“Ragionevoli” ricadute della ricerca per il servizio sanitario

Alessandro Liberati

Agenzia Sanitaria e Sociale Regionale

Università di Modena e Reggio Emilia

Contenuti

- Una premessa necessaria
- Perché valutare l'impatto della ricerca ?
- Come si valuta: quali approcci
- Quali ragionevoli aspettative ?
  - Dal sistema sanitario
  - Dal mondo dei clinici e ricercatori
- Conclusioni

La premessa: stiamo parlando di…….

"….. trovare le motivazioni politiche, culturali, scientifiche, etiche e professionali che giustificano l'impiego di risorse destinate alla tutela della salute per sostenere un'attività che ***potrà*** portare dei benefici ai pazienti ed al sistema. Ciò comporta necessariamente ***rischi di fallimento***, ***distorsioni di vario genere*** e richiede di combinare ***capacità di indirizzo*** e ***tutela della autonomia***"

A. Clarke 2002

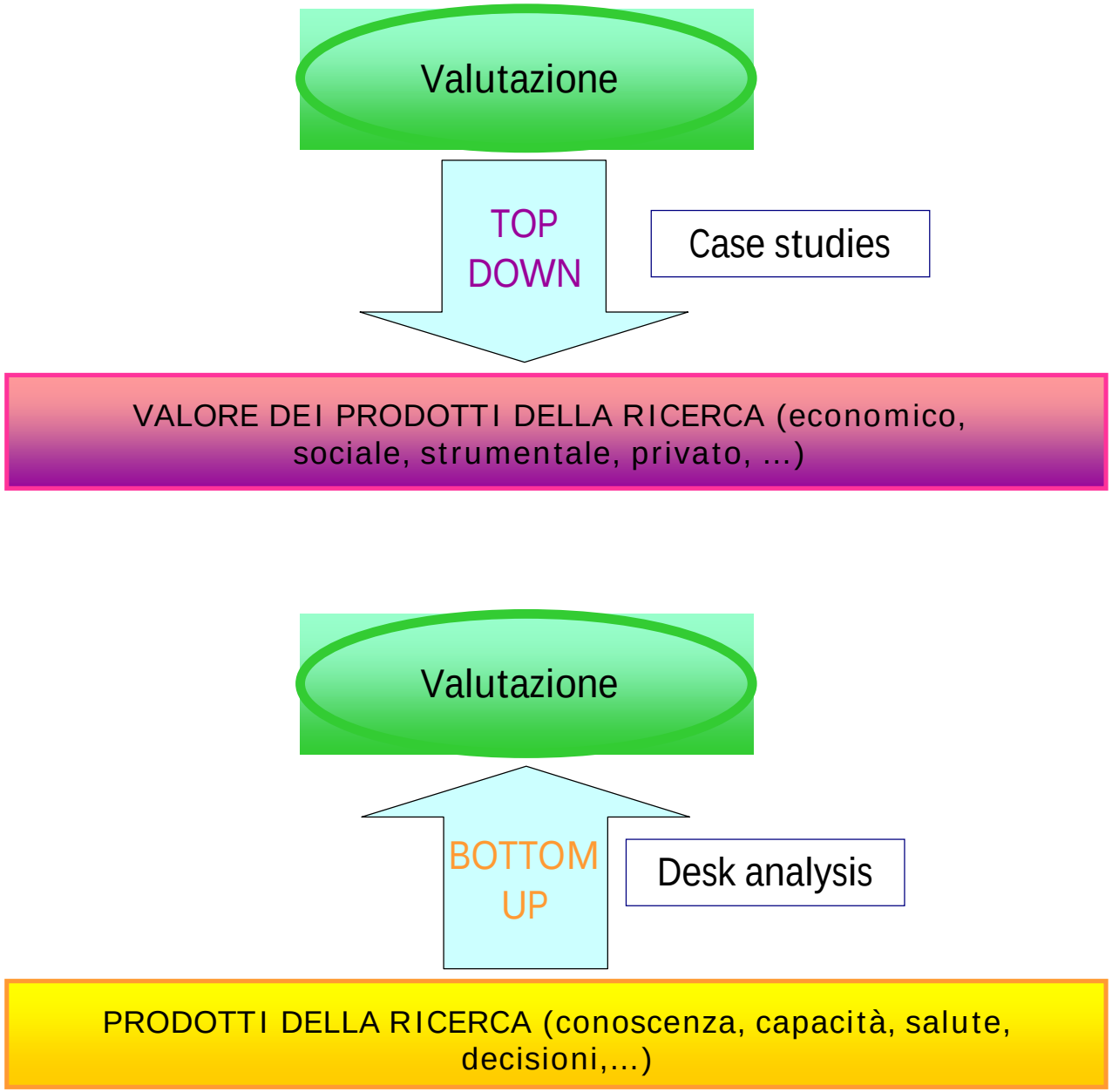
Contenuti

- Una premessa necessaria
- Perché valutare l'impatto della ricerca ?
- Come si valuta: quali approcci
- Quali ragionevoli aspettative?
  - Dal sistema sanitario
  - Dal mondo dei clinici e ricercatori
- Conclusioni

VALUTARE L' IMPATTO DELLA RICERCA BIOMEDICA

Contenuti

- Una premessa necessaria
- Perché valutare l'impatto della ricerca ?
- Come si valuta: quali approcci
- Quali ragionevoli aspettative?
  - Dal sistema sanitario
  - Dal mondo dei clinici e ricercatori
- Conclusioni

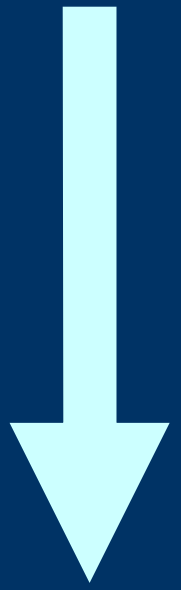

Valutazione
TOP
DOWN
Case studies
VALORE DEI PRODOTTI DELLA RICERCA (economico, sociale, strumentale, privato, ...)
Valutazione
BOTTOM
UP
Desk analysis
PRODOTTI DELLA RICERCA (conoscenza, capacità, salute, decisioni,...)

