WORKSHOP

VALUTAZIONE COMPARATIVA DI EFFICACIA E SICUREZZA TRA FARMACI

Il ruolo degli studi osservazionali

Comparative Effectiveness research: cosa abbiamo imparato

Antonio Addis, Giuseppe Traversa

Venerdì 13 giugno 2014
ore 10 - 16.30

Sala del Teatro
Complesso Monumentale Santo Spirito in Sassia
Borgo Santo Spirito, 3 - Roma

Agenzia sanitaria e sociale regionale

Regione Emilia Romagna

Agenzia Sanitaria e Sociale Regionale

Definition of CER

CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.

Annals of Internal Medicine | Medicine and Public Issues

Comparative Effectiveness Research: A Report From the Institute of Medicine

Harold C. Sox, MD, and Sheldon Greenfield, MD

Ann Intern Med. 2009;151:203-205.

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Comparative Effectiveness research: cosa abbiamo imparato?

- ✓ **Da cosa nasce il bisogno di CER**
- ✓ **Un ruolo attivo per gli enti regolatori**
- ✓ **Perché è utile la CER**
- ✓ **L'importanza di comunicare i risultati**

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Di che ricerca parliamo?

	Pure basic research		Pure applied research		Use-led basic research	
	2004–05	2009–10	2004–05	2009–10	2004–05	2009–10
Proportion of funds allocated	68·3%	59·4%	21·2%	27·2%	10·7%	13·3%

Percentages calculated with data from UK health research analysis 2009/2010.[7] Pure basic research is concerned with understanding of biological, psychological, and socioeconomic processes and functioning (underpinning research), and aetiology. Pure applied research is concerned with prevention, detection and diagnosis (but not the discovery and preclinical testing of markers and technologies), treatment assessment, disease management, and health services. Use-led basic research is concerned with development of detection, diagnosis, and treatment (including the discovery, development, and preclinical testing of biological markers, imaging technologies, and diagnostic and predictive tests).

Table 1: **Distribution of public and charitable funds for medical research in 2004–05 and 2009–10, by category of investment**

Iain Chalmers et al. Lancet 2014; 383: 156–65

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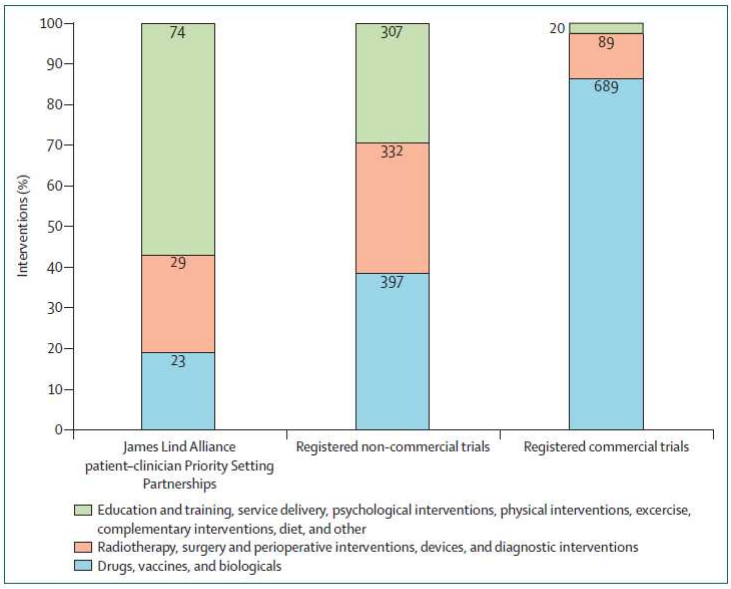

Figure 2: Interventions mentioned in research priorities identified by James Lind Alliance patient–clinician Priority Setting Partnerships[36] and in registered trials, 2003–12

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Comparative Effectiveness research: cosa abbiamo imparato?

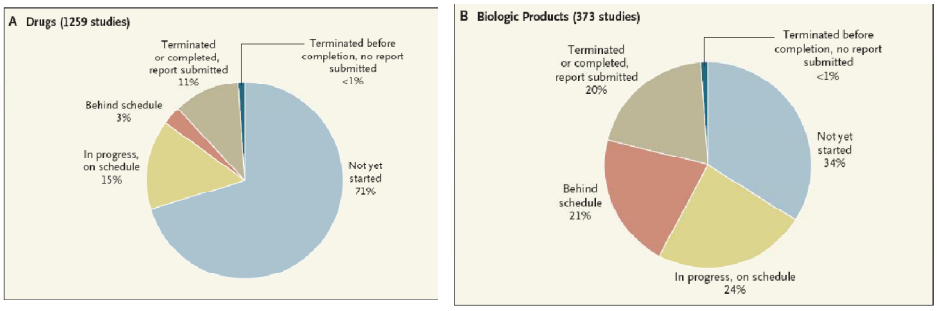
- ✓ Da cosa nasce il bisogno di CER
- ✓ **Un ruolo attivo per gli enti regolatori**
  - ✓ **Farmacovilanza attiva**
  - ✓ **Lavorare sulle open questions**
- ✓ Perché è utile la CER
- ✓ L'importanza di comunicare i risultati

Post Approval Commitments are often unaccomplished!

