

Adaptive Designs Workshop
2:30-3:30 Panel Session, Nov. 14, 2006

Recommendations and Next Steps

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From Monday: Workshop Goal

- Identify concepts and issues where there is agreement
- Identify areas where there currently is not broad agreement
- Moving forward:
 - Distinguish between issues related to
 - Statistical methodology
 - Implementation
- Panel Focus: Implementation issues

“3 Bucket” Approach

1. What is acceptable?

- In a “Confirmatory” setting:
Blinded sample size re-estimation, group sequential designs
- In a “Learn” setting: *Adaptive BY Design*, e.g. adaptive exploration of treatment strategies, learning about the dose-response
- What is required?
 - Correct statistical inference; Controlling operational bias

2. What is definitely unacceptable?

- Poorly planned, unsubstantiated, undocumented proposals
- Post-hoc adaptations

3. What requires case-by-case consideration?

- *Adaptive BY Design* in the “confirmatory phase”
 - Seamless adaptive phase II/III
- Purely Bayesian approaches in a confirmatory setting
- Can we identify aspects that we can move into Bucket #1 or #2

Key Implementation Issue: Spectrum of Blinding

■ Sponsor Involvement

- None beyond completely pre-specifying recommended decision rules
 - May better ensure trial integrity, but decision may be sub-optimal
- Limited sponsor involvement with the DMC
 - Clarify LIMITED (e.g., designated individuals distanced from trial operations receive pre-specified summary information, bound to confidentiality agreement / SOP....)
 - Better decision may be reached, but there may be a perception that trial integrity could be compromised.

■ Identify risks and processes to mitigate

Vision

- Limited sponsor involvement with the DMC will enable better decisions, and ultimately, allow for greater impact of adaptive designs on drug development....BUT
 - There MUST be a clear and important rationale for involvement
 - Appropriate processes need to be in place, and followed, to maintain the integrity of the trial.
- Allow that there may be more than ONE solution
 - Cases where limited sponsor involvement is appropriate
 - Different degrees of sponsor involvement in the decision making (e.g. only when DMC sees need to deviate from decision recommendations)

A modern review process for adaptive designs

- Should we plan for an intensified and sufficiently early and continuous interaction between FDA and sponsor to facilitate high quality planning and implementation of adaptive designs?
 - What is the process to move this forward?
- What is the method for sponsor and regulatory interaction for case-by-case issues?
 - Special Protocol Assessment Tool may not be enough

Reflections from this workshop:

- How can we generalize current DMC guidelines to incorporate adaptive designs?
 - Guidelines for sponsor interaction with DMC
 - A suggestion: “The LETTER”:
 - Sent from FDA to unblinded sponsor personnel for signature and return to FDA
- Is there potentially LESS bias in seamless phase II/III than in separate phase II followed by phase III?

- Format and content of protocol for adaptive designs
- How to share best practices
 - Checklists?
 - Sharing high quality examples

Example

- In situations where there is a clear / important rationale, can there be limited sponsor involvement with the DMC that would meet the sponsor's concerns, but with appropriate protections in place to maintain trial integrity?

Example

Scenario: Two stage seamless phase 2/3 design

Stage 1: Stop for futility OR Select doses going forward into Stage 2

Proposal: Limited sponsor involvement with DMC

Combination function fully pre-specified & possible scenarios simulated

- Agreement that statistical requirement would be met
- Summary tables of drug efficacy and safety would be shared with limited Sponsor representatives to determine futility or doses going forward

Acceptable with appropriate firewalls?

- NOTE: Potentially improved decision making & less information known about the drug than if adaptations are fully rule driven

Alternatives?