Modelli teorici

- Payback
- Impatto della ricerca
- Utilità della ricerca
- Valutazione target-specifica (modello decisionale di Lavis)
- Modello Logico di Weiss
- Valutazione dei sistemi di Health Technology Assessment
- Impatto sociale
- Balance scorecard
- Research Assessment Exercise (RAE)
- Analisi costo-benefici

Categorie di impatto (CAHS) in ordine di crescente complessità

- Avanzamento delle conoscenze
- Sviluppo di competenze e infrastrutture
- Utilità per i processi decisionali
- Miglioramento dello stato di salute
- Benefici economici e sociali



Metodologia valutativa

- Analisi bibliometrica e citazionale
- Valutazione della documentazione amministrativa
  - Interviste/Questionari
  - Database
  - Audit
  - Valutazioni economiche
- Case-studies

Valutazione ad hoc *vs* Raccolta dati

I problemi metodologici nella valutazione

- Attribuibilità
- Controfattualità
- “Finestra temporale” di valutazione
- “Double-counting”
- Considerazione selettiva dei soli effetti positivi

In sintesi….

- Area di ricerca molto “giovane” con metodologie e approcci molto disomogenei
- Solo approcci multidimensionali possono garantire una valutazione adeguata
- Metodologia ed indicatori capaci di adattarsi a tipologie di ricerca molto diverse

difficile estrapolare un “modello unico” di riferimento

Ma buone indicazioni su :

- ü dimensioni di impatto
- ü specifici indicatori
- ü ambito di applicazione
- ü metodologia necessaria per la loro valutazione

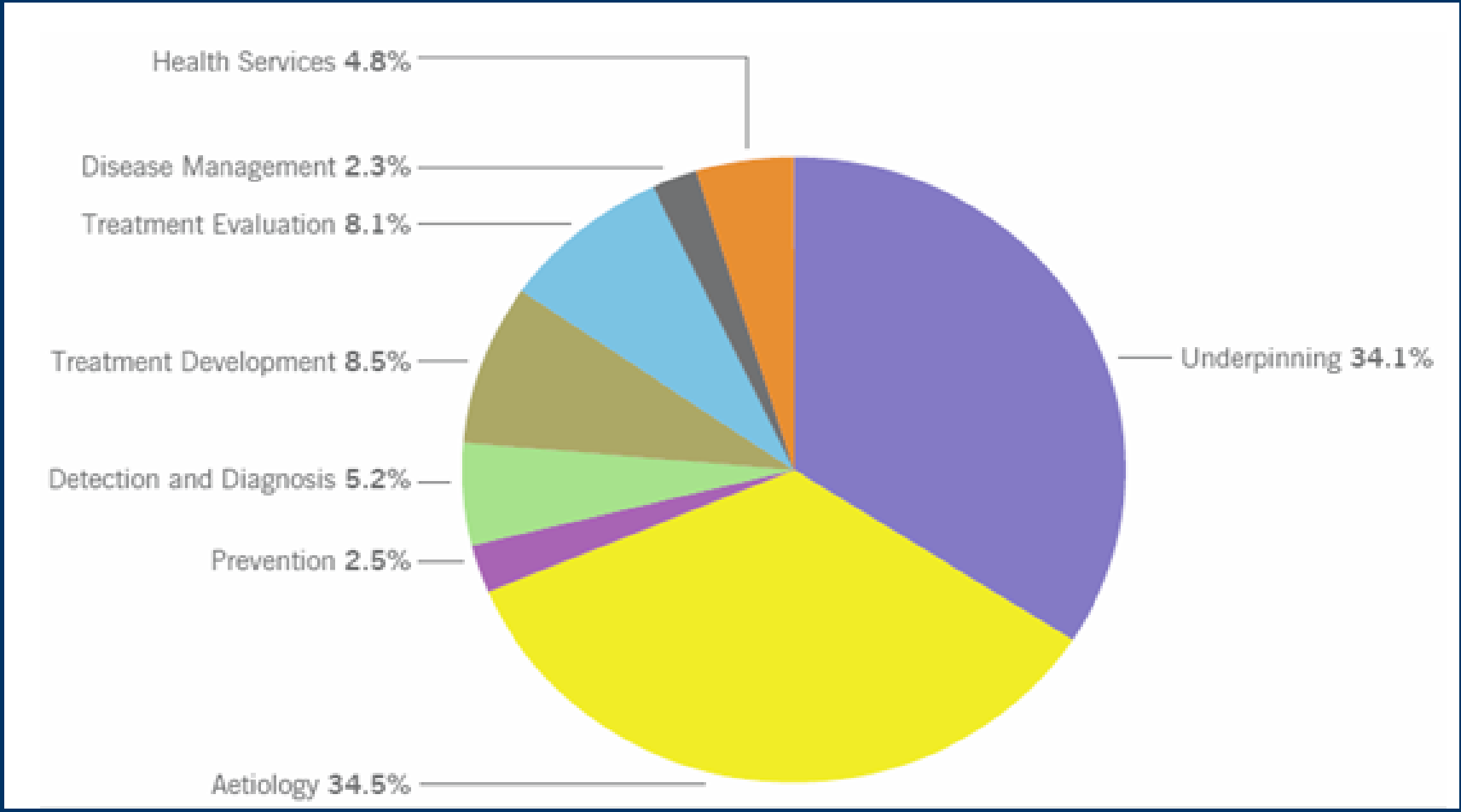
Contenuti

- Una premessa necessaria
- Perché valutare l'impatto della ricerca ?
- Come si valuta: quali approcci
- Quali ragionevoli aspettative?
  - Dal sistema sanitario
  - Dal mondo dei clinici e ricercatori
- Conclusioni

Il sostegno alla ricerca dei sistemi sanitari: potenzialità

- Bilanciare l’agenda della ricerca
- Portare a effettiva “maturità” le conoscenze
- Ridurre gli sprechi del sistema
- Identificare gli elementi utili per migliorare la qualità dell’assistenza
- Aumentare l'eticità della pratica clinica rendendo esplicite le aree di incertezza

Tipologie di ricerca finanziata UK 2004-2005



UK Clinical Research Collaboration 2006 - UK Health Research Analysis: London UKCRC

Al-Shahi R, Will RG, Warlow CP.

Amount of research interest in rare and common neurological conditions: bibliometric study

Bmj 2001;323(7327):1461-2

Amount of research interest in rare and common neurological conditions: bibliometric study

Rustam Al-Shahi, Robert G Will, Charles P Warlow

Neurologists are often accused of being interested in only rare incurable diseases. Although this may have been true in the past, today's neurologists claim to be more concerned with common disorders—but are they really?

