

Session B

Consideration for Adaptation in Confirmatory Trials

Jim Hung, FDA

Ron Marcus, BMS

Willi Maurer, Novartis

Robert Meyer, FDA

Can adaptive designs be “confirmatory” ?

- What is a **confirmatory** trial?

From ICH E9:

- **Confirmatory trial is an adequately controlled trial in which**
 - **the hypotheses are stated in advance (and the family-wise type I error is controlled)**
 - **primary objective is always pre-defined**
 - **adherence to protocols and standard operating procedures is particularly important**
 - **principal features of the planned analysis should be set out in the protocol and only a limited number of questions is addressed**
- **A trial (or parts of it) is *exploratory* if hypotheses are postulated post hoc based on inspection of the data and outside of a set of a priori stated hypotheses.**

Aspects of adaptive trials that could violate the “confirmatory” nature of a trial

- **Sample size adaptation - Blinded vs. unblinded**
 - a) Methodologies
 - b) Logistics
- **Dose selection/elimination - logistics**
- **Endpoint adaptation – when would it be appropriate?**
- **Population adaptation**
 - a) changing entry criteria
 - b) changing populations in the final analysis
- **Others?**

Blinded vs. unblinded interim analysis for adaptation decisions

- **Blinded**
 - Only for adaptation based on nuisance parameter estimates; no decisions on hypotheses intended or possible
 - No issues with confidentiality and trial integrity
 - Analysis with standard fixed design methods; little or no effect on type I error rate
- **Unblinded**
 - Measures to protect trial integrity necessary
 - Nuisance parameter and effect size estimates can be used for adaptation decisions; early rejection of hypotheses possible
 - Adjusted analysis methodology necessary
- **Other aspects?**
- **Is one of the approaches to be preferred in a confirmatory trial?**

Change or modification of primary endpoint

- **“Primary endpoint should reflect patient benefit *not* discern treatments” (EMA reflection paper)**
 - **Are there situations where it would be sensible to switch primary endpoints based on interim results ?**
 - **If yes, would this affect the confirmatory nature of the trial?**

Selection of treatment arms:

- **“Address the identification problem upfront” (EMA reflection paper)**
 - multiplicity over all initial hypotheses must be taken into account to control type I error
 - is that all that is needed?
- **Can logistical issues (drug supply management, informed consent before and after adaptation, information to investigators) decrease the confirmatory nature of a trial?**
- **To what extent is the selection bias in estimating the treatment effect a problem?**

Population adaptation in a confirmatory trial

- **Should entry criteria be changed based on interim analyses ?**
 - e.g. to concentrate on subgroup of patients (characterized e.g. by a genetic marker) that shows better treatment response
 - other reasons ?
 - If yes, should the possible changes be predefined?
- **Changing populations in the final analysis**
 - Can the primary analysis population in the final analysis be defined based on interim results?
 - If yes, why and for what reason?