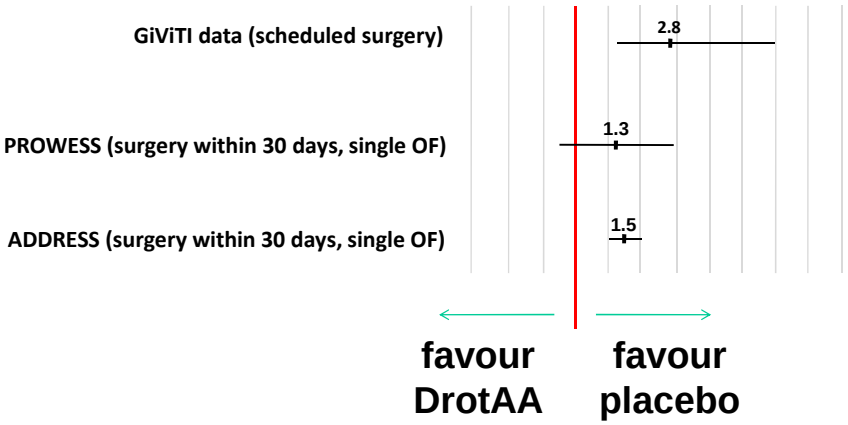
Status of Open Commitments for Postmarketing Studies Requested by the FDA, as of September 30, 2006.

Data are from the Federal R

N ENGL J MED 356;17 WWW.NEJM.ORG APRIL 26, 2007



Are GiViTI data on an harmful effect on low-risk surgical patients in line with RCTs?



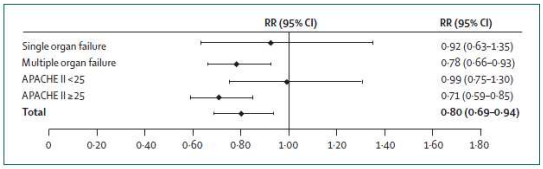


Figure 1: **PROWESS trial[10] data comparing drotrecogin alfa (activated) with placebo**
We used data from the FDA clinical review on drotrecogin alfa[11] to calculate the risk ratio (RR) and 95% CIs for patients with low and high risk of death according to the APACHE II score and the number of organ failures. Interaction test results, calculated according to Altman and Bland,[13] were p=0·045 for APACHE II score <25 versus APACHE II score ≥25 and p=0·435 for single organ failure versus multiple organ failure. The FDA clinical review,[11] reports subgroups of patients with two, three, four or five organ failures: the multiple organ failure subset was created merging data from these subgroups.

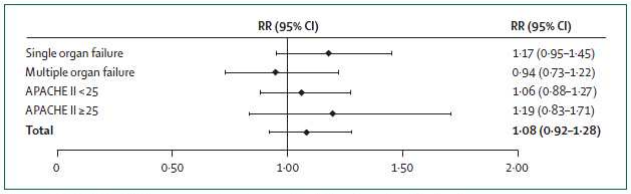


Figure 2: **ADDRESS trial[12] data comparing drotrecogin alfa (activated) with placebo**
We used data from Friedrich et al[12] to calculate risk ratio (RR) and 95% CIs for patients with low and high risk of death according to the APACHE II score and the number of organ failures.

Ad hoc studies

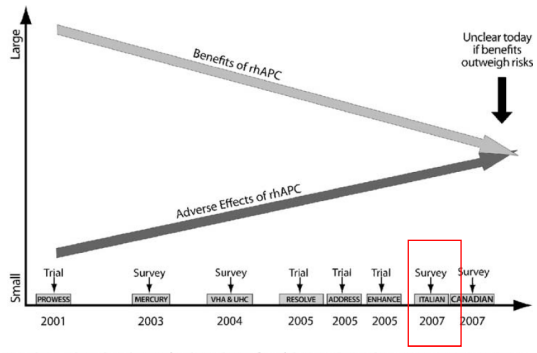
Intensive Care Med
DOI 10.1007/s00134-007-0554-x

ORIGINAL

Guido Bertolini
Carlotta Rossi
Abramo Anghileri
Sergio Livigni
Antonio Addis
Daniele Poole

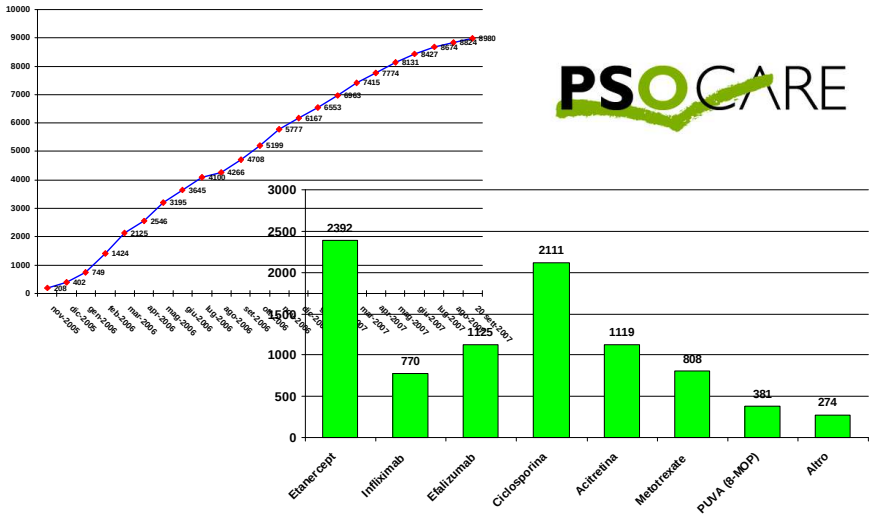
Use of Drotrecogin alfa (activated) in Italian intensive care units: the results of a

Conclusions: These results question the way in which the drug is used in everyday clinical practice and its efficacy in a selected subgroup, and reinforce the need for a new, independent, confirmatory trial to reassess the risk-to-benefit ratio of DrotAA.