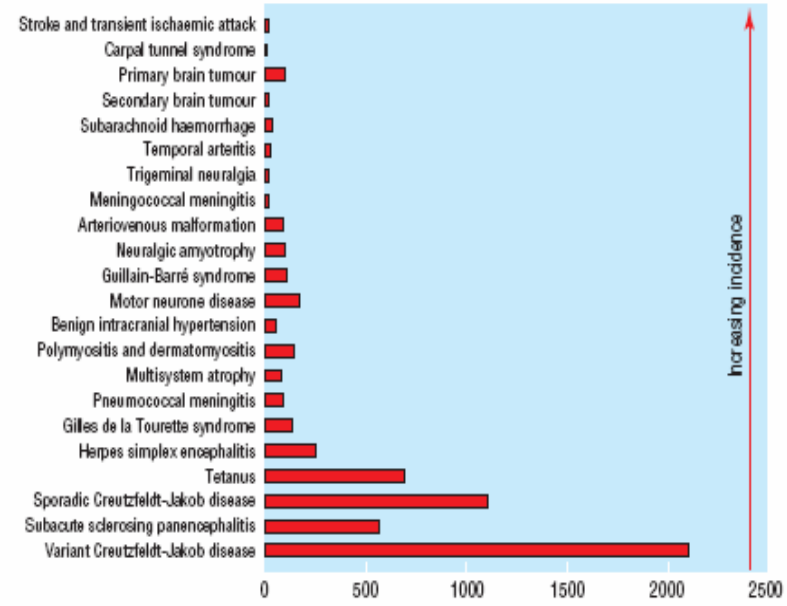
Methods and results

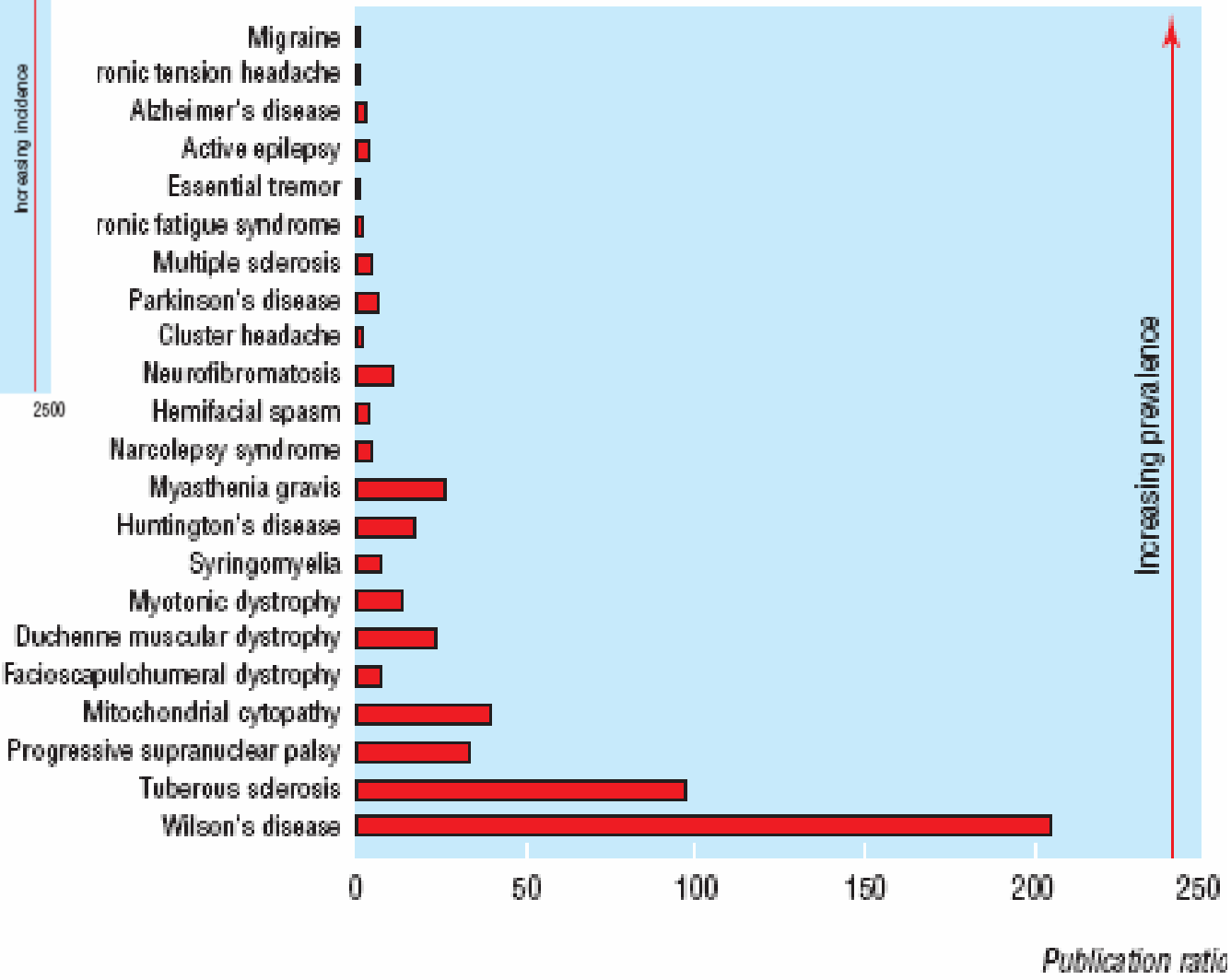
death, economic hardship, and loss of quality of life. It is recognised that funding for research into a disease should be proportional to that disease's burden on society[2]; however, conditions that account for 90% of the global burden of disease receive less than one tenth of the world's health budget.[3]

Correspondence to:
C P Warlow
CharlesWarlow@ed.ac.uk

continued over

BMJ 2001;323:1461–2





Overall, there were 42 papers about variant Creutzfeldt-Jakob disease and 4562 about stroke and transient ischaemic attack. If the publication ratio for stroke and transient ischaemic attack had been equa to that of variant Creutzfeldt-Jakob disease, clinicians and researchers interested in stroke would have had to read 525 000 papers in 1998 (about 10 000 per week)—an insufferable burden!

