La ricerca sui farmaci: alcuni temi

1. Ricerca farmacologica e non nella promozione della salute
2. La ricerca clinica come base della pratica medica
3. Eleggibilità e trasferibilità dei risultati
4. L'importanza degli esiti
5. Non sempre più è meglio
6. La necessità di infrastrutture e la qualità degli studi
7. I rischi dell'appesantimento burocratico
8. Necessità di incentivi pubblici alla ricerca for profit
9. Conditional approval e studi post marketing
10. Le ragioni a favore della ricerca indipendente
11. Una valutazione rigorosa dei progetti
12. I problemi aperti con la globalizzazione della ricerca
13. La spesa per i nuovi farmaci e i benefici attesi

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000

Earl S. Ford, M.D., M.P.H., Umed A. Ajani, M.B., B.S., M.P.H., Janet B. Croft, Ph.D., Julia A. Critchley, D.Phil., M.Sc., Darwin R. Labarthe, M.D., M.P.H., Ph.D., Thomas E. Kottke, M.D., Wayne H. Giles, M.D., M.S., and Simon Capewell, M.D.

ABSTRACT

BACKGROUND

Mortality from coronary heart disease in the United States has decreased substantially in recent decades. We conducted a study to determine how much of this decrease could be explained by the use of medical and surgical treatments as opposed to changes in cardiovascular risk factors.

N Engl J Med 2007;356:2388-98.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®
Learn and Live℠

Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000

Belgin Unal, Julia Alison Critchley and Simon Capewell

Circulation 2004;109;1101-1107; originally published online Mar 1, 2004;
DOI: 10.1161/01.CIR.0000118498.35499.B2
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000

Belgin Unal, MD, MPH; Julia Alison Critchley, DPhil; Simon Capewell, MD

Background—Coronary heart disease mortality rates have been decreasing in the United Kingdom since the 1970s. Our study aimed to examine how much of the decrease in England and Wales between 1981 and 2000 could be attributed to medical and surgical treatments and how much to changes in cardiovascular risk factors.

Methods and Results—The IMPACT mortality model was used to combine and analyze data on uptake and effectiveness of cardiological treatments and risk factor trends in England and Wales. The main data sources were published trials and meta-analyses, official statistics, clinical audits, and national surveys. Between 1981 and 2000, coronary heart disease mortality rates in England and Wales decreased by 62% in men and 45% in women 25 to 84 years old. This resulted in 68 230 fewer deaths in 2000. Some 42% of this decrease was attributed to treatments in individuals (including 11% to secondary prevention, 13% to heart failure treatments, 8% to initial treatments of acute myocardial infarction, and 3% to hypertension treatments) and 58% to population risk factor reductions (principally smoking, 48%; blood pressure, 9.5%; and cholesterol, 9.5%). Adverse trends were seen for physical activity, obesity and diabetes.

Conclusions—More than half the coronary heart disease mortality decrease in Britain between 1981 and 2000 was attributable to reductions in major risk factors, principally smoking. This emphasizes the importance of a comprehensive strategy that promotes primary prevention, particularly for tobacco and diet, and that maximizes population coverage of effective treatments, especially for secondary prevention and heart failure. These findings may be cautiously generalizable to the United States and other developed countries. **(*Circulation*. 2004;109:1101-1107.)**

Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000

Belgin Unal, Julia Alison Critchley and Simon Capewell

Circulation 2004;109;1101-1107; originally published online Mar 1, 2004;

