtzsche, MD, DrMedSci; Karmela Krleža-Jerić, MD, DSc; Asbjørn Hróbjartsson, PhD; Howard Mann, MD; Kay Dickersin, PhD; Jesse A. Berlin, ScD; Caroline J. Doré, BSc; Wendy R. Parulekar, MD; William S.M. Summerskill, MBBS; Trish Groves, MBBS; Kenneth F. Schulz, PhD; Harold C. Sox, MD; Frank W. Rockhold, PhD; Drummond Rennie, MD; and David Moher, PhD

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality. This article describes the systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, a guideline for the minimum content of a clinical trial protocol.

The 33-item SPIRIT checklist applies to protocols for all clinical trials and focuses on content rather than format. The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial. By providing guidance for key content, the SPIRIT recommendations aim to facilitate the drafting of high-quality protocols. Adherence to SPIRIT would also enhance the transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

Ann Intern Med. 2013;158:200-207. www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 8 January 2013.

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evidence

open access journal published by the GIMBE Foundation

Standards & Guidelines OPEN ACCESS

SPIRIT Statement 2013: checklist per il protocollo dei trial clinici

An-Wen Chan[1*], Jennifer M. Tetzlaff[2], Douglas G. Altman[3], Andreas Laupacis[4], Peter C. Gøtzsche[5], Karmela Krleža-Jerić[6], Asbjørn Hróbjartsson[5], Howard Mann[7], Kay Dickersin[8], Jesse A. Berlin[9], Caroline J. Doré[10], Wendy R. Parulekar[11], William S.M. Summerskill[12], Trish Groves[13], Kenneth F. Schulz[14], Harold C. Sox[15], Frank W. Rockhold[16], Drummond Rennie[17], David Moher[18]

www.gimbe.org/spirit

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Priorità raccomandazioni REWARD

- 5= Indispensabile
- 4= Priorità elevata
- 3= Priorità intermedia
- 2= Priorità bassa
- 1= Non è una priorità

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METODOLOGIA

5. Rendere pubblicamente disponibili per tutti gli studi disegnati e condotti: protocolli integrali, analisi pianificate o sequenza delle analisi previste e dati grezzi

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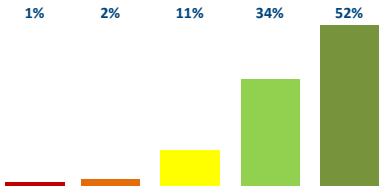
METODOLOGIA

Raccomandazione 5

Media 4.33 **DS ± 0.83**



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The problems

- Development of protocols and improvement of designs
- **Effect-to-bias ratio**: la maggior parte degli effetti terapeutici sono modesti ed è difficile distinguerli dai bias
- Reproducibility practices and reward systems

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ORIGINAL CONTRIBUTION

Empirical Evaluation of Very Large Treatment Effects of Medical Interventions

Tiago V. Pereira, PhD
Ralph I. Horwitz, MD
John P. A. Ioannidis, MD, DSc

JAMA. 2012;308(16):1676-1684

Conclusions Most large treatment effects emerge from small studies, and when additional trials are performed, the effect sizes become typically much smaller. Well-validated large effects are uncommon and pertain to nonfatal outcomes.

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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 Épistémologie 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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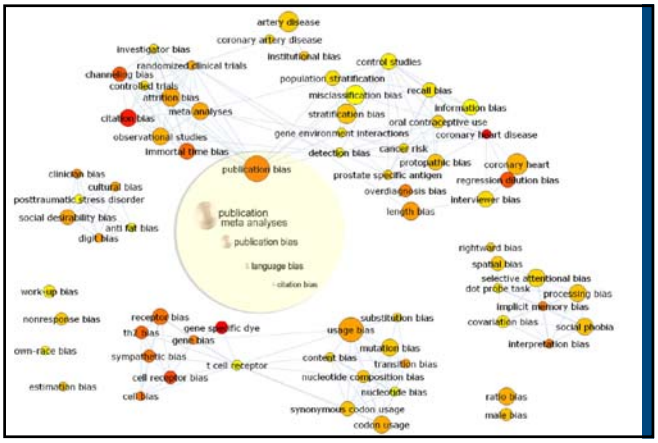