Publication ratios for 44 neurological conditions ordered by their incidence (top) and prevalence (bottom)

Il programma AIFA di ricerca sul farmaco

DOI: 10.1111/j.1365-2362.2009.02226.x

PERSPECTIVE

Feasibility and challenges of independent research on drugs: the Italian Medicines Agency (AIFA) experience

Italian Medicines Agency (AIFA) Research & Development Working Group*

KEY POINTS

- National Health Service (NHS) is becoming increasingly aware of the need to support independent research to answer some important questions for patient care in areas of scant commercial interest.
- This article reports the main features and strategies of the independent research programme on drugs launched by the Italian Medicines Agency (AIFA) in 2005.
- In the three bids launched between 2005 and 2007, a total of 151 studies have been approved for funding for a total of about 78 million Euro.
- In this article we describe the Italian legislative framework under which the programme was launched, the types of research funded and discuss how the supported studies could contribute, in an international framework, to the knowledge needed on drug efficacy, effectiveness and safety.

Eur J Clin Invest 2009

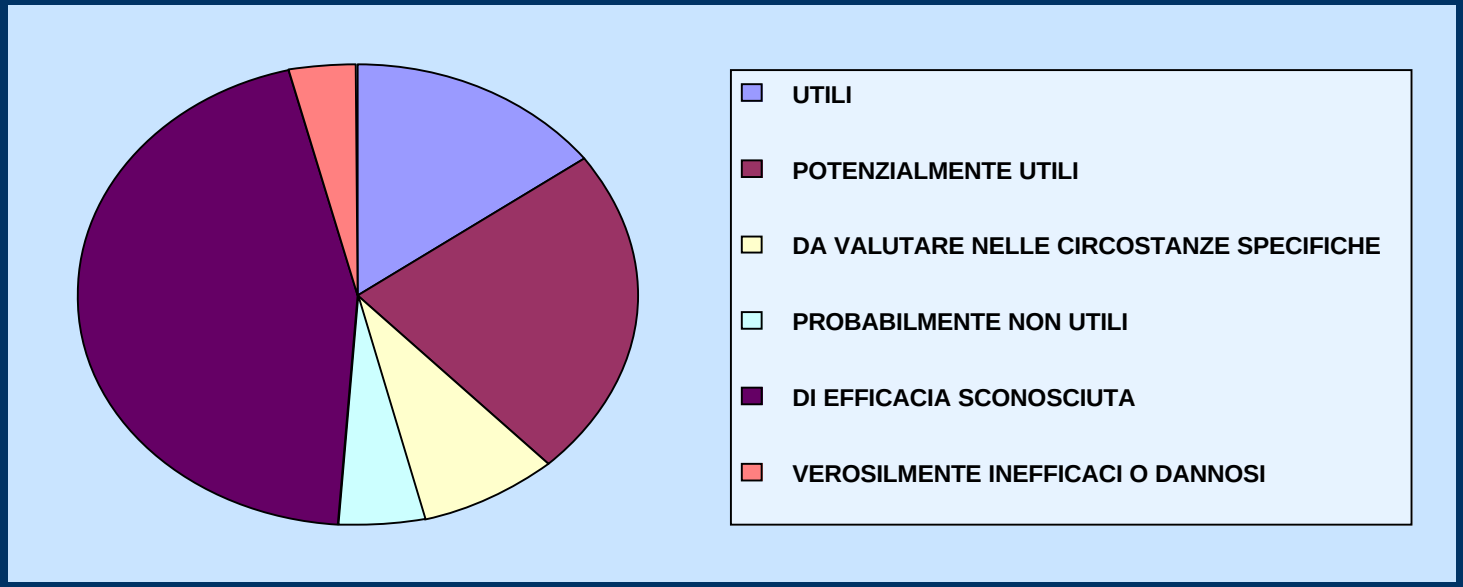
AIFA R&D Commitee - Europ J Clin Investig, 2010

La conoscenza sull' effetto degli interventi

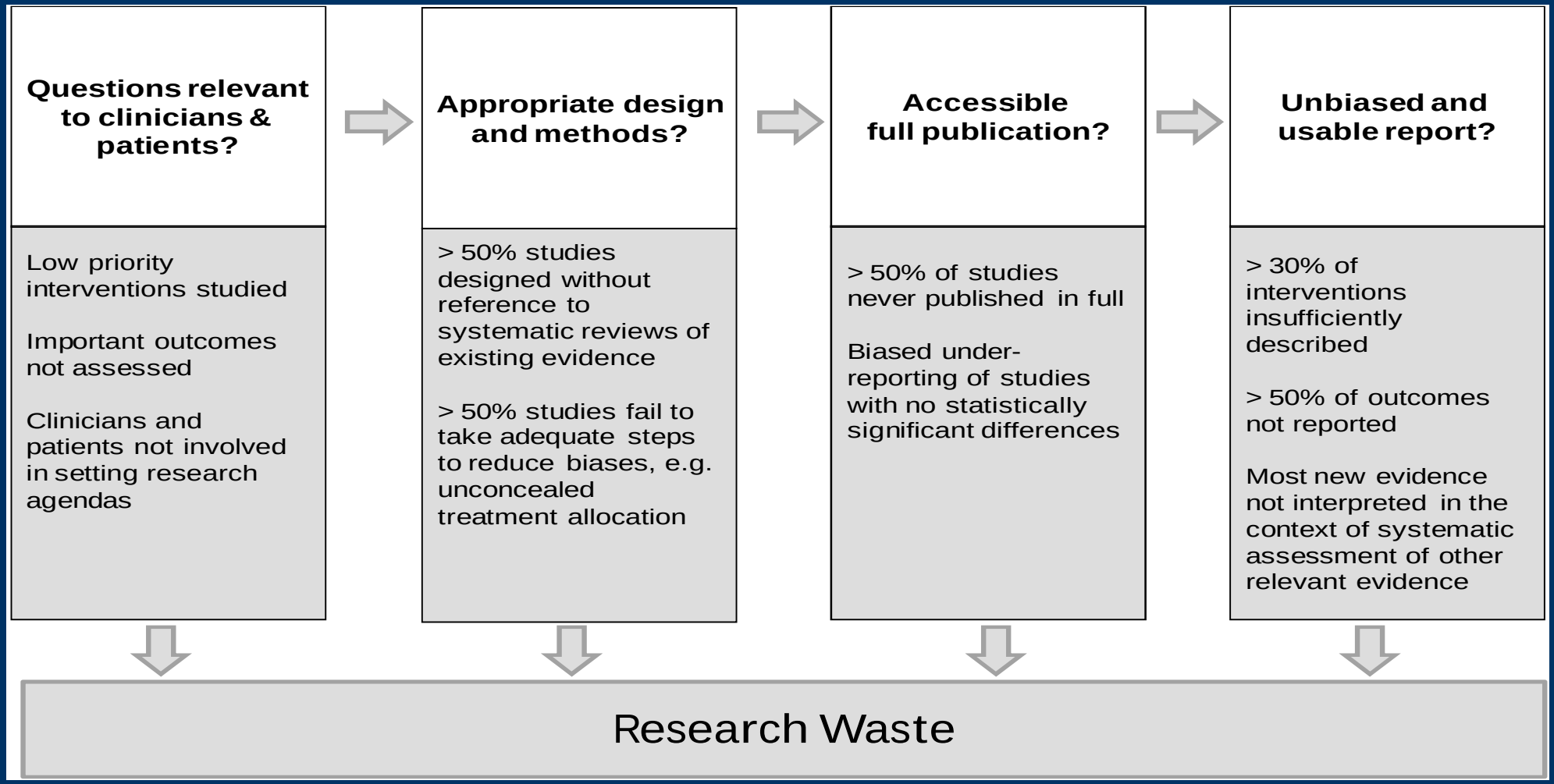
Utili	**Interventi con solide prove di efficacia e rischi inferiori ai benefici**
Potenzialmente utili	**Interventi di efficacia è plausibile ma meno chiaramente dimostrata**
Da valutare caso per caso	**Interventi nei quali va attentamente valutato profilo beneficio-rischio**
Probabilmente non utili	**Interventi sulla cui efficacia permane una considerevole incertezza**
Verosimilmente inefficaci/dannosi	**Interventi di cui è stata dimostrata l'inefficacia e potenziali rischi**