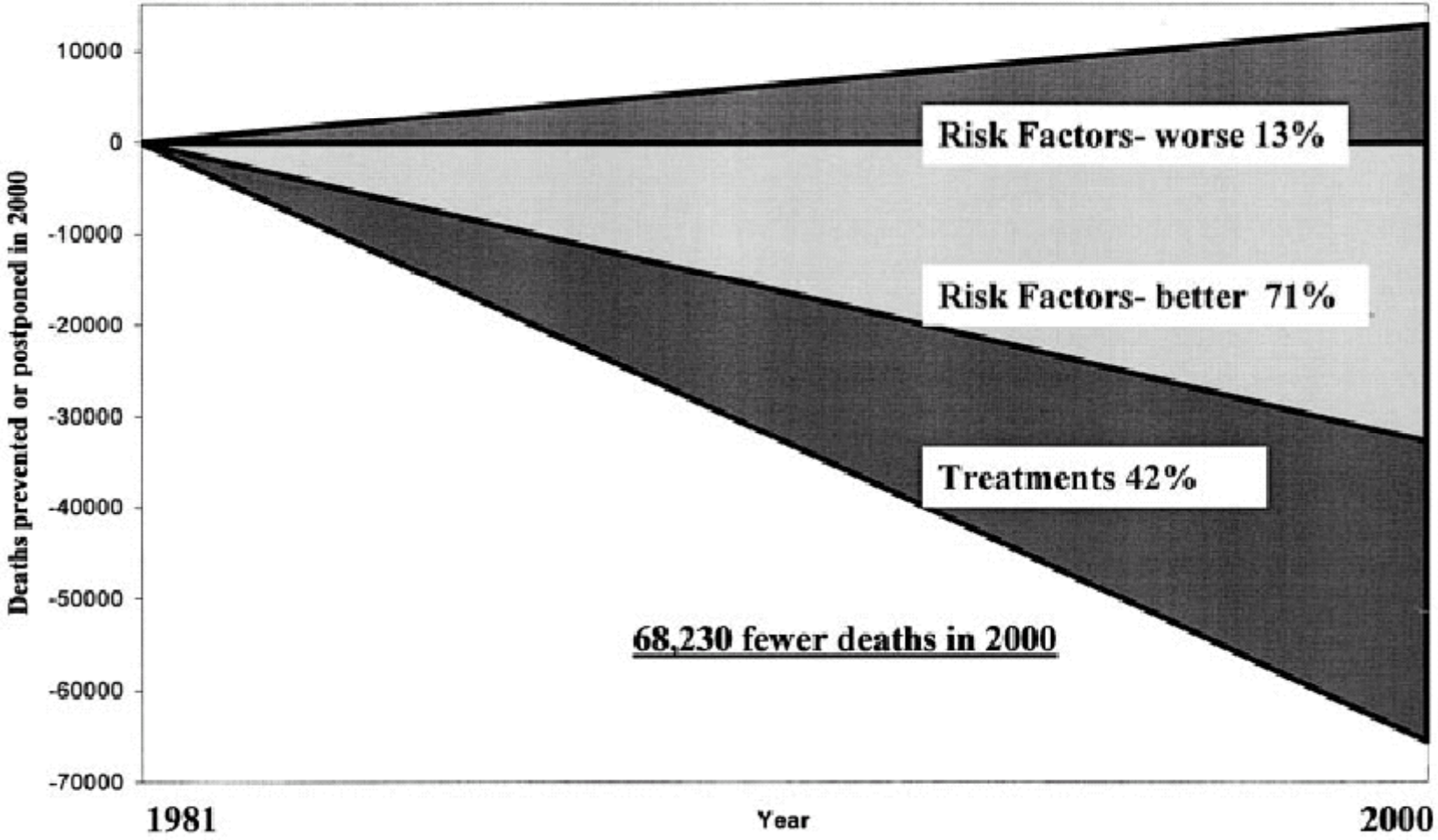


Figure 2. CHD deaths prevented or postponed by treatments and risk factor changes in England and Wales population, 1981 to 2000.

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

JAMA. 2009;301(8):831-841

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Riviste le linee guida dell'American College of Cardiology e dell'American Heart Association (ACC/AHA) pubblicate dal 1984 al 2008

Pubblicate 53 linee guida su 22 argomenti

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Tricoci et al. JAMA 2009;301(8):831-841

Livello di evidenza della raccomandazione

A: Più RCT e meta-analisi

B: Singolo RCT e studi osservazionali

C: Opinione di esperti e serie di casi

Classe (forza) della raccomandazione

Classe I: evidenza presente e/o accordo sull'efficacia

Classe II: evidenza conflittuale e/o disaccordo sull'efficacia

Class III: evidenza presente e/o accordo sul rischio o sull'inefficacia

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Tricoci et al. JAMA 2009;301(8):831-841

Risultati e conclusioni

- **Aumenta il numero di raccomandazioni ma si riduce il livello di evidenza su cui sono costruite**
  - **Stabili le raccomandazioni di classe I e aumento di quelle di classe II**
  - **La maggior parte delle raccomandazioni di classe I sono basate su livelli di evidenza minore o sull'opinione degli esperti**
- **Necessario concentrare l'attività di ricerca sulle aree carenti di evidenze ed espandere i finanziamenti della ricerca clinica**

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Tricoci et al. JAMA 2009;301(8):831-841

Implications for Research

The findings of this analysis indicate that the current system generating research is inadequate to satisfy the information needs of caregivers and patients in determining benefits and risks of drugs, devices, and procedures. The

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review

Harriette G. C. Van Spall, MD
Andrew Toren, MD
Alex Kiss, PhD
Robert A. Fowler, MD, MS

Context Selective eligibility criteria of randomized controlled trials (RCTs) are vital to trial feasibility and internal validity. However, the exclusion of certain patient populations may lead to impaired generalizability of results.

Objective To determine the nature and extent of exclusion criteria among RCTs published in major medical journals and the contribution of exclusion criteria to the representation of certain patient populations.

Data Sources and Study Selection The MEDLINE database was searched for RCTs published between 1994 and 2006 in certain general medical journals with a high impact factor. Of 4827 articles, 283 were selected using a series technique.

