DMC in the context of adaptive designs

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Outline

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Introduction: Use of DMCs

- DMC traditionally developed to monitor clinical trials to ensure patient safety
- *The purpose of data monitoring committees (DMCs) is to protect the safety of trial participants, the credibility of the study and the validity of study results (Ellenberg et al.)*
- There are two main domains an independent DMC adds to a trial
  - Ensuring the integrity of the study by keeping sponsor, trial personal and patients blinded while looking at unblinded data
  - Independent decision making avoiding conflicts of interest
- Of note, usually DMC makes recommendations to the sponsor only
- Today, DMCs are standard for confirmatory trials (blinded and open label studies)

Clinical studies with an adaptive design

Some guidance already out or in preparation on the use of adaptive designs:

- EMA: Methodological issues in confirmatory clinical trials planned with an adaptive design. Guidance document 2010
- FDA: Adaptive design clinical trials for drugs and biologics. Guidance for Industry 2019
- ICH E20 working group on adaptive designs (since 2019)

A study design is called 'adaptive' if statistical methodology allows the modification of a design element (e.g. sample size, randomization ratio, number of treatment arms) at an interim analysis with full control of the type 1 error (EMA).

Clinical studies with an adaptive design (II)

- Important: How to make design decisions during the study based on interim data without introducing statistical and operational bias
- Like an DMC for patient safety , studies with an adaptive design may require an independent committee for design adaptation
  - For exploratory studies this may be still internal (e.g. dose escalation trials)
  - For confirmatory studies this should be independent of the sponsor to limit scientific or operational bias due to sponsor unblinding
- DMC can serve also as adaptation committee
- There are discussions if a separate adaptation committee needed
  - To have specific expertise in the committee for the adaptation decision at hand
  - To separate DMC to ensure patient safety independent from adaptation decisions
  - A further committee however further complex study conduct

Clinical studies with an adaptive design (III)

- Clinical trials with an adaptive design are not new
  - Group sequential designs
  - Studies with a futility analysis
- More complex designs are
  - Sample size re-estimation designs
  - Two stage seamless adaptive designs
  - Enrichment adaptive designs
  - Master protocol adaptive designs (basket, umbrella or platform designs)
  - …
- Most frequent are group sequential designs and studies with a futility analysis

Decision making in adaptive designs and the role of DMC

- Usually, DMC serves as adaptation committee, especially for group sequential designs and designs with a futility stopping rule. Let's assume in the following that DMC will always serve for adaptation decisions
- Special aspects of DMC in adaptive designs
  - Independence for design adaptation not needed or even not wanted as the decision is a sponsor's accountability (no conflict of interest for the sponsor here!)
  - Maintaining integrity of the study when making adaptations during the trial more complex
  - For complex adaptive designs (i.e. not group sequential designs or designs with futility) DMC in reality makes the decision on behalf of the sponsor
  - In complex adaptive designs sponsors pre-specify adaptation decision by an algorithm but often with limitations

Decision making in adaptive designs and the role of DMC (II)

- For adpative designs we sometimes observe two things
  - DMC members do not want to make adaptation decision because of portfolio impact
  - Sponsor unwilling to hand complex adaptation decision over to an DMC when the decision cannot be fully prespecified
- Examples for such complex adaptive designs
  - Dose adaptation designs
  - Enrichment designs
  - Master protocol adaptive designs
  - …

Industry's and regulator's needs

- Industry wants to ensure that complex interim decisions are done in their best interest as portfolio decisions are core decisions in industry
  - For complex adaptive designs, decisions not always fully algorithmically pre-specifiable
  - When full pre-specification impossible:
    Either sponsor participates in the adaptation decision or sponsor decides against adaptive design because of adaptation process
  - Sponsor still wants minimizing confounding by the adaptation process
- Regulators primarily want minimizing confounding by the adaptation process
  - Easiest: DMC makes adaptation decision to ensure minimization of confounding and operational bias
  - Participation of sponsor in adaptation decision increases risk for impact on study conduct

Adaptation decision with sponsor participation

- Limited sponsor participation in adaptation decisions in principle possible
- There are ways to ensure minimal impact on study conduct and operational bias. For example:
  - Pre-specified data access plan
  - Strict confidentiality agreements for sponsor personal participating in the adaptation process
  - Strict separation of adaptation decision from other reviews of the DMC. Sponsor excluded from other discussions
  - Sponsor personal participating in the adaptation decision strictly excluded from further study conduct (Protocol amendments, SAP etc.)
  - Independent data coordinating center would remain in place to avoid sponsor being unblinded on patient level
  - Firewall between involved sponsor personal and study team after decision making

Adaptation decision with sponsor participation (II)

- Adaptation committees including sponsor personal however clearly more complex. Demonstration of having followed rules not easy
- There is no free lunch: Additional complexity comes with additional risk
  - Risk that things can go wrong
  - Risk that sponsor cannot demonstrate sufficiently that data confidentiality ensured when required (for example in situations where study results before and after adaptation different)
- Therefore, there needs to be a balance between benefits of having sponsor personal involved and additional risks associated with it:
  - Generally, sponsor involvement should be the exception
  - Sponsor involvement only in situations where decision really difficult to pre-specify. The rationale for such a specific situation should be outlined and discussed with all parties

Summary

- Trials with an adaptive design impact significantly DMC responsibilities
- Usually DMCs also take on task of an adaptation committee making the adaptation decision
- Usually DMC should not include sponsor personal and should stay independent. Independence for adaptation decision however not wanted (sponsor's responsibility)
- In exceptional cases for complex adaptation decisions limited sponsor involvement in adaptation decision (only) may be meaningful but comes with additional complexity and risk. In such a case specific (complex) rules need to be in place to still ensure study integrity

Literature

- Ellenberg S, Fleming T, DeMets D. Data monitoring committees in clinical trials, A practical perspective. Wiley 2003
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