Clinical Evidence

Giugno 2008



"Spreco evitabile" nell'ideazione, produzione, presentazione e disseminazione della ricerca



Contenuti

- Una premessa necessaria
- Perché valutare l'impatto della ricerca ?
- Come si valuta: quali approcci
- Quali ragionevoli aspettative?
  - Dal sistema sanitario
  - Dal mondo dei clinici e ricercatori
- Conclusioni

Aspettative dal mondo dei clinici-ricercatori

- Reagire alla mancanza di indipendenza
- Evitare la ricerca “futile” e assumersi la responsabilità della prevenzione dei bias
- Concepire la ricerca come esercizio cumulativo
- Concentrarsi su esiti clinici rilevantiù
- Identificare le aree di confine tra i diversi tipi di ricerca

Industry-Sponsored Clinical Research
A Broken System

Marcia Angell, MD

OVER THE PAST 2 DECADES, THE PHARMACEUTICA
industry has gained unprecedented control ove
the evaluation of its own products. Drug com
panies now finance most clinical research o
prescription drugs, and there is mounting evidence that the
often skew the research they sponsor to make their drug
look better and safer. Two recent articles underscore the prob
lem: one showed that many publications concerning Merck
rofecoxib that were attributed primarily or solely to aca
demic investigators were actually written by Merck employ
ees or medical publishing companies hired by Merck[1]; th
other showed that the company manipulated the data analy
sis in 2 clinical trials to minimize the increased mortalit
associated with rofecoxib.[2] Bias in the way industry
sponsored research is conducted and reported is not un
usual and by no means limited to Merck.[3]

The problem is not so much the sponsorship itself bu
the terms. Before the 1980s, industry grants to academic in-
stitutions to fund studies by faculty members gave investi-
gators total responsibility. The investigator designed the stud-
ies, analyzed and interpreted the data, wrote the papers, and
decided where and how to report the results. Generally, nei-
ther the investigators nor their institutions had other finan-
cial connections to sponsoring companies.

In recent years, however, sponsoring companies have become

to accede to drug company terms because their only clients
are drug companies. Sponsors would still prefer that their
important clinical research be conducted in academic medi-

Author Affiliation: Department of Global Health and Social Medicine, Harvard Medical School, Cambridge, Massachusetts.
Corresponding Author: Marcia Angell, MD, Department of Global Health and Social Medicine, Harvard Medical School, 651 Huntington Ave, Cambridge, MA 02115 (marcia_angell@hms.harvard.edu).

Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer

Angell M. JAMA 2008;300:1069-71

Aspettative dal mondo dei clinici-ricercatori

- Reagire alla mancanza di indipendenza
- Evitare la ricerca “futile”, assumersi la responsabilità della prevenzione dei bias
- Concepire la ricerca come esercizio cumulativo
- Concentrarsi su esiti clinici rilevanti
- Identificare le aree di confine tra i diversi tipi di ricerca

Use limited evaluative resouces where they are mostly needed

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.[6]

Department of Obstetrics and Gynaecology, Cambridge University, Cambridge CB2 2QQ

Gordon C S Smith *professor*

Department of Public Health, Greater Glasgow

...possibly avoiding futile questions

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Selective reporting of outcomes

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
Asbjørn Hróbjartsson, MD, PhD
Mette T. Haahr, BSc
Peter C. Gøtzsche, MD, DrMedSci
Douglas G. Altman, DSc

Context Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

Objective To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

Design Cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark, in 1994-1995.

Chan A-W et al. JAMA 2004;291:2457-65

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil

Results One hundred two trials with 122 published journal articles and 3736 outcomes were identified. Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Statistically significant outcomes had a higher odds of being fully reported compared with nonsignificant outcomes for both efficacy (pooled odds ratio, 2.4; 95% confidence interval [CI], 1.4-4.0) and harm (pooled odds ratio, 4.7; 95% CI, 1.8-12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

Chan A-W et al. JAMA 2004;291:2457-65

Aspettative dal mondo dei clinici-ricercatori

- Reagire alla mancanza di indipendenza
- Evitare la ricerca “futile” e assumersi la responsabilità della prevenzione dei bias
- Concepire la ricerca come esercizio cumulativo
- Concentrarsi su esiti clinici rilevanti
- Identificare le aree di confine tra i diversi tipi di ricerca

Researchers see studies as self-sufficient entities

Discussion Sections in Reports of Controlled Trials Published in General Medical Journals

Islands in Search of Continents?