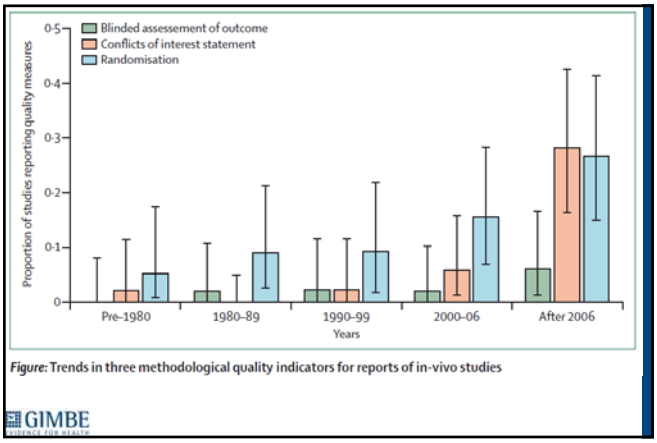

Figure: Trends in three methodological quality indicators for reports of in-vivo studies

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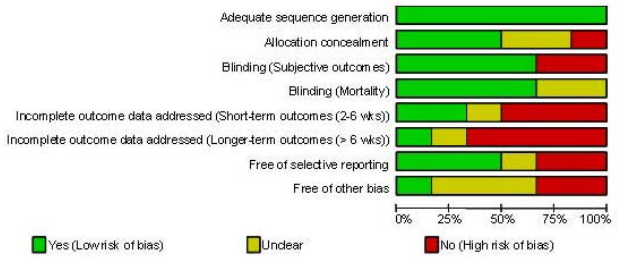
The Cochrane Collaboration's tool for assessing risk of bias



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RESEARCH

BMJ 2015;350:h809

Avoidable waste of research related to inadequate methods in clinical trials

Youri Yordanov,[1,2] Agnes Dechartres,[1,3,4] Raphaël Porcher,[1,3,4] Isabelle Boutron,[1,3,4,5] Douglas G Altman,[6] Philippe Ravaud[1,3,4,5,7]

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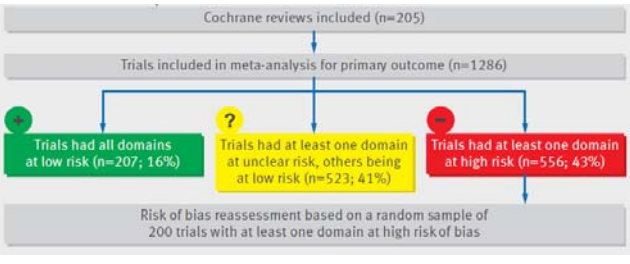

BMJ 2015;350:h809

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WHAT THIS STUDY ADDS

We found that part of the waste related to inadequate methods could have been avoided by simple and inexpensive methodological adjustments

Such adjustments could decrease the risk of bias in half of trials at high risk of bias and could transform all domains at high risk to low risk in 12% trials (95% CI 7% to 18%)

In a simulation study correcting for incomplete reporting, this avoidable waste represented 42% (95% CI 36% to 49%).