Cumulative Clinical Evidence of Risks and Benefits of rhAPC Activated Protein C in Septic Patients

Active pharmacovigilance programme



PSOCARE

PSOCARE

Dermatology

Dermatology 2008;217:365–373
DOI: 10.1159/000156599

Received: N
Accepted: A
Published o

Impact of Body Mass Index and Obesity on Clinical Response to Systemic Treatment for Psoriasis

Evidence from the Psocare Project

Luigi Naldi[a] Antonio Addis[d] Sergio Chimenti[f] Alberto Giannetti[c] Mauro Picardo[e] Carlo Tomino[d] Mara Maccarone[g] Liliane Chatenoud[a, b] Paola Bertuccio[a, b] Eugenia Caggese[a] Rosanna Cuscito[d] and the Psocare Study Centres

Abstract

Objective: Our aim was to assess the role of the body mass index (BMI) in the clinical response to systemic treatment for psoriasis. ***Methods:*** A nationwide cohort study of patients receiving a new systemic treatment for plaque psoriasis at reference centres in Italy was conducted. Information was gathered through a web-based electronic form. Patients being maintained on the same medication and with data available at 8 and 16 weeks by March 31, 2007, were eligible. The outcome was a reduction in the Psoriasis Area Severity Index (PASI) of at least 75% at follow-up compared to baseline (PASI-75). ***Results:*** Out of 8,072 patients enrolled, 2,368 were eligible and analysable at 8 weeks and 2,042 at 16 weeks. PASI-75 was achieved by 819 patients (34.5%) at 8 weeks and 1,034 (50.6%) at 16 weeks. The proportion steadily decreased with increased values of BMI. Compared to normal weight (BMI = 20–24) the adjusted odds ratio for achieving PASI-75 in obese patients was 0.73 (95% CI = 0.58–0.93) at 8 weeks and 0.62 (95% CI = 0.49–0.79) at 16 weeks. The impact of the BMI did not show remarkable variations according to the drug prescribed at entry. ***Conclusion:*** The BMI affects the early clinical response to systemic treatment for psoriasis.

Natalizumab is approved by EMA as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

patients with high disease activity despite *adequate* course of a beta-interferon.

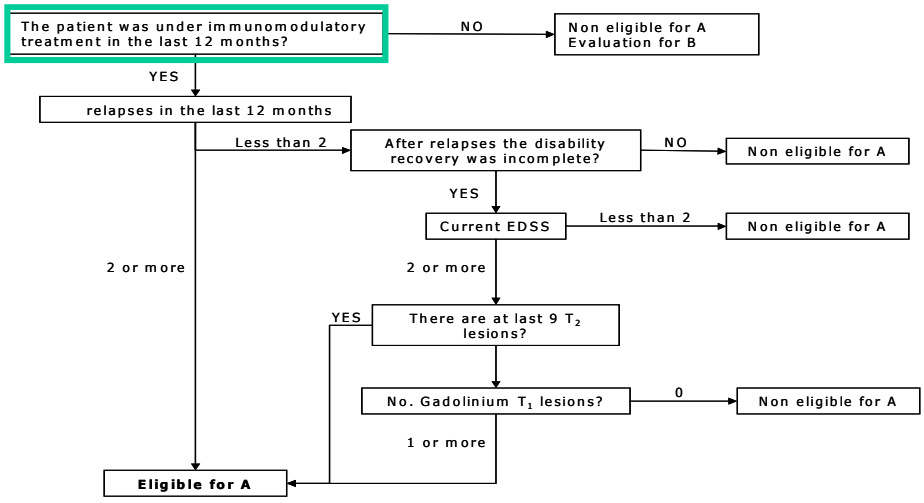
patients with rapidly evolving severe relapsing remitting multiple sclerosis.

The Italian Medicines Agency (AIFA), advised by a neurological expert panel, established more restrictive criteria to dispense and reimburse natalizumab, and organised a national registry for monitoring its safety.

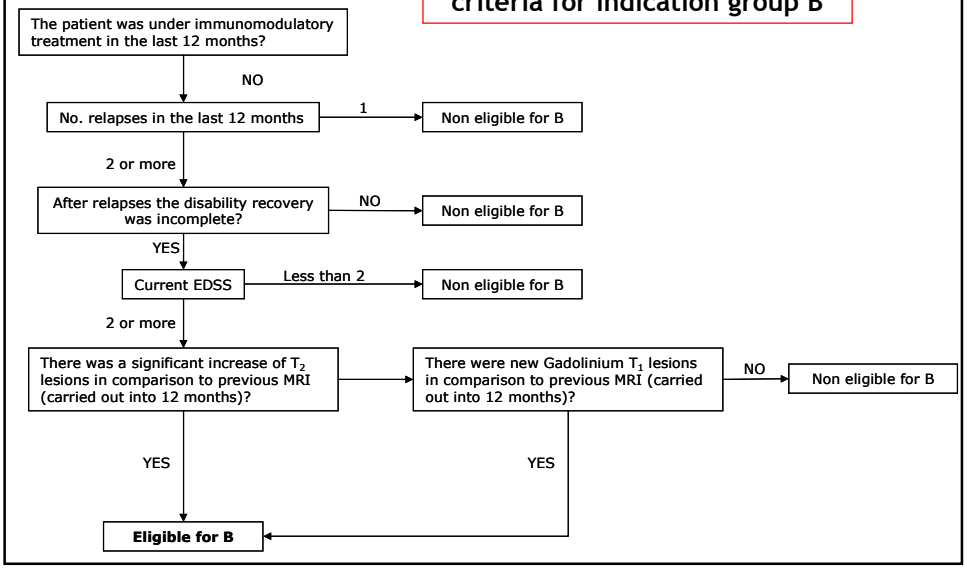
Patients group A
Patients non-responders after immunomodulatory treatment in the last *12 months*.

