The adaptive design in clinical trias: regulatory and research aspects

SISMEC Ethical Committee Working Group

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NOVARTIS

Ethics in Trials

- Clinical trials are scientific experiments in human beings.
- The performance of a clinical trial is only justified if the clinical investigators in advance consider ethical aspects and if an external ethical committee has approved the conduct of the study according to a defined protocol.
- Ethical aspects include the obligation that only the "minimum" number of patients should be entered onto the trial, which is necessary to achieve the study's primary objective given previous experience with the specific treatment.
- If the medical literature or previous experience indicates a high variability of the efficacy of treatment to be tested or if the statistical assumptions upon which the trial is based seem questionable, close monitoring of the trial conduct and its results is highly recommended. Such awareness is of particular importance if the trial treatment leads to considerable toxicity (Fosså, JCO, 2000).

Effects of monitoring

- Is the inclusion rate of patients acceptable and as expected? (Lancet, 1999)
- Is there an unexpectedly high rate of severe or life-threatening adverse events, which may indicate the premature closure of the trial?
- Is the outcome of the trial treatment comparable with that of the previous experience upon which the specific trial is based?
- Do the results of the interim analysis prove statistically significant differences between the trial treatments that exceed the differences defined by the statistical guidelines of the trial? This would warrant closure of the study. (metoprolol or simvastatin, Lancet, 1994)

Monitoring and interim analyses

Interim analyses are traditionally planned in clinical trials in order:

- to stop them as soon as serious safety concerns emerge such that the risk / benefit ratio is unlikely to be favourable (deMets, 2005)
- a treatment benefit is established reliably (Jennison, 1999)
- it is clear that no treatment effect emerges and it would be futile to continue entering patients in the trial (Piantadosi, 2007)

Other purposes of interim analyses may be (Therasse, 2006):

- to suggest changes in the design of the trial, such as changing patient inclusion criteria
- dropping an arm
- adapting a dose
- modifying the number of patients required

Statistical consequences

- FDA, EU and Japanese regulatory agencies allow for flexible designs (ICH-E9), implying a data-driven re-estimation of the sample size
- Multiple looks at interim data and stopping trials early compromises the type-1 error and/or power of the study: (McPherson, 1969) the goal is to find appropriate adjusted decision regions such that the actual error type-1 is not greater than alpha
- It might be that a penalty is paid in terms of inflated sample size (FDA – as much as 20%) is variance is higher than expected, but also deflated if investigators are facing a reduced-variability situation

EC and adaptive, GS, flexible, bayesian designs

- Control/understanding of the process
- Technical sophistication (much beyond common Medical Schools curriculum)
- Identifiability of sensitive issues
- Conflict with other open issues (equivalence, non-inferiority trials)

SISMEC workshop

The adaptive design: state of the art and paths for future research

Raphael Porcher

Département de Biostatistique et Informatique Médicale (D.B.I.M.), Hôpital St Louis, Paris

The adaptive design: issues in current research and implementation

Peter Thomas

Novartis

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

Carlo Tomino, Antonella Bacchieri, Bruno Cesana