Some considerations on when applying adaptive designs

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What are adaptive designs?

- There are a number of definitions, here is our approach: "An adaptive design is a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial design based on accumulating data from subjects in the trial"

- Adaptive designs (ADs) are applicable to both exploratory and confirmatory clinical trials

Why using adaptive designs?

- Often ADs are used to address uncertainties at the design stage (e.g. target population, outcome variability, optimal treatment for testing…)

- ADs enable modification to the trial design based on interim data

- Adaptive trials have the potential for decreased time to completion, reduced resource requirements and number of patients exposed to inferior treatments, and overall improved likelihood of trial success

Examples of common types of ADs

Different types of adaptive designs have varying levels of complexity and need to be handled differently. Examples include:

- Sample size reassessment
- Interim analyses for futility or efficacy
- Response adaptive randomisation and dropping of inferior treatment arms
- Adaptive enrichment
- “Seamless” designs

Principles for studies with an adaptive design

- Justification of an adaptive design
- Planning an adaptive design
- Limiting the chances of erroneous conclusions
- Reliability of estimation
- Maintenance of trial integrity

- The use of an independent data monitoring committee
- Adaptive designs using Bayesian methods
- Planning, conducting, and reporting simulation studies
- Early versus late drug development

Justification of an adaptive design

ICH E8 (R1):

"the essence of clinical research is to ask important questions and to answer them with appropriate studies“

“Clinical studies should be designed, planned, conducted, analysed, and reported according to sound scientific principles to achieve their objectives.”

ICH E9 discusses principles for controlling and reducing bias in the context of interventional studies

Justification of an adaptive design

- ADs involve a number of practical and operational issues (e.g. feasibility, validity, integrity, efficiency, and flexibility) which must be carefully considered

- The advantages of ADs should be clearly understood such that they outweigh the inherent risk associated with more complex designs

- The tradeoffs of an adaptive versus a non-adaptive design should be carefully evaluated to ensure that at the end the best design is chosen, especially in the context of the overall development program

Planning an adaptive design trial

- Use of the estimand framework (ICH E9 (R1)) is recommended at the design stage, to ensure alignment among trial objective, trial conduct, statistical analyses, and the reported results

- Aspects that should be pre-specified in the protocol include:
  - Anticipated number and timing of interim analyses
  - Rationale for and type of adaptation
  - Anticipated rule governing the adaptation decision
  - Statistical methods for the interim and final analysis
  - Approaches to maintain trial integrity
  - Approaches to maintain type I error control (confirmatory trials)

- Different types of adaptive designs may require different degrees of pre-specification

Limiting the chances of erroneous conclusions

- Generally, the chance of erroneous conclusions with regard to safety or efficacy should be limited
- For efficacy, the standard approach in confirmatory trials is to limit type I error (i.e. the probability of rejecting null hypotheses when true) at a pre-specified threshold
- This is also valid for ADs: ADs should address the risk of type I error probability inflation
- When Bayesian decision rules are used the situation could be more tricky (see next slides)

Reliability of estimation

- For a given estimand, an aligned method of analysis should be implemented that limits bias and variability of estimates to ensure reliable interpretation at the end of the trial
  - Estimates in AD should have no or limited bias as they are used for benefit risk assessment
- AD proposals should therefore evaluate the appropriateness of bias and variability of estimates
  - In some cases, bias and variability can be calculated analytically and in other cases, simulations may be necessary
  - For some designs, specific methods have been derived with improved reliability, and these should be used