Patients group B
Patients with rapidly evolving severe relapsing remitting multiple sclerosis.

Algorithms for Restrictive criteria for indication group A



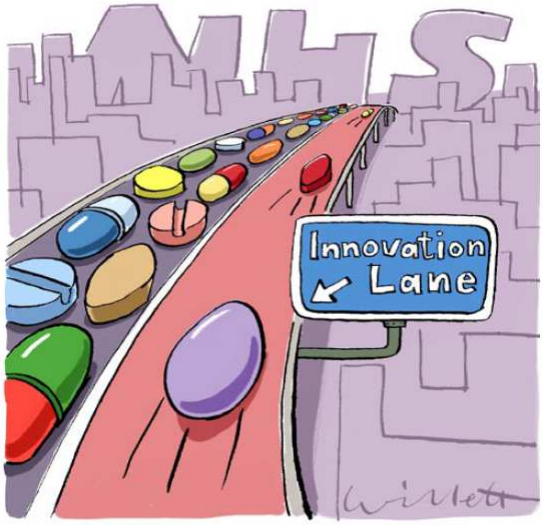
Algorithms for Restrictive criteria for indication group B



NICE and new: appraising innovation

Innovation is essential in drug development but is not cheap. **Robin Ferner, Dyfrig Hughes, and Jeffrey Aronson** examine the challenges of encouraging innovation while ensuring clinical benefit

BMJ | 30 JANUARY 2010 | VOLUME 340



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journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

The European Commission should require better medicines, not just faster reimbursements

S. Garattini & V. Bertelè

In the European Union (EU) medicines are authorised by the European Commission (EC) after a positive evaluation by the European Medicine Agency (EMA), through the centralised procedure or the national agencies through decentralised procedures. According to the EU legislation

First, the industry should be required to develop medicines to address unmet needs, whose innovative aspects are easily identifiable.

This means proving that new medicines prolong survival or improve patients' quality of life compared to available treatments, or are effective in non-responders to current therapies. This implies undertaking randomised controlled trials of adequate size, aiming at proving superiority rather than non-inferiority, using an appropriate comparator rather than placebo and addressing clinically meaningful outcome measures rather than surrogate endpoints.

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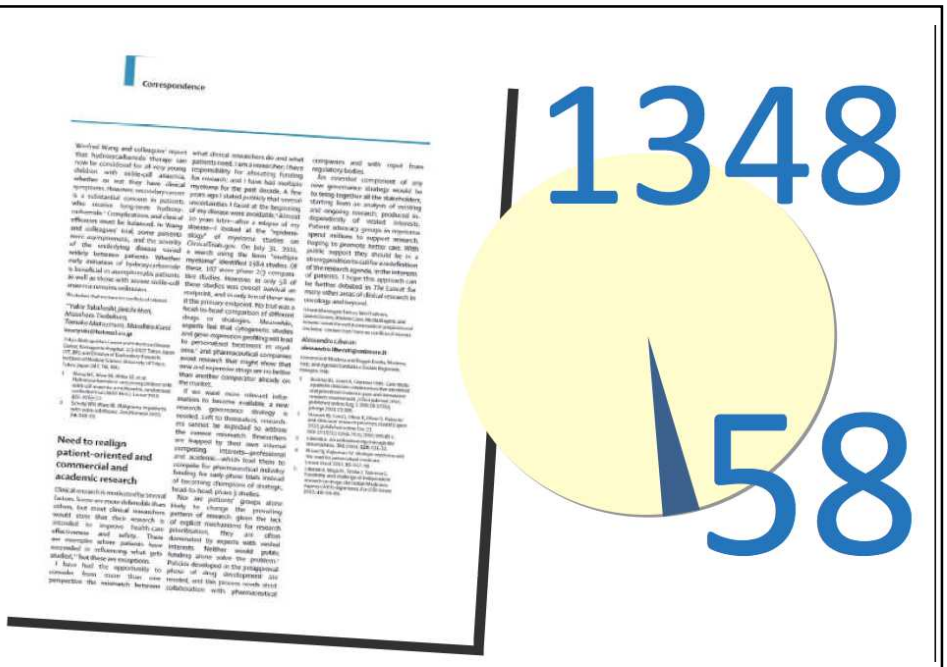
Comparative Effectiveness research: cosa abbiamo imparato?

- ✓ Da cosa nasce il bisogno di CER
- ✓ Un ruolo attivo per gli enti regolatori
- ✓ **Perché è utile la CER**
  - ✓ ***Migliorare gli standards***
  - ✓ ***Definire i quesiti***
- ✓ L'importanza di comunicare i risultati

2005-2011: in Europa sono stati registrate circa 50 nuove indicazioni terapeutiche in oncologia



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Quali temi di ricerca privilegiare in un'Agenzia regolatoria?

