

Statistical Issues of Data Monitoring Committee in Adaptive Designs

Ning Li, M.D, Ph.D.
Team Leader
CODB/OSB/CDRH

US Food and Drug Administration

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DMC Function

- Evaluate safety/efficacy – in relation to seriousness of the disease and outcome
- Monitor internal data via interim looks/analyses
- Evaluate external information that are relevant to the product
- Recommend study modifications while ensure scientific **integrity/validity**

Reasons for Data Monitoring

- Monitoring the safety of patients and quality of data
- Early termination for significant treatment benefit or safety considerations
- Early termination for lack of efficacy (i.e., futility)
- Verification of protocol assumptions
- Administrative management

DMC and Adaptive Design

- DMC may use accumulated data to recommend on how to modify aspects of the trial, without undermining study *validity* and *integrity*
- DMC needs to ensure that an adaptation is adaptive by “design”, and will not result in a change of the trial conduct and/or analysis.
- All rules for adaptive changes and for final analysis should be pre-specified in protocol and/or DMC Charter

Charter of a DMC should Cover

- When and by whom the interim analysis will be performed
- Confidentiality issue: How to keep the interim results from leaking? How to judge the impact of the interim analysis/implication?
- The decision maker (DMC or EC/Sponsor?)
 - What if the DMC's opinion is different from the sponsor's in the adaptive decision?

Stat Related Concerns for Data Monitoring

- Dependency of DMC to sponsor
 - Influence of decision making in study **modification/adaptation**
 - Questionable credibility of the study conduct
- Inflation of type I error due to multiple looks at data
- Confidentiality of interim results
 - Impact on the validity of the study
 - Impact on the ability to support a desired regulatory decision

Current Views on DMC/AD

- To ensure the integrity and validity of study results, an independent DMC is desirable.
- Use of DMC, its mission and objectives should be pre-specified in details and justified at the protocol development stage.

Current Views on DMC/AD

- Interim analyses should be pre-planned and conducted by an entity independent of the sponsor.
- Any statistical adjustment to preserve the overall type I error rate of the study should be pre-specified.
- Changes in study protocol may have substantial impact on the integrity/validity of the study.

Current Views on DMC/AD

- Early stopping a trial due to a significant benefit may **not** yield sufficiently persuasive evidence and may fail to accomplish study objectives:
 - Unstable estimates of treatment effect. Chance to observe a statistically significant benefit for an ineffective product (**unreliable interim results**)
 - Insufficient safety data to evaluate risk/benefit ratio
 - Inability to demonstrate secondary objectives.

Scenario 1

- A Randomized, double blinded study with a time to event endpoint.
- During a planned interim analysis (I=50%), the DMC found that the treatment effect was near the significant level ($p=0.02$) in favor of the new trt.
- At the final analysis, the treatment effect was reversed (to the wrong direction).
- One possible reason is that the new treatment may work at early stage but increase the risk due to long-term usage (changing hazard over time).

Questions for the panel (1)

1. How should we deal with the chance to observe a statistically significant benefit for an ineffective product based on **unreliable interim results**?
2. In which scenario you think the adaptive design is most appropriate or inappropriate?
3. How do you think the readiness for regulatory agencies to accept and approve trials with adaptive design? What kinds of conditions are necessary?

Scenario 2

- A Randomized, double blinded study with a pre-specified primary endpoint **A** and a major secondary endpoint **B**.
- During the study (w/o unblinding treatment arms), the sponsor found that the missing values for **A** was about the double comparing with that of **B**.
- The sponsor asked the DMC to look at the unblinded data to consider change primary endpoint from A to B due to missing.
- DMC refused to perform the requested unplanned interim look, but the sponsor insisted the change.
- The study might fail if **A** were used as the primary endpoint at current missing pattern but may succeed if **B**.

Questions for the panel (2)

1. Who should make the adaptation decision? DMC or the sponsor? What should be done when the DMC and the sponsor are in disagreement? Should the FDA be consulted in the adaptation decision?
2. In the current clinical trial setting (in general), how do you view the necessity and importance of adaptive design? What procedure should be followed during implementation?