Michael Clarke, DPhil; Iain Chalmers, MSc

Context.—Several journals have adopted the Consolidated Standards of Reporting Trials (CONSORT) recommendations to make assessment of the quality of randomized controlled trials (RCTs) easier. One of these recommendations is that the trial's results be discussed in light of the totality of the available evidence.

Objective.—To assess the extent to which reports of RCTs published in 5 general medical journals have discussed new results in light of all available evidence.

Design.—Assessment of the discussion sections in all 26 reports of RCTs published during May 1997 in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *The Lancet*,

systematic scrutiny. The typical discussion section usually addresses a number of dimensions, but, crucially, it is in this section that readers will look for an answer to Bradford Hill's "bottom line" question for any research article: "What does it mean, anyway?"[3] This was recognized in the CONSORT statement, which included the recommendation that trial-

.... and fail to think to the totality of evidence.....

JAMA 1998

19/26 reports ignore previous findings

Discussion Sections in Reports of Controlled Trials Published in General Medical Journals

Islands in Search of Continents?

Michael Clarke, DPhil; Iain Chalmers, MSc

Context.—Several journals have adopted the Consolidated Standards of Reporting Trials (CONSORT) recommendations to make assessment of the quality of randomized controlled trials (RCTs) easier. One of these recommendations is that the trial's results be discussed in light of the totality of the available evidence.

Objective.—To assess the extent to which reports of RCTs published in 5 general medical journals have discussed new results in light of all available evidence.

Design.—Assessment of the discussion sections in all 26 reports of RCTs published during May 1997 in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *The Lancet*,

systematic scr
sion section us
of dimensions,
section that re
swer to Brad
question for ar
does it mean, a
nized in the CO
included the re

JAMA 2002

27/30 reports ignore previous findings

Discussion Sections in Reports of Controlled Trials Published in General Medical Journals

Mike Clarke, DPhil
Phil Alderson, MBChB
Iain Chalmers, DSc

ANYONE WISHING TO INTERpret a trial needs to know how its results compare with those of similar studies, a fact recognized by the original CONSORT (Consolidated Standards of Reporting Trials) statement, which recommended that the report of a randomized trial discuss its findings in light of the totality of relevant evidence.[1] In May 1997, *Annals of Internal Medicine*, *BMJ*, *JAMA*, *The Lancet*, and *The New England Journal of Medicine* published 26 reports of randomized trials. Reports of apparently similar trials were found for 25 of these. In only 2 were a trial's results placed in the context of an up-to-

Context Reliable interpretation of the results of a controlled trial entails setting its results in the context of similar research. A previous study showed that most reports of controlled trials published in 5 general medical journals in May 1997 were deficient in this respect. We assessed the extent to which reports of controlled trials published in the same 5 journals discussed new results in light of the totality of evidence from other controlled trials.

Methods Assessment of the discussion sections in all 33 reports of randomized trials published during May 2001 in *Annals of Internal Medicine*, *BMJ*, *JAMA*, *The Lancet*, and *The New England Journal of Medicine*.

Results Three reports appeared to have been the first published trials to address the questions studied. In none of the remaining 30 reports were the results of the new trial discussed in the context of an updated systematic review of other trials. Although reference was made to relevant systematic reviews in 3 of these 30 reports, there was no integration, quantitative or qualitative, of the results of the new trials in an update of these reviews. In the remaining 27 reports, there was no evidence that any systematic attempt had been made to set the new results in the context of previous trials.

Conclusions Between 1997 and 2001, there was no evidence of progress in the proportion of reports of trials published in general medical journals that discussed the new results within the context of, or with reference to, up-to-date systematic reviews of relevant evidence from other controlled trials.

JAMA. 2002;287:2799-2801 www.jama.com

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions,

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but,

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most prominent when high-impact research is involved.

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

JAMA. 2005;294:218-228 www.jama.com

CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.[1,2]

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.[3-5] Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives most attention and dominates scien-

Results

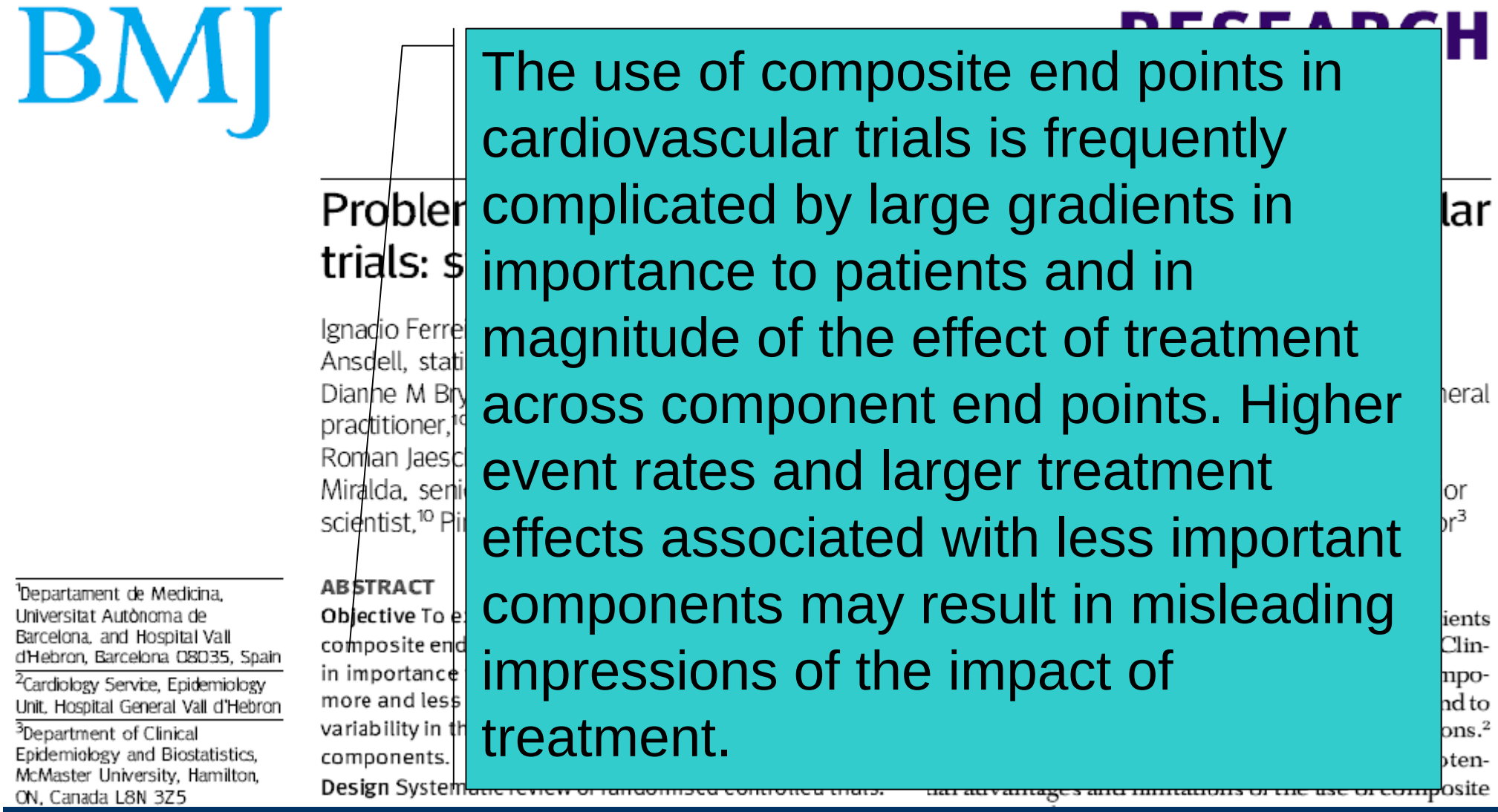
115 articles published in 1990-2003 in 3 major general medical journals (NEJM, JAMA, Lancet) and specialty journals that had received over 1000 citations each by August 2004