- I temi di ricerca promossi da un'Agenzia regolatoria dovrebbero rispondere ai seguenti requisiti:
  - la rilevanza in termini di nuove conoscenze e/o di impatto sulla pratica clinica del quesito principale dello studio
  - le potenziali ricadute per le decisioni regolatorie
  - l'interesse commerciale a condurre uno studio clinico deve essere limitato

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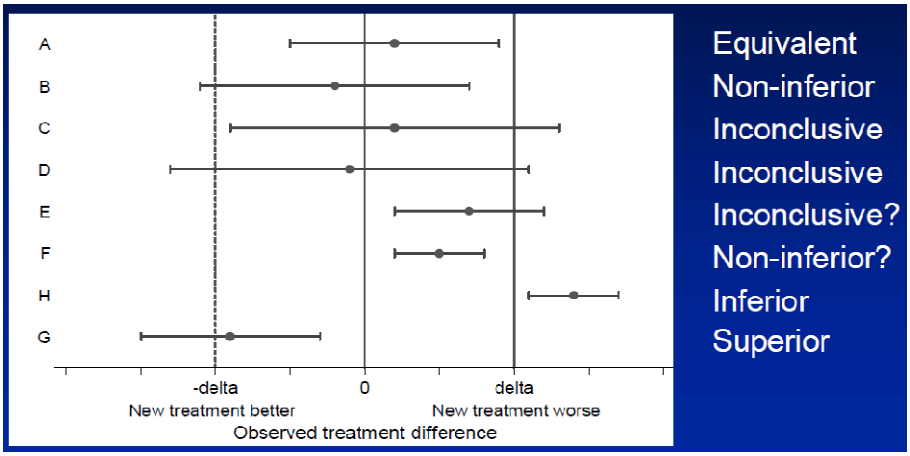
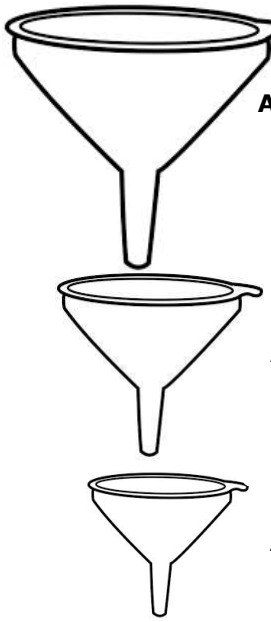
Necessità degli studi post marketing: il caso limite delle malattie rare

- Dal 2000, European Orphan Drug Legislation: oltre 900 designazioni di farmaco orfano e 60 approvazioni
- 40% dei farmaci approvati “under exceptional circumstances”
- Necessario ottenere dati più validi e a lungo termine
  - esiti clinicamente rilevanti, inclusa QoL
  - sicurezza
  - fattori prognostici

Innovativo: quali standards?





Agenzie Regolatorie Internaziona

Agenzie Regolatorie Nazionali

Agenzie Regolatorie Regionali

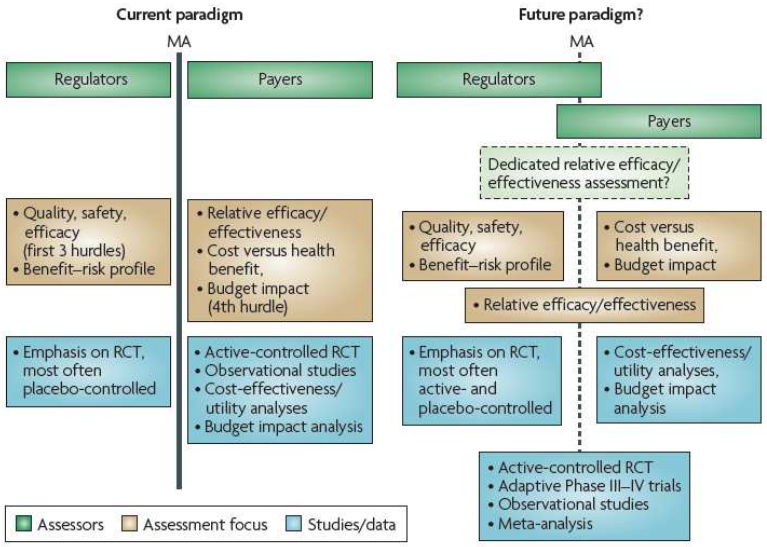
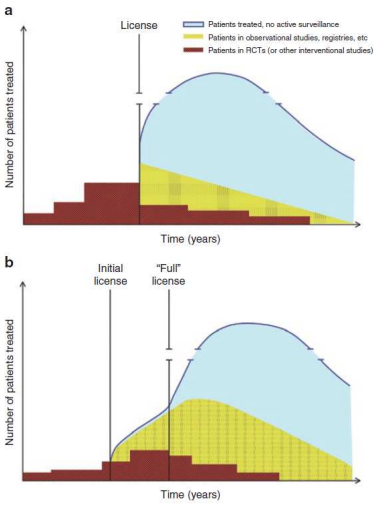


Figure 4 | **The anticipated evolution of relative efficacy assessment at the interface between drug regulatory agencies and payers.**



Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions; patient experience is captured to contribute to real-world information

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garner[8,9], P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke[16], E Pezalla[17], D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsch[2]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 91 NUMBER 3 | MARCH 2012

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I bandi AIFA negli anni 2005-2008

Area	Protocolli ammessi al finanziamento (N)			
	2005	2006	2007	2008
▪ Farmaci orfani e malattie rare	20	24	20	-
▪ Confronti fra farmaci e strategie	13	16	9	12
▪ Farmacoepidemiologia e appropriatezza	21	11	17	26
Totale progetti finanziati	**54**	**51**	**46**	**38**
Finanziamento *in milioni*	**35**	**29**	**13**	**13**

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Esempi di studi approvati in ambito materno-infantile

Valutazione della risposta anticorpale e della persistenza della memoria immunologica verso l'epatite b in coorti di bambini vaccinati con vaccini esavalenti

Identificazione del dosaggio di acido folico efficace nel ridurre le malformazioni congenite nel loro insieme, le cardiopatie congenite, la sindrome di Down. Trial clinico controllato randomizzato nelle donne in età fertile: 5 mg verso 0,4 mg di acido folico.