BMJ 2015;350:h809

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Priorità raccomandazioni REWARD

- 5= Indispensabile
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METODOLOGIA

6. Massimizzare il rapporto effetto/bias attraverso:
- aderenza a standard rigorosi nel disegno e nella conduzione degli studi
- utilizzo di ricercatori con adeguate competenze di metodologia della ricerca
- sviluppo professionale continuo
- coinvolgimento di stakeholders senza conflitti di interesse

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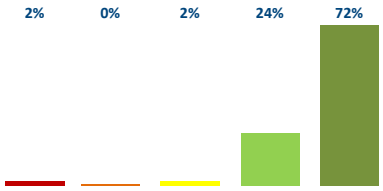
METODOLOGIA

Raccomandazione 6

Media 4.64 **DS ± 0.72**



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The problems

- Development of protocols and improvement of designs
- **Effect-to-bias ratio**: la maggior parte degli effetti terapeutici sono modesti ed è difficile distinguerli dai bias
- **Reproducibility practices and reward systems**

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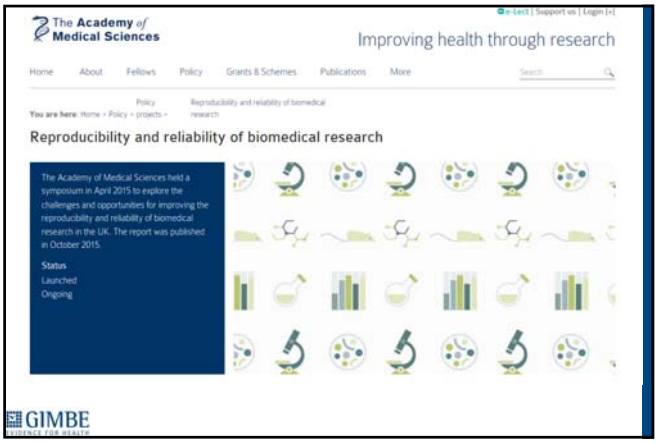

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METODOLOGIA

7. Incentivare (con finanziamenti, riconoscimenti accademici o di altra natura) pratiche di riproducibilità e studi riproducibili e sensibilizzare sulla necessità di replicare la ricerca

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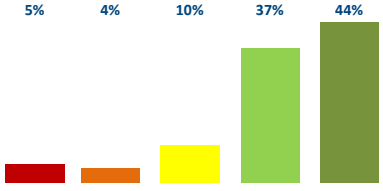
METODOLOGIA

Raccomandazione 7

Media	DS
4.10	± 1.07



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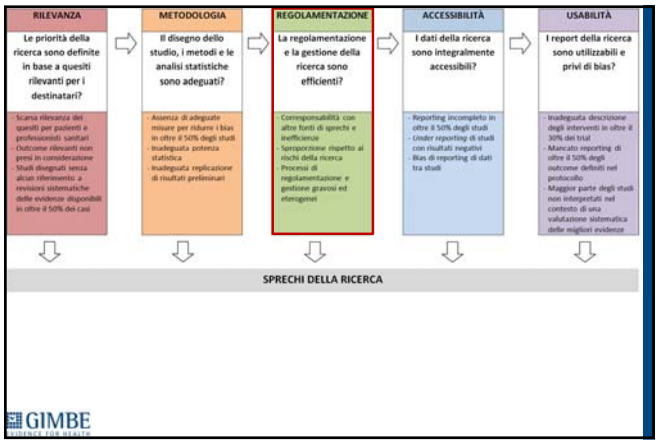

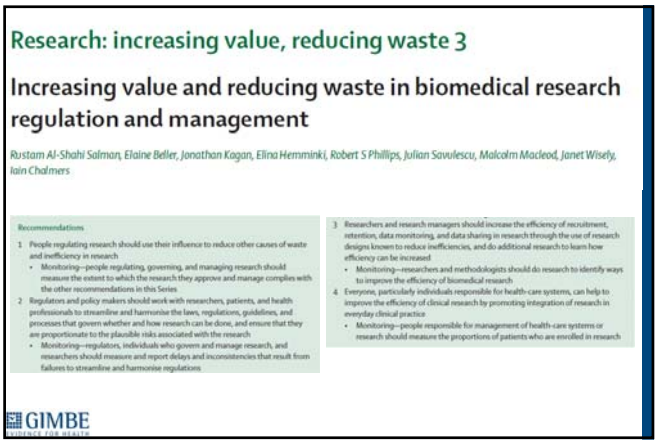

REGOLAMENTAZIONE

La regolamentazione e la gestione della ricerca sono efficienti?