RANDOMIZED CONTROLLED trials (RCTs) are generally accepted as the most unbiased measures of efficacy for new

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review

Harriette G. C. Van Spall, MD
Andrew Toren, MD
Alex Kiss, PhD
Robert A. Fowler, MD, MS

RANDOMIZED CONTROLLED trials (RCTs) are generally accepted as the most unbiased measures of efficacy for new

Context Selective eligibility criteria of randomized controlled trials (RCTs) are vital to trial feasibility and internal validity. However, the exclusion of certain patient populations may lead to impaired generalizability of results.

Objective To determine the nature and extent of exclusion criteria among RCTs published in major medical journals and the contribution of exclusion criteria to the representation of certain patient populations.

Data Sources and Study Selection The MEDLINE database was searched for RCTs published between 1994 and 2006 in certain general medical journals with a high impact factor. Of 4827 articles, 283 were selected using a series technique.

Background

- ✓ **Criteri eleggibilità selettivi aumentano la fattibilità e la validità interna dei trial**
- ✓ **Tuttavia, esclusioni ingiustificate possono portare a ridurre la generalizzabilità dei risultati**

Obiettivi

- ✓ **Verificare la natura dei criteri di esclusione applicati in RCT pubblicati su riviste mediche generaliste**

Metodi

- ✓ **Rivisto un campione di 283 articoli (a partire da 4827) pubblicati nel periodo 1994-2005**

Risultati

(Van Spall et al, JAMA 2007;297:1233-1240)

- ✓ **RCT con almeno un criterio poco giustificato: 84%**
- ✓ **Principali criteri di esclusione poco giustificati:**
  - ✓ **Età <16: 60%**
  - ✓ **Età >65: 38%**
  - ✓ **Gravidanza; allattamento: 32%; 14%**
  - ✓ **Comorbidità mediche non specificate: 31%**
  - ✓ **Uso di farmaci: 54%**
- ✓ **Si osserva un miglioramento: la proporzione di criteri poco giustificati è passata da 37% nel periodo 1994-1998 al 26% nel periodo 1999-2005**

BMJ

doi: 10.1136/bmj.39136.682083.AE

RESEARCH

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

Ignacio Ferreira-González, research fellow,[1] Jason W Busse, research associate,[3] Diane Heels-Ansdell, statistician,[3] Victor M Montori, associate professor,[5] Elie A Akl, assistant professor,[6] Dianne M Bryant, clinical epidemiologist,[8] Pablo Alonso-Coello, general practitioner,[9] Jordi Alonso, general practitioner,[10] Andrew Worster, associate professor,[3] Suneel Upadhye, associate member,[3] Roman Jaeschke, clinical professor,[4] Holger J Schünemann, associate professor,[7] Gaietà Permanyer-Miralda, senior consultant,[2] Valeria Pacheco-Huergo, research fellow,[1] Antònia Domingo-Salvany, senior scientist,[10] Ping Wu, senior scientist,[11] Edward J Mills, assistant professor,[12] Gordon H Guyatt, professor[3]

EDITORIALS

Composite and surrogate outcomes in randomised controlled trials

Composite end points may mislead—and regulators allow it to happen

RESEARCH p786

Nick Freemantle
professor of clinical epidemiology and biostatistics

In this week's *BMJ*, Ferreira-González and colleagues report that clinical trials may mislead if they use composite end points.[1] For example, a statement that an intervention reduces a composite end point of cardio- to restrict the number of tests undertaken and limit the type 1 error to preserve the overall error rate for the trial. To do this, the type 1 error is allocated to different outcomes, most simply through the specification of a

G. Traversa

BMJ
doi: 10.1136/bmj.39136.682083.AE

RESEARCH

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

Metodi:

- ✓ **Revisione sistematica degli RCT su interventi cardiovascolari, con end point compositi, pubblicati su 6 riviste**
- ✓ **Singoli end point categorizzati come: fatali, critici, maggiori, moderati, minori**

Risultati:

- ✓ **Gli end point meno rilevanti tendono a sovrastimare l'efficacia degli interventi**

