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

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 usable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment.

Trisha Greenhalgh, dean for research impact1, Jeremy Howick, senior research fellow2, Neal Maskey, professor of evidence informed decision making3, for the Evidence Based Medicine Renaissance Group.

Omission bias

Necessary Research
Planned Research
Published Research
Necessary Research
Necessary Research

Planned Research

Published Research

BIAS

Not valid
Not relevant
Not applicable

Best evidence

COIs

Avoidable waste in the production and reporting of research evidence

THE LANCET

“By ensuring that efforts are invested with rigor from start to finish, the research community might protect itself from the wasted efforts that could undervalue the conflicted motivations of capital and policy, and perhaps real value for money for charitable giving and taxpayer through increased value and reduced waste.”
"Wasters" in Life Sciences Research in 2010

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


Biomedical research: increasing value, reducing waste

How should medical science change?

Comment

Life sciences research in 2010

US$ 240.000.000.000

85% wasted
L'inefficienza della ricerca di base

1 intervention used widely
5 resulted in licensed clinical interventions by 2003
103 claimed that new discoveries had clear clinical potential
>25,000 reports in 6 basic science journals 1979-83

Translation of Highly Promising Basic Science Research into Clinical Applications

Despina G. Contopoulou-Ioannidou, MD, Evangelia E. Ntari, MD, John P. A. Ioannidis, MD

PURPOSE: To evaluate the predictions of and factors 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 therapeutics or preventative promise. Each case was evaluated for whether the promising finding resulted in relevant uncontrolled clinical trials and clinical use. Measures included the time to publication of clinical trials and trials favoring outcome, "positive" trials, and licensed clinical use.

RESULTS: By October 2002, 25 of the promising technologies had resulted in at least one published randomized trial, 19 of which led to the publication of a clinical positive randomized trial. Five basic science findings are currently licensed for clinical use, but only one has been used extensively for clinical indications. Promising technology that did not lead to a published human study within 10 to 12 years was unlikely to be tested in humans subsequently. Some forms of evidence involve in the basic science publication of an unmet need for clinical experimentation, accounting for the precise by about eightfold 90% confidence interval: 3 to 10) 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; 114:677–80. © 2003 by Elsevier Inc.
**Limitato riferimento a revisioni sistematiche**

<table>
<thead>
<tr>
<th>May, 2009 (n=29)</th>
<th>May, 2012 (n=34)</th>
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<tr>
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<td>5</td>
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<tr>
<td>Contains an updated systematic review that was used to inform trial design</td>
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</tr>
<tr>
<td>Previous systematic review dismissed that was not used in trial design</td>
<td>20</td>
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<tr>
<td>Contains references to other randomised trials</td>
<td>4</td>
</tr>
<tr>
<td>Does not contain references to other randomised trials or claims to be the first trial</td>
<td>9</td>
</tr>
</tbody>
</table>


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

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**What Makes Clinical Research Ethical?**

Edward J. Emanuel, MD, PhD
David Walker, PhD

JAMA. 2003;289:2709-2711

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**Research: increasing value, reducing waste 2**

*Research* and *increasing value, reducing waste in research design, conduct, and analysis*

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**METODOLOGIA**

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

- Mancata adozione di misure adatte per ridurre il 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
- È 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
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

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

Publication bias in clinical research

*Lancet* 1991;337:867-72

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10 esempi clamorosi

- Oseltamivir
- Rosiglitazon
- Gabapentin
- TGN1412
- Paroxetin
- Lorcanide
- Rofecoxib
- Celecoxib
- Ezetimibe–simvastatin
- Vitamin A and albendazole
Quali sprechi?

EU-funded health research from 1998-2006

- 6 billion of euros → 50% unpublished

Goworthy MJ et al. Lancet 2012

Quali effetti su morbilità e mortalità?

- Rofecoxib 100,000 heart attacks in 1999-2004 (US)
- Lorcanide 50,000 deaths per year in 1980s (US)

Research: increasing value, reducing waste 5

Reducing waste from incomplete or unusable reports of biomedical research

Paul Glasziou, Douglas Altman, Patrick Sweeney, Annabel Boutron, Mike Clarke, Steven Howes, Susan Wair, David Clarke, Elizabeth Magee

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

Fig 2: Percentage of studies with sufficient description of treatment initially (based only on the published paper) and after supplementary information was obtained
Abstract
38%, 49%

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

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

Discussion
50%

Data
Almost all

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

Figure 2: Percentage (and number) of trials that set their results in the context of other trials. Percentage and number of trials reported in the context of other trials by year. Data from references 55 and 75.

Abstract
Trials: reporting effect size and confidence interval (95%), no mention of adverse effects (49%).

Methods
Trials: 40-50% inadequate treatment descriptions; 15% missing number of trials and duration; 15% missing on one or more questions.

Results
Clinical trials: outcomes missing: 50% efficacy and 60% harms outcomes per trial incompletely reported. Animal studies: number of animals and raw data missing (54%, 92% age and weight missing 24%). Diagnostic studies: missing age and sex (40%).

Discussion
Trials no systematic attempt to set new results in context of previous trials (59%).

Data
Trials: most data never made available, author held data at about 7% per year.

Figure 3: Estimates of the prevalence of some reporting problems (see publication column, figure 2).
Regulation of Therapeutic Research is Compromising the Interests of Patients

• 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

Tre motivazioni principali

Necessarie azioni e reazioni

• Utilizzare checklist standardizzate e condivise a livello internazionale per valutare i protocolli delle sperimentazioni cliniche
• Richiedere il numero di registrazione del trial per confermare in maniera definitiva l'approvazione delle sperimentazioni cliniche

Azioni

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)

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?