

XI Riunione annuale Network Cochrane Italiano
Roma, 28 Novembre 2006

AREE DI INCERTEZZA IN MEDICINA
come identificarle e promuovere la ricerca necessaria

**II SESSIONE : Quale rapporto tra incertezza scientifica
e indirizzo della ricerca**

Enrico Geraci

L'incertezza per il ricercatore clinico

The U.S. National Institute of Health (NIH) defines “Clinical Research” to include :

- patient oriented research including mechanisms of human disease, clinical trials and new technology development;**
- epidemiologic and behavioral studies;**
- outcomes and health services research.**

(DeMaria AN, *JACC* 23003; 41: 2000-2001)

The many facets of “uncertainty” in clinical research

(with reference to randomized trials [RCTs] on drugs)

1. Uncertainty about priorities in clinical research.

The approach to this problem in the context of *independent* research is very different from that of *industry-promoted* research...

To assess priorities in clinical research

Independent research : Clinicians know quite well the grade of importance / urgency of research in their specific areas. A simple way of identifying areas lacking information to guide clinical practice, would be to look at recommendations of grade II-a or II-b in current clinical guidelines...

However, it is not easy to coordinate the requests of funds for research coming from multiple areas and to draw up a satisfying scale of priorities.

Only recently in Italy an ad hoc central authority has been established, and public funds for independent clinical research have become available [Martini's talk]. And to define an acceptable scale of priorities one must evaluate not only the importance of each potential research but also its grade of feasibility in terms of costs, other practical issues, ethical problems, etc. [Liberati's talk].

To assess priorities in clinical research

Industry-promoted research (now also called “contract research”): In this type of clinical research, priorities are assessed essentially for profit purposes, looking mainly at marketing strategies.

In pharmacotherapeutic research, for example, important clinical trials on innovative drugs (such as ezetimibe or torcetrapib, to cite very recent examples) stay side by side with trite trials on “me too” drugs (e.g. the twentieth dihydropyridine calcium-channel blocker).

2. Uncertainty about the feasibility of really independent clinical research.

RCTs are expensive, and those focusing on drugs are mostly funded by industry. Clinical research just *funded* (not directly promoted) by industry implies anyway problems of external influence upon investigators, even if they consider themselves fully independent. And clinical research *promoted* by industry is, as just said, almost always piloted more by profit than by desire of science advancement...

Torcetrapib and Atorvastatin - Should Marketing Drive the Research Agenda ?

Jerry Avorn, M.D.

NEJM June 23, 2005

“Pfizer trials will study torcetrapib only in combination with the company’s widely used atorvastatin (Lipitor)...

The current trial designs may not optimally meet the scientific needs of prescribers, the clinical needs of patients, the economic needs of payers, or the regulatory needs of policymakers. But they superbly meet the business needs of the sponsor - to create new knowledge in a way that will protect the market share of the largest drug company’s most important product [Lipitor]”.

3. Uncertainty as equipoise (balance, equilibrium) felt by investigators of the starting trial about the relative values of the treatments to be compared.

For ethical reasons, a status of equipoise is necessary before running an RCT, but that position is not mandatory for every single investigator, provided that a condition of so called “clinical equipoise” (recognized widespread uncertainty, or balanced opinions, within the community of clinicians) is present concerning the treatments to be compared.

**4. Uncertainty about the persistence of equi-
poise during the development of the study. If
an interim analysis of the current trial and /
or fresh results of similar trials show that one
treatment is clearly superior, the Steering Commi
ttee of the trial (with the consent, or even by
input, of the independent Data & Safety Moniti
ng Board [DSMB]) should consider the pre
mature arrest of the trial, or at least a modificati
on of the study protocol (if that is possible
and sufficient to protect patients' interest).**

**Sometimes this issue is incorrectly managed,
with consequent harm to enrolled patients...**

Unethical placebo assignment in clinical trials of thrombolysis

Enrico Geraci, JACC 1992; 20: 1302-3 (Letter)

Meta-analysis by Yusuf et al, 1985; GISSI-1, February 1986; ISAM, April 1986 : *clear proof that systemic thrombolysis reduces deaths in AMI.*

Western Washington (SK) : Anticipated arrest of the enrolment in the trial (timely : July,1986) due to results of other trials.