BMJ
doi: 10.1136/bmj.39136.682083.AE

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

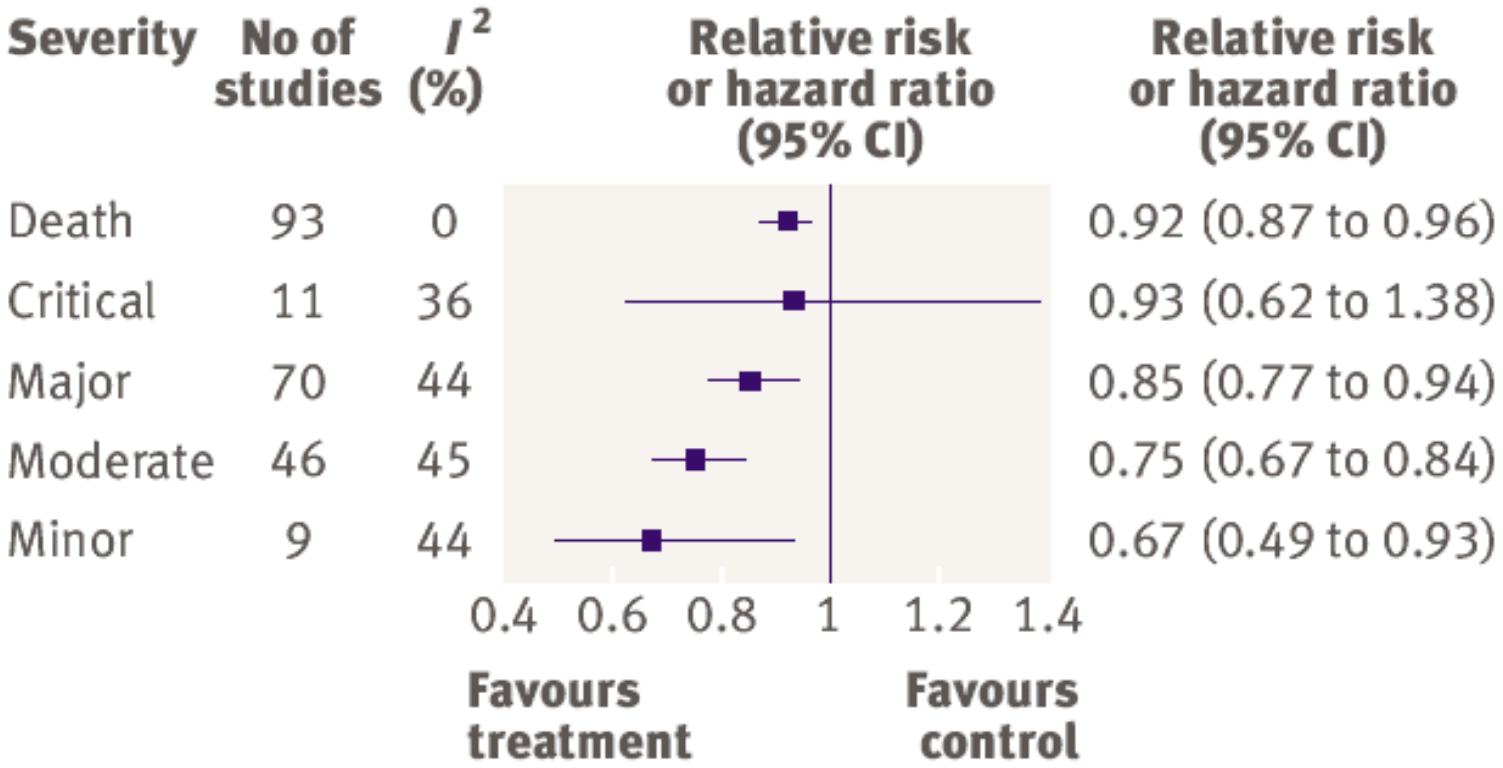


Fig 2 | Variability in magnitude of the effect of intervention across categories of importance to patients

BMJ
doi: 10.1136/bmj.39136.682083.AE

RESEARCH

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials

- ✓ **Spesso la significatività statistica è raggiunta solo aggiungendo gli end point di minore importanza**
- ✓ **Gli end point compositi sono utili se i singoli end point sono relativamente omogenei per:**
  - ✓ **importanza per i pazienti**
  - ✓ **effetto sulla riduzione del rischio relativo**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 5, 2009 VOL. 360 NO. 6

Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer

Jolien Tol, M.D., Miriam Koopman, M.D., Annemieke Cats, M.D., Ph.D., Cees J. Rodenburg, M.D., Ph.D., Geert J.M. Creemers, M.D., Ph.D., Jolanda G. Schrama, M.D., Frans L.G. Erdkamp, M.D., Ph.D., Allert H. Vos, M.D., Cees I. van Groeningen, M.D., Ph.D., Harm A.M. Sinnige, M.D., Ph.D., Dirk J[illegible]ger, M.Sc., M[illegible] M.Sc.,

EDITORIAL

Targeted Therapy for Advanced Colorectal Cancer — More Is Not Always Better

Robert J. Mayer, M.D.

