SISMEC
The adaptive desing in clinical trials: regulatory and research aspects

Roundtable: issues in homogeneity and current evaluation of adaptive designs in clinical studies by ethical committees

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"Adaptive" / "Flexible" Designs

1)-Sample Size Re-estimation: the originally planned sample size may not be appropriate (greater variability, different response rate).

2)-Termination / Adaptation of a treatment arm: dose or treatment schedule are not optimal as a result of an interim analysis).

3)- Adaptation of the statistical methodology (a formal statistical plan can be released before breaking the randomization code – ICH E9).

“Adaptive” / “Flexible” Designs

4)- Change inclusion / exclusion criteria (recruitment rate too slow / selection of subgroups) but target population changes.

5)-Response Driven Adaptive Designs (change of primary endpoint: composite endpoint ill-specified, treatment effect on other variables, responder definition).

6)-Change of study objective from superiority to non-inferiority or vice versa (can be foreseen in the protocol: CPMP/ EWP/2158/99, CPMP/EWP/482/99).

“Adaptive” / “Flexible” Designs

7)-Seamless designs (Phase I / II, Phase II / III).

"Adaptive" / "Flexible" Designs

Meeting: "Pharmaceutical Research": working group (IBS-GR, Aachen, 28 April, 2005)

Meeting: "Multiple Methods": working group (IBS-GR, Basel, October, 2005)

Workshop on Adaptive Designs (IBS – Berlin, September 28-29, 2006)

IBS's 3rd International: Adaptive Designs for Clinical Trials, May 10-11, 2007, Cambridge, MA.

"Adaptive" / "Flexible" Designs

FDA: "Innovation or Stagnation ? – Challenge and Opportunity on the Clinical Path to New Medical Products (March, 2004 – replaced: http:www.fda.gov/oc/initiatives/criticalpath/)

"main focus is that there has been a slowdown, not the expected acceleration in innovative medical therapies reaching patients and that the medical product path is becoming increasingly challenging, inefficient and costly."

"Adaptive" / "Flexible" Designs

FDA: "Innovation or Stagnation ? – Challenge and Opportunity on the Clinical Path to New Medical Products (March, 2004 – replaced: http:www.fda.gov/oc/initiatives/criticalpath/)

"FDA's view is that the situation is critical and we need to act now to improve the development process in many areas and impact public in a positive way".

"Adaptive" / "Flexible" Designs: **Goals**

1. Adaptive/flexible designs allow some type of mid-study changes (prospectively planned) in order to maximize the chance of success of the trial while properly preserving the type I error because some planning parameters are imprecisely known.
2. Enrich trials with subgroups of patients having genomic profiles likely to respond or less likely to experience toxicity.

"Adaptive" / "Flexible" Designs:

Adaptive/flexible designs should ***NOT*** be viewed as a remedy for insufficient planning; rather they should be implemented based upon realistic understandings of some limitations in knoweledge at the design stage, and how knowledge contained in accruing data might be useful to enhance some aspect of the trial.

Comitato Etico: COMPETENZE

D.M. 12 / 5 / 2006 G.U. N. 194 del 22 / 8 / 2006
2.4 La composizione dei comitati etici deve garantire le qualifiche e l'esperienza necessaria a valutare gli aspetti etici, scientifici e metodologici degli studi proposti.

I componenti dei comitati etici devono avere una documentata conoscenza e / o esperienza nelle sperimentazioni cliniche dei medicinali e nelle altre materie di competenza del comitato etico.

Comitato Etico: RIFERIMENTI

5.2 La valutazione etica, scientifica e metodologica degli studi clinici :

- D.L.vo n. 211 del 15/7/ 2003,
- Dichiarazione di Helsinki nella sua versione più aggiornata,
- Convenzione di Oviedo (7/4/97, n.145 28/3/01)
- Le norme di buona pratica clinica (GCP)
- Le linee guida aggiornate dell'Agenzia Europea per la valutazione dei medicinali (EMEA) in tema di valutazione dell'efficacia dei medicinali…
- La "larga bibliografia" esistente in materia…

Il PARERE del Comitato Etico

Scientific and Ethical Evaluation:
THE CLINICAL RELEVANCE

Analysis of the actual situation:

- **kind of pathology considered in the CCT**
- **kind, "efficacy" and burden of the "standard"**
- **actual possibility of improving the clinical results of the "standard"**

Il PARERE del Comitato Etico

Scientific and Ethical Evaluation:
THE CLINICAL RELEVANCE

Analysis of the new proposed procedure:

- appropriateness of the aims and of the rationale
- the sensible expectations:
  - efficacy / safety against the "standard"
  - methodological improvement
  - costs (time, organization)
  - burdens for the patients, researchers, hospitals, and society