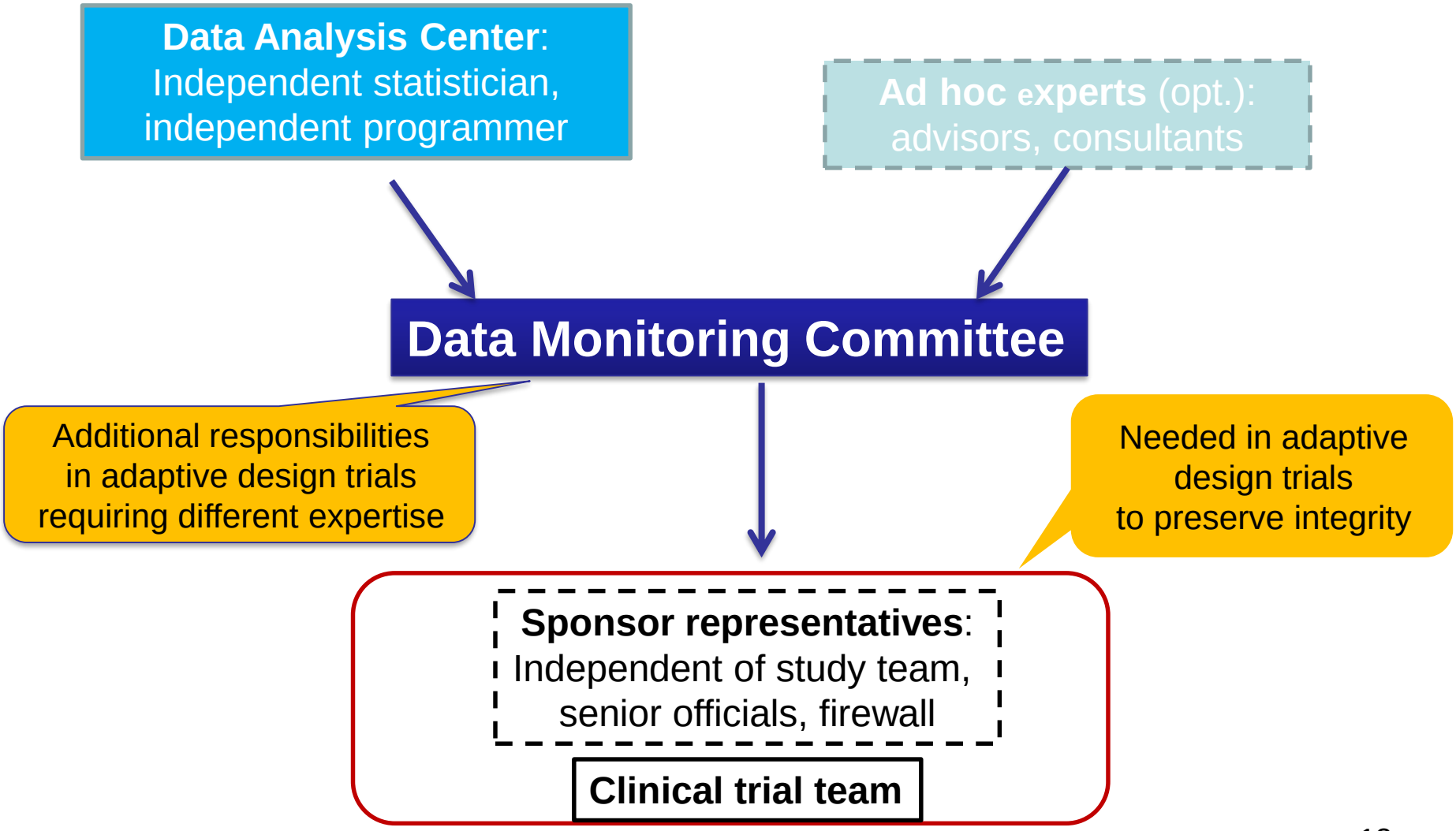
Maintenance of trial integrity

- Knowledge of interim results (whether individual or treatment group level) has the potential to introduce bias or influence the conduct of the study and interpretation of study results
- Integrity of a trial should be maintained such that it achieves its objectives in a timely, reliable, and ethical manner. All adaptations include a risk to change conduct of the trial
- Information distributed to a broader audience on type of interim adaptations and outcome should be minimized