Chemotherapy, Bevacizumab, and Cetuximab in Metastatic Colorectal Cancer

Jolien Tol, M.D., Miriam Koopman, M.D., Annemieke Cats, M.D., Ph.D., Cees J. Rodenburg, M.D., Ph.D., Geert J.M. Creemers, M.D., Ph.D., Jolanda G. Schrama, M.D., Frans L.G. Erdkamp, M.D., Ph.D., Allert H. Vos, M.D., Cees J. van Groeningen, M.D., Ph.D., Harm A.M. Sinnige, M.D., Ph.D., Dirk J. Richel, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Jeroen R. Dijkstra, B.Sc., Marianne E. Vink-Börger, M.Sc., Ninja F. Antonini, M.Sc., Linda Mol, M.Sc., Johan H.J.M. van Krieken, M.D., Ph.D., Otilia Dalesio, M.Sc., and Cornelis J.A. Punt, M.D., Ph.D.

Tol et al., NEJM 2009;360:563-72

Metodi

- ✓ **Valutata l'efficacia dell'aggiunta di cetuximab alla terapia di confronto (capecitabine, oxaliplatin, and bevacizumab)**

Risultati

- ✓ **"The addition of cetuximab resulted in significantly shorter progression-free survival and inferior quality of life"**
- ✓ **Non si è osservato alcun vantaggio neppure nei pazienti con gene K-RAS di tipo wild-type**

EDITORIAL

Targeted Therapy for Advanced Colorectal Cancer — More Is Not Always Better

Robert J. Mayer, M.D.

NEJM 2009;360:623-625

- ✓ The findings of Tol and colleagues serve as a reminder that antitumor activity observed in preclinical and also uncontrolled clinical contexts may not be validated when examined in randomized trials
- ✓ … combining multiple forms of targeted therapies may not be analogous to combining different types of cytotoxic chemotherapy …
- ✓ Finally, these results underscore the fundamental importance of subjecting hypotheses to carefully conducted clinical trials
- ✓ As was observed in this situation, more is not always better

JAMA®

Online article and related content current as of April 3, 2009.

FDA's Science Infrastructure Failing

Bridget M. Kuehn

JAMA. 2008;299(2):157-158 (doi:10.1001/jama.2007.53)

http://jama.ama-assn.org/cgi/content/full/299/2/157

"Underinvestment has left the Food and Drug Administration with outdated technology and other problems that interfere with its duty to protect the public's food and medical supplies"

VOLUME 26 · NUMBER 15 · MAY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Statement on Minimum Standards and Exemplary Attributes of Clinical Trial Sites

Robin Zon, Neal J. Meropol, Robert B. Catalano, and Richard L. Schilsky

From Michiana Hematology Oncology, South Bend, IN; Fox Chase Cancer Center; Coalition of Cancer Cooperative Groups, Philadelphia, PA; and University of Chicago, Chicago, IL.

Submitted December 7, 2007; accepted January 30, 2008; published online ahead of print at www.jco.org on April 7, 2008.

Reviewed and approved by the American Society of Clinical Oncology Board of Directors, October 11, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Neal J. Meropo, MD, Fox Chase Cancer Center, 333 Cottman Ave, Room C307, Philadelphia, PA 19111; e-mail: nj_meropol@fccc.edu.

ABSTRACT

Purpose
To describe both minimum requirements for a site conducting quality clinical trials and attributes of an exemplary site.

Methods
Minimum requirements and exemplary attributes were selected based on literature review, prevailing regulatory requirements, and consensus among a group of community and academic clinical researchers.

Results
To provide guidance to oncologists who wish to conduct patient-oriented research, recommendations are made to assist in the development and implementation of high-quality research programs with the priority of protecting the welfare and rights of trial participants. A quality research site complies with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the accepted international ethical and scientific quality standards for designing, conducting, recording, and reporting trials involving human participants. Recognizing that many research sites conduct clinical trials in compliance with accepted GCP standards, supplemental attributes of an exemplary research site that exceed the GCP criteria are also described. These attributes include diversification of clinical trial mix, high accrual activity, participation in the trial development process, maintenance of high educational standards, quality assurance, multidisciplinary involvement in the clinical trial process, and promotion of clinical trial awareness programs.

Necessari standard minimi per garantire una ricerca clinica di qualità

- ✓ **Si diffonde fra le società scientifiche l'esigenza di promuovere la qualità della ricerca clinica**
- ✓ **Il programma dell'American Society of Clinical Oncology (ASCO) per stabilire standard minimi e indici di eccellenza per i centri clinici, quali:**
  - ✓ **diversification of clinical trial mix**
  - ✓ **high accrual activity**
  - ✓ **participation in the trial development process**
  - ✓ **maintenance of high educational standards**
  - ✓ **quality assurance**
  - ✓ **multidisciplinary involvement in the clinical trial process**