Il PARERE del Comitato Etico

Scientific and Ethical Evaluation:
THE SCIENTIFIC RELEVANCE

- the rigour of the adopted method
- objectivity
- reproducibility of the results
- the procedures can be verified
- the results have to be compared

Il PARERE del Comitato Etico

ETHICAL EVALUATION:

- adequacy and completeness of the written information to the patients (Informed Consent)
- the procedure for obtaining the written Informed Consent
- the principle of the individual ethics
- the principle of the collective ethics
- the principle of the autonomy of the patient

Il PARERE del Comitato Etico

IL PARERE del Comitato Etico:

- *Feasibility of the study*
- *Assurance (medical - legal aspects)*
- *Costs (Art. 6 D.M. 15/5/2006)*
- *Enrollment of the patients*
- *The transparence of the information (art. 5.c D.M. 12/5/2006)*

"Adaptive" / "Flexible" Designs

How Ethical Committees can consider:
Clinical Relevance,
Scientific relevance,
Ethical issues of "Adaptive" / "Flexible" Designs?

Actual and unresolved problems about:

- **sequential designs**
- **non-inferiority designs**
- **study interruptions (efficacy, futility)**
- **designs "switching from superiority to non-inferiority"** (CPMP / EWP / 482 / 99):
- **protocols amendements**

Ethical Committees *and* "Adaptive" Designs

1)-Sample Size Re-estimation: the originally planned sample size may not be appropriate (greater variability, different response rate)

The statistical method has to be fully specified in the protocol of the CCT together with the maximum allowable sample size;
The starting clinically relevant difference has to remain clinically meaningful;
If the adaptation criterion is completey specified in advance, a more efficient fixed information design may be available.

Ethical Committees *and* "Adaptive" Designs

Case Study: Protocol XX for treatment of LLC.
First sample size calculation: approximately 624 patients (312 patients per treatment group)
Second sample size calculation: approximately 550 patients (275 patients per treatment group) according to the results from independent trials on the overall response rate and CR rate.

A change from an external information does not require an adaptive design, for the modification is independent from the data.

Ethical Committees *and* "Adaptive" Designs

2)-Termination / Adaptation of a treatment arm: dose or treatment schedule are not optimal as a result of an interim analysis)

Highy recommended / acceptable in Phase II designs, if it is the case (toxicity,no response); Practically not applicable in Phase III CCT.

It requires the re-allocation of the unused α to the remaining arms for comparisons.

Ethical Committees *and* "Adaptive" Designs

3)- Adaptation of the statistical methodology (a formal statistical plan can be released before breaking the randomization code – ICH E9)

This is a "borderline adaptive aspect"

It is required that a statistical plan considering the possible solutions (statistical models) according to the data is written in the study protocol.

Ethical Committees *and* "Adaptive" Designs

4)- Change inclusion / exclusion criteria (recruitment rate too slow / selection of subgroups) but target population changes.
A very frequent "informal design adaptation" in pratically every protocol amendment.

Usually, only minor changes are and can be accepted.
It is possible to consider statistical methods to model the population deviations by using some covariates but what is the **clinical meaning** of these results ?

Ethical Committees *and* "Adaptive" Designs

5)- Response Driven Adaptive Designs (change of primary endpoint: composite endpoint ill-specified, treatment effect on other variables, responder difinition).

PEACE trial: revascularization was added to its composite endpoint (Pfeffer et al., 1998)

RUTH trial: the Ex.Comm. added "hospitalization for coronary syndrome" to its composite (Mosca et al., 2001)

At least, the added component has to lay in the same putative biological pathway as the other components, but it is consistent with the first judgement of the clinical relevance ?

Ethical Committees *and* "Adaptive" Designs

6)-Change of study objective from superiority to non-inferiority or vice versa (can be foreseen in the protocol: CPMP/ EWP/2158/99, CPMP/EWP/482/99)

Problems with this kind of trials:

-how to select the trials relevant to define the margin
-how to choose the non-inferiority margin
-how to deal with assay sensitivity
-how to analyze data in presence of noncompliance
-how to write the Informed Consent when the endpoint is a clinically important outcome

It is sensible to increase the difficulty of interpreting their results in making them adaptive ?

“Adaptive” Designs

Logistics and Implementation
Software Tools (statistical and data input)
Monitoring, Analyzing and Reporting

Members of Ethical Committees have to be informed and the biostatistician has to acquired a specific knowledge.

It can argued that the EC of the coordinating center is involved in the active conduct of an “Adaptive Design” and that “its decision” (jointly with Ex.Comm., DSMC) is communicate to the ECs of the participating centers.