- Corresponsabilità con altre fonti di sprechi e inefficienze
- Sproporzione rispetto ai rischi della ricerca
- Processi di regolamentazione e gestione gravosi ed eterogenei

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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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Warning to trial protocols…

- …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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Tabella 2. Protocolli di trial a rischio di alimentare gli sprechi della ricerca, senza migliorare la salute dei pazienti

Red flag	Media (DS)*
Mancato riferimento a revisioni sistematiche per giustificare la necessità dello studio	3.22 (± 0.70)
Misurazione di outcome surrogati, di rilevanza clinica non provata	3.38 (± 0.73)
Proprietà dei dati mantenuta dallo sponsor	3.20 (± 0.89)
Confronto vs placebo in presenza di trattamenti efficaci	3.56 (± 0.76)
Disegno di non inferiorità	3.01 (± 0.77)
Trial di disseminazione	3.28 (± 0.75)

*Valori calcolati secondo uno score di rischio 1-4 (1= nessuno; 2=lieve; 3= moderato; 4= elevato)

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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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REGOLAMENTAZIONE

8. I soggetti coinvolti nella regolamentazione della ricerca, forti del loro ruolo, dovrebbero limitare altre cause di sprechi e inefficienze

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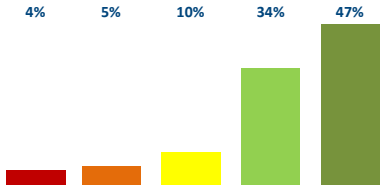
REGOLAMENTAZIONE

Raccomandazione 8

Media 4.14 **DS ± 1.07**



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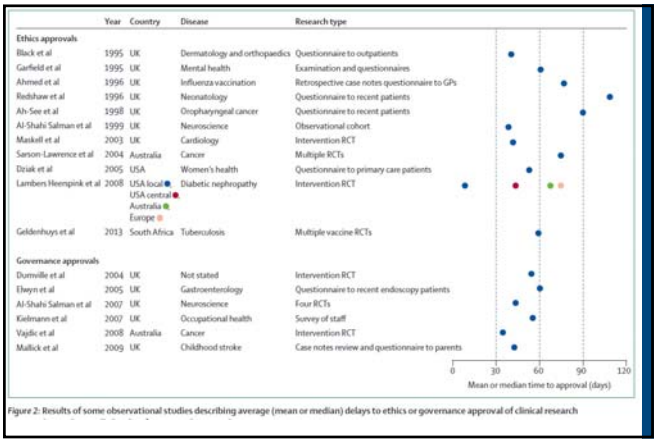
Panel 1: An example from Sweden of the bureaucracy involved in applications for central research ethics committee approval

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



	Year	Country	Disease	Research type
Ethics approvals				
Black et al	1995	UK	Dermatology and orthopaedics	Questionnaire to outpatients
Garfield et al	1995	UK	Mental health	Examination and questionnaires
Ahmed et al	1996	UK	Influenza vaccination	Retrospective case notes questionnaire to GPs
Redshaw et al	1996	UK	Neonatology	Questionnaire to recent patients
Ah-See et al	1998	UK	Oropharyngeal cancer	Questionnaire to recent patients
Al-Shahi Salman et al	1999	UK	Neuroscience	Observational cohort
Maskell et al	2003	UK	Cardiology	Intervention RCT
Sarson-Lawrence et al	2004	Australia	Cancer	Multiple RCTs
Dziak et al	2005	USA	Women's health	Questionnaire to primary care patients
Lambers Heerspink et al	2008	USA local, USA central, Australia, Europe	Diabetic nephropathy	Intervention RCT
Geldenhuys et al	2013	South Africa	Tuberculosis	Multiple vaccine RCTs
Governance approvals				
Dunville et al	2004	UK	Not stated	Intervention RCT
Elwyn et al	2005	UK	Gastroenterology	Questionnaire to recent endoscopy patients
Al-Shahi Salman et al	2007	UK	Neuroscience	Four RCTs
Kielmann et al	2007	UK	Occupational health	Survey of staff
Vajdic et al	2008	Australia	Cancer	Intervention RCT
Mallick et al	2009	UK	Childhood stroke	Case notes review and questionnaire to parents

