Challenges for maintaining integrity of results in adaptive studies

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Current data monitoring practices

- Review of accruing unblinded data by a *Data Monitoring Committee* is a common feature in clinical trials.
- Typical motivations:
  - safety monitoring
  - formal group sequential plan allowing stopping for efficacy
  - lack of effect / futility judgments
- Current procedures and conventions governing interim monitoring are a sensible starting point for addressing similar issues in adaptive trials.

Confidentiality / regulatory perspective

- As described, e.g., in the FDA DMC guidance document (2006), access to interim results and unblinded data should be strictly controlled:
  - Such access diminishes the ability of trial personnel / sponsor to manage the trial in a manner that is completely objective.
  - Such knowledge could introduce subtle, unknown biases into the trial, perhaps causing changes in characteristics of patients recruited, administration of the intervention, endpoint assessment, etc.

Issues / distinctions for adaptive trials

- Adaptive trials will certainly require review of accruing data, and for an additional purpose:
  - *to implement adaptations which will govern some aspect of the conduct of the continuing trial.*
- What differences might there be in operational models relative to more familiar monitoring situations?
- Who will be involved in the analysis, review, decision-making, implementation processes?

Role of the DMC

- A DMC is a natural party to consider for an adaptation role
  - they're already allowed access to interim results
  - independence, objectivity
- Is this an *optimal* role for the DMC?
  - possible conflict / mismatch with their more familiar responsibilities?
  - experience in the types of decisions called for.
- Possible misunderstanding: what changes can a DMC implement *pro-actively*?

From FDA draft adaptive guidance (2010)

- An adaptive trial "*includes a prospectively planned opportunity for modification of one or more specified aspects of the study . . .*"
- Prospective "*means that the adaptation was planned (and details specified) before data were examined in an unblinded manner . . .*"

What's "*planned*", "*specified*"?

- What degree of specification is needed?
  - depends on the nature of the trial and adaptation
  - not necessarily a *rigid algorithm*
  - sufficient specification is required to allow the potential changes to be embedded within a valid and interpretable statistical scheme.

More from FDA adaptive guidance

- DMC as the *"implementer"* :
  - *". . . a DMC . . . can help implement the adaptation decision according to the prospective adaptation algorithm, but it should not be in a position to otherwise change the study design except for serious safety-related concerns that are the usual responsibility of a DMC."*
- *Planning* is key - acting within the structure of a well-developed plan, and barring conflict with their primary responsibilities, a DMC can be a natural party to play a role in implementing adaptations.

Single vs separate decision boards

- Should adaptation decisions be made by a party different from a DMC having more familiar roles?
- Can the right decisions of both types be fully *independent* of each other?
- What if there could be some potential *conflict*?
- Planning should aim to ensure that adaptations are sensible in the *full context* of the trial.
- All relevant perspectives should be represented among the decision makers.

Sponsor involvement?

- Current practices generally withhold interim information from study sponsors.
- Might sponsors be uneasy about major decisions with critical long-term implications being totally in the hands of an external party?
  - e.g., for decisions traditionally sponsor responsibilities and / or where sponsor perspective was relevant.
- PhRMA group (*DIJ 2006*): *minimize* the amount of information that would satisfy sponsor interests (including as an option: *none!*):
  - good DMC, sound plan, extensive prior discussions, clear rationale for any access, etc.

"*Back calculation*"

- Even with perfect confidentiality processes, changes within a trial will generally be *visible* to some degree.
- What might this tell observers about the *interim results which led to the adaptation*?
  - Can this convey a degree of information that violates the confidentiality conventions and could compromise trial integrity?

- *Note*: even adaptations which do not convey such information might have potential to modify some aspect of the conduct of the trial.