Johns Hopkins (SK), TPAT (t-PA), TEAHAT (t-PA) : Anticipated arrest (but more or less late : March,1987; December,1987; May,1988 !) “due to results of other trials”.

TICO (t-PA), AIMS (APSAC) : Anticipated but late arrest (July,1987; December,1987) “due to interim analysis” (other trials not considered !).

ECSG-V (t-PA), ASSET (t-PA), Esbjerg (t-PA) : Closed as initially planned (December,1987; March,1988; July,1988 !!).

Some of these trials started after the publication of GISSI & ISAM results!

Of note, the proof of thrombolysis efficacy in AMI had been obtained using the relatively cheap SK, and it was essential, for the industry producing the much more expensive t-PA, to achieve an independent proof of efficacy for that drug too. On the whole, thousands of AMI patients in these trials continued to be assigned to placebo though it had become already evident that systemic thrombolysis is lifesaving.

The Steering Committees and the DSMBs of those trials were highly censurable, but what the cardiological community was looking at ?

In contrast, some RCTs are interrupted prematurely for reasons other than patient protection, mainly because

- the sponsor industry realizes that the investment is not worthwhile, or money is no more available, or**
- the findings of an interim analysis of this one, or the results of other trials, indicate that the new treatment is better, *even if the advantage is not so clearcut that investigators or DSMB would stop anticipately the study.* The sponsors impose the premature interruption of the trial to immediately fuel their marketing strategies or for fear that data accretion could not confirm the superiority.**

5. Uncertainty about how to process and present the findings of the trial : Intention-to-treat or per-protocol analysis ? Absolute or relative end-point reduction ? etc.

These doubts are not always genuine indeed, and the search for optimal processing and presentation of trial's data is often market-driven and / or is guided by investigators' desire to best enlighten the results of their work (and to increase the chances of publication in a prestigious medical journal).



- SOMETIMES I HAVE TO GO THROUGH
MANY DIFFERENT STATISTICIANS TO
GET THE RIGHT RESULTS.

6. Uncertainty about the applicability of the trials results into clinical practice : only to trial-like patients, or even to other categories ? One example is that of the expensive DES (drug-eluting [coronary] stents), which in the RCTs resulted better than the cheaper bare-metal stents (because of a lower incidence of early restenosis), but are now suspected of favouring late in-stent thrombosis. Probably this problem arises mainly from the large use of DES, in clinical practice, even in patients with coronary anatomy different from that of patients enrolled in the trials (“off protocol” use).

The many issues facing regulatory bodies and clinicians for appropriately and quickly transferring the research results into clinical practice, have recently prompted in U.S.A. the creation of a number of dedicated “Translational Medicine Institutes” (TMIs), funded by NIH but placed within centres of excellent clinical practice and research (e.g. at Duke University Medical Center, where the TMI will be directed by Robert Califf, a most renowned clinical investigator in Cardiology).

TRANSLATIONAL MEDICINE INSTITUTES

funded by NIH National Center for Research Resources

“...to streamline how we move diagnostic technologies, preventive efforts, and therapies that prove effective in clinical trials, into the hands of physicians and other health care providers in caring for patients.”

7. Uncertainty about the validity of the trial results in the near future, as similar studies could subsequently show weaker effects of the winning treatment, or even fully contradict the results of this trial.

Moreover, the post-trial follow up could modify the initial conclusions, as in the case of DES trials (it is not certain that the large off-protocol use of DES accounts for the *whole* incidence of late in-stent thrombosis).

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P.A. Ioannidis

JAMA 2005; 294: 218-228

I have so far underlined the many perils and harms due to the heavy interference of drug industry in clinical research. Yet it is proper to recognize that without Big Pharma many essential advances in pharmacotherapy would not have been achieved.

But I can't resist temptation of a last dig...

**HARLOT plc (How to Achieve
positive Results without actually
Lying to Overcome the Truth)**

In this humorous article (*BMJ, December 20, 2003*) David Sackett and Andrew Oxman offer the opportunities of the (obviously fictitious) HARLOT agency, that “will provide a comprehensive package of services to trial sponsors who don’t want to risk the acceptance and application of their products and policies amid the uncertainties of dispassionate science.”