Migliorare le competenze a sostegno della ricerca clinica

- ✓ **Competenze a sostegno della ricerca clinica e dell'attività dei Comitati etici:**
  - **Competenze GCP**
  - **Competenze metodologiche di epidemiologia e statistica**
- ✓ **Diverse opzioni disponibili a livello di:**
  - **Istituzione (es., unità di ricerca clinica, quality team)**
  - **Associazioni scientifiche (es., Anmco, Gimema, Aiom)**
- ✓ **Necessità di un'azione coordinata fra i diversi attori (AIFA, Ministero, Regioni, IRCCS, associazioni ecc.)**

Regulation—the real threat to clinical research

Recent changes to research governance were intended to ensure that clinical trials are safe and effective. But **Paul Stewart and colleagues** argue that the regulatory burden is now obstructing high quality science

BMJ 2008;337:1085-1087

Personal experience and feedback from many clinical researchers indicates that a major hurdle to undertaking clinical research is the ever increasing bureaucracy attached to the process. It is now the biggest single threat to the UK clinical research base and warrants immediate action. Earlier threats—lack of researchers and capacity—have been addressed through major investment by interested parties including the Medical Research Council, Wellcome Trust, other charities, and the Department of Health. However, anyone taking up one of the new academic specialist registrar posts created to encourage clinical academic training is likely to spend the entire 12 month fellowship trying to obtain regulatory approval for any clinical research project. Drug companies are experiencing similar difficulties. The UK has slipped from one of the most attractive to one of the least attractive places to undertake clinical trials as a result of ignoring warnings at the start of the decade that companies cannot afford long delays in approval and initiation.[1,2] We illustrate the effect of recent regulation with two anecdotes from our experience.

Case 1

In November 2004, AS sought ethical approval (under the old system) for a single centre, double blind, placebo controlled crossover comparison of glucose tolerance in two established classes of antihypertensive drugs, beta blockers, and thiazide diuretics. The ethics committee submission was approved with no changes at the end of November 2004, and approval from the trust's research and development department was obtained in parallel. A paper request for clinical trials authorisation was submitted in early January 2005 and approved in February 2005. The first patient visit was in the same month.

In July 2007, we decided to add another phase to the study using the licensed potassium sparing diuretic amiloride. This decision followed reports that high dose amiloride was more effective than bendroflumethiazide (one of the trial drugs) in hypertension and that raising potassium concentrations may protect against diabetes mellitus.[3,4] AS submitted a

BMJ 2008;337:1085-1087

Gli obiettivi delle linee guida GCP sono sacrosanti

- ✓ **Tutelare la sicurezza, il benessere, e i diritti dei soggetti coinvolti nella sperimentazione**
- ✓ **Garantire che i dati acquisiti e i risultati finali siano accurati**

E' necessario evitare che le GCP diventino e/o siano avvertiti come un inutile fardello burocratico

BMJ 2008;337:1085-1087

Recommendations to cut research bureaucracy

A single and simple web based submission form for all research studies

Automatic indemnity by National Institute for Health Research for all research protocols involving NHS patients

A national and consistent ethical review process

Medicines and Healthcare Products Regulatory Agency to focus on its remit to ensure medicines work and are safe

- ✓ **Alcune raccomandazioni sono problemi comuni: ad es., una valutazione affidabile da parte dei CE**
- ✓ **In altri casi l'AIFA ha già adottato provvedimenti: ad es., il CTA form**
- ✓ **Sono comunque necessari ulteriori interventi per ridurre il carico burocratico**

N ENGL J MED 354;5 WWW.NEJM.ORG FEBRUARY 2, 2006

Adopting Orphan Drugs — Two Dozen Years of Treating Rare Diseases

Marlene E. Haffner, M.D., M.P.H.

Related article, page 462

- ✓ **Un intervento pubblico mirato e coordinato può creare ricadute di rilievo: il caso dei farmaci orfani**
- ✓ **Orphan drug act: approvato negli USA nel 1982**
- ✓ **In 24 anni approvati 282 farmaci**

chronic diseases. Examples include ovine digoxin immune Fab (Digibind) for the treatment of life-threatening digitalis intoxication; ceramide trihexosidase–α-galactosidase A (Fabrazyme) for the treatment of Fabry's disease, a lipid-storage disorder; and nitisinone (Orfadin) for the treatment of type 1 tyrosinemia, a metabolic disorder caused by the lack of the enzyme fumarylacetoacetate hydrolyase, which, if left untreated, results in hepatic carcinoma, often before four years of age.

bmj.com

Orphan drugs and the NHS: should we value rarity?