"*Information conveyed*" - examples

- Planned dropping of treatment arm(s), as in so-called *seamless phase II/III trials*
  - Results which lead to a decision remain confidential
  - PhRMA group (*DIJ* 2006): argued that the potential for bias is generally quite limited
  - Often, not really dissimilar to many conventional *futility* judgments
- Sample size re-estimation (*unblinded*)
  - Would seem to be more of a concern
  - In general, weaker treatment effects lead to larger SS increases

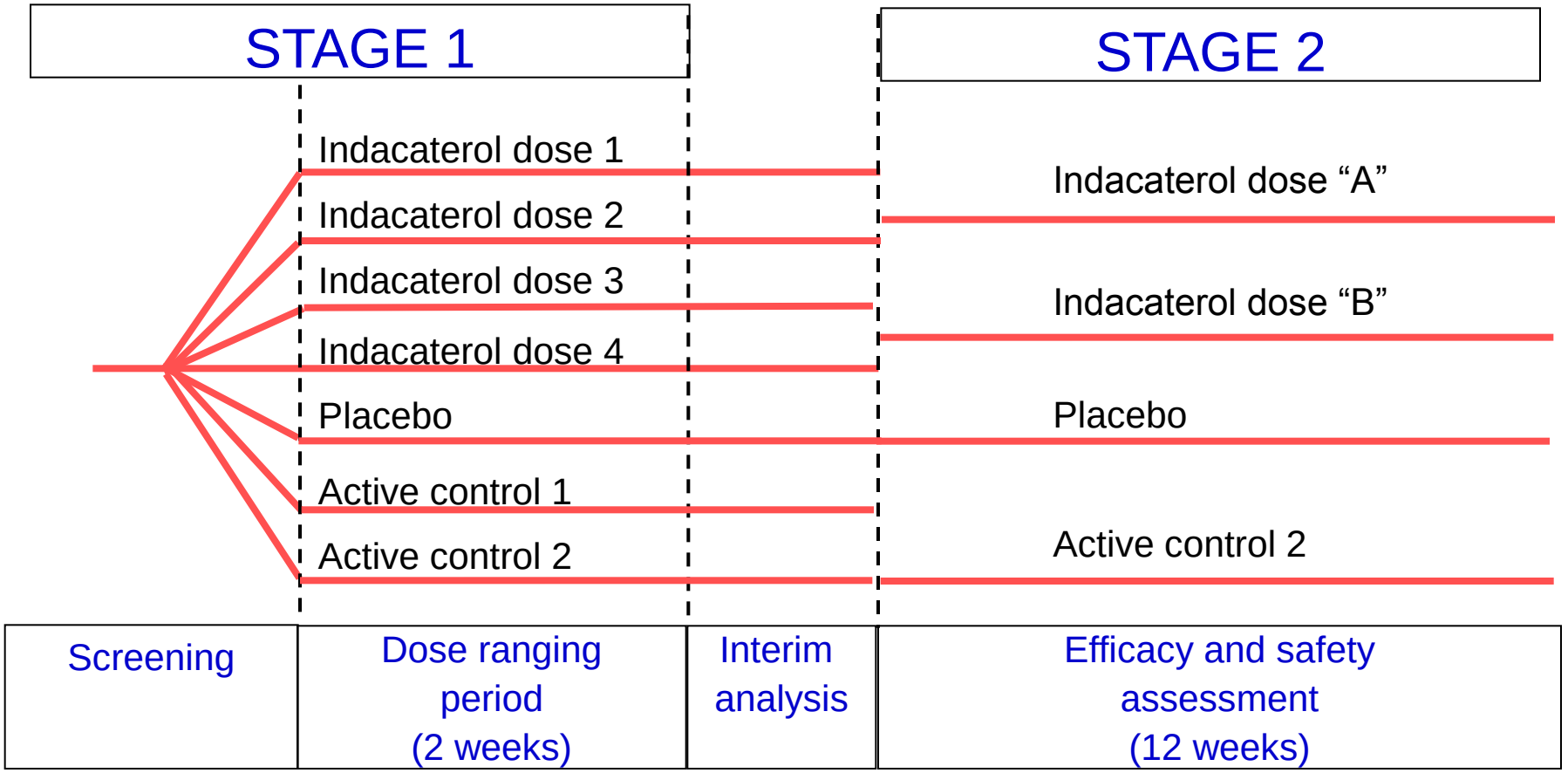
Remedies?