45/49 reported evaluations of health care interventions claimed that they were effective

By 2004 5/6 non randomised studies and 9/39 randomised trials were already contradicted or found to be exaggerated

Aspettative dal mondo dei clinici-ricercatori

- Reagire alla mancanza di indipendenza
- Evitare la ricerca “futile” e assumersi la responsabilità della prevenzione dei bias
- Concepire la ricerca come esercizio cumulativo
- Concentrarsi su esiti clinici rilevanti
- Identificare le aree di confine tra i diversi tipi di ricerca


BMJ

RESEARCH

Probler … lar
trials: s…

Ignacio Ferre…
Ansdell, stati…
Dianne M Bry… neral
practitioner,[1…
Roman Jaesc…
Miralda, seni… or
scientist,[10] Pi… or[3]

[1]Departament de Medicina, Universitat Autònoma de Barcelona, and Hospital Vall d'Hebron, Barcelona 08035, Spain
[2]Cardiology Service, Epidemiology Unit, Hospital General Vall d'Hebron
[3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada L8N 3Z5

ABSTRACT

Objective To e… ients
composite end… Clin-
in importance … mpo-
more and less … nd to
variability in th… ons.[2]
components. …oten-
Design Syste… tial advantages and limitations of the use of composite

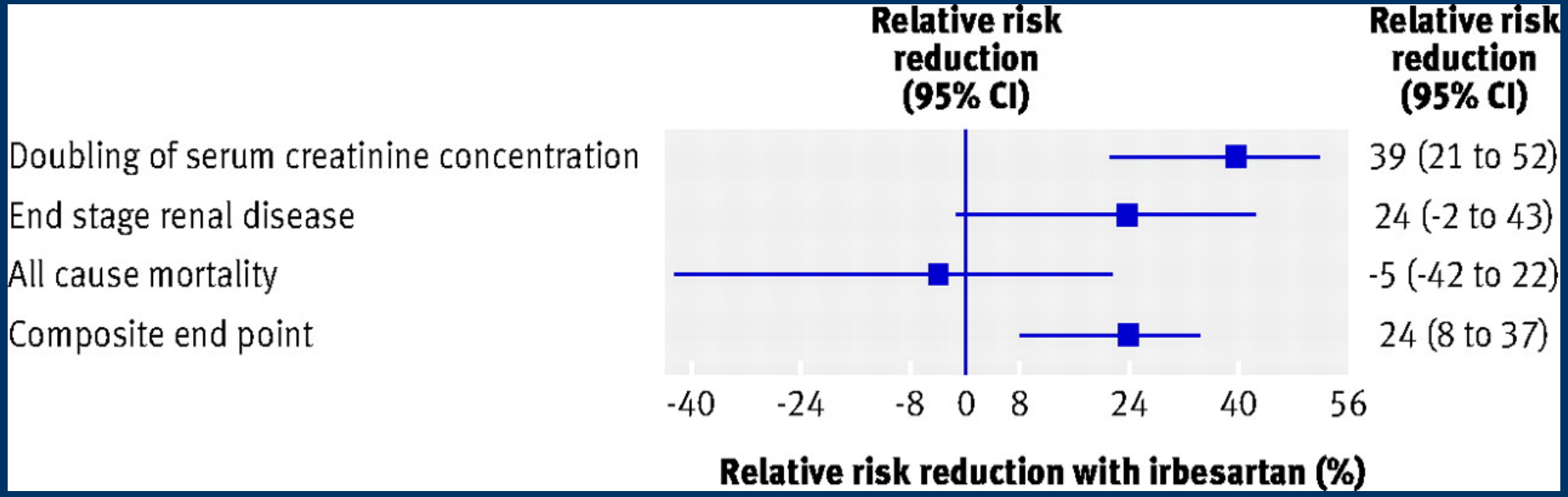
The use of composite end points in cardiovascular trials is frequently complicated by large gradients in importance to patients and in magnitude of the effect of treatment across component end points. Higher event rates and larger treatment effects associated with less important components may result in misleading impressions of the impact of treatment.