The use of an independent data monitoring committee (DMC)

- DMCs should primarily ensure the safety of patients in the trial, and help assure the scientific validity of the trial results
- DMC must fully understand the trial, the motivations and details of the monitoring, and their specific role
- DMCs can naturally have an important role in adaptive clinical trials for recommending pre-planned adaptations but a separate adaptation committee is also possible
- Adaptations informed by non-comparative data (e.g., blinded sample size re-estimation) typically does not require a DMC
- In confirmatory trials sponsors should be excluded and kept fully blinded. Exceptions are possible but increase risk for bias. Interim analysis should be done by an independent data coordination center

The use of an independent data monitoring committee



Adaptive designs using Bayesian methods

Two types of adaptive designs using Bayesian methods:

1. Adaptive designs with frequentist inference for the analysis may use Bayesian methods to specify adaptation rules
   - For example, futility stopping may be based on Bayesian predictive power, or sample size adaptations may use informative priors on nuisance parameters
   - Requirements for such designs (e.g., Type I error rate control) are the same as for adaptive designs where adaptation rules do not rely on Bayesian methods
2. Adaptive designs using Bayesian inference by providing the posterior distributions of targeted estimands on which decision criteria are based
   - For example, leveraging external data via informative prior distribution and making interim and final efficacy assessments based on posterior probabilities of efficacy
   - Require consideration of issues that do not arise in designs that use frequent inference (next slide)

Adaptive designs using Bayesian methods

Considerations for adaptive designs using Bayesian inference:

- Construction or prior distributions
  - Use of weakly informative priors is largely uncontroversial
  - For non-informative prior distributions, it is critical to document upfront details about the source of the prior information, its relevance to the adaptive design, and strategies to mitigate prior-data conflicts
- Decision criteria
  - Definition of trial success with an adaptive design using Bayesian inference has to be pre-specified through adequate decision criteria
  - Thresholds should be selected such that the success criteria are clinically meaningful and meet common levels of the operating characteristics
  - Results based on the posterior distribution should always be complemented by results when considering study data only
- Operating characteristics
  - Simulations will often be necessary for evaluating operating characteristics
  - When using informative priors, operating characteristics (e.g., type I error rate, power) are only of interest for scenarios that are consistent with the prior (outside type I error will usually not be controlled)

Planning, conducting, and reporting simulation studies

- Major use of simulations in adaptive designs is to estimate operating characteristics of a trial design (e.g., type I error rate, reliability of estimates, adaptation rules) or a development approach
- Importantly, in most cases simulations can only support type I error control, not prove it. Therefore, analytical methods are always preferred
- Simulation studies need to be rigorously planned, conducted, and documented
- Points to consider for the simulation study include:
  - Objective and questions
  - Operating characteristics
  - Design options (i.e., under control of the trialist)
  - Current state of information to inform scenarios (next bullet)
  - Scenarios (i.e., ‘what-if’ scenarios not under control of the trialist)
  - Implementation, including data generating process
  - Documentation of simulation approach and results

Early versus late drug development

- Adequate control of erroneous conclusions in early development as important as in late development
- ADs in early stage development appear easier than in late stage as responsibility of adequate trial conduct and decision making is with the sponsor:
  - Hypothesis testing generally less important in early development
  - Participation of internal staff in adaptation decision easier as no need to demonstrate compliance with rules to the outside
- Adaptive designs in early development can be more complex and handle more research questions

Discussion

- In a setting where ADs can be justified, ADs can lead to a variety of advantages compared to conventional clinical trials. But adaptations need to be pre-planned and carefully executed
- ADs involve a number of practical and operational issues
- The relative importance of the different advantages and challenges will depend on the phase of development
- Reliability of estimation, type I error inflation, and trial integrity are major concerns in ADs and therefore careful planning is required to address these at the design stage
- Some topics (e.g., use of Bayesian methods) need more discussion

Questions?