Christopher McCabe, Karl Claxton and Aki Tsuchiya

BMJ 2005;331;1016-1019

Table 1 Examples of ultra-orphan drugs

Condition	Drug	Status	Annual cost/ patient (£)
Congenital sucrase isomaltase deficiency	Sacrosidase	Licensed	3 800
Essential thrombocytopenia	Anagrelide	Licensed	4 295
Gastrointestinal stromal tumours	Imatinib	Licensed	28 500
Gaucher's disease	Miglustat	Licensed	58 400
Gaucher's disease	Imiglucerase	Licensed	70 100
Fabry's disease	Agalsidase	Licensed	109 600
Mucopolysaccharidosis 1	Laronidase	Licensed	311 000
Hereditary tyrosinaemia (type 1)	Orfadin (organic chemical)	Licensed	Unknown
Hunter syndrome	Idursulfas	Early clinical trials	Unknown
Mucopolysaccharidosis VI	Aryplase	Licence applied for	Unknown
Niemann-Pick's disease	OGT 923	Early clinical trials	Unknown

bmj.com

Orphan drugs and the NHS: should we value rarity?

Christopher McCabe, Karl Claxton and Aki Tsuchiya

Summary points

- The appraisal framework already supports the use of lower evidential standards for orphan drugs
- The costs of production and the value of innovation cannot justify special treatment for orphan drugs
- Arguments about the measurement and valuation of health outcomes apply equally to orphan drugs and drugs for more common conditions
- Valuing health outcome more highly for rare conditions is incompatible with other equity principles and theories of justice
- The cost effectiveness of orphan drugs should be treated in the same way as for other technologies

JAMA®

Online article and related content current as of April 3, 2009.

Benefits and Risks of Drug Treatments: How to Combine the Best Evidence on Benefits With the Best Data About Adverse Effects

Jan P. Vandenbroucke; Bruce M. Psaty

JAMA. 2008;300(20):2417-2419 (doi:10.1001/jama.2008.723)

THE CENTRAL THEME OF THE INSTITUTE OF MEDICINE report on the US drug safety system was the need for a life cycle approach to drug evaluation: both the benefits and the risks need to be evaluated and integrated during the entire market life of a drug.[1] The Food

La sorveglianza post marketing

- ✓ **Committment per le aziende al momento dell'approvazione**
- ✓ **Studi osservazionali post marketing**
  - **Registri sull'uso appropriato**
  - **Follow up a lungo termine sulle ADR**
  - **Studi comparativi sul place in therapy nella pratica clinica corrente**

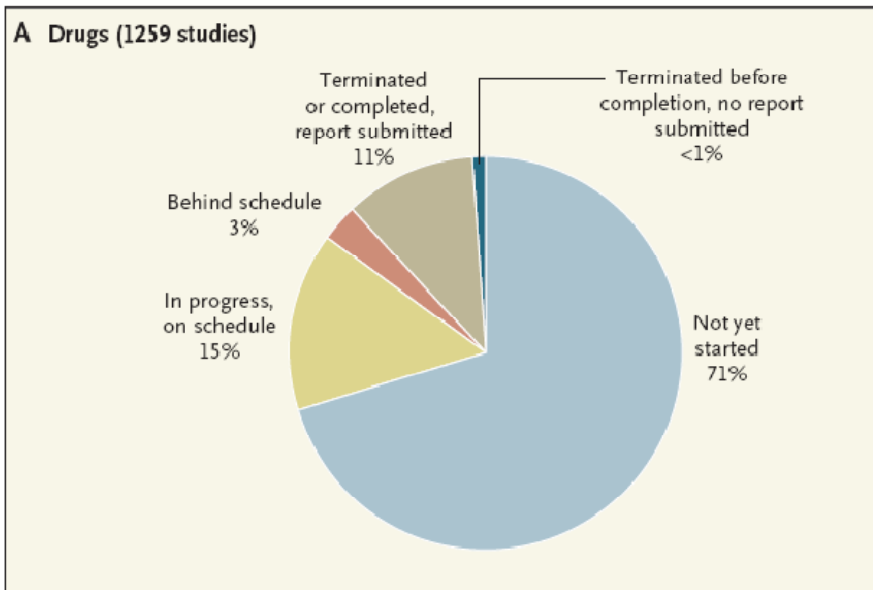
Non-compliance con i post-marketing commitments