Ferreira-González I et al. BMJ 2007;334:786

Composite end points

SR of 114 cardiovascular RCTs published in 6 core journals between January 2002 and June 2003 including at leats one composite endpoint relevant to the patient

es. ibesartan *vs* amlodipina [NEJM 2001;345:851-60]

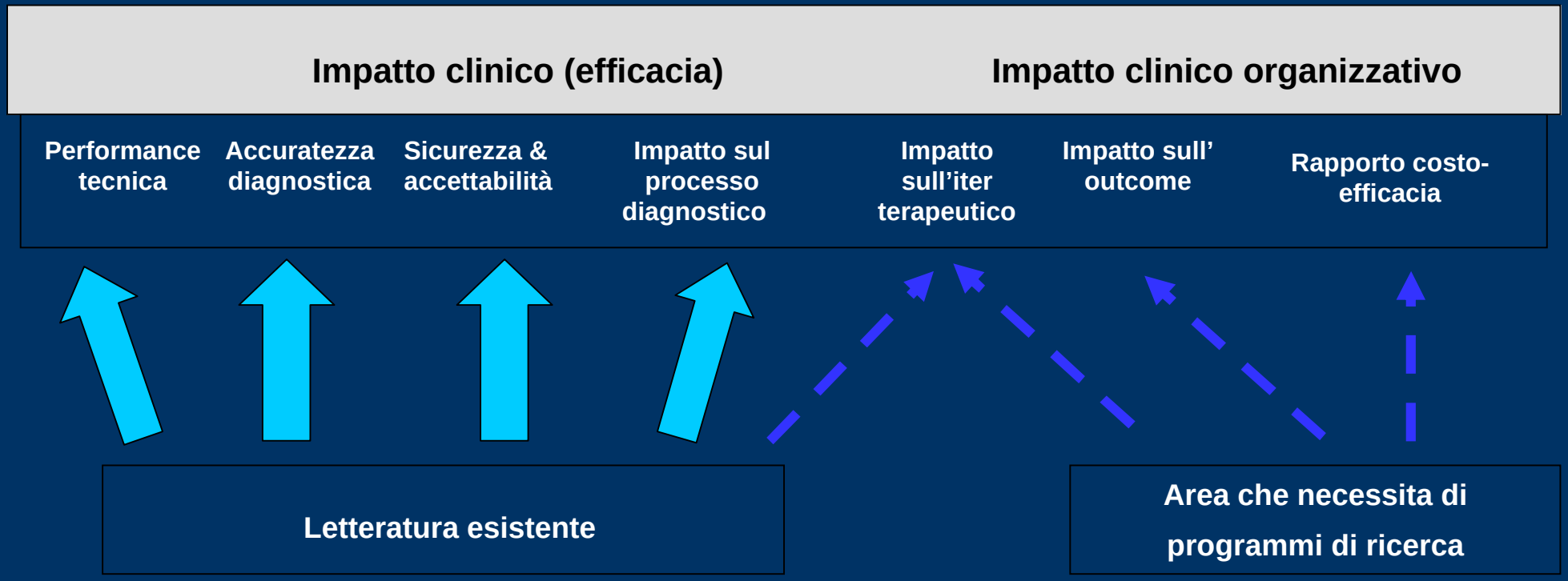


Ferreira-González I et al. BMJ 2007;334:786

Aspettative dal mondo dei clinici-ricercatori

- Reagire alla mancanza di indipendenza
- Evitare la ricerca “futile” e assumersi la responsabilità della prevenzione dei bias
- Concepire la ricerca come esercizio cumulativo
- Concentrarsi su esiti clinici rilevanti
- Identificare le aree di confine tra i diversi tipi di ricerca

“Evidence profile” per un test di valutazione diagnostica

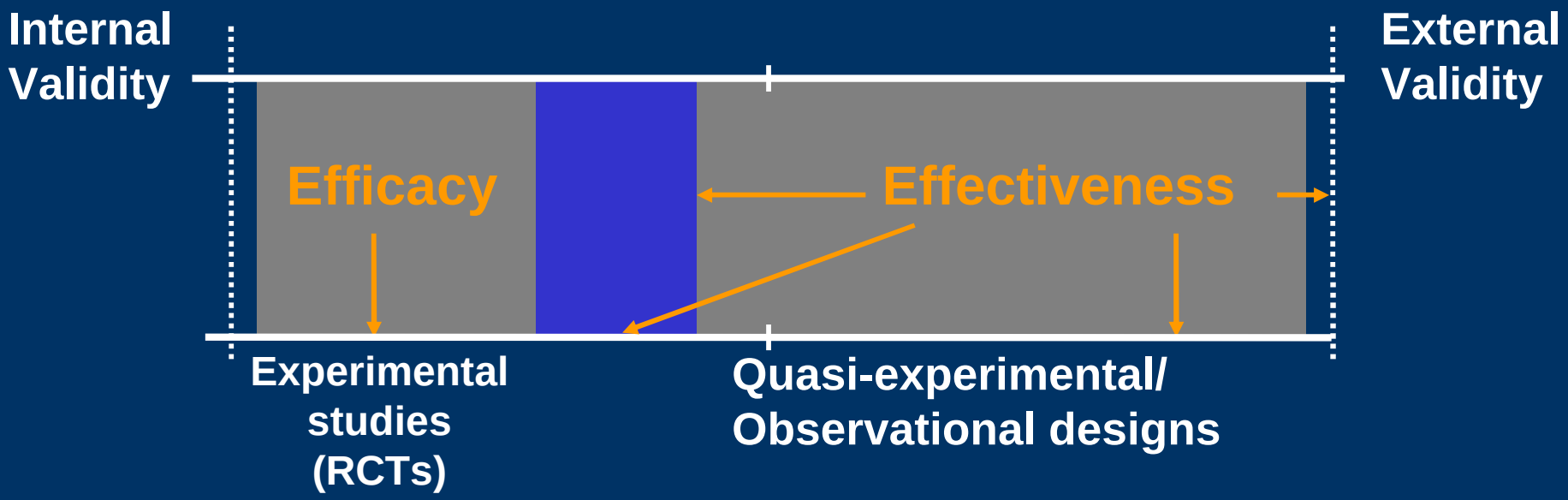


Aree nelle quali esistono studi primari, revisioni sistematiche Technology Assessment report

Aree nelle quali è prioritario svolgere programmi prospettici di ricerca clinica

Efficacy *and* Effectiveness *studies have different priorities*

The continuum in the assessment of health interventions



Most studies fall within this continuum though with different emphasis and informative values

Riflessioni conclusive

- Valutare l'impatto della ricerca è possibile ma molto complesso (tempi, metodologie ecc.)
- Governance per orientare le priorità
- Evitare gli errori più comuni (concettuali e metodologici), ormai abbastanza noti
- Rendere l'attività di ricerca parte integrante della pratica clinica (anche attraverso politiche regolatorie)
- Necessità di strategie nazionali e internazionali e di adeguati finanziamenti

Un’alternativa... alla research governance