- Not always easily solvable, and this issue should be kept in mind in designing adaptive trials.
- Can we quantify or characterize the risk of certain types / degrees of information conveyed?
  - e.g., familiar group sequential schemes convey *some* information, but we're comfortable with that.
- Partial remedies may fit some circumstances
  - Can some details of the adaptation algorithm be not broadly disclosed?
  - Can knowledge of the changes made be restricted?

Example – *INHANCE* study

- Adaptive trial for dose selection and to provide confirmatory evidence in COPD patients
- 7 arms: 4 doses of indacaterol, 2 active controls, placebo
- Analysis for dose selection based on 2 week FEV_1 data in an initial cohort of patients
- 2 doses selected for continued enrollment, along with placebo and one of the active controls
- Final evaluation: 12 week FEV_1 using *all patients from both stages* in the continuing arms
  - success criteria properly adjusted for the design.

INHANCE scheme

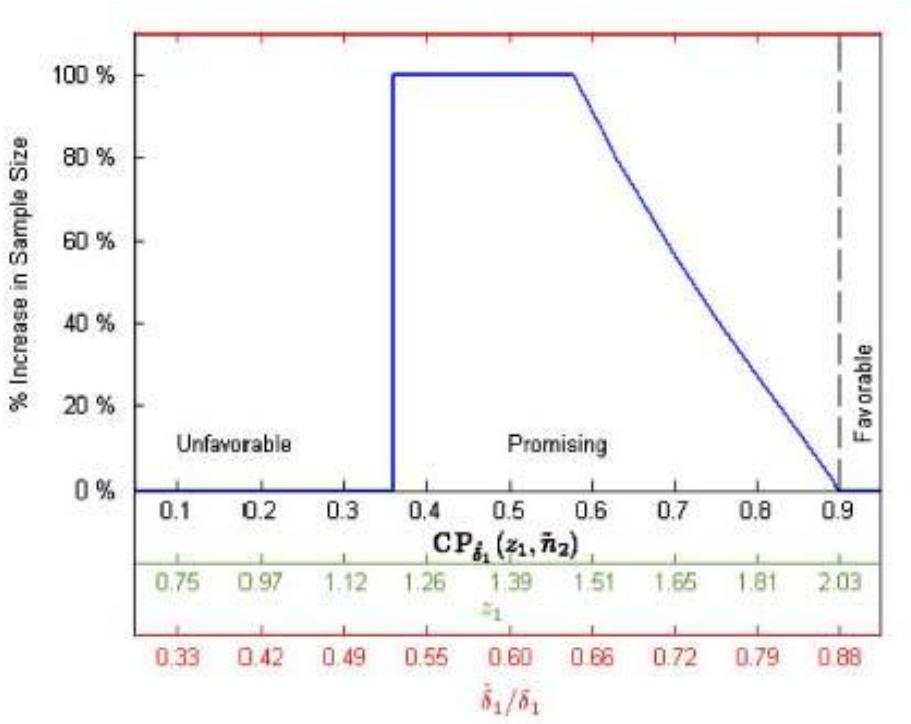


INHANCE DMC set-up

- Complex dose selection algorithm was developed, supported by extensive *simulations*, that all parties felt should suffice.
- Expert DMC was charged; sponsor was satisfied that decision could be made without information supplied to sponsor and trial team, other than doses selected.
- In case some *unexpected* issue arose during review which might cast doubt on the adequacy of the algorithm, the DMC could *confidentially* discuss with pre-designated sponsor contact personnel
  - *contingent*, at the DMC's discretion
  - {this contact never took place}.

SSR example: "*promising zone*"

- From Mehta-Pocock, *Stat Med* 2011



- Question: does this convey *serious* information?

Summary

- The principles are generally pretty clear:
  - Pre-planning is *essential*
  - Decision makers possess all relevant expertise for the responsibilities with which they are charged.
  - Access to results is minimal to meet the needs.
  - Separation of results from those with trial management functions.
- Information apparent to observers (or potential for adaptations to otherwise impact trial conduct):
  - somewhat a matter of judgment and hard to quantify, but an aspect that should not be overlooked.