

Adaptive Design and DMC




Questions

- Who should see interim results used to make adaptations? Who will be involved in the decision making process?
 - Should decisions about design changes be relegated entirely to a DMC? DMC and sponsor? Other?
 - If the sponsor views data as informative to make design changes, should investigators and patients have access to this information also?

Discussion

- Confidentiality of Phase II Results Greater with Phase II/III Design
- Probably Need Substantial Sponsor Involvement in Adaptive Decisions
 - DMCs Already Make Big Decisions in Traditional Trials – Are Adaptive Decisions Really Different?
 - Sponsor Unlikely to Abdicate Authority
 - DMCs May Be Unwilling to Accept Responsibility
 - Can a DMC Make Subtle Risk/Benefit Decisions Without Sponsor Involvement?
- Maintain Firewall Within the Sponsor – Separate Group Within Sponsor Makes Adaptive Decisions
 - Will This Work in a Small Company?
 - Does This Maintain the Perception of Independence to the Outside World?

Questions

- How should these processes differ from more familiar interim monitoring practices?
 - Can DMC specific documents (protocols with algorithms spelled out in detail) unknown to others, address some of these concerns?
 - Should a separate group make adaptive decisions?
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Discussion

- If Arm Dropped for Safety Need to Inform Participants
 - What if Arms Are Dropped for Other Reasons?
- What About Having Sponsor-Only Involved in Phase II Decisions, With DMC Introduced for Phase III only?
 - Asking a DMC to Commit to the Life of a Phase II/III Trial May Be Too Much
- DMC May Require Additional Skills for Adaptive Decisions
- Will We Have Enough DMC Members?
 - Need to Train a New Generation
- TMC Instead of DMC?

Questions

- How can this be implemented while maintaining trial integrity and validity?
 - Are there instances where adaptive decisions (pre-specified algorithm) can unblind the study?
 - Can knowledge of interim results introduce biases into the trial?
 - What firewalls should be in place to maintain trial integrity?

Discussion

- Change in Patient Mix (eg., From M/F to Only M) – Global Null Hypothesis May Be Difficult to Interpret
- Informed Consent Is Contract With Patient
 - Is It Sufficient to Inform Them That Adaptive Decisions Might Be Made?
- Updating the Informed Consent
 - Modifying Trial During “White Space”
 - Can This Lead to Discontinuations?