0 30 60 90 120
Mean or median time to approval (days)

Figure 2: Results of some observational studies describing average (mean or median) delays to ethics or governance approval of clinical research

16 EvidenceLive
University of Oxford **June 22 - 24 2016**

Waste in independent drug research in Italy: a cross-sectional study

Nino Cartabellotta
GIMBE Foundation

Results: time gap

Mean (± SD) 515 (± 318) days*
Range 7-2.058 days*

Grant approval → Contract with AIFA → Ethical approval → Administrative approval§ → Start

*Data available for 140/204 (69%) studies
§From the research center of the PI

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Per prepararsi al Regolamento EU

- Utilizzo dei dati della ricerca clinica
- Assicurazione per la sperimentazione clinica
- Protezione dei dati personali pazienti
- Utilizzo materiale biologico residuo a scopo di ricerca
- Idoneità centri partecipanti a sperimentazioni cliniche
- Valutazione delle sperimentazioni e comitati etici

La ricerca no profit e il SSN

- Ruolo della ricerca no profit per il SSN
- Formazione per la ricerca: metodologia, procedure
- Sistemi premianti, re-investimento utili da ricerca
- Figure professionali di supporto alla ricerca

Priorità raccomandazioni REWARD

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REGOLAMENTAZIONE

9. Enti regolatori e policy maker dovrebbero collaborare con ricercatori, pazienti e professionisti sanitari per snellire e armonizzare normative, regolamenti, linee guida e processi che regolano approvazione e conduzione della ricerca, assicurando che siano proporzionati ai rischi verosimili per i partecipanti

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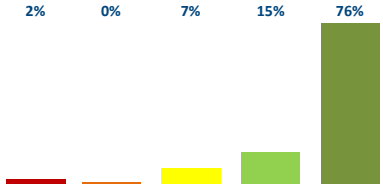
REGOLAMENTAZIONE

Raccomandazione 9

Media 4.62 **DS ± 0.80**



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REGOLAMENTAZIONE

10. Ricercatori e soggetti coinvolti nella gestione della ricerca dovrebbero:

- aumentare l'efficienza dei processi di reclutamento, mantenimento, monitoraggio e condivisione dei dati della ricerca, utilizzando disegni di studio in grado di ridurre le inefficienze
- condurre ulteriori studi sui metodi per aumentare l'efficienza

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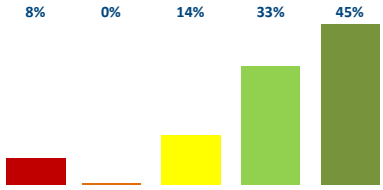
REGOLAMENTAZIONE

Raccomandazione 10

Media 4.09 DS ± 1.12



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REGOLAMENTAZIONE

11. Tutti, in particolare chi gestisce organizzazioni sanitarie, possono contribuire a migliorare l'efficienza della ricerca clinica, promuovendo l'integrazione dei suoi risultati nella pratica clinica quotidiana

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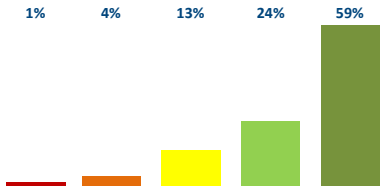
REGOLAMENTAZIONE

Raccomandazione 11

Media 4.35 DS ± 0.92



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SPECIAL COMMUNICATION

What Makes Clinical Research Ethical?

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

JAMA. 2000;283:2701-2711

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Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.