

THE ROLE OF DATA MONITORING COMMITTEES IN IMPLEMENTING ADAPTIVE DESIGNS

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DMCs AND ADAPTATION

- DMCs are all about adaptation
- Role of DMC is to ensure trial is safe for participants and question being addressed remains meaningful
- DMC may recommend changes based on pre-specified considerations, or ad hoc
 - Pre-specified: early stop for efficacy, harm, futility
 - Ad hoc: modifying dose, adding new risk to informed consent, changing entry criteria

IMPLICATIONS OF ADAPTATION

- Issues with adaptive designs depend on what type of change is being made
- When change conveys information about the emerging results that could affect the future conduct of the trial, concerns about trial integrity arise

TYPES OF CHANGES

- Dropping one or more treatment arms
 - Selecting optimal dose
 - Selecting optimal regimen
- Dropping or adding a subgroup
 - Dropping group with excess toxicity
 - Adding group once safety established for other subgroups
- Changing an endpoint
- Changing the allocation ratio
- Changing the sample size

TYPES OF TRIALS

- Trials not intended to provide definitive information about safety and/or efficacy
 - Phase 1
 - Phase 2
- Trials that could form the basis for product approval or changes in practice

WHAT CHANGES RAISE MINIMAL CONCERNS?

- Changes in an exploratory trial
- Changes in "pivotal" trials for which the adaptation
 - Would reveal no information about the likely outcome for any participant
 - Would have no effect on final inference

EXAMPLES

- Dropping an arm
 - provides no information about how a remaining participant will respond
 - equipoise presumed to still exist for those continuing to be entered
- Changing the endpoint
 - could affect inference if done with knowledge of interim results

EXAMPLES

- Changing the allocation ratio
 - May be done to increase proportion on superior treatment arm
 - In open label study will provide information on emerging result
 - In double-blind study may also provide information if changes in drug ordering and distribution are required
- Increasing sample size
 - provides information that potential benefit is smaller than anticipated
 - provides information about likely participant outcomes

DMCs AND CONFIDENTIALITY

- DMCs can (and currently do) make recommendations for protocol changes on the basis of adaptive rules specified in the protocol—eg, early stopping based on pre-specified boundaries
- If the protocol change raises the concerns noted earlier, the fact that the DMC is the group recommending the change doesn't mitigate the concern
 - Action taken as result of recommendation is what reveals the information

SPECIFIC QUESTIONS

- Who will perform the interim analyses?
 - Usual approach—independent statistician is optimal
- Should there be any sponsor involvement in the adaptive decision?
 - Usual approach—DMC makes recommendation, sponsor must accept or reject.

SPECIFIC QUESTIONS

- How is a recommended adaptation implemented so that the trial continues to run smoothly?
 - Would have to be case by case—thought through and specified in advance
- How will the sponsor ensure that the interim results are not widely known?
 - For some types of adaptation, such as sample size increases, it probably can't

MY QUESTIONS

- Would sponsors be willing to offer a CRO an open account in order to implement adaptations requiring additional resources in a way that keeps sponsors blinded?
- If not, would access of sponsor personnel to information revealing something about emerging data, even if limited to a small number, affect the credibility of the trial?