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Esempi di studi approvati di interesse neurologico

- A randomized controlled trial of alteplase (rt-PA) vs standard treatment in acute ischemic hemispheric stroke in patients aged more than 80 years, where thrombolysis is initiated within 3 hours after stroke onset
- Multicenter randomized controlled study of azathioprine versus interferon beta- in relapsing-remitting multiple sclerosis
- Alzheimer's Disease (AD) and antipsychotics: a long term, multicentre, double blind, randomised clinical trial
- A prospective study on long-term outcome and potential usefulness of an intervention aimed at reducing adverse effects in patients with refractory epilepsy sclerosis

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Esempi di studi approvati di interesse oncologico

- FATA – First Adjuvant Trial on all aromatase inhibitors in early breast cancer. A phase 3 study comparing anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen), as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer
- A randomized trial investigating the role of FOLFOX-4 regimen duration (3 versus 6 months) and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer

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Le ricadute della ricerca indipendente

- Contributo alla conoscenza e alla pratica clinica
- Decisioni regolatorie
- Rafforzamento della capacità di ricerca nel SSN
  - dalla scrittura di un protocollo alle pubblicazioni
  - la creazioni di infrastrutture di sostegno
  - opzione aggiuntiva agli studi sponsorizzati

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Negli USA, i 100 temi della Comparative Effectiveness Research

INSTITUTE OF MEDICINE

REPORT BRIEF • JUNE 2009

Initial National Priorities for Comparative Effectiveness Research

Clinical research provides health care providers with information on the natural history of disease, clinical presentations of disease, and diagnostic and treatment options. Consumers, patients, and caregivers also require this information to decide how to evaluate and treat their conditions. All too often, the information necessary to inform these medical decisions is incomplete or unavailable, resulting in more than half of the treatments delivered today without clear evidence of effectiveness. This uncertainty contributes to great variability in managing clinical problems, with costs and outcomes differing markedly across the country.

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Il piano Obama e i temi della CER: confronto con la ricerca AIFA 2005-08

Comparative effectiveness research (CER)

- 100 temi
  - Nel 40% il confronto include anche i farmaci
  - Circa il 50% di questi temi sono stati inclusi negli anni passati nei bandi AIFA

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Come scegliere i progetti: gli obiettivi delle procedure di valutazione

1) Promuovere il merito:

- Rilevanza e innovatività dell'idea di base
- Appropriatezza del disegno di studio
- Adeguatezza dell'organizzazione

2) Promuovere un'erogazione trasparente ed efficiente

3) Promuovere la qualità dei progetti nel tempo:

- Linee guida, feed back e attività di sostegno ai ricercatori

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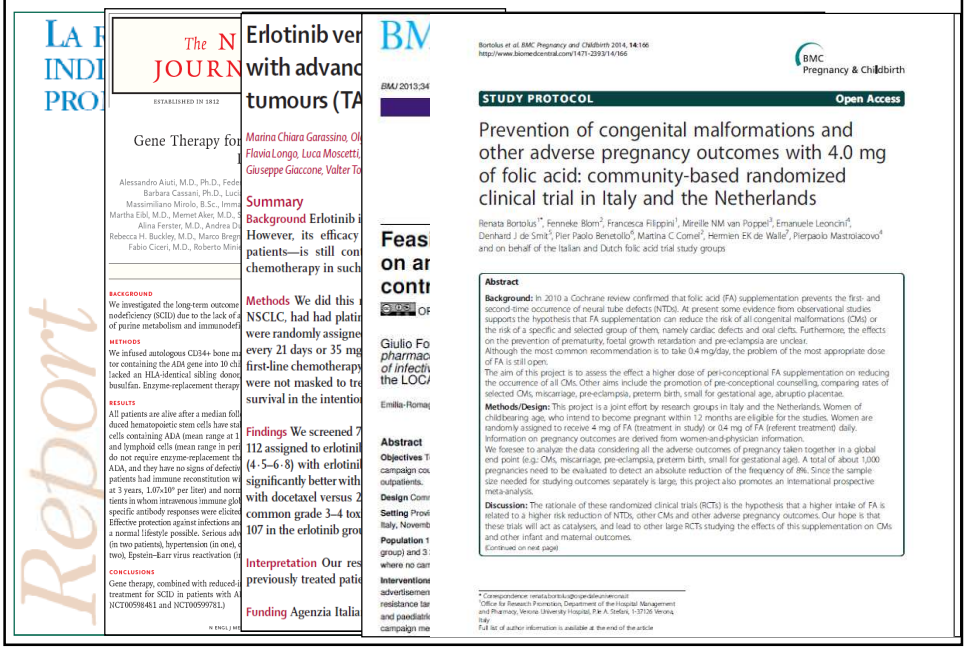
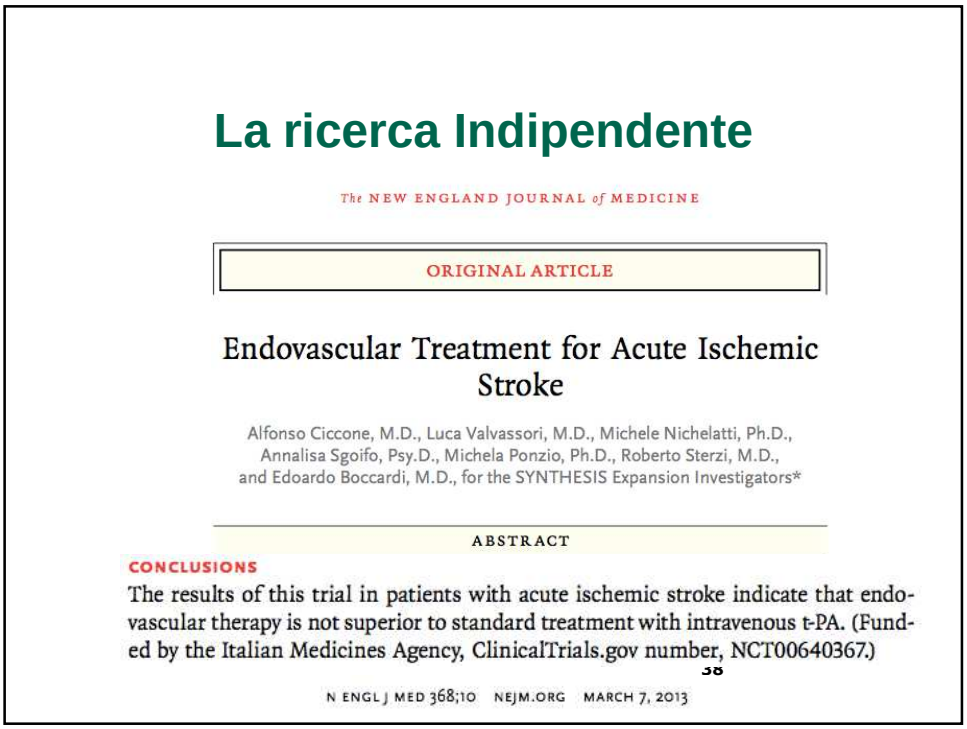
Il meccanismo di selezione: l'esempio dei bandi AIFA 2005-2008