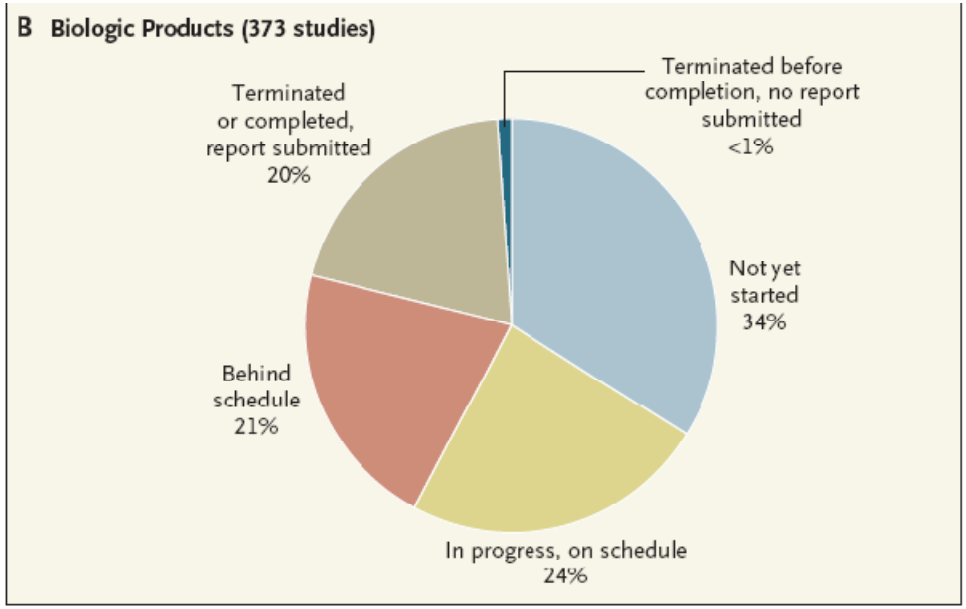
Paying for Drug Approvals — Who's Using Whom?

J. Avorn. N Engl J Med 2007;356:1697-1700

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

Data are from the Federal Register.





Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Tricoci et al. JAMA 2009;301(8):831-841

Implication for research

There is limited sponsorship of trials to address questions of comparative effectiveness or routine clinical practice. The problem of how to generate funding for research addressing practical clinical questions that do not involve a marketable product is currently unresolved. Parties with an

Le motivazioni della ricerca indipendente

- ✓ **<u>Pazienti</u> poco rappresentati nelle sperimentazioni: ad es., bambini, donne in gravidanza, anziani con polipatologia, malattie rare**
- ✓ **<u>Temi</u> poco rappresentati nelle sperimentazioni: ad es., i confronti testa a testa e/o con farmaci fuori brevetto, il place-in-therapy in una strategia terapeutica (farmacologica e non), il follow up a lungo termine, end point hard**

Necessità di una valutazione rigorosa dei progetti di ricerca: l'esperienza dell'AIFA

- ✓ **Lettere di intenti: valutazioni singole da parte di almeno 3 componenti della CRS**
- ✓ **Discussione plenaria e votazione**

- ✓ **Protocolli finali: valutazione da parte di Study session (per il bando 2008 con 21 esperti, in maggioranza stranieri, diversi dalla CRS)**
- ✓ **Per ciascun protocollo:**
  - ✓ **3 reviewer (con commenti scritti e votazione da casa)**
  - ✓ **Discussione plenaria e votazione**

Totale progetti finanziati nei bandi AIFA 2005-2007

Area	Progetti finanziati	
	N	%
✓ Farmaci orfani e malattie rare	64	42
✓ Confronti fra farmaci e strategie	38	25
✓ Farmacoepidemiologia e appropriatezza	49	32
Totale	151	100

Finanziamento: circa 78 milioni di euro nel triennio

La globalizzazione della ricerca

SOUNDING BOARD

Ethical and Scientific Implications of the Globalization of Clinical Research

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D.

NEJM 2009;306:816-823

SOUNDING BOARD

NEJM 2009;306:816-823

Ethical and Scientific Implications of the Globalization of Clinical Research

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D.

- ✓ **Analisi di 300 articoli (NEJM, Lancet e JAMA), 1995 e 2005**
- ✓ **Più che raddoppiati i paesi con almeno un centro clinico in una sperimentazione**
- ✓ **La proporzione di sperimentazioni cliniche multinazionali che abbiano coinvolto più di 10 paesi: dal 4,7% del 1995 all'11,7% del 2005**
- ✓ **La proporzione sul totale dei trial condotti si è ridotta:**
  - ✓ **negli USA da 53,8% a 42,6%**
  - ✓ **insieme USA e Europa occid. da 93,8% a 85,1%**
- ✓ **Aumentano le sperimentazioni nei paesi meno sviluppati**

SOUNDING BOARD

NEJM 2009;306:816-823

Ethical and Scientific Implications of the Globalization of Clinical Research

Seth W. Glickman, M.D., M.B.A., John G. McHutchison, M.D., Eric D. Peterson, M.D., M.P.H., Charles B. Cairns, M.D., Robert A. Harrington, M.D., Robert M. Califf, M.D., and Kevin A. Schulman, M.D.

- ✓ **Implicazioni di tipo etico**
  - ✓ **ruolo dei CE**
  - ✓ **uso del placebo e confronti inadeguati**
  - ✓ **acquisizione consenso informato**
  - ✓ **compenso per la partecipazione**
  - ✓ **verifiche sulla conduzione degli studi**
- ✓ **Implicazioni in termini di trasferibilità**
  - ✓ **minore coinvolgimento di soggetti affetti da polipatologie e politrattamenti**
  - ✓ **informazioni sul profilo genetico**