- Lettere di intenti: Commissione Ricerca e Sviluppo Aifa
- Protocolli finali: Study session (per il bando 2008 con 21 esperti, in maggioranza stranieri, diversi dalla CRS) con ruolo decisionale
- In entrambe le fasi di valutazione: linee guida per la revisione e regole scritte per evitare i conflitti di interesse

La ricerca indipendente è produttiva!



La ricerca Indipendente



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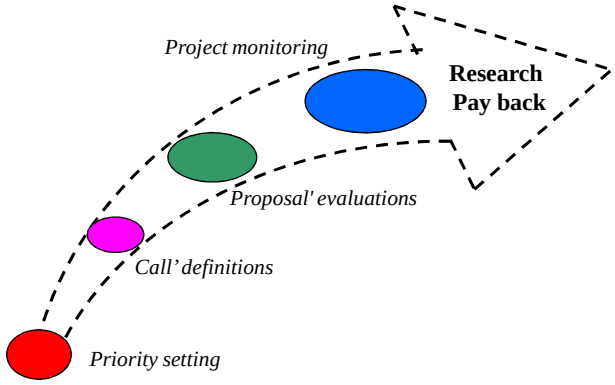
Focusing on better research for better health



Regional Health Services

Alcuni problemi aperti

- Come coordinare le attività:
  - Nazionale-regionale e fra regioni
- Come dare continuità e diffondere criteri di valutazione trasparenti
- Come sostenere/costruire le capacità di ricerca nel SSN
- Come promuovere la qualità degli studi senza aggravi burocratici

Attenzione a non derogare sulla qualità degli studi

- La domanda di fondo: … ma dopo la pubblicazione dei risultati un mio collega sarà convinto che sia utile modificare una pratica clinica?
- Integrare competenze cliniche e metodologiche

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L'Esempio Bandi AIFA

Tematica	N. Lettere di intenti	Studi potenzialmente non eleggibili sulla base del titolo	Note
A1	72	8	studi osservazionali/costo efficacia
A2	8	1	studio osservazionale
A3	17	1	studio osservazionale
A4	40	39	studi su farmaci NON riconducibili alla tematica (biosimilari)
A5	22	9	studi osservazionali/farmacocinetica/costo efficacia
A6	26	10	studi osservazionali
A7	10	2	studi osservazionali
A8	10	1	studio osservazionale
A9	10	1	studio osservazionale
A10	15	15	Studi su biomarkers
Totale	230	87 (38%)	

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L'Esempio Bandi AIFA

La tematica A 4, richiede

Confronti fra farmaci o strategie terapeutiche in pediatria e geriatria: ottimizzazione dell'uso dei farmaci biosimilari per l'apparato respiratorio, gastro-enterico, cardiovascolare, endocrino, neurologico (con particolare riferimento a patologie cerebrovascolari e neurodegenerative) e per le malattie psichiatriche.

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How should medical science change?

In December, 2013, Randy Schekman received a Nobel Prize in Physiology or Medicine for his codiscovery (with James Rothman and Thomas Südhof) of the cellular machinery regulating vesicle traffic. He used the occasion to launch a ferocious attack against what he called "luxury journals"—*Nature*, *Science*, and *Cell*. Although he didn't mention *The Lancet*, *JAMA*, or *The New England Journal of Medicine*, it probably isn't unreasonable to think he would include us in his definition of "luxury journal". This is what he wrote in *The Guardian*: "These luxury journals are supposed to be the epitome of quality, publishing only the best research. Because funding and appointment panels often use place of publication as a proxy for quality of science, appearing in these titles often leads to grants and professorships. But the big journals' reputations are only partly warranted. While they publish many outstanding papers, they do not publish only outstanding papers. Neither are they the only publishers of outstanding research."[1] Schekman and his lab are now boycotting those luxury journals and he is encouraging other scientists to do the same.

Another 2013 Nobel Laureate, Peter Higgs, won the physics prize (along with François Englert) for the theoretical discovery of a mechanism that helps us understand the origin of mass. In an interview, also with *The Guardian*, Higgs described himself as an "embarrassment" to his Edinburgh University department because he published so little: "Today", he said, "I wouldn't get an academic job. It's as simple as that. I don't think I would be regarded as productive enough."[1]

There is clearly a strong feeling among many scientists, and not only Nobel Prize winners, that something has gone wrong with our system for assessing the quality of scientific research. Does the fault lie with myopic university administrations led astray by perverse incentives or with journals that put profit and publicity above quality? The likely answer is that it is a mix of both. But perhaps the discussion provoked by the latest Nobel awards needs to be widened still further. Perhaps all of us engaged in the enterprise we call "science" need to pause and reflect on the present state of what we do.

In 2009, we published a Viewpoint by Iain Chalmers and Paul Glasziou called "Avoidable waste in the production and reporting of research evidence", which made the extraordinary claim that as much as 85% of research investment was wasted.[3] It seemed an unbelievable figure. But the useful discussion their paper triggered led to a spate of seminars and meetings to explore what could be done about what all agreed was a wholly unsatisfactory situation—wi by scientists, poor study de that was inaccessible and fir selective reporting and othe now publish addresses thes than the paper we published paper make specific recom value of—and reduce waste f

Our belief is that re societies, school and univ medical associations, and their editors) can use this to examine more forensi what they do—the purpo communication—and whe most value for the time anc *The Lancet* Research: Increa Series, is not intended to matters. Consideration sho organisers to raising these meetings—these issues ma in research. One special vi is the 4th World Research held in Rio de Janeiro, Braz that gathering will be "Rese improving systems to pro one of the key subjects of th

Randy Schekman asked th "luxury journals" last year: '

Published Online

Comment

Biomedical research: increasing value, reducing waste

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Of 1575 reports about cancer prognostic markers published in 2005, 1509 (96%) detailed at least one significant prognostic variable.[1] However, few identified biomarkers have been confirmed by subsequent research and few have entered routine clinical practice.[2] This pattern—initially promising findings not leading to improvements in health care—has been recorded across biomedical research. So why is research that might transform health care and reduce health problems not being successfully produced?

Global biomedical and public health research involves billions of dollars and millions of people. In 2010, expenditure on life sciences (mostly biomedical) research was US$240 billion.[3] The USA is the largest funder, with about $70 billion in commercial and $40 billion in governmental and non-profit funding annually,[4] representing slightly more than 5% of US health-care expenditure. Although this vast enterprise has led to substantial health improvements, many more gains are possible if the waste and inefficiency in the ways that biomedical research is chosen, designed, done, analysed, regulated, managed, disseminated, and reported can be addressed.

In 2009, Chalmers and Glasziou[3] identified some key sources of avoidable waste in biomedical research. They estimated that the cumulative effect was that about 85% of research investment—equating to $200 billion of the investment in 2010—is wasted. This amount was calculated without consideration of the inefficiencies in the regulation and management of research. Although some real progress with the issues they identified has been made [5,6] at the present

others (table). Through consideration of these drivers, the economic, social, cultural, and political conditions that have shaped the research environment can be understood.[7]

Economic forces are important. Industry seeks to maximise profit by bringing new products to market and by protecting and expanding market share. In industry-funded clinical research, commercial motives can control the study design and comparators, and so-called seeding trials (in which the purpose is to promote familiarity with a new drug rather than generate knowledge) can be done for marketing purposes.[8] The economic motivations of industry do much to characterise health as a commodity that can be bought, which informs and distorts the motivations of other actors. The profit motive is central to everything with which industry is involved, including its interactions with seemingly independent researchers and clinicians.[9]

Equally, advertising, publication charges, and charges for reprints make journal publication a highly profitable business, and attempts to maximise income are not always consistent with an ambition to publish only reports about research of the highest quality and relevance. Although peer review is supposed to uphold the quality of publications and grants awarded, the costs of the system are substantial,[10] raising questions about its cost-effectiveness.[10]

Governments and politicians have an important role. Funding is needed for research in areas important for the protection and restoration of human health even when the prospects for commercial profit are poor or

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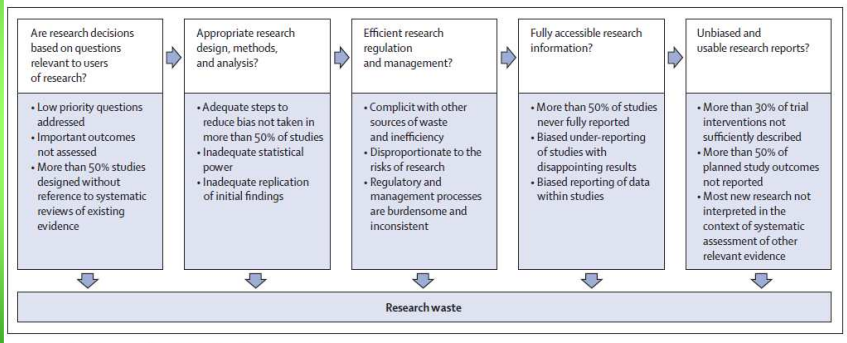

Figure: Avoidable waste or inefficiency in biomedical research

Macleod MR, et. Al *Lancet*. 2014;383:101-4

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